Current Concepts in Dermatology

Alpesh Desai, D.O., FAOCD
Activity Chair

Acknowledgement of Commercial Support

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Continuing Medical Education Statements

This activity will change your practice and improve patient outcomes!

AOA Statement:
The American Osteopathic College of Dermatology is accredited by the American Osteopathic Association to provide osteopathic continuing medical education for physicians.The American Osteopathic College of Dermatology designates this activity for a maximum of 25 AOA Category 1-A credits and will report CME and specialty credits commensurate with the extent of the physician's participation in this activity. October 16-18, 2015

AAD Statement:
The American Osteopathic College of Dermatology Current Concepts in Dermatology (Activity #698100) is recognized by the American Academy of Dermatology for 25 AAD Recognized Credit(s) and may be used toward the American Academy of Dermatology's Continuing Medical Education Award. October 16-18, 2015

ACCME Statement:
"The American Osteopathic College of Dermatology is currently seeking accreditation by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians."
October 16-18, 2015

American Osteopathic College of Dermatology
Mission Statement &
Continuing Medical Education Needs Assessment

The Continuing Medical Education Activity of the American Osteopathic College of Dermatology will support enhance and advance new models of academic excellence and community health care.

The objectives of this organization are:

1. To maintain the highest possible standards in the practice of dermatology
2. To stimulate study and to extend knowledge in the field of dermatology
3. To promote a more general understanding of the nature and scope of the services rendered by osteopathic dermatologists to the other divisions of medical practice, hospitals, clinics, and the public.
4. To contribute to the best interests of the osteopathic profession by functioning as an affiliated organization of the American Osteopathic Association

Purpose

The purpose of the CME activity is to provide AOA-accredited continuing medical education activities to inform the dermatologist physician. The activity will provide a mechanism by which its constituents can improve competency, maintain board certification, and cultivate lifelong learning. CME will provide physicians with the opportunity to further develop their knowledge through individual and group learning activities. The Continuing Medical Education Committee will monitor the quality of all activities conducted by the AOCD.

Content Areas

The content of CME activities produced by the AOCD is determined and initiated by its members. The CME activity approves the activities based upon needs assessment data to ensure that all offerings present current, state-of-the-art information. Specific areas of emphasis include: (1) state-of-the-art clinical information, (2) health systems administration, (3) public health issues, (4) educational methodology, (5) professionalism in medicine, (6) cultural proficiency.

Target Audience

The primary target audience of the CME activities conducted by the AOCD are the dermatologist physician members. The activity serves community physicians, volunteer clinical faculty, academic clinicians, and students affiliated with the AOCD. The activity will also actively seek to broaden its audience through developing affiliations with CME providers on the national level.

Types of Activities

The core activities presented by the CME activity are live conferences. The activity actively encourages member to develop enduring materials as an evolving tool for continuing education. The activity is committed to exploring the development of its capacity to expand resources in other educational techniques, including Web-based activities and point-of-care technologies.

Expected Results

As a result of participation in the AOCD Continuing Medical Education activity, practicing clinicians will have access in obtaining assistance in the correction of outdated knowledge, the acquisition of new knowledge in specific areas, mastering of new skills, and the changing of attitudes or habits, etc.

These objectives will be achieved in a setting which is evidence-based, culturally sensitive, and free of commercial bias. The AOCD is committed to the practice of continuing activity improvement. The AOCD will actively explore new educational technologies, develop collaborative relationships with other CME providers, and seek to build the capacity to evaluate competency-based outcomes among the clinicians we serve.

Accreditation:
The AOCD is accredited by the American Osteopathic Association.

Meeting Objectives:
The 2015 Fall Meeting will provide a diversified CME activity focusing on the art and science of dermatology. Information will be presented through lectures and scientific paper presentations. Attendees will be updated on a broad range of new developments in dermatology and acquire a better understanding of advances in medical and surgical therapies. They will also gain greater insight into current trends in practice management as well as financial and medical/legal challenges facing today's clinician.

Needs Assessments:
The activity was developed based upon the needs of physicians within the association identified through: (1) an activity evaluation/survey provided to meeting participants at both our annual and midyear meeting, (2) recommendations received through the mail, email, or by phone, (3) recommendations from previous activity chair, and (4) new advances in dermatologic treatment identified in major publications or research studies. The Board of Trustees also meets to discuss previous conferences and to provide additional topics and potential speaker contacts.

Faculty Disclosure:
As a sponsor accredited by the AOA, it is the policy of the AOCD to require the disclosure of anyone who is in a position to control the content of an educational activity. All relevant financial relationships with any commercial interests and/or manufacturers must be disclosed.

Disclosure of Commercial Support of CME:
As you undoubtedly know from the national media, there has been much discussion concerning the relationships between CME sponsors, faculty and commercial companies providing support of CME.

Both the American Osteopathic Association and the Committee on Continuing Medical Education have adopted regulations for ethical actions in this area which the American Osteopathic College of Dermatology endorse and have adopted for all our educational activities.

Please be assured that having an affiliation with a company does not imply in any way that something is wrong or improper; however, we want to inform attendees that such a relationship exists.

Should you have any questions regarding the facilities, handouts, activity content, or concerns about CME compliance with the AOA "Uniform Guidelines," feel free to contact the AOCD representative:

Marsha A. Wise, BS
Executive Director
P.O. Box 7525
Kirksville, MO 63501
660-665-2184
800-449-2623

Unresolved issues regarding compliance with the AOA "Uniform Guidelines" can be brought to the attention of the AOA Division of CME by calling: 800-621-1773, or by writing: AOA CME Office

142 East Ontario Street, Chicago, IL 60611

Meeting Faculty & Needs Assessments

Rick Lin, DO, FAOCD
Dr. Rick Lin is a board-certified dermatologist practicing in McAllen, TX since 2006. He is the only board-certified Mohs micrographic surgeon in the Rio Grande Valley region.

Dr. Lin earned his Bachelor degree in Biology at the University of California at Berkeley and received his medical degree from University of North Texas Health Science Center at Fort Worth in 2001. He also graduated with the Master in Public Health Degree at the School of Public Health of the University of North Texas Health Science Center. He then completed a traditional rotating internship at Dallas Southwest Medical Center in 2002.

In 2005, he completed his dermatology residency training at the Northeast Regional Medical Center in Kirksville, Missouri in conjunction with the Dermatology Institute of North Texas. Dr. Lin served as the chief resident of the residency training program for two years. He was also the resident liaison for the American Osteopathic College of Dermatology for two years prior to the completion of his residency. In addition to general dermatology and dermatopathology, Dr. Lin received specialized training in Mohs micrographic surgery, advanced aesthetic surgery, and cosmetic dermatology.

Dr. Lin is board-certified by American Osteopathic Board of Dermatology in the primary specialty of dermatology. He also holds the certification of added qualification for Mohs micrographic surgery from the Bureau of Osteopathic Medical Specialists of the American Osteopathic Association and the American Osteopathic Board of Dermatology.

As a leader in the field of dermatology, he is currently serving on the Board of Trustees for American Osteopathic College of Dermatology. He also chairs the Information Technology Committee of the Texas Osteopathic Medical Association and is the President for District 14. Dr. Lin also serves on several advisory boards for different pharmaceutical companies and contributes his opinion to the development of new medications.

Disclosures: No disclosures

Alpesh Desai, DO, FAOCD
Dr. Alpesh Desai is a leading board-certified dermatologist who specializes in all aspects of adult and pediatric dermatology, including general, surgical and cosmetic dermatology. He shares excellent academic and professional credentials, as well as a genuine commitment to sharing knowledge and experience with both his professional colleagues and his patients. It comes as no surprise that he has been named as one of Houston's Best Physicians by Health & Fitness Sports Magazine in 2007, 2008 and 2009.

A Houston native, Dr. Desai returned to the area after successfully completing a surgical internship and dermatology residency in southern California. In 2006, he was selected among several of his peers to take over one of Houston's most prestigious dermatology practices. With the help of his brother Dr. Tejas Desai, he expanded the practice to include Mohs micrographic surgery, cosmetic procedures and clinical research trials. At Heights Dermatology and Aesthetic Center, the mission has been to utilize the emerging technology to deliver advanced patient care with a personal and caring touch.

His long list of professional affiliates includes memberships at the local and national levels, including the Texas Medical Association, Harris County Medical Society, and American Academy of Dermatology. Dr. Desai is also a leader in the field of dermatology and conducts many clinical research trials in dermatology. He also provides free dermatology care to local charities and was recently awarded an Honor of Distinction by the Asian American Physician Association for his contribution and dedication to Southeast Asia Orphanages.

As a well-recognized expert in his field, Dr. Desai has been frequently featured in print and broadcast media. He has been on numerous radio interviews discussing dermatological issues ranging from psoriasis to cosmetic procedures. Furthermore, he continues to contribute back to his medical community by authoring multiple medical articles, manuscripts, and texts currently in print.

He is actively sought for civic, local, and national speaking engagements, where his goal has always been to educate and advance the care of dermatology diseases and skin cancer prevention.

Disclosures: No disclosures

Will Kirby, DO, FAOCD
Board-certified dermatologist, Dr. Will Kirby, has a degree in biology from Emory University. He received his medical degree from Nova Southeastern University and completed his first year of postgraduate training in internal medicine at Mount Sinai Medical Center. His dermatology residency training took place in association with Western University/Pacific Hospital where he was honored by being selected to serve as chief resident in the Department of Dermatology. Academically, Dr. Kirby proudly serves as a Clinical Assistant Professor of Dermatology at Western University of Health Science and as a Clinical Assistant Professor in the Department of Internal Medicine, Division of Dermatology, for Nova Southeastern University. He is also an expert reviewer for the Osteopathic Medical Board of California in dermatology.

Dr. Kirby lectures at national medical conventions, publishes articles in peer reviewed medical journals, authors and co-authors medical text book chapters and has the prestigious honor of serving on the editorial advisory board of popular dermatological publications including the Dermatologist and the Journal of Aesthetic and Clinical Dermatology. He has served as the national spokesman for Johnson & Johnson's Neutrogena Dermatologics and Kimberly Clark's Truist Skin Care lines.

A licensed osteopathic physician and surgeon in the state of California since 2002, Dr. Kirby is recognized as a Fellow by the American Osteopathic College of Dermatology. He is currently a member of the American Osteopathic College of Dermatology (AOCD) and the American Osteopathic Association (AOA). In the past, Dr. Kirby has held membership in the American Medical Association (AMA), the American Society for Laser Medicine and Surgery (ASLMS), the American Society of Dermatologic Surgery (ASDS) and the American Academy of Dermatology (AAD). Having appeared on more than 35 different television shows, Dr. Kirby was a featured physician on E! Entertainment Television's "Dr. 90210" and has frequently been seen on "The Doctors," where he showcases his dermatology practice. Other TV appearances have included "The Young & The Restless," "LA Ink," "The Real Housewives of Orange County," "Regis & Kelly," "The Talk" and "Chelsea Lately" and has appeared on QVC more than 100 times. Dermatologist, professor, spokesman, researcher and author, Dr. Kirby is well-recognized as one of the country's leading dermatologists!

Laser Tattoo Removal
Objectives:
1. Discuss the history of laser tattoo removal
2. Provide suggested treatment and parameters
3. Discuss future implications

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Development of new technology.
4. Advances in medical knowledge.

References:

- "Unanticipated Ink Retention Following Tattoo Removal Treatment". The Journal of Clinical & Aesthetic Dermatology. July 2013:27-31.
- "A Proposed Scale to Assess Tattoo Removal Treatments". The Journal of Clinical & Aesthetic Dermatology. March 2009: 32-37.

Core Competencies: 2, 3, 4, 7

Disclosures: No disclosures

Matt Leavitt, DO, FAOCD

Dr. Matt Leavitt is a board-certified dermatologist and the Founder and Chief Medical Officer of Advanced Dermatology & Cosmetic Surgery (ADCS), the country's largest dermatology practice. Additionally, he is Founder and Chairman of Ameriderm, a division that provides billing and collections services for dermatology practices outside of ADCS.

Dr. Leavitt also founded Medical Hair Restoration (MHR), which he grew into national practice for surgical hair transplantation that became the second largest hair restoration practice in the country. Dr. Leavitt now holds the office of Executive Medical Advisor with Bosley, the largest hair restoration group in the world, due to the merger of MHR and Bosley.

Dr. Leavitt has served as President of the American Osteopathic College of Dermatology (AOCD) and as Advisor and Trustee for the North American Academy of Cosmetic and Restorative Surgery. He is a founding father of the American Board of Hair Restoration Surgery, where he served as its first vice president. The group administers board examinations and establishes standards for hair transplant surgeons. He was also the founder of the World Hair Society. Additionally, Dr. Leavitt was one of the founding members and is currently the president, of the Hair Foundation.

As clinical advisor for Merck Pharmaceutical, Dr. Leavitt was among the original physicians selected to study the effects of the hair-growth drug Propecia on hair transplantation. Dr. Leavitt is currently a member of the advisory boards and national speaker for Abbott and Allergan, both pharmaceutical companies specializing in dermatology products. Formerly, he was a member of the advisory boards of Pfizer (now Johnson & Johnson) Consumer Health, manufacturers of Rogaine. He was selected by the National Educational Foundation to train other physicians nationwide on the use of Botox and was a member of Connetic's Clinical Advisory Board, a company noted for its development of skin, dermatology and scalp related medications. Since 2005, Dr. Leavitt has served as a special consultant to Lexington International, manufacturers of the Hairmax LaserComb.

Dr. Leavitt currently is a Clinical Assistant Professor in Dermatology for University of Central Florida, University of Florida and NOVA Southeastern University. Additionally, he is a preceptor for NOVA University's Physician Assistant Training Program. He is often requested to speak at Dermatology Grand Rounds at the University of Florida and the Florida Society of Dermatology Physician Assistants.

Dr. Leavitt's vision led to the development of Advanced Dermatology & Cosmetic Surgery's research division which has undertaken numerous studies for major pharmaceutical companies.

Dr. Leavitt is recognized both nationally and internationally as an accomplished author, clinical researcher, surgeon and lecturer on the subject of hair loss. He has been sought after to speak on hair loss and dermatology to diverse groups amongst which are the AOCD, American Academy of Cosmetic Surgery, American Academy of Dermatology, American Hair Loss Council, Premier Hair Show, European Cosmetic Surgeons, ISHRS, Masters Teaching Workshop in Mexico, the Multi-Specialty Foundation for Facial Aesthetic Surgical Excellence and the American Association of Anti-Aging.

Dr. Leavitt's physician group was originally selected to research and evaluate the CO2 laser and again chosen as a beta site to study the practicality and use of the Erbium laser on hair transplantation. He was the 2002 recipient of the prestigious 'Golden Follicle,' an award presented by nomination from an elite group of leaders and peers involved in hair transplantation surgery, known as the International Society of Hair Restoration Surgery (ISHRS), and selected for two consecutive years for the Milestone Award by the Italian Society of Hair Restoration. In 2002, he was also elected to the Board of Governors of the ISHRS, where he served until 2009.

Dr. Leavitt is a founder and 17 time chairman of the annual Live Surgery Workshop, which is acclaimed worldwide for its scope of training doctors in hair transplant and cosmetic surgery, its scientific presentations by the Who's Who in the field of hair research and cosmetic procedures and for the showcasing of innovative surgical techniques, procedures and patented instruments. Dr. Leavitt is credited with originating 'crosshatching,' and the 'zipper' closure, techniques used in hair transplantation as well as inventing several surgical instruments. He has received three research grants from ISHRS and was a recipient of two educational monographs where he collaborated with a group of other physicians to develop teaching and instructive programs for doctors.

Dr. Leavitt has penned numerous articles for dermatology, hair and cosmetic journals and has served three times as editor for special hair loss editions of the International Journal of Cosmetic Surgery. He published a chapter on "Corrective Hair Surgery" in the first edition of Hair Restoration, a medical textbook, and a chapter on "Follicle Facts" in the fourth edition of the book. In 2004, he authored chapters on "Scalp Anatomy" and "The Consultation Process" in the fourth edition of another textbook, Hair Transplantation. He is also the author of three chapters in

the upcoming 5th Edition of Hair Transplantation and published a chapter on LLLT (low-level laser therapy) in the laser textbook, Lasers and Non-Surgical Rejuvenation. He has also published for the consumer, Women and Hair Loss: A Physician's Perspective, which has been reviewed and acclaimed by such readers as Richard Simmons, and referenced as a source material in medical books.

Dr. Leavitt has been interviewed by Forbes, Men's Vogue, Parents Magazine, International Herald Tribune, MD News, Cosmetic Surgery Times, 20/20, WGN radio, New Beauty, Healthy Aging, Playboy, MuscleMag and Men's Health. He has appeared on America's Health Network, CBS's "The Early Show," The Learning Channel, plus numerous local news programs nationwide. He has been interviewed by the Orlando Business Journal and USA Today regarding the Hairmax Lasercomb as well as appearing on NBC iVillage regarding acne and skin care. Most recently, Dr. Leavitt has been selected by ACG (the Association for Corporate Growth) for the 2010 award for outstanding corporate business. The Florida Medical Business Journal selected Dr. Leavitt as the recipient of the Physician Business Leadership award in 2003, and deemed his Advanced Dermatology & Cosmetic Surgery offices as the "Best Dermatology Practice" in 2004. Florida Business Week has honored the dermatology practice several times for its management, patient care and for Dr. Leavitt's achievements. He has co-sponsored five annual charity golf tournaments benefiting Ronald McDonald House and the Crohn's and Colitis Foundation (CCFA) in Orlando, Florida. In 2009, he was asked to be Chair of the CCFA Take Steps chapter in Orlando, a post he continues to hold.

A graduate of the University of Michigan and Michigan State University College of Osteopathic Medicine, Dr. Leavitt completed his residency at Ohio University Grandview Medical Center.

Female Hair Loss
Objectives:
1. Discuss and identify the various causes and etiology of female hair loss
2. Discuss and identify treatments and/or therapies for female hair loss
3. Discuss hair transplantation as a treatment for female hair loss and determine when it is appropriate

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Availability of new medication(s) or indication(s)

References:
- 4th ed. Hair transplantation, Unger, pgs. 516-524.
- 5th ed. Hair transplantation, Unger, pg 37.
- ISHRS.org
- hairfoundation.org.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: A-Z Surgical/George Tiemann, Allergan, Lexington

Dan Ladd, DO, FAOCD
Dr. Daniel Ladd, is the Medical Director and Founder of Tru-Skin™ Dermatology in Austin, Texas. He earned his B.A. from the University of Texas at Austin and received his medical degree from Des Moines University in 1999. He completed his dermatology residency at the Northeast Regional Medical Center in Kirksville, Missouri in conjunction with the Dermatology Institute of North Texas in 2004. In addition to being board-certified in general and cosmetic dermatology, Dr. Ladd is also board-certified in Mohs micrographic surgery.

He is a member of the American Academy of Dermatology, American Osteopathic College of Dermatology, the American Society of Dermatologic Surgeons and the American Society of Cosmetic Dermatology and Aesthetic Surgery, as well as a Member of the American Society of Mohs Surgery. Dr. Ladd is a lifetime member of the Skin Cancer Foundation's Amonette Circle, an elite group of the country's foremost dermatologists and Mohs surgeons who have made a commitment to skin cancer education and prevention.

Solo Strategies: The Future is Still Bright
Objectives:
1. Increase attendee knowledge of future patient demographics

2. Increase attendee knowledge of future skin cancer burden
3. Discuss strategies to meet future skin cancer burdens in a way that is ethical and profitable

Needs:
1. New advances in dermatologic treatment
2. New methods of diagnosis or treatment
3. Availability of new medication(s) or indication(s)
4. Development of new technology
5. Advances in medical knowledge
6. Legislative, regulatory, or organizational changes effecting patient care

References:

- Census Bureau 2012, Sun Protection. Cancer Trends Progress Report 2009/2010 Update. National Cancer Institute.

Core Competencies: 2, 3, 5, 6

Disclosures: No disclosures

John Cangelosi, MD

Dr. John Cangelosi received his medical degree at the University of Texas Health Science Center at Houston after which he successfully completed an AP/CP pathology residency and dermatopathology fellowship at the University of Texas Medical Branch (Galveston, TX). Dr. Cangelosi is board-certified in dermatopathology by both the American Board of Dermatology and the American Board of Pathology. After dermatopathology board certification, Dr. Cangelosi founded Sagis, PLLC, an entirely physician-owned subspecialty diagnostic pathology laboratory located in Houston, TX. Sagis, PLLC has rapidly grown to be one of the largest dermatopathology laboratories in Texas.

Dr. Cangelosi has performed research in such topics as cutaneous adnexal tumors, histiocytic tumors, cutaneous t-cell lymphomas and non-melanoma skin cancers, and has published in various pathology journals including the American Journal of Dermatopathology, Journal of Cutaneous Pathology and Archives of Pathology and Laboratory Medicine. He has also written a book chapter about cutaneous tumors in Dermatology, A Pictorial Review (McGraw-Hill Medical Publishing). Dr. Cangelosi currently holds academic positions at both the University of Texas Medical Branch and the University of North Texas/TCOM and regularly teaches dermatopathology to both pathology and dermatology residents at numerous residency programs in Texas. Dr. Cangelosi currently holds medical licenses in numerous states including Texas, Indiana, Utah, Arizona, Florida, Oklahoma, Kansas, Illinois and Louisiana. He also holds professional membership in numerous medical societies including the American Academy of Dermatology, The American Society of Dermatopathology, College of American Pathologists, United States and Canadian Academy of Pathology and the American Medical Association.

Benign or Malignant: What Does the Pathology Say?
Objectives:
1. Inform audience that clinically benign lesions can sometimes end up malignant histologically
2. Inform audience that it is important to have low threshold for biopsy if lesion is rapidly growing or long standing and recently changed
3. Discuss as much clinical information as possible and ensure optional clinical-pathologic correlation

Needs:
1. New methods of diagnosis or treatment.
2. Advances in medical knowledge.

References:

- Scaly Erythematous Lesion in a patient with extensive solar damage. Malignant Melanoma In-Situ, amelanotic type. Arch Dermatol. 1996 Oct;132(10):1239,1242.
- Acneiform Primary Cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma with prominent necrosis. J. Cutan Pathol, 2015 Apr;42(4):265-70.

Core Competencies: 2, 3, 4, 6

Disclosures: Sagis, PLLC

Shelly Friedman, DO, FAOCD, FISHRS
In Arizona, the name Dr. Shelly Friedman is synonymous with hair restoration. With 29 years of experience treating more than 16,000 patients—including celebrities, royalty, politicians, CEO's—he has been called one of the top ten hair transplant doctors in the country.

Dr. Friedman has dedicated his medical career to becoming a true specialist in hair restoration surgery. He is the Founding President of the American Board of Hair Restoration Surgery, the certifying board for hair transplant surgeons. Dr. Friedman believes that hair transplantation is a surgical specialty in itself and like other medical specialties, it requires professional oversight to protect the public from inexperienced surgeons. He has lectured extensively nationally and internationally at hair restoration and dermatology seminars. He has also taught his surgical techniques at live surgery workshops.

Dr. Friedman has been very generous with his time and knowledge, training a number of well-known hair transplant physicians. Dr. Friedman not only performs the latest hair restoration techniques but also has advanced the practice of hair transplantation with his own innovative ideas and skills.

Update on Androgenetic Alopecia: Surgical and Non-Surgical Treatments
Hair loss is one of the most common problems seen in a dermatology office. Dermatologists need to be well-versed in both surgical and non-surgical modalities.

Objectives:
1. Provide an update on treatment modalities for androgenetic alopecia in males and females
2. Discuss low-level laser therapy for assisting the physician in treatment patients non-surgically

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Development of new technology.
4. Advances in medical knowledge.

References:

- Friedman, SA. "Not Your Father's Hair Transplant". Aesthetic Practitioner News, July-Aug 2009;4(4).
- Friedman, SA. "To Bald or not To Bald, That is the Question" 2010.

Core Competencies: 2, 3, 6

Disclosure: Capillus, LLC

Suzanne Sirota-Rozenberg, DO, FAOCD
Dr. Sirota-Rozenberg is currently the program director for the dermatology residency training program at St. John's Episcopal Hospital in Far Rockaway, NY. She graduated from NYCOM in 1988, did an Internship and Family Practice residency at Peninsula Hospital Center and a residency in dermatology at St. John's Episcopal Hospital. She holds Board Certifications from ACOFP, ACOPM – Sclerotherapy and AOCD.

Osteopathic Review in Dermatology and Practice Management
Objectives:
1. Discuss the osteopathic approach to dermatology
2. Discuss the correlation between the tenets of osteopathy
3. Discuss practical aspects of running a practice

Needs:
1. Advances in medical knowledge.
2. Legislative, regulatory, or organizational changes effecting patient care.

References:

- *JAOCD*
- *JAOA*

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

Lloyd Cleaver, DO, FAOCD
Dr. Lloyd Cleaver, DO founded the Cleaver Dermatology Clinic in 1986. Dr. Cleaver completed his internship and residency at the Navy Regional Medical Center in San Diego, CA. He is a graduate of Kirksville College of Osteopathic Medicine. He is also a board-certified dermatologist, Fellow of American Osteopathic College of Dermatology and board-certified in Mohs micrographic surgery.

A leader in medical education, Dr. Cleaver is a Professor of Dermatology at the Kirksville College of Osteopathic Medicine/A.T. Still University and Assistant Dean of Continuing Medical Education at the Kirksville Osteopathic Medical Center/A.T. Still University. He serves as Vice Chair for the Certification Committee of American Osteopathic Association and has been Vice Chair and is currently Secretary to the American Osteopathic Board of Dermatology. He is a Past President of the Kirksville Osteopathic Alumni Association and a Past President of American Osteopathic College of Dermatology.

Osteopathic Continuing Certification Update
Objectives:
1. Provide an understanding of the OCC process that ensures osteopathic physicians are current in their specialty.
2. Discuss the five components of OCC which include: Unrestricted License, Lifelong Learning, Cognitive Assessment, Practice Performance, Continuous AOA Membership

Needs:
1. Ensuring college membership understands new requirements for accreditation and maintenance of our board certification.

References:
- http://www.osteopathic.org/inside-aoa/development/aoa-board-certification/Pages/osteopathic-continuous-certification.aspx

Core competencies: 1, 3, 5, 6

Disclosures: No disclosures

David Herold, MD
Dr. David Herold is one of the few board-certified radiation oncologists in the country to have specialized in the treatment of skin cancer using therapeutic radiation. He has practiced both in general and specialty radiation oncology in Palm Beach County since 1999 and has served for over a decade as the Medical Director of Jupiter Medical Center Department of Radiation Oncology and the Palm Beach Cancer Institute - Center for Radiation Oncology.

Dr. Herold completed his radiation oncology residency training at the prestigious Fox Chase Cancer Center in Philadelphia. He had the privilege of working under the direct teaching and guidance of pioneering radiation oncologists including Gerald Hanks, MD, Barbara Fowble, MD, Robert Lee, MD, Benjamin Movsas, MD and Eric Horowitz, MD He spent time during residency training to learn specialized radiation techniques with experts at MD Anderson Cancer Center in Houston and Thomas Jefferson University Hospital and Children's Hospital of Pennsylvania in Philadelphia.

After serving as chief resident at Fox Chase Cancer Center, he began working in private practice at Jupiter Medical Center. Over the next fifteen years he established countless radiation oncology programs, protocols and treatment plans and diligently cared for hundreds of cancer patients. He has earned a reputation for radiation expertise, professionalism and a kind, compassionate old-fashioned style of care. He completed his internship in internal medicine at Northwestern University – Evanston Hospital in Evanston, IL and attended the University College of Medicine in Gainesville, FL. He attained his undergraduate degree from Cornell University in Ithaca, NY. He also spent a year abroad studying psychology and neurophysiology at Oxford University in England before attending medical school.

Dr. Herold pioneered the skin cancer program at Jupiter Medical Center and was responsible for all aspects of the radiation oncology program. He has refined the management of skin cancer treatment using advanced radiation techniques.

The Art of Radiotherapy: Skin Cancer Removal Without a Trace
This lecture is designed to educate clinicians on the use of radiation therapy in the management of BCC/SCC cancers.

Objectives:
1. Review the historical perspective of x-ray therapy
2. Discuss patient selection for radiation
3. Discuss the many radiation options/techniques available

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Development of new technology.
4. Advances in medical knowledge.

Reference:
- Int. J. Radiation Oncology Biol. Phys. Vol 51. No 3 pp 748-755, 2001.
- Int. J. Radiation Oncology Biol. Phys. Vol 52. No 4 pp 973-979, 2002.

Core Competencies: 2, 3, 4, 6

Disclosures: No disclosures

John P. Minni, DO, FAOCD
Dr. John Minni is board-certified in dermatology. He graduated, with honors, from Nova Southeastern College of Osteopathic Medicine in Fort Lauderdale, FL. He completed his internship at Union Hospital/St. Barnabas Healthcare System in New Jersey. He then returned to Florida and completed both family medicine and dermatology residencies at Columbia Hospital and the VA Medical Center in West Palm Beach, FL. Dr. Minni also served as chief resident in dermatology.

Between residencies, Dr. Minni practiced family medicine at the Palm Beach County Health Department while training residents, interns and medical students.

Prior to medical school, Dr. Minni attended the University of Notre Dame as a Notre Dame Scholar and graduated with honors with a B.S. in Biology.

Therapeutic Update
This lecture will discuss newer therapeutic approaches in dermatology for acne, rosacea, psoriasis, eczema and other disorders.

Objectives:
1. Review new therapies in dermatology
2. Review pertinent side effects
3. Discuss results

Needs:
1. New advances in dermatologic treatment.
2. Availability of new medication(s) or indication(s).
3. Advances in medical knowledge.

References:
- *JCAD*
- *JAAD*
- *Current Dermatologic Therapy* Wolverton Text
- *Cutis* 5 part series Rosacea guidelines

Core Competencies: 1, 2, 3, 6

Disclosures: No disclosures

Carlos Nousari, MD
Carlos Nousari, MD is nationally and internationally recognized as a leading authority in dermatoimmunology. He is a clinician, a researcher and a prolific author in the areas of dermatoimmunology, dermatopatholgy and immunofluorescence. In particular, he has conducted extensive research in autoimmune blistering diseases, connective tissue disorders and vasculitides.

Prior to joining Dermpath Diagnostics in June 2004, Dr. Nousari served as co-director of the Division of Immunodermatology at Johns Hopkins Medical Institute in Baltimore, MD, and as chairman of the Department of Dermatology and Director of Dermatopathology and Immunodermatology at the Cleveland Clinic Florida in Weston. Dr. Nousari is currently the program director of the Broward Health Medical Center Dermatology Residency Program. He also serves as the Medical Director at Dermpath Diagnostics South Florida and the Director of the Institute for Immunofluorescence. Dr. Nousari is a Professor of Dermatology at the University of Miami, University of Florida and Nova Southeastern University where he runs an immunobullous clinic.

Urticarial Dermatitis: Urticaria or Mimicker?
Urticaria is a common dermatoses. Increased understanding of clinicopathologic correlation of urticarial and its mimickers will help the practicing dermatologists, dermatology residents and dermatopathology fellows to expand on their differential diagnoses, and provide improved standards for their patients.

Objectives:
1. Discuss the identification of histologic subtypes of urticaria and its mimickers
2. Discuss the diagnostic role of histology and immunofluorescence in urticarial dermatitides
3. Discuss immunopathology as a guide for therapy of common and serious urticarial dermatitides

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Advances in medical knowledge.

References:

- Fitzpatrick's Dermatology in General Medicine – Immunosuppressive and Immunomodulatory Drugs, Ch. 258, p. 2853-64, 5th ed.
- Clinical and Basic Immunodermatology – Cutaneous Vasculitis, Ch. 19, page 277-96, 1st edition, 2008.
- Nousari HC, Anhalt GJ. Pemphigus and bullous pemphigoid. Lancet. 1999 Aug 21;354(9179):667-72.

Core Competencies: 2, 3, 6

Disclosures: No disclosures

Mark Lebwohl, MD
Dr. Mark Lebwohl graduated summa cum laude from Columbia College in 1974 and graduated from Harvard Medical School in 1978. He completed residencies in internal medicine and dermatology, both at Mount Sinai. Dr. Lebwohl has been practicing dermatology since 1983. He is professor and chairman of the Kimberly and Eric J. Waldman Department of Dermatology of the Icahn School of Medicine at Mount Sinai. Dr. Lebwohl is the President of the American Academy of Dermatology. Dr. Lebwohl is chairman emeritus of the Medical Board of the National Psoriasis Foundation. He is the founding editor of Psoriasis Forum as well as a medical editor of the bulletin of the National Psoriasis Foundation, Psoriasis Advance. He is editor of the Dermatology Section of Scientific American Medicine. Dr. Lebwohl has chaired numerous symposia and has written, edited, or co-edited several books including Psoriasis, Mild-to-Moderate Psoriasis, and Moderate-to-Severe Psoriasis. He has authored or co-authored over 500 publications including peer-reviewed articles, invited articles and book chapters. Dr. Lebwohl is actively involved in clinical trials of many new dermatologic treatments.

Osteopathic Dermatology in an Allopathic World
Objectives:
1. Practice management

Needs:
1. Legislative, regulatory, or organizational changes effecting patient care.

References:
- "The Future of Dermatology Practices" Dermatology World, 2014 March.
- "Dermatology Incorporated" Dermatology World, 2012 August.
- "Building Our Advocacy Arm's Muscle" Dermatology World, 2015 August.
- "Dermatology's Advocacy Achievements are No Accident" Dermatology World, 2015 July.

Core Competencies: 5, 6, 7

Disclosures: AbGenomics, AbbVie, Amgen, Anacor, Aqua, Canfite Biopharma, Celgene, Clinuvel, Coronado Biosciences, Ferdale, Lilly, Janssen Biotech, Leo Pharmaceuticals, Merz, Novartis, Pfizer, Sandoz, Valeant.

Brad Glick, DO, FAOCD

Dr. Brad P. Glick, is a Board Certified Dermatologist and Dermatologic Surgeon practicing in Margate and Wellington, Florida. He performs a blend of dermatologic, surgical and aesthetic procedures. Dr. Glick graduated from Emory University with a B.A. in chemistry and received his M.P.H. from the Emory University School of Public Health. He earned his medical D.O. degree with honors at Nova Southeastern University. His internship in internal medicine was performed at South Broward Hospital and his residency in family medicine was performed at Wellington Regional Medical Center and the Palm Beach County Public Health Unit, West Palm Beach, FL. Dr. Glick's dermatology residency training was performed at the Greater Miami Skin and Laser Center at Mount Sinai Medical Center, Miami Beach, FL, where he earned certificates in dermatologic, Mohs micrographic and laser surgery.

Dr. Glick is a Diplomate of the American Osteopathic Board of Dermatology, American Osteopathic Board of Family Practice and National Board of Osteopathic Medical Examiners. He held staff positions at University of Florida College of Medicine, Nova Southeastern University College of Osteopathic Medicine, Northwest Medical Center, Coral Springs Medical Center and Mount Sinai Medical Center. Dr. Glick has served as the Director of Dermatology Residency Training at Wellington Regional Medical Center. Dr. Glick is an Assistant Clinical Professor of Dermatology at the Herbert Wertheim College of Medicine at Florida International University.

Dr. Glick has been the author of numerous publications including journal articles and textbook chapters. He is a guest lecturer for the Abbvie, Amgen, Galderma, Valeant, Medicis and Merz Pharmaceutical Speakers Bureaus and has received numerous honors during his career. Dr. Glick is the Past President of the American Osteopathic College of Dermatology (AOCD), President of the Foundation for Osteopathic Dermatology (FOD) and Past President of the Broward County Dermatologic Society. Dr. Glick offers his patients comprehensive dermatologic care as well as specially formulated skin care products for use as part of a physician supervised skin care regimen.

Biologic/Psoriasis Update

Objectives:
- Properly define psoriasis as a systemic disease
- Identify specific comorbid conditions associated with psoriasis
- Discuss the current treatment algorithm for the management of psoriasis
- Discuss the mechanism of action of the latest psoriasis therapies

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Availability of new medication(s) or indication(s).
4. Development of new technology.
5. Advances in medical knowledge.

References:
- Lebwohl, MG et al. "Patient Perspectives in the Management of Psoriasis: Results from the Population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey". JAAD 2014; 70(5)871-81.
- Armstrong, AW et al. "Undertreatment Treatment Trends & Treatment Sissatisfaction Among Patients with Psoriasis and Psoriatic Arthritis in the US". JAMA Dermatol 2013; 149(10):1180-85.

Core Competencies: 2, 3, 4, 5, 6, 7

Disclosures: Abbvie, Amgen, Galderma, Valeant, Medicis, Merz Pharmaceutical

Clifford Lober, MD, JD
Dr. Lober received his M.D. degree from Duke University School of Medicine in 1974. He then completed his internship at Mayo Clinic in 1977 and his residency at the University of Tennessee in 1982.

Dr. Lober has been in the full-time private practice of dermatology in Kissimmee, FL, for 29 years. He is Adjunct Associate Professor of Medicine in the Department of Dermatology and Cutaneous Surgery at the University of South Florida.

Dr. Lober has received four Presidential Citations from the American Academy of Dermatology and was named "Surgeon of the Year" in 1992 by the Florida Society of Dermatology and Dermatologic Surgeons. He was awarded the first ever "Distinguished Service Award" by the Florida Society of Dermatology and Dermatologic Surgery. Dr. Lober has served on the Board of Directors of the AAD and chaired its section on Health Practice, Policy and Research. He is currently Chairman of the Carrier Policy and Medical Liability Task Force.

The Best Malpractice Defense - Informed Consent
This lecture will review informed consent, stress what should be discussed in a properly executed consent and what may not need to be mentioned, and review exceptions to informed consent.

Objectives:
1. Inform attendees that a signed piece of paper alone is not informed consent
2. Discuss what a good informed consent should contain
3. Discuss what does not have to be conveyed in informed consent

Needs:
1. Legislative, regulatory, or organizational changes effecting patient care

References:
- Legal Medicine, seventh edition, by Mosby Elsevier. "Ensuring Informed Consent"
- Dermatology World, August 2013, pg. 8.

Core Competencies: 4,5

Disclosures: No disclosures

Lisa Swanson, MD
Dr. Swanson is a board certified dermatologist. She was born in New Orleans, LA and raised in Scottsdale, AZ. She attended college at the University of Colorado at Boulder, graduating with honors as an English major. After that, she obtained her medical degree from Tulane University School of Medicine in New Orleans. She performed her internship at Mayo Clinic in Scottsdale, AZ and went on to complete her dermatology residency at Mayo Clinic in Rochester, MN. She recently completed a fellowship in pediatric dermatology at Phoenix Children's Hospital in Arizona.

New Updates in Pediatric Dermatology
This lecture will entail common pediatric dermatology conditions and their treatments. Attendees will gain exposure to commonly misdiagnosed pediatric dermatology conditions. Attendees will learn new treatment options for common pediatric dermatology conditions.

Objectives:
1. Identify common causes of contact dermatitis in children
2. Discuss new treatments for hemangiomas and pyogenic granulomas
3. Provide attendees with some new tools to manage atopic dermatitis in children

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Availability of new medication(s) or indication(s).
4. Advances in medical knowledge.

References:
- "Treatment of Pediatric Pyogenic Granulomas using B-Adrenergic Receptor Antagonists". Lara Wine Lee, et al. Pediatric Dermtology, March/April 2014; Vol 31, Number 2:pg. 203-207.
- "Genital Melanocytic Nevi in Children: Experience in a Pediatric Dermatology Practice". Reagan Hunt, et al. JAAD March 2014 Vol 70 Number 3:pg. 429-434.

Core Competencies: 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

Francisco Kerdel, MD

Dr. Francisco A. Kerdel is the founder of Florida Academic Dermatology Centers. He is nationally and internationally renowned as one of the leaders in medical dermatology. Patients are referred to his practice from throughout the United States, Latin America and the Caribbean. Many of these patients are referred from other dermatologists in recognition of his clinical expertise and innovative approaches to treatment.

He attended the St. Thomas Hospital Medical School, London University, United Kingdom. Dr. Kerdel completed his dermatology residency at Harvard Medical School, Boston, MA where he was chief resident during the year 1983-1984. He completed Fellowships at Guy's Hospital, London, England and New York University School of Medicine, New York, NY. He is Director of Dermatology Inpatient at The University of Miami Hospital, Miami, FL, and former Professor of Dermatology at the University of Miami.

Dr. Kerdel is the current Treasurer-General of the International Society of Dermatology and the Foundation for International Dermatologic Education. Other society memberships include the American Academy of Dermatology, Society for Investigative Dermatology, American Dermatological Association, Cuban, Broward, Miami and Florida Societies of Dermatology.

Dr. Kerdel has been chosen an Honorary Member of the Venezuelan, Argentinean and Chilean Societies of Dermatology and a corresponding member of the Venezuelan Academy of Medicine. Over 150 scientific articles, 33 books and book chapters and 20 abstracts have been authored by Dr. Kerdel.

As an invited speaker, Dr. Kerdel has spoken at national meetings and at international meetings worldwide. He has been a visiting professor in the United States, Japan, Portugal, Italy, Australia, Brazil, Chile, Spain, England, Venezuela, Colombia, Uruguay and Mexico.

Larkin Community Hospital Grand Rounds Cases
This lecture will provide attendees with a useful form of inpatient dermatology grand rounds implemented by Larkin Community Hospital.

Objectives:
1. Discuss new inpatient dermatology unit descriptions
2. Discuss new format for implementing grand rounds
3. Provide interesting case discussions

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Development of new technology.
4. Advances in medical knowledge.

References:
- Case studies seen at Grand Rounds.

Core Competencies: 2, 3, 4, 5, 6

Disclosures: Amgen, Galderma, Janssen Biotech, AbbVie, Pfizer, Novartis, Astrozeneca, Valeant, Celgene

Reagan Anderson, DO, FAOCD
Dr. Reagan Anderson specializes in general dermatology and in Mohs micrographic surgery for the treatment of skin cancer. After graduating from Rampart High School in Colorado Springs, Dr. Anderson moved to Vancouver, British Columbia where he attained his Bachelor of Science and Biology from the University of British Columbia and a Master of Christian Studies degree from Regent College.

Dr. Anderson was then invited to attend the founding Osteopathic Medical School, Kirksville College of Osteopathic Medicine. Upon matriculation, Dr. Anderson was commissioned in the United States Navy where he spent the majority of his time serving the United States Marine Corps as the First Reconnaissance Battalion Surgeon. Dr. Anderson left the military in order to pursue dermatology. During his three-year dermatology residency at the Michigan State University Consortium/Oakwood Southshore Medical Center, he was actively involved in academic pursuits which included national and international lecturing as well as publishing several dermatologic articles. From October 2008-October 2009 Dr. Anderson represented all osteopathic dermatology residents as the resident liaison for the American Osteopathic College of Dermatology.

Since opening the Colorado Dermatology Institute in July, 2010, Dr. Anderson has been recognized as a board-certified dermatologist by the American Osteopathic Board of Dermatology; as a Fellow Member of the American Society of Mohs Surgeons; and is one of approximately 40 Mohs surgeons in the U.S. to attain the prestigious American Osteopathic Board of Dermatology Certificate of Added Qualification in Mohs micrographic surgery. Dr. Anderson is on staff at Memorial and Penrose/St. Francis hospitals and is a member of the El Paso County Medical Society and the Colorado Springs Osteopathic Foundation. He is also an assistant professor at Rocky Vista University College of Osteopathic Medicine in Parker, CO and in conjunction with Rocky Vista University, has founded the Colorado Dermatology Institute/Rocky Vista University Dermatology Residency program–the only one of its kind in Southern Colorado.

Teodor Huzij, DO, FACN
Dr. Teodor Huzij is a graduate of the Kirksville College of Osteopathic Medicine, and he completed an Air Force combined residency in family practice and psychiatry. He served in the U.S. Air Force for nine years. After his military service concluded, Dr. Huzij completed an NMM/OMM plus One Residency at the University of New England in Biddeford, ME.Dr. Huzij is osteopathically board certified in psychiatry and NMM/OMM and is an Assistant Professor of Osteopathic Manipulative Medicine at Rocky vista University College of Osteopathic Medicine. He is also an examining board member of the American Osteopathic Board of Neurology and Psychiatry. Dr. Huzij provides osteopathic psychiatry in his private practice where he specializes in the interface of mental health and manual medicine as well as faith and psychiatry.

What is an Osteopathic Dermatologist Anyway?
This lecture will describe osteopathic principles and practice and how that relates to dermatology.

Objectives:
1. Define what an Osteopathic Dermatologist is
2. Encourage new thought on treatments
3. Start a dialogue of what osteopaths offer the world of dermatology

Needs:
1. New advances in dermatologic treatment.
2. New methods of diagnosis or treatment.
3. Development of new technology.
4. Advances in medical knowledge.

References:

- "Defining the DO" Dermatology World, 2015 June.
- "Dermatology Incorporated" Dermatology World, 2012 August.

Core Competencies: 3, 4, 5, 6

Dr. Anderson's Disclosures: Novartis, Abbvie, Kao, Galderma
Dr. Huzij's Disclosures: No disclosures

RMOPTI/Colorado Dermatology Institute
Benign Epidermal and Dermal Tumors

Objectives:
1. Recognize the most common epidermal and dermal nevi/tumors
2. Identify related syndromes and refer to the appropriate specialists
3. Correlate clinical and histological findings

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge

References:
- Dermatology (Bolognia), Third Edition. Elsevier. 2012.
- Andrews' Diseases of the Skin, 11th Edition. 2011.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

OPTI-West/Chino Valley Medical Center
Premalignant and Malignant Tumors

Objectives:
1. Boards-related material on premalignant tumors
2. New treatment approaches for selected malignant tumors
3. Treatments options for patients at high risk of malignant conditions

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Schwartz, RA, Keratoacanthoma. J Am Acad Dermatol 1994; 30: 1-19.
- Gandini S, Sera F, Cartruzza MS, et al. Meta-Analysis of Risk Factors for Cutaneous Melanoma: II Sun Exposure. European Journal of Cancer 2005; 41: 45-60.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

OPTI-West/Aspen Dermatology
Cysts

Objectives:
1. To histologically differentiate between different cysts
2. What different conditions can include cysts
3. Effective treatment

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology

References:
- Elston, Ferringer. Requisites in Dermatology. Dermatopathology. Sydney: Saunders Elsevier, 2008.
- Elder. Lever's Histopathology of the Skin. Philadelphia: Lippincott Williams & Wilkins, 2005.

Core Competencies: 2, 3, 6

Disclosures: No disclosures

OPTI-West/Silver Falls Dermatology
Acne and Related Conditions

Objectives:
1. Basic science of acne pathogenesis
2. Different acneiform conditions
3. Alternative acne treatments

Needs:
1. New advances in dermatologic treatment
2. New methods of diagnosis or treatment

References:
- Smith R, Mann N, et al. The Effect of a High-Protein, Low Glycemic-Load Diet Versus a Conventional, High-Glycemic-Load Diet on Biochemical Parameters Associated with Acne Vulgaris: A Randomized, Investigator-Masked, Controlled Trial. J Am Acad Dermatol. 2007;57(2):247-256
- Bowe, WP. Probiotics in Acne and Rosacea. Cutis. 2013;92:6-7

Core Competencies: 1, 2, 3, 7

Disclosures: No disclosures

LECOM/Alta Dermatology
Psoriasis: A Therapeutic Update

Objectives:
1. Understand the pathogenesis of psoriasis
2. Review some of the available treatment options for psoriasis
3. Using osteopathic principles, hightlight a "whole-person approach to psoriasis treatment

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Bolognia, Jean. "Psoriasis." Dermatology, 3rd ed. Philadelphia: Elsevier Saunders, 2012.
- Jain, Sima. Dermatology Illustrated Study Guide and Comprehensive Board Review. New York: Springer. 2012. 83-84.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

Advanced Desert Dermatology
Review of Granulomatous, Metabolic and Depositional Diseases

Objectives:
1. How granulomatous, metabolic and depositional diseases present clinically
2. Understand the pathogenesis of granulomatous, metabolic and depositional diseases
3. First and second line treatments of granulomatous, metabolic and depositional diseases

Needs:
1. New methods of diagnosis or treatment

References:

- Kapoor R, Piris, A, Saavedra AP, et al. Wolf Isotopic Response Manifesting as Postherpetic Granuloma Annulare: A Case Series. Arch Pathol Lab Med. 2013; 137(2): 255-258
- Lecha M, Puy G. Deybach JC. Erythropoietic Protoporphyria. Orphanet J Rare Dis. 2009; 4:19

Core Competencies: 2, 3

Disclosures: No disclosures

Affiliated Dermatology
Erythemas and Purpuras

Objectives:
1. To be familiar with the varying figurative erythemas
2. To be able to differentiate the varying pigmented purpuras
3. Identify systemic associations with figurative erythemas and pigmented purpuras

Needs:
1. Advances in medical knowledge
2. New methods of diagnosis or treatment

References:

- Sardana, K., Sarkar, R., & Sehgal, V. (2004, July) Pigmented Purpuric Dermatoses: An Overview
- Mir, A., Terushkin, V., Fischer, M., & Meehan, S. (2012, December). Erythema Annular Centrifugum.

Core Competencies: 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

South Texas Osteopathic Dermatology
Vesiculobullous Diseases

Objectives:
1. Understand general features of vesiculobullous lesions that occur in the skin and oral mucosa
2. Understand the etiology of blister forming dermatoses
3. Know diagnostic aspects and treatment of blister forming conditions.

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:

- Lebwohl, M.G. (2013). Treatment of Skin Disease: Comprehensive Therapeutic Strategies. New York, NY: Elsevier
- Bolognia, J, Jorizzo, J, Schaffer, J. (2012). Dermatology, 3rd Edition. Saunders Publishers.

Core Competencies: 2, 3, 6

Disclosures: No disclosures

UNTHSC/TCOM
Pregnancy Dermatoses

Objectives:
1. Identify physiologic changes of the skin, hair, and nails that occur during pregnancy
2. Describe the pathophysiology and diagnose skin disease specific to pregnancy
3. Manage and treat dermatoses of pregnancy

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Obstetrics and Gynecologic Dermatology, 3e, Black, Martin
- Dermatology, 3e, Bolognia, Jean

Core Competencies: 2, 3

Disclosures: No disclosures

Oakwood Southshore Medical Center
Vasculitides and Vaso-Occlusive Disease

Objectives:
1. Become familiar with the classification of cutaneous vaculitides and vaso-occlusive disease
2. Understand which systemic manifestations may be associated with cutaneous vasculitides and vaso-occlusive disease
3. Review key clinical features which aid in diagnosis of vasculitides and vaso-occlusive disease

Needs:
1. New advances in dermatologic treatment
2. Advances in medical knowledge
3. New methods of diagnosis or treatment

References:
- Micheletti R, Werth V. Small Vessel Vasculitis of the Skin. Rheum Dis Clin North Am. 2015;41(1):21-32
- Wysong A, Venkatesan P. An Approach to the Patient with Retiform Pupura. Dermatol Ther. 2011;24(2):151-72

Core Competencies: 2, 3, 6, 7

Disclosures: No disclosures

MSUCOM/Lakeland Regional Medical Center
Eosinophilic and Neutrophilic Dermatoses

Objectives:
1. Be able to recognize key clinical features of important neutrophilic & eosinophilic dermatoses
2. Be able to order & utililized the necessary labs, imaging, and other tests to diagnosis important neutrophilic & eosinophilic dermatoses
3. Be able to effectively manage and treat important neutrophilic & eosinophilic dermatoses

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Legislative, regulatory, or organizational changes effecting patient care

References:

- Long H, Zhang G, Wang L, Lu Q. Eosinophilic Skin Disease: A Comprehensive Review. Clin Rev Allergy Immunol. 2015 Apr 1.
- Alavi A, Sajic D, Cerci F, Neutrophilic Dermatoses: An Update. Am J Clin Dermatol. 2014 August 26.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

Botsford Hospital/McLaren-Oakland
Cutaneous Manifestations of Systemic Disease

Objectives:
1. Cutaneous diagnostic criteria for systemic diseases
2. Common cutaneous presentations of systemic diseases
3. Clinical interdisciplinary approach to multi-organ diseases

Needs:
1. Advances in medical knowledge

References:

- Kota SK, Jammula S, Kota SK, Meher LK, Modi KD, Necrobiosis Lipoidica Diabeticorum: A Case-Based Review of Literature. Indian J Endocrinol Metab. 2012; 16(4):614-20
- Byun CW, Yang SN, Yoon JS, Kim SH. Lofgren's Syndrome: Acute Onset Sarcoidosis and Polyarthralgia: A Case Report. Ann Rehabil Med. 2013:37(2):295-9

Core Competencies: 2, 3, 7

Disclosures: No disclosures

St. Joseph Mercy Health System
An Update on Alopecia

Objectives:
1. Discuss the key findings in both cicatricial and non-cicatricial alopecias
2. Review the pathogenesis and diagnostic algorithms for alopecias
3. Discuss current and emerging therapeutic options for alopecias in literature

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology

References:

- Baibergenova A, Donovan J. Lichen Planopilaris: Update on Pathogenesis and Treatment. Skin Med 2013;11(3):161-5
- Craiglow BG, King BA. Killing Two birds with One Stone: Oral Tofacitinib Reverses Alopecia Universalis in a Patient with Plaque Psoriasis. J Invest Dermatol. 2014 Dec;134(12):2988-90.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

Still OPTI/Northeast Regional Medical Center
Neuropsychocutaneous Disorders

Objectives:
1. Review common neuropsychocutaneous diseases
2. Discuss treatment options

Needs:
1. Advances in medical knowledge

References:
- Bolognia, Jorizzo, Rapini. Dermatology. Ch 8 – Psychocutaneous Diseases. Pg 109
- Bolognia, Jorizzo, Rapini. Dermatology. Ch 8 – Psychocutaneous Diseases. Pg 111

Core Competencies: 2, 3

Disclosures: No disclosures

LECOM/Tri-County Dermatology
Oral Diseases in Dermatology

Objectives:
1. What are the most common diseases of oral mucosa
2. How to recognize and manage diseases of the oral mucosa in the dermatology clinic
3. How certain oral lesions can be associated to other systemic or dermatological diseases.

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology
6. Legislative, regulatory, or organizational changes effecting patient care

References:
- Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's Disease. N Engl J Med. 1999 Oct 21. 341(17):1284-91.
- Stafford Gary L, Lynch Dennis. Hairy Tongue. http://emedicine.medscape.com/article/1075886-overview.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

O'Bleness Memorial Hospital
Nail Diseases

Objectives:
1. What are the most effective treatments for onychomycosis according to the current literature
2. What are some effective non-prescription alternatives for nail disease treatment
3. Identify and categorize the various fungal nail diseaeses and their most common causes

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Bolognia, J. Dermatology 3rd Ed. p. 1145
- Wolverton, S. Comprehensive Dermatologic Drug Therapy 3rd Ed. p. 55

Core Competencies: 2, 3, 6, 7

Disclosures: No disclosures

University Hospitals Regional Hospital
Photodermatoses

Objectives:
1. Causes of endogenous and exogenous photodermatoses
2. Vitamin D levels and photodermatoses
3. Updates on treatments of photodermatoses

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology

References:
- Clin Dermatol, 2014 Jan-Feb; 32(1):73-9
- Br J Dermatol, 2014 Dec; 171(6):1478-86

Core Competencies: 1, 2, 3, 6

Disclosures: No disclosures

Lewis Gale Hospital - Montgomery
Infectious Disease: Viral Infections

Objectives:
1. How to recognize and differentiate viral exanthems
2. Which viral infections should be treated with oral antiviral medication
3. Various clinical presentations the human herpes virus family can cause

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge

References:
- Bolognia, J.L., et al. Dermatology, 3rd Edition. Elsevier, 2012.

Core Competencies: 2, 3

Disclosures: No disclosures

OMNEE/Sampson Regional Medical Center
Infectious Diseases: Bacterial Infections

Objectives:
1. Identification of common bacterial skin infections
2. Treatment recommendations: Use of antibiotics and concern about antibiotic resistance
3. Post-operative infections in skin surgery

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Bolognia, JL, Jorizzo JL, Schaffer JV. Dermatology, 3rd Edition. Chapt 74. 2012.

Core Competencies: 2, 3, 6

Disclosures: No disclosures

PCOM/North Fulton Hospital Medical Campus
Infectious Disease: Fungal Infections

Objectives:
1. Differentiate between the following fungal forms: yeasts, molds, and dimorphic fungi
2. Correlate clinical and laboratory findings related to opportunistic, cutaneous, and systemic mycoses.
3. Assess the uses of multiple antifungal therapeutic agents.

Needs:
1. New methods of diagnosis or treatment.
2. Development of new technology.
3. Advances in medical knowledge.

References:
- Bolognia Dermatology, 2nd Edition. P. 1158-1160
- Andrews' Diseases of the Skin. Clinical Dermatology. P. 306-307

Core Competencies: 2, 3

Disclosures: No disclosures

Palisades Medical Center
Pediatric Dermatology: Neonatal Dermatology

Objectives:
1. Neonatal eruptions of the newborn
2. Vesicopustual neonatal dermatoses
3. Reactive neonatal erythemas

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Cohen, Bernard. Atlas of Pediatric Dermatology. London: Mosby, 1951. Chapter 2, Neonatal Dermatology; p. 38.
- Bolognia J, Jorizzo JL, Rapini RP. Dermatology 2nd Ed Vol 1. London: Mosby; c2003 Chapter 34; Vesiculobullous and Erosive Diseases in the Newborn; p. 523.

Core Competencies: 2, 3

Disclosures: No disclosures

St. John's Episcopal Hospital
Pediatric Dermatology: Papulosquamous and Eczematous Dermatoses

Objectives:
1. How to accurately describe and diagnose many pediatric papulosquamous and eczematous dermatoses
2. How to compose a reliable list of differential diagnoses based on lesion morphology and distribution
3. How to treat a variety of pediatric papulosquamous and eczematous dermatoses with multiple therapeutic options.

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Legislative, regulatory, or organizational changes effecting patient care

References:
- Bolognia, Jean L, et al. (2012). Third Edition Dermatology. Volume 1. Pp 206. St. Louis: Mosby
- Paller, Amy S; Mancini, Anthony J. (2011) Fourth Edition Hurwitz Clinical Pediatric Dermatology. Pp 73. Saunders: British Library Cataloguing in Publication Data.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

St. Barnabas Hospital
Pediatric Dermatology: Pigmented Lesions

Objectives:
1. Recent advances in pigmented lesions diagnosis in the pediatric population
2. Appropriate evidence-based approach to management of pediatric pigmented lesions
3. How to utilize dermoscopy as a diagnostic tool in approaching pediatric pigmented lesions

Needs:
1. New advances in dermatologic treatment
2. Advances in medical knowledge
3. New methods of diagnosis or treatment

References:
- Alikhan et al. Congenital Melanocytic Nevi: Where Are We Now? Part I. Clinical Presentation, Edpidemiology, Pathogenesis, Histology, Malignant Transformation, and Neurocutaneous Melanosis. JAAD. Oct. 2012.
- Pizzichetta et al. Morphologic Changes of a Pigmented Spitz Nevus Assessed by Dermoscopy. JAAD. July 2002.

Core Competencies: 2, 3

Disclosures: No disclosures

Lehigh Valley Health Network
Pediatric Bullous Disease: Update and Current Treatment Strategies

Objectives:
1. Current understanding of the pathophysiology of pediatric bullous disease
2. Current diagnostic techniques used in pediatric bullous disease
3. Current treatment strategies in pediatric bullous disease

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment

References:
- Hammers, C., Stanley, J. Desmoglein-1, Differentiation, and Disease. J Clin Invest. 2013;123(4):1419-22
- Salud, C., Nicholas, M. Chronic Bullous Diseases of Childhood and Pneumonia in a Neonate with VATERL Association and Hypoplastic Paranasal Sinuses. J Am Acad Dermatol. 2010;62(5):895-6.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

NSUCOM/Largo Medical Center
Pediatric Melanocytic Lesions of the Skin and Nails

Objectives:
1. To improve general knowledge of pediatric melanocytic lesions
2. Discuss the various etiologies and appropriate management for melanonychia striata in the pediatric population
3. Increase understanding of accurate diagnosis and treatment of various melanocytic lesions in children.

Needs:
1. New advances in dermatologic treatment
2. Advances in medical knowledge

References:
- Hurwitz Pediatric Dermatology textbook
- May 2015 Issue of the Journal of American Academy of Dermatology (JAAD)

Core Competencies: 2, 3, 6, 7

Disclosures: No disclosures

NSUCOM/Broward Health Medical Center
Pediatric Dermatology: Tumors of Fat, Muscle and Bone

Objectives:
1. The most common pediatric tumors of fat, muscle and bone
2. Epidemiology, pathogenesis, clinical features, and treatment of pediatric tumors of fat, muscle and bone
3. The board relevant dermatopathology and differential diagnosis of pediatric tumors of fat, muscle and bone

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology

References:
- Wyers MR. Evaluation of Pediatric Bone Lesions. Pediatric Radiol 2010; 40:468
- Yildiz C, Erler K, Atesalp AS, Basbozkurt M. Benign Bone Tumors in Children. Curr Opin Pediatr 2003; 15:58

Core Competencies: 2, 3, 6, 7

Disclosures: No disclosures

West Palm Hospital
Pediatric Vascular Disorders

Objectives:
1. Distinct features of infantile hemangiomas that enable differentiation from other vascular anomalies in children
2. Indications for treatment of infantile hemangiomas
3. Available options in the treatment of infantile hemangiomas and vascular malformations

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology

References:
- Bolognia J, Jorizzo J, Schaffer J, eds. Dermatology 3rd Ed. Amsterdam, Netherlands: Elsevier: 2012; Chapter 103
- You H, Kim H, Kim B, Kim M, Ko H. Propranolol to Treat Infantile Hemangioma (IH) in Patients with Congenital Heart Disease. J Am Acad Dermatol. 2015 May; 72(5):912-4.

Core Competencies: 2, 3, 6

Disclosures: No disclosures

NSUCOM/Larkin Community Hospital
Goltz Syndrome

Objectives:
1. Defining clinical features of focal dermal hypoplasia
2. Genetics and pathogenesis
3. Diagnostic work up, treatment and management of disease

Needs:
1. New advances in dermatologic treatment
2. Availability of new medication(s) or indication(s)
3. Advances in medical knowledge
4. New methods of diagnosis or treatment
5. Development of new technology

References:
- Stevenson D, Chirpich M, Hanson H, et al. Goltz Syndrome and PORCN Mosaicism. International Journal of Dermatology, Dec 2014, 53(12):1481-1484
- Mallipeddi R, Chaudhry S, Darley C, Kurwa H. A Case of Focal Dermal Hypoplasia (Goltz) Syndrome with Exophytic Granulation Tissue Treated by Curettage and Photodynamic Therapy. Clinical & Experimental Dermatology. Mar 2006, 31(2):228-231.

Core Competencies: 1, 2, 3, 4, 5, 6, 7

Disclosures: No disclosures

Thursday, October 15

8:00 a.m. - 12:00 p.m.	AOCD Board of Trustees Meeting
12:00 p.m. - 1:00 p.m.	AOCD Leaders Luncheon
1:00 p.m. - 5:00 p.m.	Resident In-Training Exam
1:00 p.m. - 5:00 p.m.	Private Practice Forum
4:00 p.m. - 6:00 p.m.	Exhibitor Set Up & Registration
4:00 p.m. - 8:00 p.m.	AOCD Program Directors Meeting

Friday, October 16

6:30 a.m. - 7:30 a.m.	Breakfast with Exhibitors
7:30 a.m. - 8:30 a.m.	*Laser Tattoo Removal* **Will Kirby, DO, FAOCD**
8:30 a.m. - 10:00 a.m.	*Female Hair Loss* **Matt Leavitt, DO, FAOCD**
10:00 a.m. - 10:30 a.m.	Break with Exhibitors
10:30 a.m. - 11:30 a.m.	*Solo Strategies: The Future is Still Bright* **Daniel Ladd, DO, FAOCD**
11:30 a.m. - 1:00 p.m.	AOCD Business Meeting/Lunch
1:00 p.m. - 1:30 p.m.	Break with Exhibitors
1:30 p.m. - 2:30 p.m.	*Benign or Malignant: What Does the Pathology Say?* **John Cangelosi, MD**
2:30 p.m. - 3:30 p.m.	*Cutting Edge on Androgenetic Alopecia* **Shelly Friedman, DO, FAOCD**
3:30 p.m. - 4:30 p.m.	*Osteopathic Review in Dermatology and Practice Management* **Suzanne Sirota Rozenberg, DO, FAOCD**
4:30 p.m. - 5:30 p.m.	*Osteopathic Continuous Certification* **Lloyd Cleaver, DO, FAOCD**
7:00 p.m.	Presidential Celebration (Ticketed Event)

LASER TATTOO REMOVAL

William Kirby, D.O., FAOCD

Text Book Chapters

- **Kirby W**, Lasers and Energy Devices for the Skin, Second Edition. Chapter 4: *Tattoo Removal*. Ed. Goldman, Fizpatrick, Ross, Kilmer. CRC Press. Pgs: 74-93. May 21, 2013. ASIN: 1841849332. ISBN-13: 978-1841849331
- **Kirby W**, Kartono F, Small R. Dermatologic and Cosmetic Procedures in Office Practice. *Tattoo Removal with Lasers*. Elsevier. Chaper 30. Pgs: 367-376. September, 21st, 2011. ISBN: 978-1- 4377-0580-5

Journal Articles

- **Kirby W**, Chen C, Desai A, Desai T. Causes and Recommendations for Unanticipated Ink Retention Following Tattoo Removal Treatment. *The Journal of Clinical and Aesthetic Dermatology*. July 2013: 27-31.
- **Kirby W**, Alston D. Successful Treatment of a Traumatic Tattoo on the Ala Following the Removal of a Nose Piercing. *Dermatologic Surgery*, July 2013;1–2
- **Kirby W**, Tantillian M, Desai A, Superficial Frostbite Masquerading as Ecthymosis fro Improper Cryotherapy Use After Q-Switched Laser Tattoo Treatment *Dermatologic Surgery*, Available on-line in December 2013. (Print publication date June 2013
- **Kirby W**, Holmes E, Desai A, Desai T. Best Clinical Practices in Laser Tattoo Removal: Tips for improving patient outcomes and managing patient expectations. *The Dermatologist*, June 2012: 23-28
- **Kirby W**, Chen C, Desai A, Desai T. Successful Treatment of Cosmetic Mucosal Tattoos Via Q-Switched Laser. *Dermatologic Surgery*, December 2011: 1767-1769.
- **Kirby W**, Kotsikas A, Desai A, Desai T. Undesired Pigmentary Alterations Associated with Quality-Switched Laser Tattoo Removal Treatment: A Retrospective Study and Review of the Literature. *Skin & Aging*. August 2010: 38-
- **Kirby W**, Kaur R, Kartono F, Desai A, Desai T. Research letter: Paradoxical Darkening and Removal of Pink Ink Tattoo. *Journal of Cosmetic Dermatology*. 9, 2010;149 – 151.
- **Kirby W**, Desai A, Desai T. Tattoo Removal: Wiping the Slate Clean. *Skin & Aging*January/February 2010: 36-40.
- **Kirby W**, Kartono F, Desai A, Desai T. Treatment of Bullo in Three Patients After Treatment with a Q-Switched laser. *The Journal of Clinical and Aesthetic Dermatology*. January 2010: 39-41.
- Kaur R, **Kirby W**, Maibach H. Cutaneous Allergic Reactions to Tattoo Ink. *Journal of Cosmetic Dermatology*. December 2009: 304-309
- **Kirby W**, Desai A, Desai T. The Kirby – Desai Scale: A Proposed Scale to Assess Tattoo-removal Treatments. *The Journal of Clinical and Aesthetic Dermatology*. March 2009: 32-37.
- **Kirby W**, Kartono F, Passalacqua, et al. Inflammatory Linear Verrucous Epidermal Nevus (ILVEN): A Case Report and Review of the Literature. *Journal of the American Osteopathic College of Dermatology*. 2007: 22-23
- Desai T, May L, **Kirby W**, et al. Evaluation of the SilkPeel System in Treating Erythematotelangiectatic and Papulopustular Rosacea. *Cosmetic Dermatology*. January 2006; 31-37.
- **Kirby W**, Desai T, Horowitz D. Effective Tattoo Removal Treatments. *Skin & Aging*. October 2005: 68-75.
- **Kirby W**, Desai T, Kartono F. Tattoo Removal Techniques. *Skin & Aging*. September 2005: 50-57.

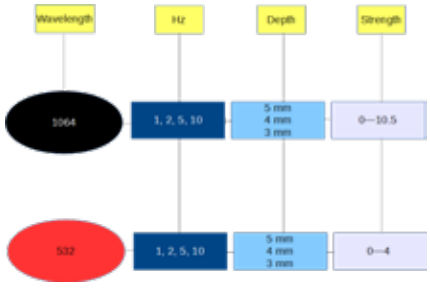
How does laser tattoo removal work?

Tattoo removal works by breaking up ink particles trapped in the dermis. To achieve this, the laser is pulsed over the tattoo, directing light energy into the ink.

The energy is absorbed by the tattoo ink particles, which instantly shatter into tiny fragments.

***If the ink does not absorb the light from the laser, the ink does not shatter, and the tattoo will not be removed.

Laser Tattoo Removal Components



Wavelength

- A wavelength of light is measured in nanometers
- Different laser wavelengths are needed to remove different colors of tattoo ink.
- Some tattoo pigments absorb some wavelengths of light better than others.
- When deciding your settings, you first need to think about what wavelength is appropriate

The Gold Standard for Tattoo Removal Contains Two Wavelengths

- 1064: Targets black very effectively, but can be effective for all colors to a degree.
- 532: Targets red, pink, orange, yellow, brown, and sometimes purple.
- **TOGETHER, THESE WAVELENGTHS ARE DERIVED FROM AN ND:YAG CRYSTAL, THE GOLD STANDARD FOR TATTOO REMOVAL**

Wavelengths and Skin Types

1064 nm

- The "all color", "all skin type" wavelength
- Great for most skin types with the exception of very dark pigments such as a skin type VI

532 nm

- Only appropriate for lighter skin tones because it targets red ink and brown pigment which is the color of melanin.
- Greater risk of hypopigmentation.

Other Wavelengths of Light

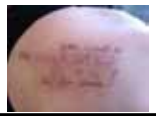
- 694 (The "Ruby") Used for blue and stubborn black
- 755 (The "Alexandrite") Used for greens and blacks
- 585/650 Dye Barrels: These barrels are placed on the end of some devices to convert wavelengths that target blue and green ink. They are not as effective as the Ruby or Alexandrite.
- These wavelengths are also to be used on lighter skin tones only, as they increase risk for hypopigmentation or hyperpigmentation as well.

"What is hypopigmentation?" you ask…

- Hypopigmentation is a decrease in the skin's melanin, or the loss of skin color.

- Conversely, hyperpigmentation is a darkening of the skin

- Both can be present as well



Q-switched vs. Pico vs. Femto

- Q-switched = quality switch, one billionth of a second, measured in nanometers (includes Nd:YAG, Ruby, and Alexandrite)
- Pico = one trillionth of a second (includes Nd:YAG, Alexandrite)
- Femto = 10 to the 15th power

Speed: Measured in Hertz

- How fast do you want your laser to pulse during treatment?
- As a general rule, you choose 10 hz to make things comfortable for your patient and to make the treatment fast.
- Smaller tattoos in delicate places may require a slower pulse rate. Your options are:
- 1 hz, 2 hz, 5 hz, and 10 hz.

Depth: Measured in millimeters (mm)

- The larger the spot size of your laser beam, the deeper the penetration into the ink, the more efficacious your treatment.
- 5 mm is the deepest.
- 4 mm is a medium depth
- 3 mm is the most shallow.

***As a general rule, use the deepest spot size possible with the amount of joules needed to produce a positive clinical reaction.

Energy: (Measured in Joules: J/cm2)

1064

- 5 mm: 0—3.6 J/cm2
- 4 mm: 3.7—6.6 J/cm2
- 3 mm: 6.7—10.5 J/cm2

532

- 5 mm:
- 4 mm:
- 3 mm:

Desired Clinical Reactions

- Snapping
- Frosting
- Mild localized edema
- Petechiae

Snapping

- An audible snap is sometimes all you need to know that your treatment is working.
- It sounds much like a rubber band snapping against the skin
- Sometimes this is the only reaction you want to see on darker skin types. Too much clinical reaction can cause skin discoloration or scarring.

Frosting

Results from Frosting

Frosting Continued

- Frosting is the biggest indicator that your treatment is effective.
- It indicates that you have broken the bond between the ink particles.
- The body will then begin absorbing those particles and digesting them.

Mild Localized Edema

- Mild edema can occur approximately 5 minutes after your treatment pass.
- This is an indication that the body has recognized mild trauma and is beginning to heal the area.
- It can occur with or without the presence of frosting and/or petechiae.

Petechiae

Petechiae

- Pinpoint, round spots that appear on the skin as a result of bleeding.
- Commonly appear in clusters and looks like a rash
- Normal in laser tattoo removal and tend to resolve within one to two weeks.

Pre-care

- Sun avoidance
- Avoiding light sensitizing medications prior to treatment
- Keep area moisturized with vaseline or aquaphor every day
- Make sure it is at least 6 weeks between your treatments and no sooner; or 6 weeks since you had your tattoo placed before beginning treatments
- No accutane for the last 6 months
- Area is clean/dry/intact
- No chance of pregnancy

Post-Care

- Moisturize
- Ice on and off for the first 24 hours post treatment
- Avoidance of any activity that would increase body heat
- No popping of blisters
- Follow up with provider if suspected infection

Proper Follow Up

- All new patients merit a next day follow up phone call no matter the procedure. If the patient is not reachable by phone, an email should be sent and documented.

Returning patients should be called as well, but not necessarily emailed, as a rapport should be strong enough to support leaving a voicemail only.

**ALWAYS follow up with concerned patients right away.

Consultation Components

- The three "Ps": Pain, Procedure and Price
- Introduction
- Form a bond
- Make an assessment
- Determine how many treatments it will take using the Kirby-Desai Scale (See handout, observe presentation.)
- How long does it take?
- How does it feel?
- Aftercare

The KIRBY-DESAI Scale

How to determine how many treatments it will take to remove any given tattoo

KD Scale Continued

- The average number of treatments it takes to remove a tattoo varies based on a number of factors.
- The average of the KD Study was 10 treatments with a SD of 2.65.
- Let's walk through the scale.

KD Scale: Skin Type

KD Scale: Location

KD Scale: Amount of Ink

KD Scale: Layering

TABLE 6. Tattoo Layering and Kirby-Desai score

TATTOO LAYERING	POINTS IN THE KIRBY-DESAI SCALE
No	0
Yes	2

KD Scale: Scarring

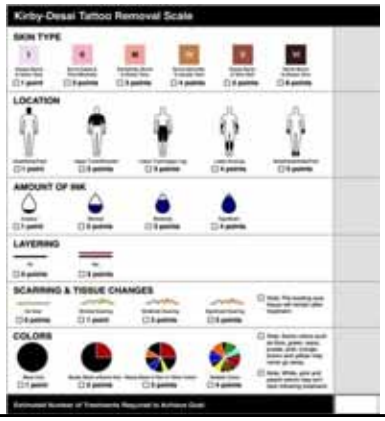
TABLE 5. Scarring and tissue change amount and Kirby-Desai score

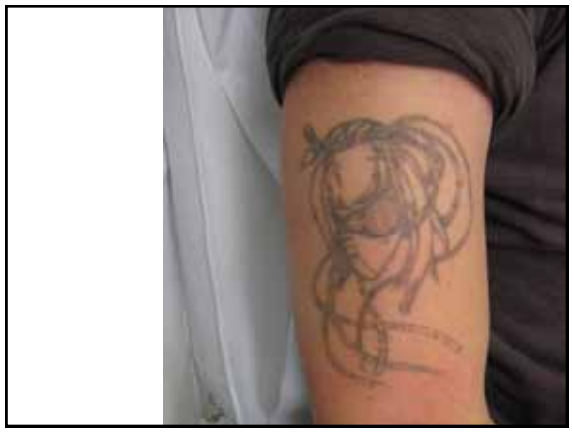
SCARRING AND TISSUE CHANGE AMOUNT	POINTS IN THE KIRBY-DESAI SCALE
No Scar	0
Minimal amount of scarring	1
Moderate amount of scarring	3
Significant amount of scarring	5

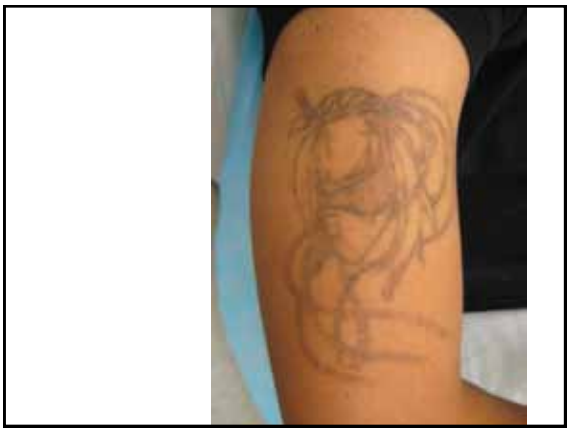
KD Scale: Ink Color

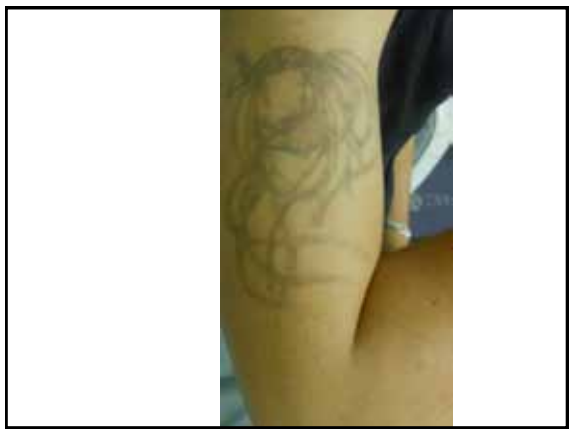
TABLE 3. Tattoo pigment color and Kirby-Desai score

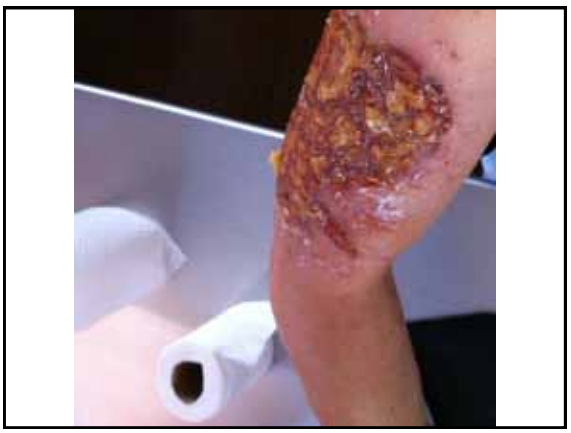
COLOR OF PIGMENT(S)	POINTS IN THE KIRBY-DESAI SCALE
Black only	1
Mostly black with some red	2
Mostly black and red with other colors	3
Multiple colors	4

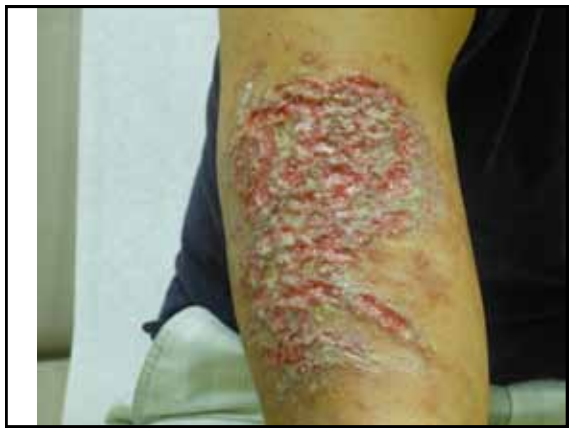


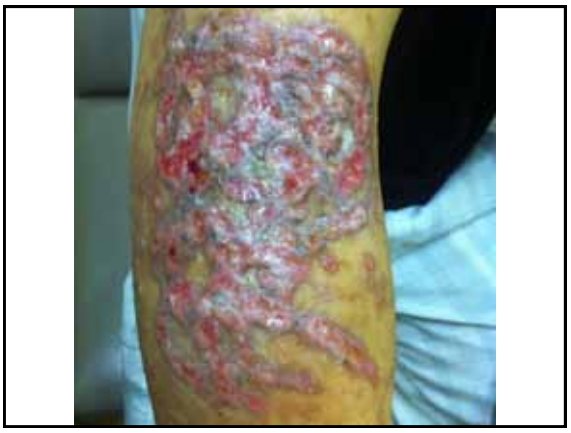


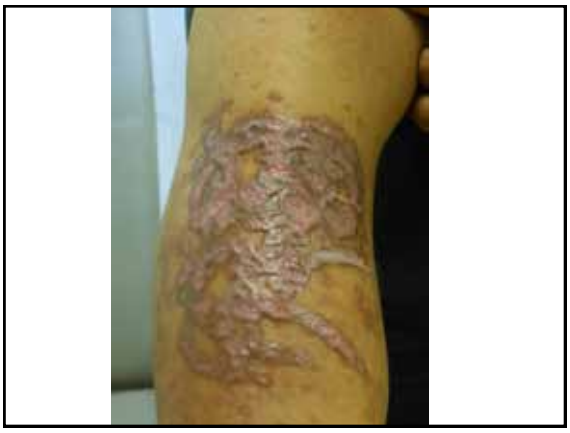


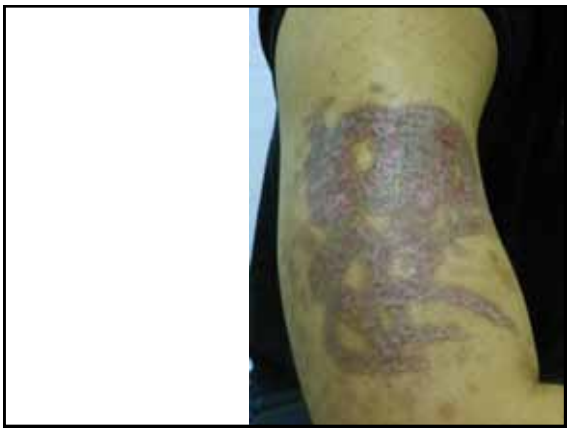


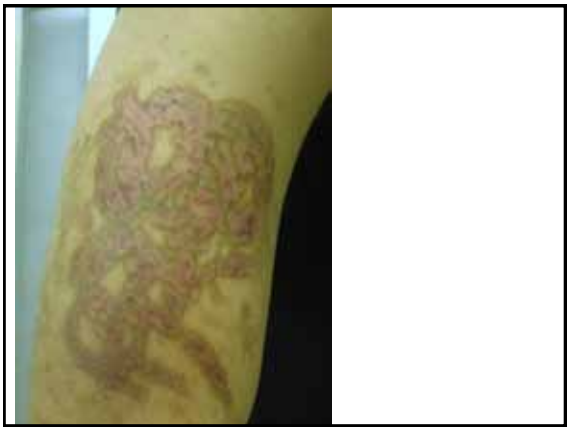












Questions?

Thank you for listening!

Solo Strategies: The Future is Still Bright

By Daniel J. Ladd Jr, DO

Financial Disclosure

- No relevant financial disclosure

Going Solo: What is your personality?

- Do you think of yourself as an entrepreneur?
- Do you "think outside the box"?
- Are you willing to work harder & longer hours?
- Do you like being told what to do? Leader? Follower?

Going Solo: What is your personality?

- What is your comfort level with financial risk?
- Are you comfortable delegating tasks?
- Do you enjoy teaching? New employees? How good are you at managing an employee?
- Remember: YOUR TEAM = YOU in your patient's eyes

Going Solo: What's Your Personality?

- Be a nice doctor.
- Introduce yourself.
- Shake hands.
- Make eye contact.
- Listen to the whole story: faster than interrupting
- Understand the patient doesn't usually care what the name of the rash or tumor is, but is often totally concerned about:
- 1) How quickly it can be cured
- 2) Whether it can be cured or managed
- 3) How it will affect social and business events in their near future.
- Manage these 3 items and you'll have a patient for life.

Going Solo: What is your personality?

- Do you have "Santa Claus" syndrome, ie want everyone to be happy?
- Do you avoid conflict at all costs?
- How attached do you become to staff?
- Healthy distance is actually a really good thing
- There's a reason Santa Clause doesn't give presents to his elves.
- Keeping interpersonal boundaries is critical to success.
- Be honest with yourself.
- If you're not firm but fair, hire someone who is.

Going Solo: What's your personality?

- I really wanted to "steer my own ship" after residency so working for someone else really and truly wasn't an option for me.
- The following is simply my vision of where the future of dermatology is headed and how solo practices can still not only exist but run at a profit.
- My greatest downfall was Santa Claus Syndrome, so I simply hired an office manager who was "The Anti-Claus"
- Dramatic pause…..

The Anti Claus

Important decisions in going solo

- Location, location, location
- Lease or purchase?
- Bank: Business Plan
- Buy existing practice or start from scratch?
- Type of practice: General? Cosmetic?
- Procedure heavy or light?
- EHR system – which one?
- Embracing new technologies?
- To Lase or not to Lase?
- Choosing an office manager

Location

- My personal experience
- Purchased an existing practice in Austin, Texas in 2004.
- Most Derms prefer metropolitan, plenty to do, culture, events etc.
- Metropolitan = Extremely high competition, low $$$
- Opened a rural satellite in 2006 and growth skyrocketed.
- Farmers and ranchers = major skin cancer population.
- Major skin cancer population means more procedures = more $$$
- You can have both! However, starting with Rural makes sense.

Location: Buildout

- Waiting room
- 3 exam rooms, Lab, autoclave
- Does every room need a sink?
- Procedure room, Office, Nurses station
- If you lease there is often a restroom by the elevators or in a common space.
- Keep costs low but remember waiting area is the patient's "First Impression" of YOU.
- EHR: Modernizing Medicine: EMA is derm-centric and it is very helpful in successfully maneuvering Meaningful Use, ICD-10, PQRS, E-Rx etc.

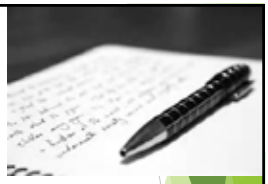
Lease or purchase?

- Leasing is all I've ever done
- Advantages:
- Quick start up. Very important to generate revenue quickly.
- Less expensive than purchasing in the short run (at start up)
- LEAN & MEAN is a great way to start any business plan.
- Repairs are landlord's responsibility
- Every few years you get updated: leasehold improvements
- Recommend having any lease reviewed by an attorney
- Disadvantages:
- Rent doesn't build equity. Renting doesn't build a retirement plan.

Lease or purchase?

- Purchase is a good option to build value over the years.
- May want to arrange locum tenens work to tide you over during the months and months and months of construction.
- Remember that construction deadlines are often inaccurate.
- Often things "come up" that delay your construction and make choosing an opening day difficult.
- Whether you go lease or purchase join the local Chamber of Commerce and have a grand opening event. Helps introduce you to the community

Bank: Business Plan



- This is a very helpful exercise. Allows you to:
- Put it on paper: like a "to do" list
- Allows you to estimate start up costs
- Start visualizing how you'd like your practice to grow
- SWOT
- Strengths, Weaknesses, Opportunities, Threats
- Plenty of studies demonstrate high demand for dermatology services
- Forces you to think like a business person rather than a physician
- (Also allows you to borrow money to start your practice)

Bank: Business Plan

- Once you get your loan & the build out begins:
- Shop around for affordable/used medical supplies & equipment
- Hiring/Recruitment: consider outsourcing
- Really need to hire as good a manager as you can find for admin/front office
- YOU MUST MANAGE THIS EMPLOYEE
- Hire as good an MA as you can find for back office/clinic

"Watch costs and the profits take care of themselves"

Bank: Business Plan

- Visit every local doctor in your area in person. Bring donuts or kolaches.
- Let them know you are brand new and have minimal wait times to get patients in and seen.
- Bring Business Cards with you everywhere you go!!!!
- Get to know the doctors.
- Making a connection is more important than "selling" them on anything.
- Be genuine, be yourself.
- Be well groomed. Firm handshake. Eye contact.
- Once you see a referred patient send a note to PCP. I think this is a great use of dictation services. Sending long EHR notes is actually harder on your referring doc than a personalized dictated note.

Changing Landscape: Expanding Cancer Burden

- Remember that the baby boomers will create a huge demand for skin cancer services
- Mohs surgery is a great revenue generator and a nice thing to offer patients if you are so inclined.
- Maybe you'd really rather not do Mohs….
- Surface Radiation is also a nice thing to offer patients: Allows you to treat skin cancers you would normally send out for Mohs. Keeps revenues under your roof. Patients love it. Excellent cosmetic results.
- I offer patients Mohs or Surface Radiation = happy patients.
- Highest cure rates: surgical and non-invasive.
- I chose to focus on cancer treatment because it is rewarding & profitable.

Changing Landscape: Expanding Cancer Burden

- The number of Americans over 65 will double from
- 40.2 million in 2010 to
- 88.5 million in 2050
- The number of Americans over 85 will triple from
- 6.3 million in 2015 to
- 17.9 million in 2050
- Reference: Census Bureau, 2012
- GENERAL DERM WILL MOVE CLOSER TO GERIATRIC DERM

Changing Landscape: Expanding Cancer Burden

- Between 40 and 50 percent of Americans who live to age 65 will have either BCC or SCC at least once.
- Reference: Sun Protection. Cancer Trends Progress Report 2009/2010 update. National Cancer Institute
- Based on these facts we can estimate that by 2050 dermatologists will be treating double the number of skin cancers we treat now, around 10 million cases a year.

Changing Landscape: Expanding Cancer Burden

- We can also estimate that 1 in 4 or about 2.5 million of those NMSCs will be difficult and complex enough in nature to be treated with Mohs micrographic surgery.
- Since we have no plan in place to double the number of Mohs surgeons we have, nor do we have a plan to add another 8 hours to our work day, it seems unlikely that we'll be able to supply adequate access to the highest quality of care for the American elderly population that suffers from difficult or complex BCC and SCC cases on our current trajectory.

Rates of Comorbidity by Age

Age	Sex	Diagnosis	%	Year	Study
71+	M,F	Alzheimers/Dementia	13.9	2013	NSLTCP
NH	M,F	Alzheimers/Dementia	50.0	2013	NSLTCP
65+	M,F	Pre-Diabetes	50.0	2015	CDC Website
60-79	M	Cardiovascular Disease	69.1	2015	AHA Stats
60-79	F	Cardiovascular Disease	69.7	2015	AHA Stats
65+	M,F	Any Cancer	24.0	2012	Profile, AOA
65+	M,F	Diabetes	20.0	07-10	Profile, AOA
65+	M,F	Hypertension	72.0	07-10	Profile, AOA
Adults	M,F	Overweight or Obese	68.8	09-10	NHANES

NSLTCP - National Study of Long Term Care Providers
CDC - Centers for Disease Control
AHA - American Heart Association
Profile, AOA - A Profile of Older Americans: 2012
NHANES - National Health and Nutrition Examination Survey 2009-2010

Surface Radiation

- Can treat most anatomic sites that we currently use for Mohs
- You don't have to be a Mohs surgeon to perform it
- Patients don't have to interrupt anticoagulation medications
- Excellent cosmesis especially on the nose
- Below the knee (circulation) hands (utility)
- Works very well as an alternative to Mohs surgery, not as a replacement.
- Mohs surgeons can only do a finite number of cases per day
- Problem: Knowledge Gap: radiation therapy hasn't been widely used in dermatology for many years. Mohs cure rates were excellent and our specialty expanded surgically to adapt to this new technique

Surface Radiation

- Educational push is already underway
- ASCO – American Cutaneous Oncology Society
- Mark Nestor, MD, Clay Cockerell, MD
- Excellent organization, however, we need RTTs!
- RADIATION THERAPY TECHNOLOGIST
- These professionals are well versed in the safe and effective delivery of radiation. Rad Oncs use them as a matter of course to help them deliver their prescribed regimens.

Surface Radiation

How does this work?
You create the "Radiation Prescription"
Includes size of lesion plus the clinical margin
Lead shield size (protects normal surrounding skin)
Applicator size (delivers the radiation)
Special shielding (thyroid, mastoid, corneal, intranasal, concavities, eye)
Patient position, photographs
Indications/medical necessity, number of fractions
Usual total dose is between 4000-5000 cGy

How is surface radiation a Solo Strategy?

- After you create the prescription an RTT can deliver the fractions to 30 or so patients per day as long as you (or in some states a mid level) are on site.
- This creates an ancillary revenue stream while you are seeing General Derm patients or performing Mohs or Botox/Fillers, whatever
- 20-30 patients generating revenue for 8-13 treatments in 1 exam room using 1 extra employee (RTT)
- You can market this to your community and colleagues as a Pain Free, Scalpel Free, Non-Invasive skin cancer treatement!
- Patients love it!
- Ethically a good thing to offer elderly patients with multiple co-morbidities
- Excellent cosmesis means more word of mouth referrals

Solo Strategies: Passive Revenue Streams

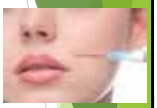
- Slide Prep: hire a histotech to prep slides.
- Up front cost is not unreasonable, can purchase used equipment
- Solo Strategy wise this is another passive revenue stream.
- Research: better pay for doing what you do already. Time, yes, planning yes, but a nice pay off.
- Remember: there are only so many hours in the day. Any way you can generate revenue without taking away those hours from patient care is a prudent financial strategy.

Solo Strategies: Billing, Discussing money with patients

- Know your top 10 minor procedure codes like the back of your hand
- Know how to accurately choose surgical codes
- Modernizing Medicine's EMA helps, but you must still know the underlying codes to make sure you are documenting accurately. Otherwise fear of the machine will likely cause you to undercode.
- Large deductibles: means biopsies, cryo and surgeries will be OUT OF POCKET.
- Patients need to understand OUT OF POCKET before the procedure occurs.
- Cheat sheet "fee schedules" for top 20 codes inside exam room cabinet doors is a smart, fast way to LEVEL with patients.
- Keeps everyone aware. Nobody likes surprises at the front desk. Helps create a plan of care that the patient can adhere to.

Solo Strategies: Extending Your Reach

- Hiring and training mid level providers
- Adding additional clinics in rural (high demand) areas.
- Hair transplantation, Leg Vein ablation
- Lasers, Mini-Facelifts
- Nurse Cosmetic Injectors (or mid levels) esp
- if you're not the "cosmetic" type
- Research: Pharmaceutical companies are paying you to
- diagnose and treat (which you are already doing)
- Private label skin care products
- Body Sculpting Technologies
- Chemical Peels/Aesthetician for IPL etc.

Solo Strategies: Overarching Principles

- HAVE FUN, HAVE A SENSE OF HUMOR
- More procedures = more revenue
- More locations = more revenue
- More providers = more revenue
- More ancillary passive revenue streams = more revenue
- More revenue = insulates you from reimbursement changes
- Choose some sort of cosmetic endeavor to add to your
- practice and learn it well: Educate, Publish, Lead
- Balance revenue with patient care, both are equally important

Solo Strategies: Overarching Principles

- Join leadership of AOCD, attend AOCD meetings
- Learn "the real deal" from your colleagues.
- There are a ton of decisions to make in these changing times.
- In hard times it is important to stick together.
- Pay attention to your Online Reputation: eMerit
- Collect patient emails for an eNewsletter with regular discounts.
- Keep Cancer as a priority in your practice: it matters most to people.
- KEEP CRACKER JACKS, FIRE WING NUTS

Solo Strategies: Hiring/Firing Employees

- CRACKER JACKS:
- These are keepers.
- They make your life easy.
- Don't complain
- Anticipate your needs
- Team players.

Solo Strategies: Hiring/Firing Employees

- WINGNUTS:
- These people must be fired
- as soon as they declare
- themselves (which they always do)
- They make your life miserable.
- They complain
- Fail to complete tasks
- Not team players.

Conclusion

General Dermatologists still have a wealth of opportunities to take advantage of in the pursuit of a solo practice.

Insight into your true personality is the key.

Entrepreneur is not right or wrong, it is just who you are (or are not)

Entrepreneurs must manage their office manager.

Entrepreneurs must hire cracker jacks and fire wing nuts.

Entrepreneurs must understand billing very clearly.

Entrepreneurs must be able to successfully marry good patient care with profitability in an ethical and logical manner.

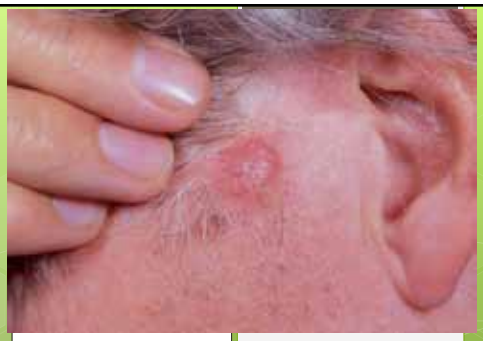
Avoid "Santa Claus Syndrome"

YOU ARE THE ASSET. EVEN IF YOU FAIL, YOU'LL BE ABLE TO RECOVER.

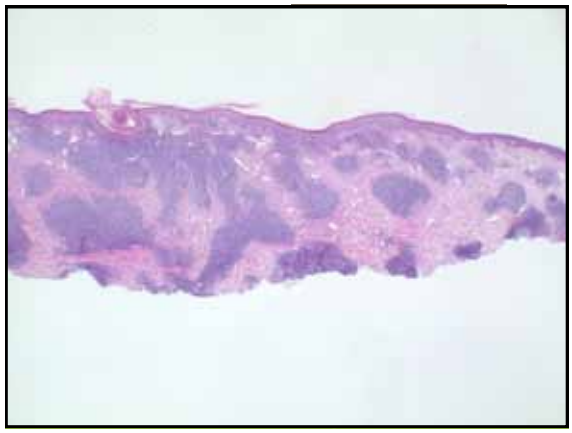
Live Long and Prosper….

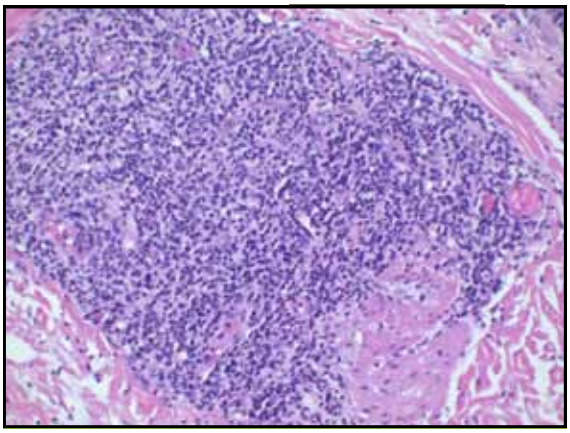
Benign or Malignant What Does The Path Say?

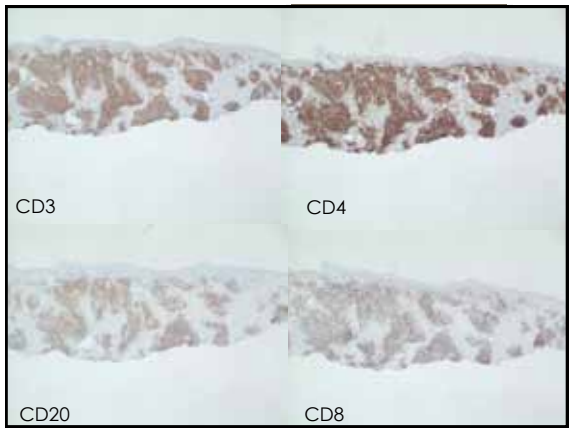
John Cangelosi, MD
Sagis, PLLC



64 yo male presents with a 3 year history of a slowly growing, 1.5 cm pearly plaque on the left sideburn.

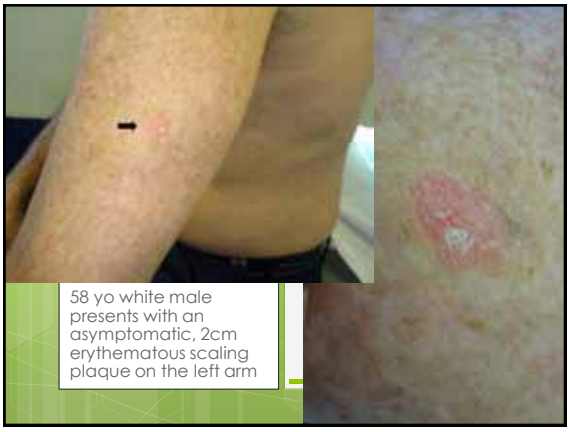




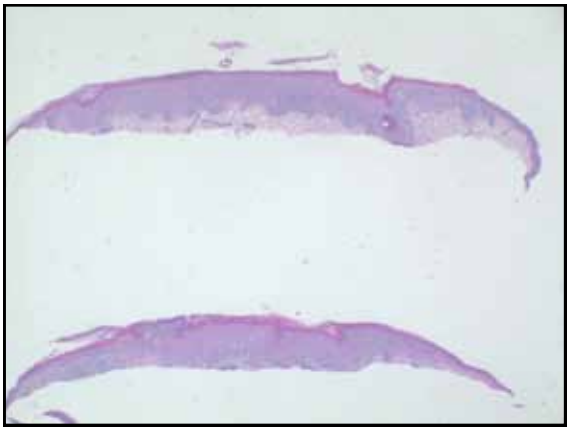


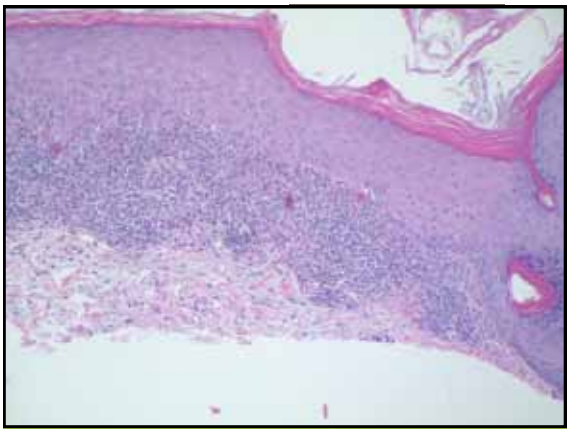
CD4+ Small/Medium Sized Pleomorphic T-cell Lymphoma

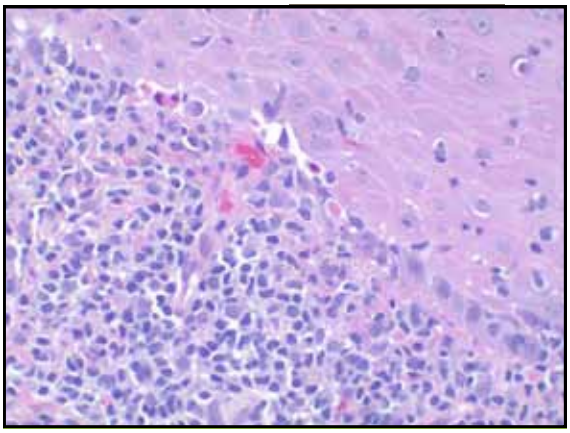
- Rare, 2-3% of all primary cutaneous lymphomas
- Solitary plaque or nodule on face, neck, or upper trunk (lower extremity rare)
- Usually asymptomatic
- Favorable prognosis with 5-year survival rate of 60 – 80%
- Solitary skin lesions have an excellent prognosis (surgical excision or radiotherapy)
- Multiple/larger lesions more aggressive



58 yo white male presents with an asymptomatic, 2cm erythematous scaling plaque on the left arm

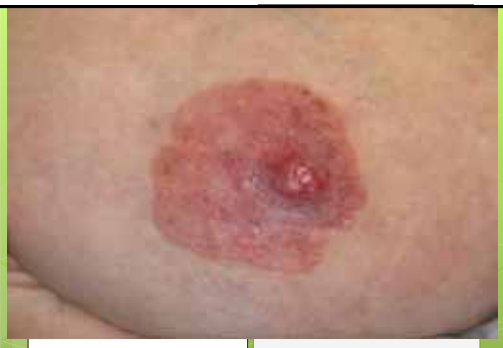




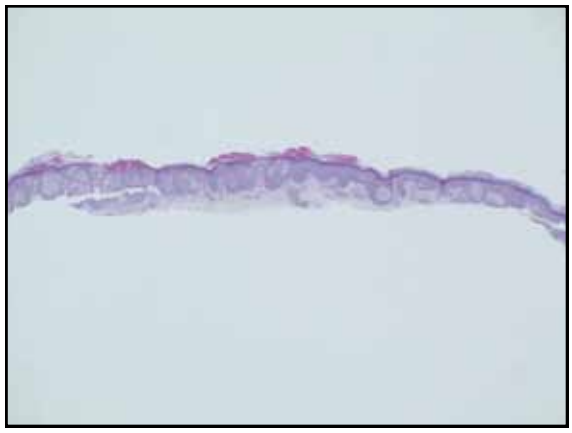


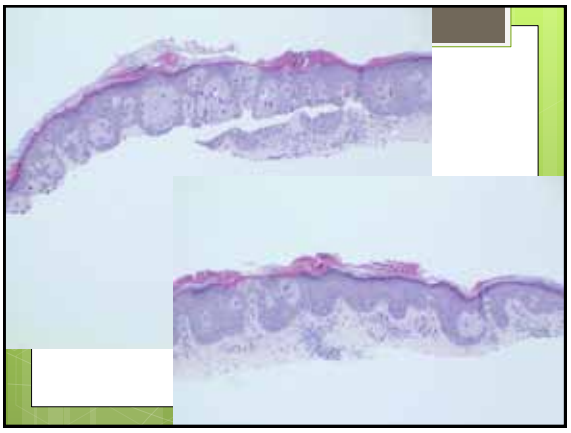
Benign Lichenoid Keratosis

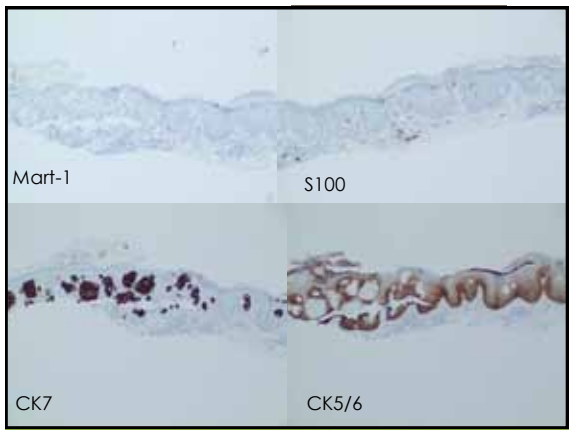
- Short duration
- Predilection for face (cheeks and nose), forearm and dorsal hand, upper trunk, and neck
- Predominately Caucasian
- Females > Males
- 4 – 7th decade

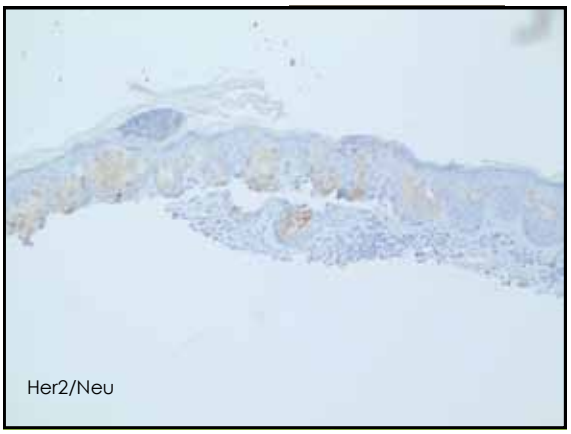


44 yo female with rash on right areola.



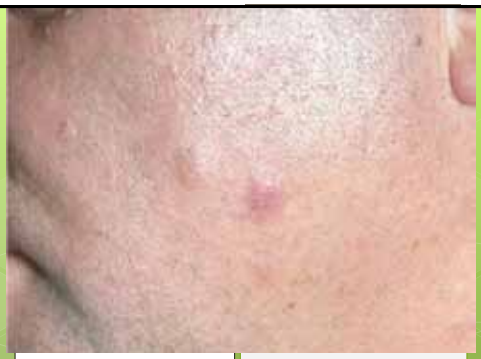




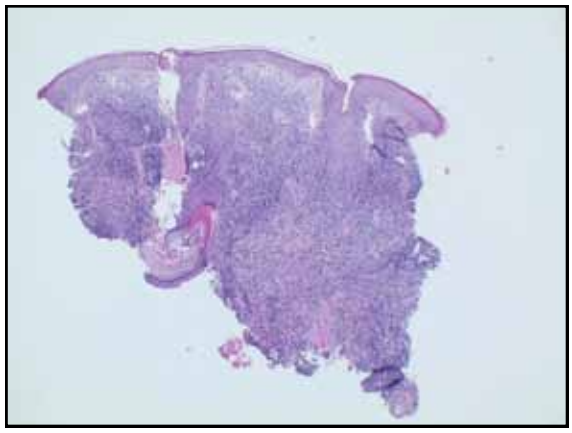


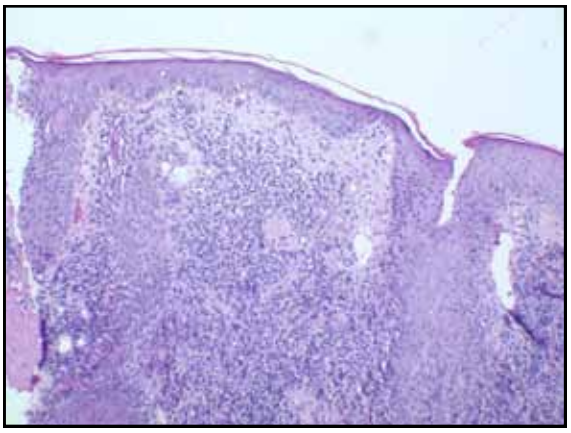
Paget's Disease of the Nipple

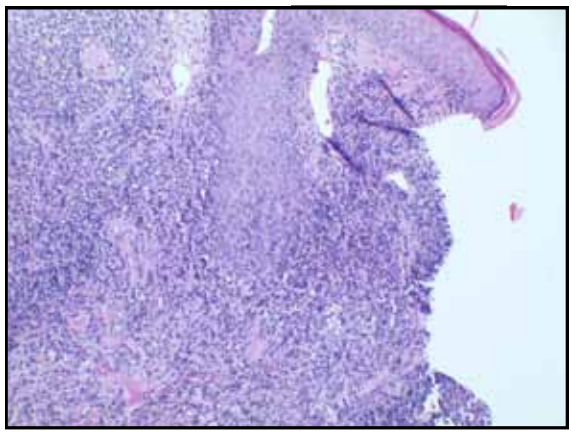
- Almost always associated with carcinoma of the breast
- Dermatosis results from spread of tumor via the lactiferous ducts to the surface epithelium
- Breast carcinoma can be in situ or invasive at time of presentation
- Usually unilateral presentation

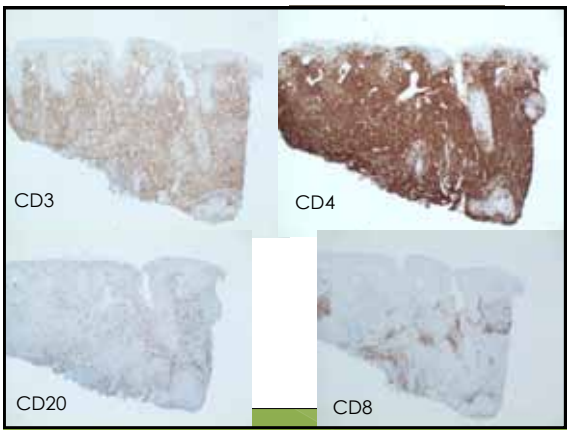


45 yo male with growing lesion on left cheek



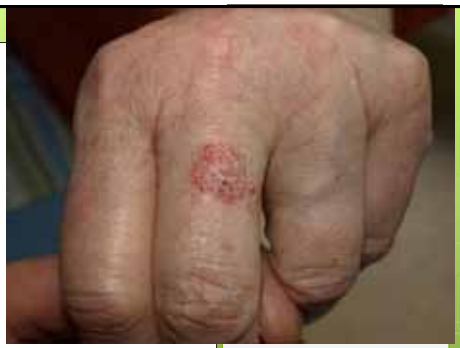




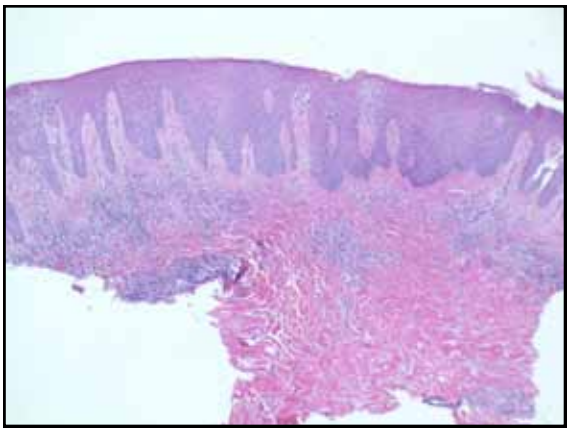


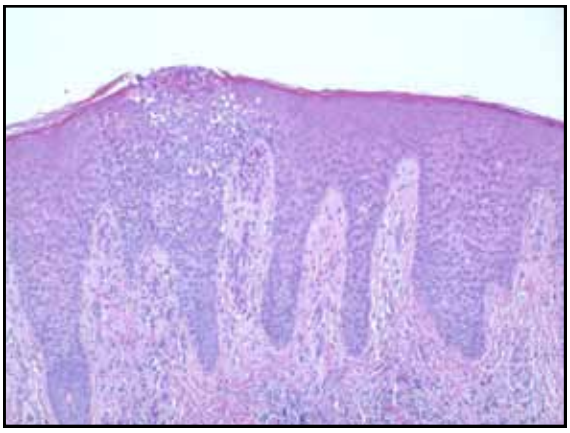
Folliculotropic Mycosis Fungoides

- Preferential location is head and neck region
- Follicular mucinosis often
- Usually minimal epidermotropism
- More refractory to treatment than classic MF
- Worse survival rates than classic MF (68% at 5 years, 26% at 10 years)



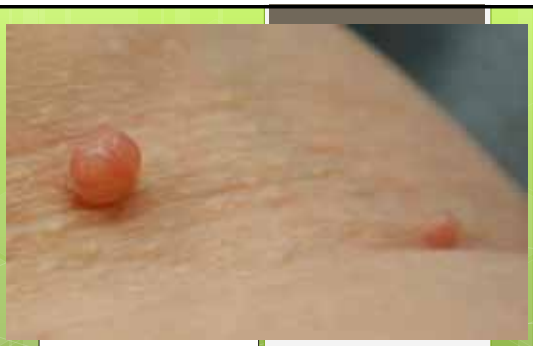
67 yo white male with rash on left middle finger refractory to over the counter topical steroids



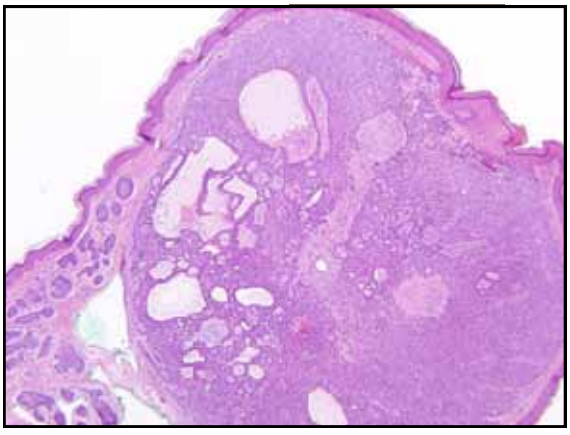


Psoriasis

- Familial disease in 1-3% of the population
- Most common on scalp, trunk, buttock, elbows, and knees
- Least common on the face (UV light improves disease)
- Nail dystrophy
- Psoriatic arthritis in 1/3 of patients

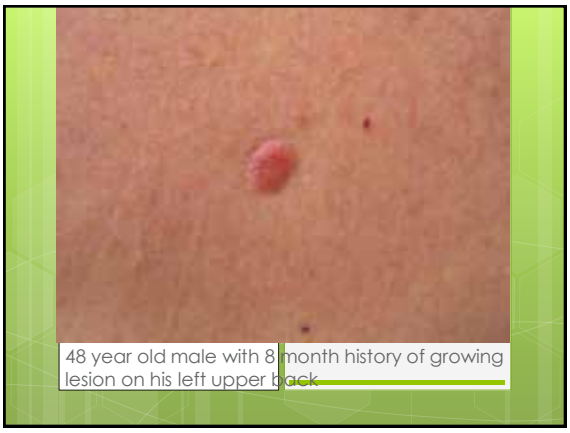


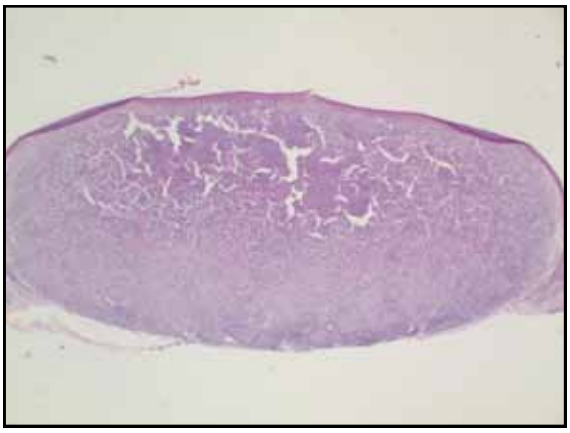
46 yo female presents with two pedunculated papules in the right antecubital fossa

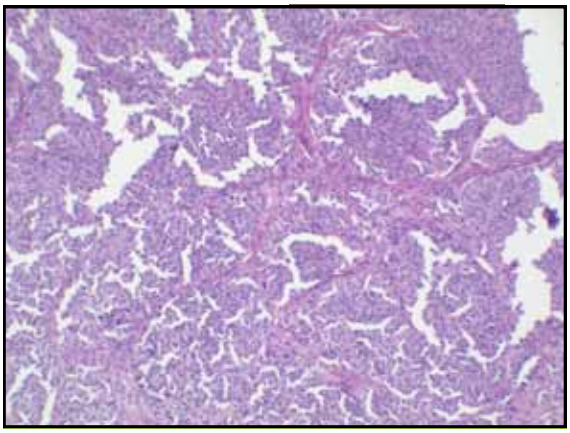


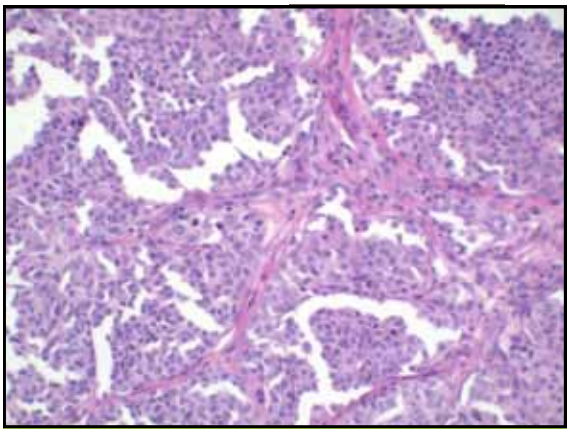
Basal Cell Nevus Syndrome

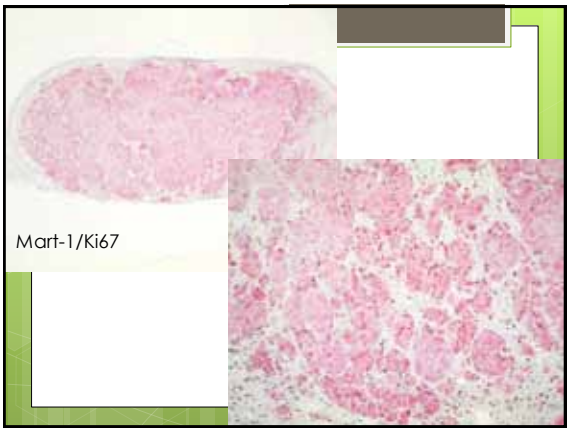
- Autosomal dominant
- Early onset, multiple basal cell carcinomas
- Odontogenic keratocysts, palmoplantar pits, falx cerebri calcifications, medulloblastomas, hydrocephalus, cataracts
- Mutation of chromosome 9 in the PTCH gene
- Should consider biopsy of acrochordon-like lesions in young patients


48 year old male with 8 month history of growing lesion on his left upper back





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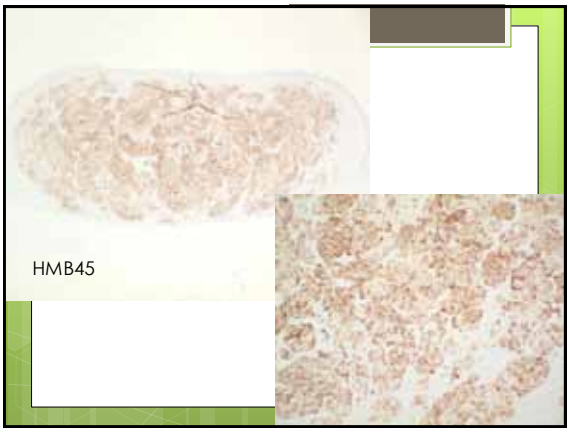
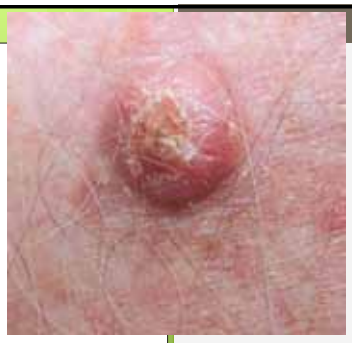

HMB45

Amelanotic Melanoma

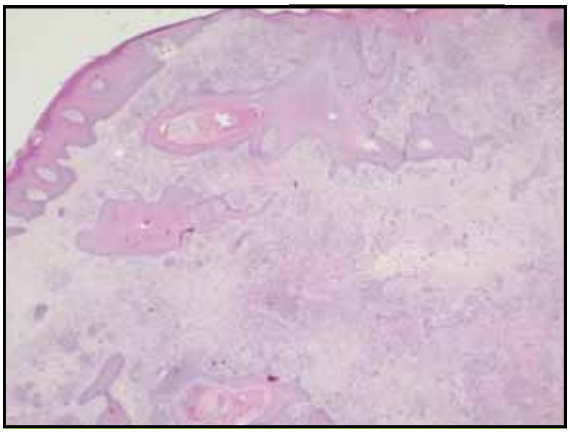
- 5% of melanomas
- Often misdiagnosed (eczema, seborrheic keratosis, Bowen's disease, basal cell carcinoma, angiofibromas, etc)
- Often leads to poor prognosis when diagnosed late
- Breslow thickness (not Clark Level) and ulceration are the most dominant predictors of survival (same for all melanomas)
- Mitotic rate also plays a role in staging

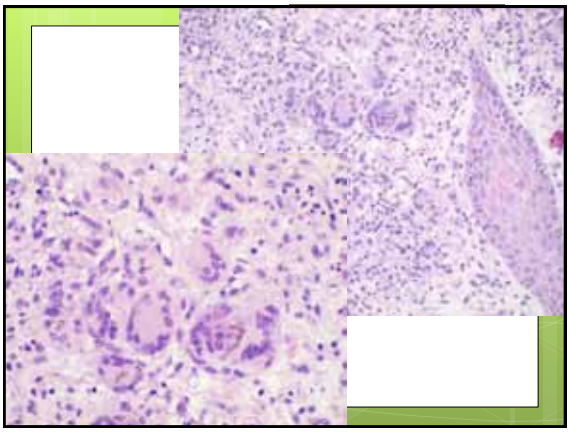
Melanoma Staging

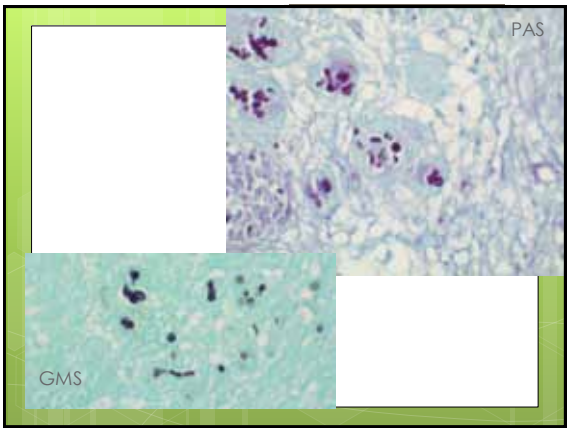
- Tis – In-situ
- T1a – Invasive but less than 1.0mm Breslow without ulceration and <1 mitosis/mm2
- T1b – Less than 1.0mm Breslow but ulceration and/or >1 mitosis/mm2
- T2a – 1.01-2.0mm thick without ulceration
- T2b - 1.01-2.0mm thick with ulceration
- T3a/b - 2.01-4.0mm thick with/out ulceration
- T4a/b – Greater than 4.0mm thick with/out ulceration



62 yo female presents with a 1.3 cm lesion on her left arm



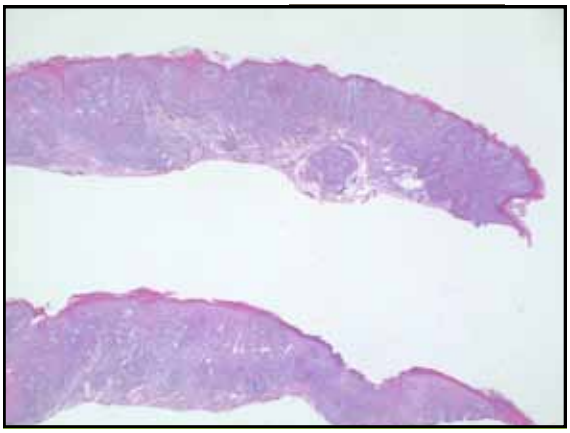


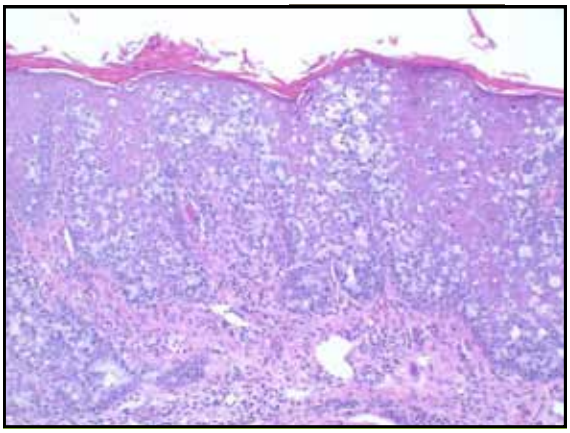


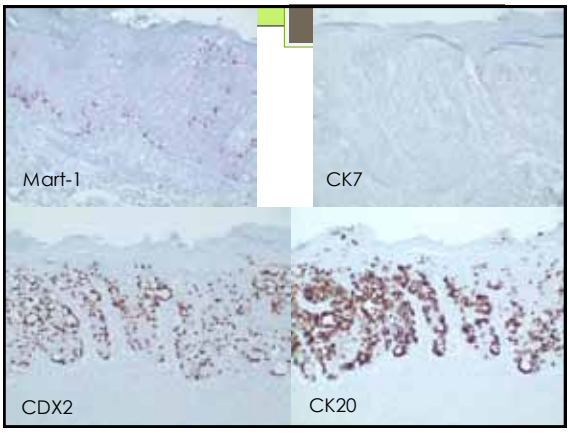
Chromohyphomycosis

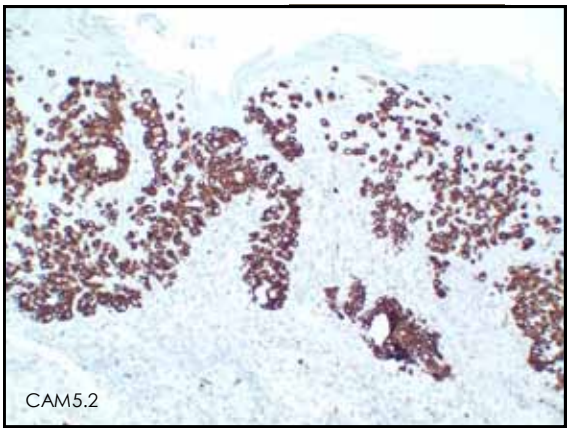
- Infection by fungal family Dematiaceae (brown or black fungi)
- Fungi with brown septated hyphae
- Common saprophytic forms found in soil and decomposing vegetation
- Trauma is the gateway for infection

53 year old female with a pruritic perianal rash



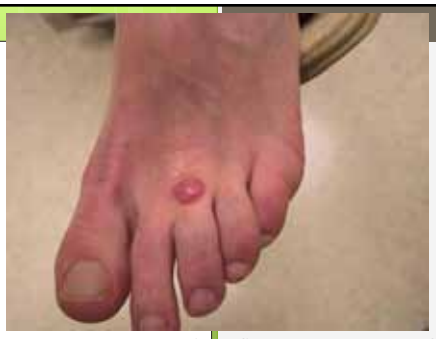




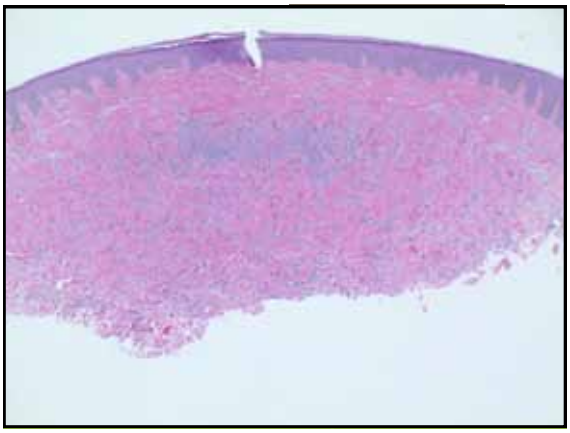


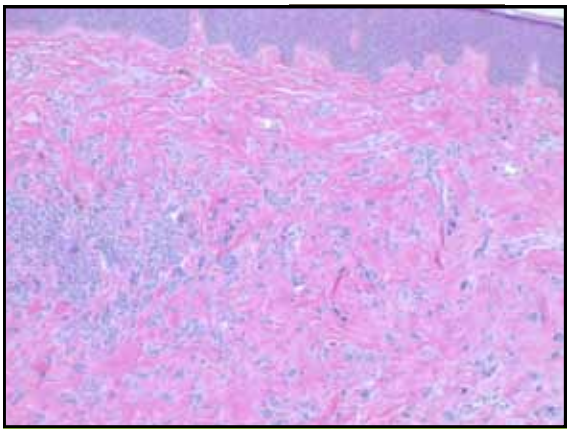
Extramammary Paget's Disease

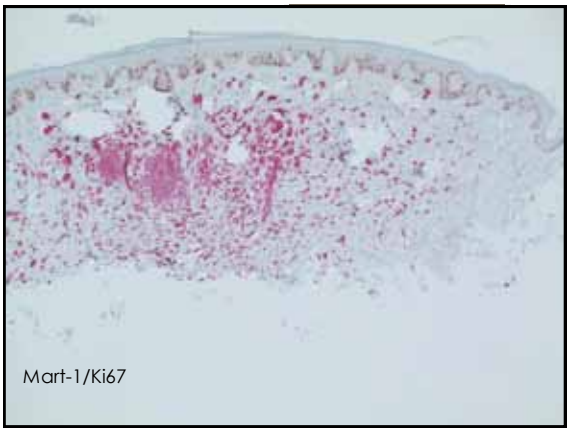
- Majority of cases represent an in situ malignancy derived from intraepidermal sweat ducts
- Minority of cases represent an epidermotropic metastasis from a distant malignant neoplasm (rectum, bladder, urethra, prostate or endocervix)
- 1/3 of perianal lesions are associated with a rectal adenocarcinoma
- Overall association with an internal malignancy is 15%



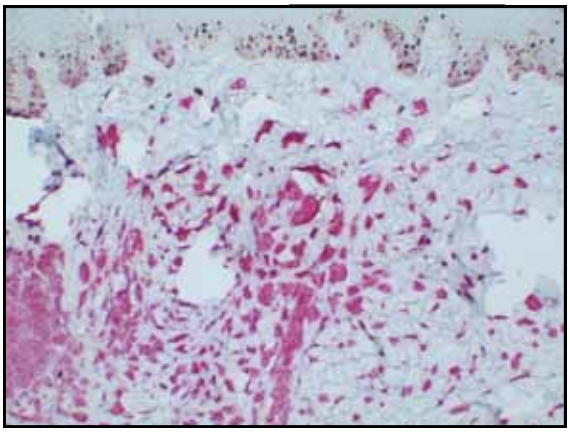
38 yo male presents with a firm papule on the left dorsal foot

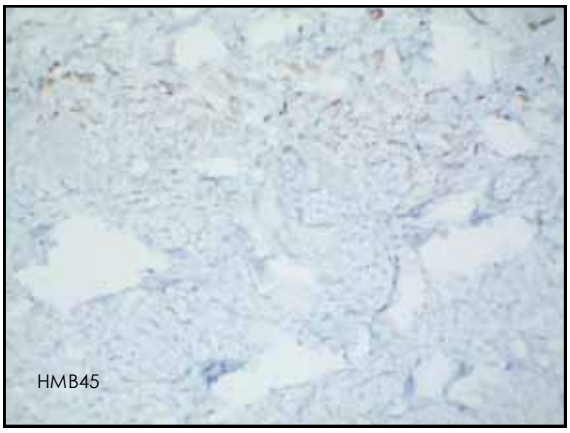






Mart-1/Ki67



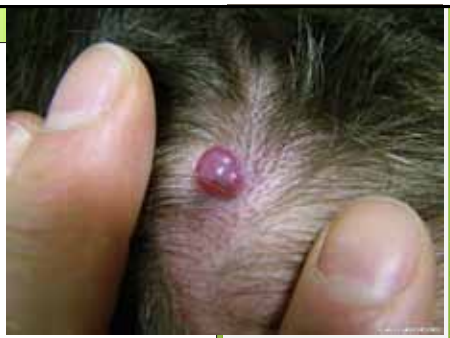


Spitz Nevus

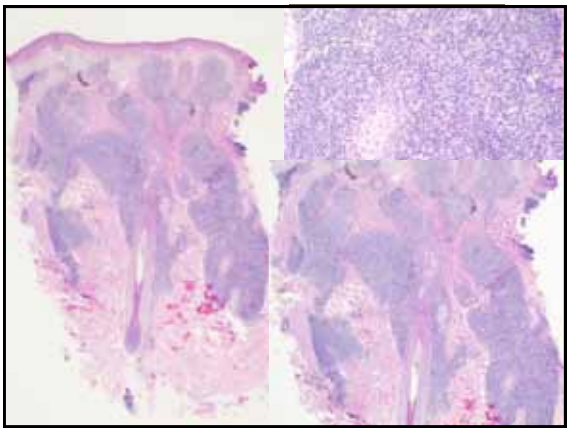
- Benign melanocytic nevi
- 50% occur in children younger than 10yo
- 70% diagnosed during first 2 decades of life
- Differential diagnosis includes atypical Spitz tumor and Spitz-type melanoma
- If older patient, additional molecular tests may be needed

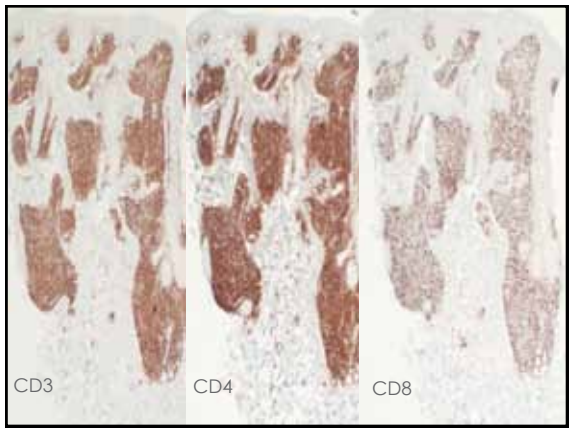
NeoSITE Melanoma Test

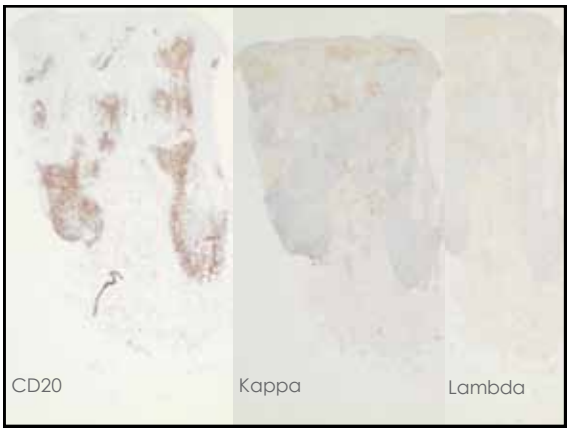
- Proprietary fluorescent in-situ hybridization (FISH) test
- Neogenomics Laboratories
- Homozygous loss of 9p21 (spitzoid melanomas)
- Gain of cMYC locus at 8q24 (amelanotic melanoma)
- Gene amplification at CCND1 region on 11q13 and RREB1 region on 6p25



52 yo male presents with a firm red papule on the scalp

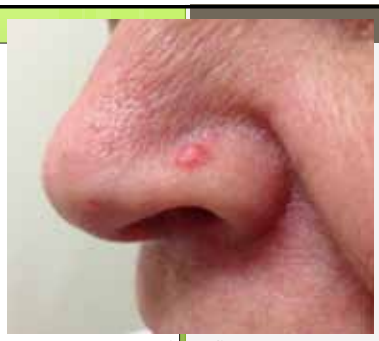




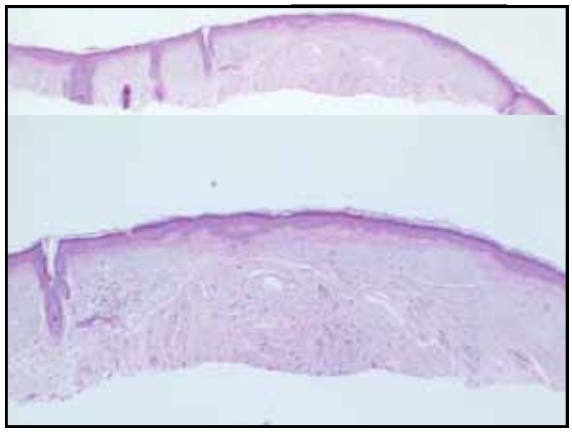


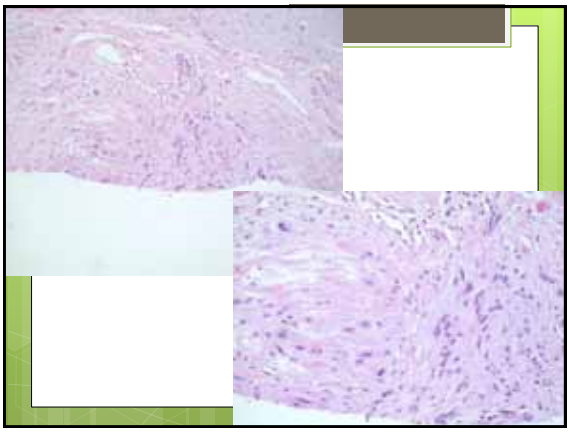
Cutaneous Lymphoid Hyperplasia (CLH)

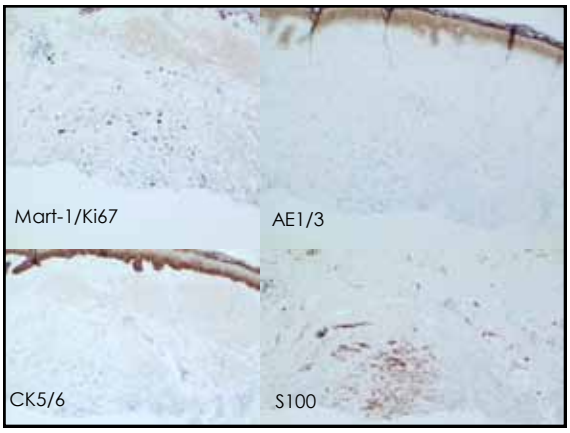
- AKA "pseudolymphoma"
- B-cell (typical CLH, angiolymphoid hyperplasia, Kimura's and Castleman's diseases)
- T-cell (T-cell CLH, lymphomatoid contact dermatitis, and lymphomatoid drug eruption)
- Both may represent exaggerated reactions to external antigens (bug, tattoo, zoster, trauma)
- T/B cell gene rearrangement studies can help
- Follow for persistence at site or evolution of lesions elsewhere



62 yo male presents with a firm papule on the left nasal ala present for several months



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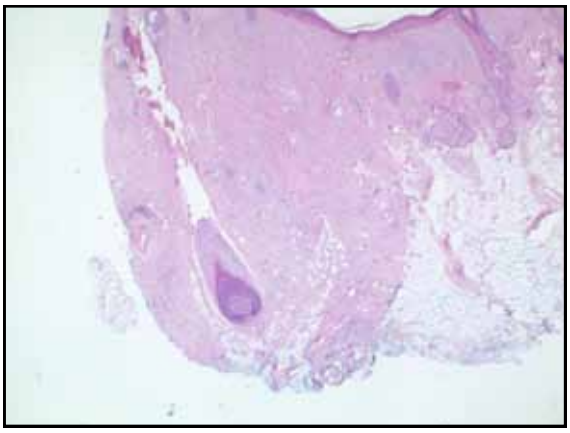

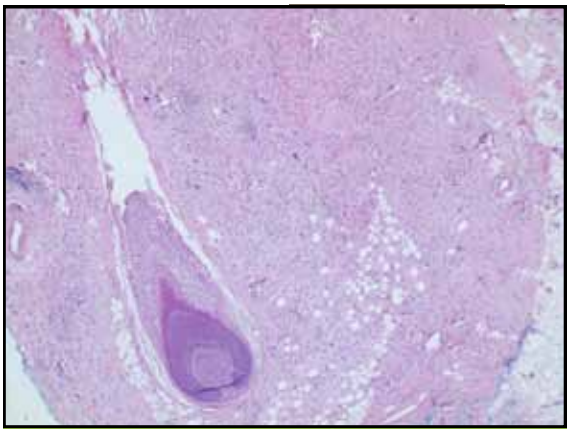

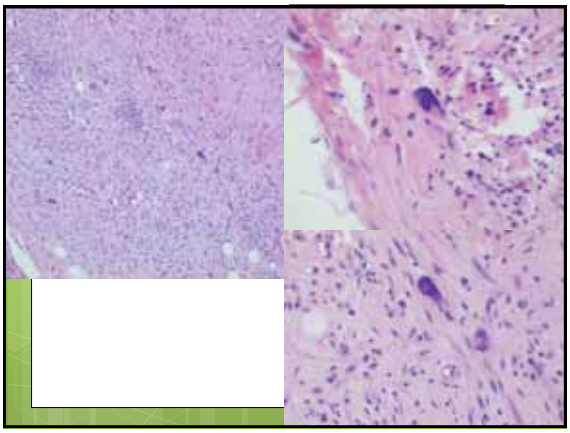

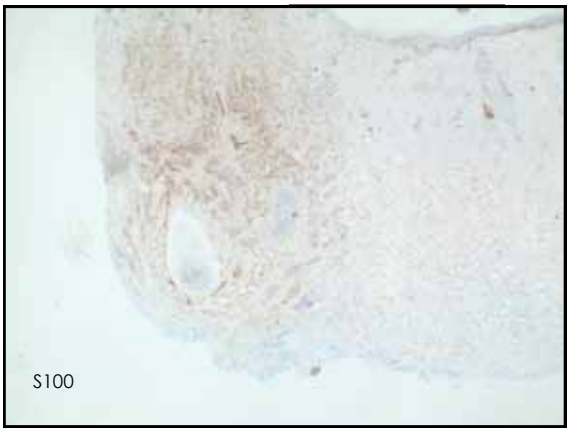
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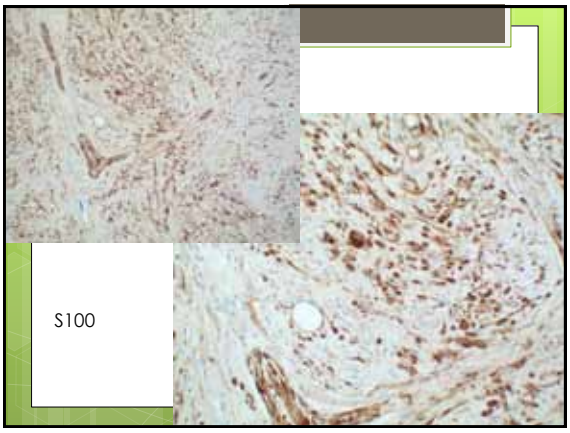

S100

Desmoplastic Melanoma

- Rare variant of spindle cell melanoma
- Most frequently on sun damaged skin in the elderly
- Uncommon, less than 4% of melanomas
- Different clinical behavior than normal melanomas
- Higher tendency for persistent local growth and less nodal metastasis
- 5 year survival from 70-90%

OMM and Dermatology

Suzanne Sirota Rozenberg, D.O.
FAOCD
Program Director
St. John's Episcopal Hospital

October 16, 2015

Objectives

- Review osteopathic tenets
- Review the connection of tenets to dermatology
- Role of OMM in dermatology
- Review specific disease states

OMM and Dermatology

What is the connection between OMM and Dermatology?

Dermatology

study of skin, its structure, functions, and diseases

OMM

•Developed 130 years ago by physician A.T. Still

•Strong emphasis on the inter-relationships of the body's nerves, muscles, bones, and organs

•The philosophy of treating the whole person

•All of the body's systems work together, and that disturbances in one system may impact function elsewhere in the body

*patients with skin conditions may benefit from OMT as adjunctive therapy (stasis dermatitis, brachioradialis pruritis, notalgia paresthetica)

OMM

- Central to osteopathic medicine are the following 4 principles:

Review of Osteopathic principles

Principle 1: The body is a unit

-skin disease may affect the mind (ie: acne vulgaris, psoriasis, vitiligo, melasma)

-the mind may cause or exacerbate cutaneous disease (ie: delusions of parasitosis, trichotillomania, pruritus)

Review of osteopathic principles

Principle 2: The body is capable of self-regulation self-healing, and health maintenance.

-some skin disease have immunologic basis for pathogenesis (ie: psoriasis, atopic dermatitis, vitiligo, alopecia areata)

-self-limited skin diseases illustrate the body's abililty to heal (ie: pityriasis rosea, granuloma annulare)

-skin disease can be actively prevented (ie: skin cancers)

Review of osteopathic principles

Principle 3: Structure and function are interrelated

-defects in skin structure result in skin disease (ie: bullous impetigo, bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa variants)

Review of Osteopathic principles

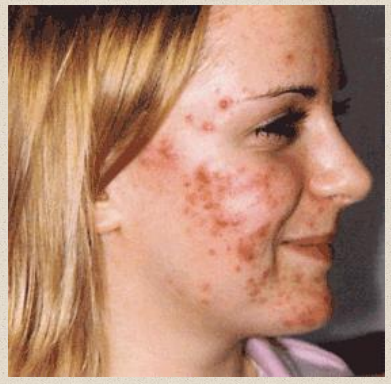
Principle 4: Rational treatment is based on an understanding of the 3 main principles.

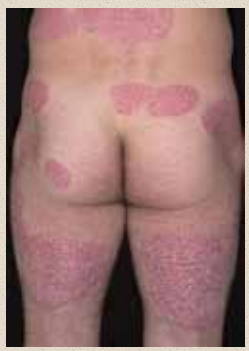
-examine the patient as a whole (ask about their lifestyle, diet, occupation)

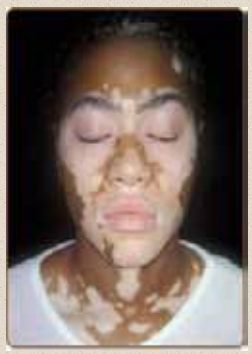
-understand the cutaneous signs of internal diseases (acanthosis nigricans, recurrent dermatophyte infections, eruptive xanthomas, pruritus).

…the practice of dermatology is based upon a visual approach to clinical disease, with the development of an appreciation of recurrent patterns and images (Jean Bolognia, 2008)

Let's review some common dermatological diseases/ conditions and see how we can apply OMM principles to help with disease management.

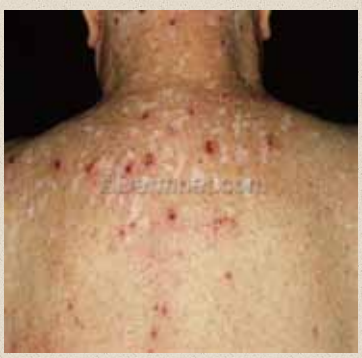






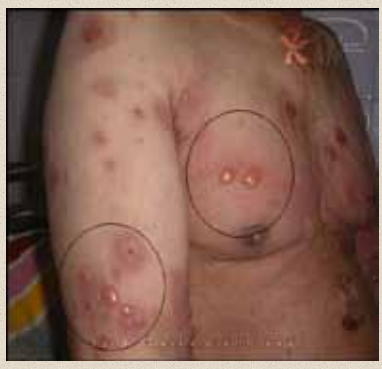
Principle 1

- **The body is a unit**
- Skin disorders have a psychological impact
- Teenager with acne ridiculed by peers, an elderly gentleman with large BSA involvement of psoriasis embarrassed to be out in public, a dark skinned pt with vitiligo feels culturally stigmatized
- Dermatology Life Quality Index; Psoriasis Disability Index
- Treatment can include counseling



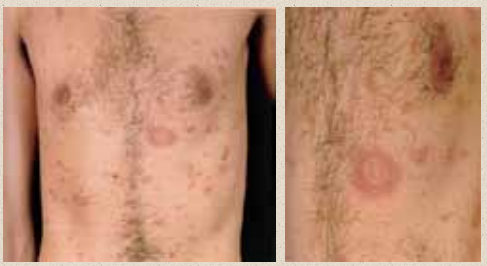
Principle 1

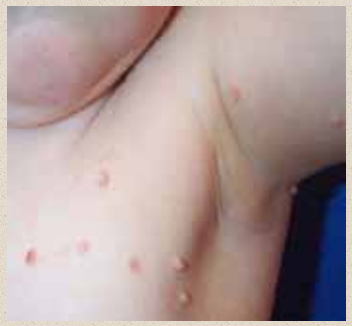
- The mental state may cause or exacerbate cutaneous disease
- Seen in disorders such as trichotillomania, neurotic excoriations, acne excoriee, and body dysmorphic disorder
- Some studies suggest that depression is a modulating factor for physical stimuli such as pruritus and factitial skin disease may be a sign of underlying psychiatric illness
- Management should include a psychiatric evaluation



Principle 2

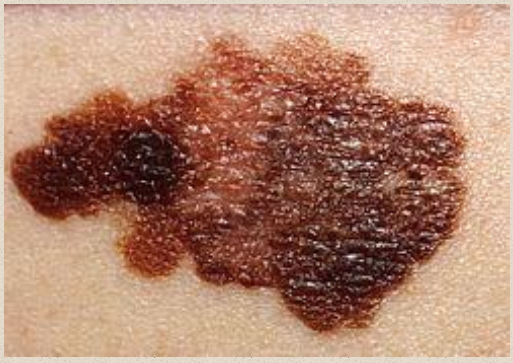
- **The body is capable of self-regulation, self healing, and health maintenance**
- Skin diseases have an immunologic basis for pathogenesis, seen in autoimmune blistering diseases to connective tissue diseases
- Treatment aimed at helping the body to regain its ability to self-regulate and self-heal using modalities such as immunosuppresive drugs and UV light therapy





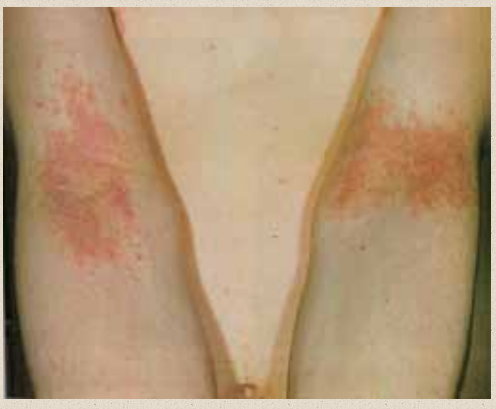
Principle 2

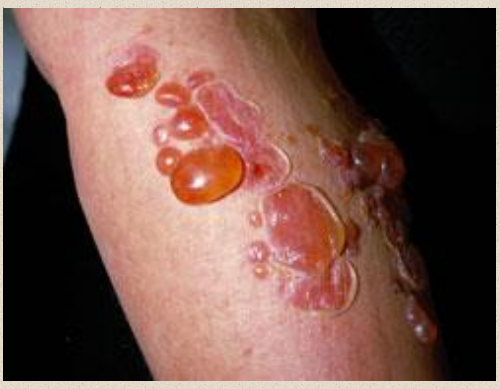
- Examples of pityriasis rosea and molluscum contagiosum
- Without direct medical intervention, the body's innate ability to heal will clear those disorders
- Treatment is symptomatic



Principle 2

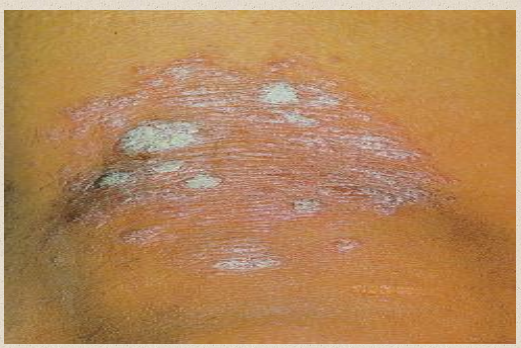
- Skin disease can be actively prevented
- Inquire about lifestyle, family history of skin cancer, use of sunscreen/sunblock
- Management aimed at photoprotection and those with family hx to be regularly examined





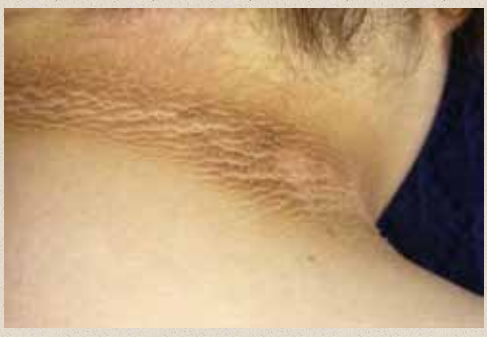
Principle 3

- **Structure and function are interrelated**
- Defect in epidermal skin barrier implicated in atopic dermatitis
- Dysfunction of target structural proteins may result in autoimmune blistering dermatoses



Principle 4

- **Rational treatment is based on understanding of the 3 main principles**
- Need to examine the patient as a whole
- Skin disease have an immunologic basis for pathogenesis
- Psoriasis: Inquire about stress or recent trauma; be aware of association with metabolic syndrome



Principle 4

- Cutaneous signs of internal disease
- Acanthosis nigricans is associated with insulin resistance
- Management aimed at blood glucose control, follow up with PMD and weight loss

Osteopathic Manipulative Treatment

- Patients with skin disorders may benefit from OMT as adjunctive therapy
- Dermatoses with neurologic component may be complicated by abnormal spine mechanics
- On the PE, palpate the thoracic spine and paraspinal musculature for possible functional abnormalities
- Techniques: myofascial release, rib raising, muscle energy

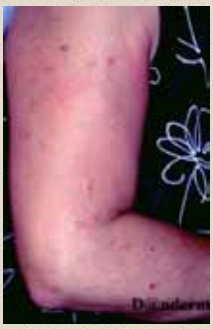
Osteopathic Manipulative Treatment

- Primary hyperhidrosis may be aggravated by autonomic dysfunction
- OMT directed at normalizing the sympathetic chain will be helpful
- Techniques: OA release, sacral inhibition

Osteopathic Manipulative Treatment

- Dysesthesia syndromes: brachioradialis pruritus- cervical rib or cervical nerve root impingement; notalgia paresthetica-nerve impingement
- May benefit from manipulation of the spine
- Techniques: myofascial release, muscle energy, counterstrain

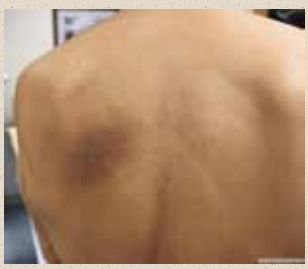
Brachioradialis Pruritus



Osteopathic Manipulation in Brachioradial Pruritis

- Patients have altered sensation in the distribution of the posterior cutaneous nerve of the arm that supplies the skin over the brachioradialis muscle
- Corresponds to C5-C8
- Presence of a cervical rib or cervical nerve root impingement may contribute to altered cutaneous sensation
- Treatment of cervical arthritis and cervical spine manipulation provides relief

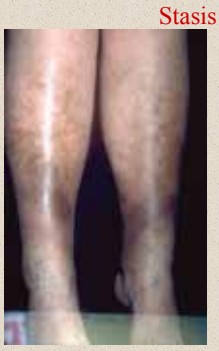
Notalgia Paresthetica

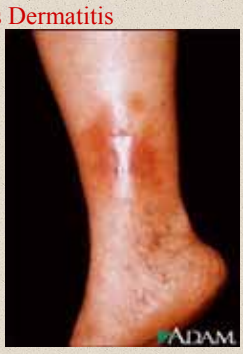


Osteopathic manipulation in Notalgia Paresthetica

- Uncommon pruritic condition seen most commonly in middle aged women
- Etiology unclear, may be associated with cervical radiculopathy
- Affecting mainly the interscapular region(especially the T2-T6 dermatomes
- OMT may decrease the sensation of neuropathic pain/itch

Stasis Dermatitis

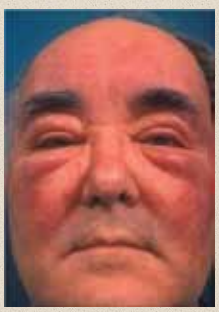




Osteopathic manipulation in Stasis Dermatitis

- Common condition seen in older patients with cardiac insufficiency and venous incompetence
- Due to gravity and increased hydrostatic pressure leading to leaky vessels
- Hemosiderin deposits in the skin of lower extremities causing hyperpigmentation
- Lymphatic pump/effleurage may decrease edema and thus improve condition and decrease the incidence of venous stasis ulcers

Morbus Morbihan



Osteopathic manipulation in Morbus Morbihan

- Uncommon condition characterized by a hard, nonpitting edema of the central face
- Unclear whether this condition is a distinct disease or a rare complication of rosacea
- Locally pre-existing impaired lymphatic drainage plays a crucial role in the progression
- Effleurage and thoracic duct release may be beneficial

PUPPP (Pruritic, urticarial, papules & plaques of pregnancy)

OMM in PUPPP (Pruritic, urticarial, papules & plaques of pregnancy)

- Osteopathic manipulation may offer some relief of symptoms while avoiding potentially harmful medications
- Remove restrictions to lymphatic flow using rib raising techniques
- Paraspinal inhibition
- Open the thoracic inlet
- Promote and augment lymphatic flow with relaxation of abdominal diaphragm and use of lymphatic pump techniques

Conclusion

- Dermatology is a multifaceted specialty and incorporates the 4 major osteopathic principles into daily practice
- To treat the whole patient, dermatologists evaluate the psychological impact of a disease, the relationship between structure and function resulting in cutaneous disease, and the body's ability to self-regulate
- Osteopathic manipulation has definite benefits to our dermatology patients
- Numerous opportunities for case reports and research on the benefits of osteopathic manipulation in the field of dermatology

References

1. Use of Complementary Medicine in Among Outpatients with Dermatologic Conditions within Yorkshire and South Whales, United Kingdom. Baron et. al; JAAD, 2005. Vol 52(4), P589-594.
2. Persistant Erythema and Edema of the Midthird and Upper Aspect of the Face (Morbus Morbihan): Evidence of hidden Immunologic Contact Urticaria and Impaired Lympthatic Drainage. Wohlrab et. al; JAAD 2005, Vol 52(4), P595-602.
3. Foundations of Osteopathic Medicine. Robert Ward, Executive Editor, Williams and Wilkins, 1997.
4. Osteopathic Considerations in Systemic Dysfunction. Kuchera M and Kuchera W, Greyden Pres, 1994.
5. Forearm Neuropathy and Pruritis, Massey EW, Massey JM. South Med J. Oct 1986: 79(10): P1259-1260.
6. Dermatology. Bolognia, Jean et. al, Volume One, Mosby, 2003
7. Andrews' Diseases of The Skin. Tenth Edition, Saunders Elsevier, 2006.

Practical Practice Management

Suzanne Sirota Rozenberg, DO FAOCD
Department of Dermatology
Program Director
St. John's Episcopal Hospital

- No conflict of interest

OBJECTIVES

- How to be happy and succeed in practice
- Pearls to make your life easy
- Keep smiling and enjoy life

NEGOTIATE

- Lease payments
- Percentages for billing
- Interest rates
- …..staff

LOCATION

- Location Location Location - MAXIMIZE
- Opening an office
- Advertising
- Don't spread yourself too thin

BUNDLE

- Bundle packages to get better deals
- I.e., Henry Schein AAD member pricing, member buying programs, match prices
- Share overhead
- Maximize resources
- Bundle cosmetic services

SUBLET SPACE

- Passive income
- I.e., nutritionist, aestheticians

RE-EVALUATE

- Annually
- Insurance policies
- Pension plan
- Loans/lease payments
- Equipment
- Employees
- Advertising

OFFICE MEETINGS

- Huddle
- Delegate
- Emergency situations….Be PREPARED! I.e., hurricane

SPECIALTY SERVICES

- Specialty Pharmacies
- Pre-Authorization
- Drug Representatives
- Office products

STAFF

- Be efficient
- Don't overstaff
- Multi-task when possible
- Office manager must know all aspects of office
- Educating your staff about all services available
- Treat staff with respect; offer all services available to them
- THEY REPRESENT YOU!

IDIOMS OF MINE

- Do not let the practice run you, YOU run the practice
- Don't bite off more than you can chew
- Love going to work!


THANK YOU!

Saturday, October 17

6:00 a.m. - 7:00 a.m.	Breakfast with Exhibitors
7:00 a.m. - 8:30 a.m.	*Great Cases from Osteopathic Institutions*
8:30 a.m. - 9:30 a.m.	*The Art of Radiotherapy: Skin Cancer Removal Without a Trace* **David Herold, MD, MBA**
9:30 a.m. - 10:30 a.m.	*Therapeutic Update* **John Minni, DO, FAOCD**
10:30 a.m. - 11:00 a.m.	Break with Exhibitors
11:00 a.m. - 12:00 p.m.	*Urticarial Dermatitis: Urticaria or Mimicker?* **Carlos Nousari, MD**
12:00 p.m. - 1:30 p.m.	Lunch served to lecture attendees
12:00 p.m. - 12:30 p.m.	*Osteopathic Dermatology in an Allopathic World* **Mark Lebwohl, MD**
12:30 p.m. - 1:30 p.m.	*Biologic/Psoriasis Update* **Brad Glick, DO, FAOCD**
1:30 p.m. - 2:30 p.m.	*The Best Malpractice Defense - Informed Consent* **Clifford Lober, MD, JD**
2:30 p.m. - 3:00 p.m.	Break with Exhibitors
3:00 p.m. - 4:00 p.m.	*New Updates in Pediatric Dermatology* **Lisa Swanson, MD**
4:00 p.m. - 5:00 p.m.	*Larkin Community Hospital Grand Rounds Cases* **Francisco Kerdel, MD**
5:00 p.m. - 5:30 p.m.	CLIA Proficiency Exam

Therapeutic Update

John Minni, DO, FAOCD
Waters Edge Dermatology
Stuart, FL

Objectives

- Explore new therapies pertaining to many common diagnoses of dermatology
- Review updates on previous therapies
- Explore changes in treatment paradigms for common dermatologic conditions
- Review how to incorporate these changes into practice

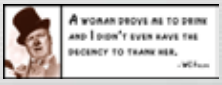
Disclaimer

- I am a speaker and/or consultant for
  - Galderma
  - Abbvie
  - Janssen
  - Novartis
  - Pharmaderm
  - Leo
- Many of statements are my experiences etc. and very well be off label
- I am not going to review data verbatim

Outline

- Rosacea
- Acne (antibiotic use)
- Psoriasis
- Atopic Dermatitis
- Cutaneous Oncology (Melanoma, BCC, & AK)
- Alopecia
- Onychomycosis
- Urticaria
- Cosmetics

Rosacea



Topical Ivermectin

- Topical ivermectin 1% (Soolantra) indicated for inflammatory lesions of rosacea
  - Activity against parasites, scabies, bed bugs, and demodex
  - Exact mechanism unknown for rosacea
  - Contraindicated in turtles and some canines
- Immediate and long term efficacy - 27% reported good improvement in 2 weeks and continued benefit in year long study
- Excellent vehicle (~ Cetaphil) which boosts its anti-inflammatory benefits
- Significant improvement over metronidazole 0.75% cream bid which had been the standard of therapy
- Fewer side effects than azelaic acid cream

- Experience with Soolantra
  - Excellent patient satisfaction
  - Getting now close to a year of follow up with some and doing well
  - So far access has been good but as we all know could end
  - Off label uses
    - Acne especially for "sensitive skin"
    - Seborrhea
    - Delusions of parasitosis
    - Pruritus (part of a treatment plan I use)
      - TAC cream, fexofenadine Qam, doxepin Qhs, permethrin and/or ivermectin, and Sarna lotion OTC soaks

Brimonidine

- Topical brimonidine 0.33% (Mirvaso)for persistent facial redness of rosacea
- First used for open angle glaucoma (Alphagan) and ocular hypertension
- Alpha 2 adrenergic agonist which leads to peripheral vasoconstriction

- Experience
  - Very hit or miss whether patient will like it
  - Works very well but many caveats
    - May work too well
    - Not great for telangiectatic or poikiloderma of Civatte
    - Does not always last 12 hours
    - Rebound can be great in some
    - Patient must be very good at applying

Rosacea Summary

- I use extended release doxycycline 40mg (Oracea) or doxycycline 20 bid
- Various topical treatments
  - Dapsone (Aczone), metronidazole gel, azelaic acid (Finacea), sulfur based therapies (cream, wash shampoo)
  - Treat underlying seborrheic dermatitis as well
  - Also examine for atopic dermatitis in patient as this will aid in vehicle choices
- Compliance is critical with any chronic dermatitis

Acne

Adapalene 0.3% and BPO 2.5%

- Topical for acne featuring adapalene 0.3% and benzoyl peroxide 2.5% (Epiduo forte)
- Indicated for acne vulgaris (no niches etc)
- Perfect for combination minded providers and can be used on patients with even severe acne
- I do not use this very often since I limit my patient's use of irritating BPO to cleansers
- Plenty of success stories with it and it is nice to have some dosing maneuverability within a proven product

Antibiotic Use

- We are getting bombarded with non medical sources of antibiotics and the threat of resistance has intensified (agriculture, industry, etc) as well as medical sources
- For the vast majority of patients a sub-antimicrobial dose of oral antibiotics should be used
- If a patient is on antibiotic for more than 3-6 months new regimen should be sought (AAD recommendations)
- We have oral meds which work very well below the antimicrobial threshold - Oracea (also its generic extended release doxycycline) & Periostat (doxy 20mg bid)

Antibiotic use

- Minocycline
  - dizziness, pigment alterations, auto-immune hepatitis, drug induced lupus
- Doxycycline
  - photodermatitis, nausea/vomiting
- Sulfamethoxazole/Trimethoprim
  - life threatening drug eruptions, contraindicated with methotrexate

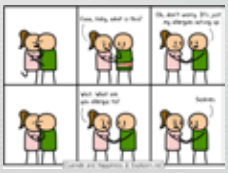
Sources

- http://www.cdc.gov/drugresistance/threat-report-2013/
- https://www.aad.org/dw/monthly/2015/august/overusing-acne-antibiotics#allpages
- https://www.whitehouse.gov/the-press-office/2015/06/02/fact-sheet-over-150-animal-and-health-stakeholders-join-white-house-effo

Adalimumab

- Recently received indication for hidradenitis suppurativa
- Different dosing plan than for psoriasis and psoriatic arthritis
- 160mg at day 0, 80 at day 14 then 40 q 14 days
  - Can also break up initial and second doses over 2 days
- About 50% response which is remarkable considering very few things work for this disease state

Psoriasis



Update to biologics

- Another year of extensive use another year of good safety data (PSOLAR)
  - no safety spikes with ustekinumab, etanercept, adalimumab or any biologics used for psoriasis
  - Every year at AAD will release another year of data
- Still we are not using enough of them for our patients
  - combination of provider apathy, managed care, patient education, misleading information, and complexity of disease states
- Each year more data revealing co-morbidities with psoriasis and by not treating sufficiently we are doing a disservice
- New agents coming as well

Apremilast

- Oral apremilast (Otezla) indicated for plaque psoriasis and psoriatic arthritis (Sept. 2014 and March 2014) - 30mg bid
- Inhibitor of phosphodiesterase 4 and also of TNF-a in synovium (why both indications)
- $22,500 a year for treatment
- 33% PASI 75 at week 12 - sustained for a year
- Achieved ACR 20 38% at week 12 and continued to improve over one year of therapy

Apremilast

- Side effects - nausea, vomiting, weight loss, diarrhea, headaches, and worsening of depressed mood
- I have about 15-20 patients on it and growing nearly daily
- Use the starter pack to get patients used to nausea which resolves
- All have been successful with treatment but by no means as effective as TNF or IL12/23
- Using it combination with TNF and IL12/23 and now have my first on methotrexate, ustekinumab, and apremilast
- Being upfront with side effects and expectations has led to rather smooth implementation in my practice

Secukinumab

- Secukinumab (Cosentyx)is indicated for plaque psoriasis
- Inhibitor of Interleukin-17A
- Dosing 300mg every week for 4 weeks then monthly pens are 150mg (latex tips)
- Cost $46,000 - which may be the most expensive
- 82% PASI 75, 59% PASI 90, sustained PASI 75 for one year as well

Secukinumab

- Side effects - check for TB, infections especially yeast as its theoretical effect on neutrophils, exacerbation of Crohn's disease, latex allergic patients beware of dispensing pen tip
- We have patients in our practice utilizing it with great results
- Since its new and doesn't seem to offer any major benefits it is being used as a 3rd or 4th line agent
- As safety data continues to be revealed will feel more confident about it

Atopic Dermatitis

Look Familiar?

Atopic Dermatitis

Investigational

- Topical
  - PDE4 inhibitors
  - JAK inhibitor - Janus from Roman mythology
    - "just another kinase" - family of tyrosinase inhibitors
    - Tofacitinib ointment
  - Oral PDE4 inhibitor as well (Otezla)

Investigational

- Dupilumab which blocks IL4 and 13 (asthma as well)
  - may be a game changer as it has effect clinically and at the molecular level
  - studies still underway but very encouraging 85% of adults with at least 50% improvement in 12 weeks
  - side effect profile encouraging with an actual decrease in serious skin infections
- Other targets include IgE, IL 17, 21, 22, 31(overlap with psoriasis)

Cutaneous Oncology

Melanoma

- New approval nivolumab (PD-1) which is part of the checkpoint inhibitors (pembrolizumab) AND ipilimumab as part of a combination therapy
- 50% patients have V600 BRAF mutation which would enable use of vemurafenib and dabrafenib which have increased overall survival
- BRAF + agent with a MEK inhibitor have increased overall survival and progression free survival
- Combination therapies have become more widely used and more and more patients are being put on these (oncologists)

Side Effects

- Since we do not per se write or deliver these new systemics for metastatic melanoma our familiarity with these agents may not be sufficient
- Cutaneous side effects of these medicines however, we should be familiar
- Vemurafenib (Zelboraf) and dabrafenib (Taflinar)
  - produce SCC's especially KA's. Treat with excision. Do not stop therapy.
  - New primary melanomas are also a possibility
  - By addition of a MEK inhibitor this side effect may be mitigated
  - Photo distributed dermatitis and alopecia also seen

Side Effects continued

- Trametinib (Mekinist)
  - acneiform eruption
  - treat as acne
- Ipilimumab
  - vitiligo
  - diffuse morbilliform rash
- Pembrolizumab (Keytruda) and nivolumab (Opvido)
  - diffuse rash with eosinophilia
  - vitiligo
  - mucosal irritation

Basal Cell Carcinoma

- Sonidegib (Odomzo) oral treatment for locally advanced BCC (Novartis)
- Same hedgehog pathway as vismodegib (Erivedge)
- Sonidegib study is BOLT
- Vimodegib study is STEVIE
- Have not used it yet but have used vismodegib several times with success
- Side effects - all of my patients have discontinued because of these:
  - dysgeusia, alopecia, muscle spasms, nausea, weight loss
  - however clinical results have been great - only time will tell if durable response

Actinic Keratosis

- New warning about severe reactions with the use of ingenol mebutate (Picato) when not used correctly
- I have used ingenol mebutate extensively since its release and have had excellent results when patients use it correctly
- Side effects do occur similar to using other topical field therapies for actinic keratoses
- Do not use topical corticosteroids to relieve the symptoms

Alopecia

- For female patterned do not neglect spironolactone
  - new data confirms safety especially at low doses (25-100mg a day)
  - routinely testing potassium etc not as much as a concern
  - may help with acne as well
- For male
  - Low level light therapy (600-800 nm) might be another therapy with some limited success
  - new devices are on the market but none of them stand out in efficacy

Onychomyosis

Efinacazole

- Topical Efinacazole (Jublia), a triazole, indicated for onychomycosis
- Not very effective so limit use to mild cases in my practice
- 17.8 & 15.2% compared to 3.3 & 5.5% for placebo in its studies - still not great numbers but its something

Tavaborole

- Topical tavaborole (Kerydin) indicated for onychomycosis of the toenails once daily for 48 weeks
- Unique mechanism of action Leucyl-tRNA synthetase inhibition
- Also utilizes boron (naturally occurring element)
  - helps with shape of molecule which can help with delivery
  - in an of itself an anti-inflammatory and has been used in household products before (Borax 20 mule)
- Have used this extensively with some remarkable results
- Studies almost mirror that of efinacazole but I have a feeling Kerydin's new MOA has given it more in clinical results

Urticaria

Omalizumab

- Injectable omalizumab (Xolair) indicated for chronic urticaria not responsive to antihistamine therapy also indicated for allergic asthma
- Results were good
  - 15% to 9% & 22% to 5% complete response at week 12 with around 40% complete relief of symptoms
  - most common side effects were nasopharyngitis, headache, sinusitis, URI
  - must be monitored in office during injection for potential hypotension (anaphylaxis)
  - Pregnancy B

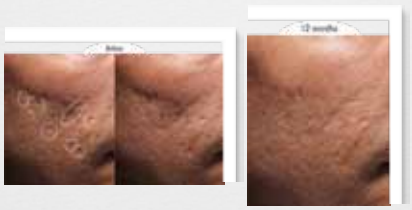
Omalizumab

- Method of action
  - Humanized monoclonal antibody IgG that binds to IgE
  - Lowers free IgE (paradoxically it raises serum IgE so be aware if you check this)
  - By this method the receptors become down regulated
  - How this exerts its effect clinically on urticaria is unknown
- We have had decent success (6 patients)
  - Well tolerated
  - No issues getting covered somehow
  - What I have learned that true chronic urticaria is rare and many times underlying issue remains

Cosmetics

BellaFill
Bovine collagen and PMMA

- First material to be indicated for correction of acne scars (severe, atrophic, distensible) on the face in patients over 21
- 2006 indicated for nasolabial fold correction for up to 5 years
- Bovine collagen and PMMA
  - Poly methyl methacrylate microspheres
  - collagen provides immediate correction while the PMMA is there for further collagen production
- Must have skin test prior to using



Taken from their website

Summary

- This is a modest presentation of some of the newer therapies dermatology providers can utilize
- Begin to change the way to approach rosacea and acne patients
- Lets all be mindful of antibiotic use
- Many of aspect of dermatology has received new items
- Luckily most of them have been effective
- Dermatology and Immunology seems to more and more woven as biologic therapies are extending to psoriasis, atopic, and oncology.

New Updates in Pediatric Dermatology

Elizabeth (Lisa) Swanson, MD
Advanced Dermatology
Rocky Mountain Hospital for Children
National Jewish Hospital

Disclosures

- Speaker
  - Valeant
- Advisory Board Representative
  - Valeant
  - Allergan
  - Ranbaxy/Sun

What's New In Atopic Dermatitis?

Atopic Dermatitis Standard Treatment

- Sensitive skin care
  - ALL free and clear detergent, no dryer sheets/fab soft
  - Dove sensitive skin or cetaphil soap
  - Vanicream/Vaseline/Aquaphor as moisturizers
  - Robathol bath oil
  - Bleach baths
- Topical steroids- always do OINTMENTS in little kids
  - HC 2.5
  - Triam 0.1
  - Fluocinonide 0.05
  - Clobetasol 0.05

Atopic Dermatitis Standard Treatment

- Topical steroid burst for severe eczema/significant flares
  - Clobetasol bid for 4 days
  - Fluocinonide bid for 10 days
  - Triamcinolone bid until clear or followup appt

Atopic Dermatitis Standard Treatment

- Scalp options
  - DermaSmoothe oil at bedtime
    - Peanut oil, shower cap
  - Clobetasol foam
- Steroid sparing agents
  - Tacrolimus-generic
  - Elidel- philidor
  - Black Box warning
    - Newest studies show no association between malignancy and pimecrolimus (JAMA Derm June 2015)
    - Pts with atopic dermatitis have a slightly increased risk of lymphoma (that correlates with severity of eczema)

Atopic Dermatitis
Natural Therapy

- Coconut oil
  - Has good antibacterial properties, but doesn't seem to help the eczema itself
- Sunflower seed oil
  - Does appear to help with eczema- difficult to find a good preparation
  - Aroma Workshop in Chicago
  - hello@aromaworkshop.com
  - Patients can call 773-871-1985
  - 8 oz spray bottle for $22 plus $5.50 shipping

Atopic Dermatitis
Prevention

- Probiotics
  - Taken by a child with eczema appear to have no impact
  - But if a pregnant woman takes probiotics 2 weeks prior to having a baby and for 3 mos after having the baby, it reduces the risk of eczema in that baby by 20-30%
- Vitamin D
  - Some studies in the past suggested that vitamin D supplements could help eczema
  - Recent study looked at staph colonization and correlation with serum 25(OH)D level
  - Patients with low vitamin D had more staph colonization (SPD July/Aug 2015)

Atopic Dermatitis
New Therapies on the Horizon

- AN2728- Boron based ointment
  - inhibits phosphodiesterase-4 activity (PDE4) and decreases production of proinflammatory cytokines
  - Applied bid
  - 65% of patients in preliminary studies were clear/almost clear
  - Studied in kids >2 yrs old
- Oat Based Sterile Emollient cream
  - Used for maintenance in atopic dermatitis
  - BID x 3 mos and kids had fewer flares, less use of topical steroids

Atopic Dermatitis
New Therapies on the Horizon

- Topical Tofacitinib (JAK 1/3 inhibitor)
  - In phase 2 study for eczema
- Cyclosporine weekend therapy
  - 5 patients who were on cyclosporine 5 mg/kg/day but couldn't get weaned off
  - Tried just using cyclosporine 5 mg/kg/day on weekends
  - Worked well for all but 1 out of the 5
- Dupilumab
  - Anti-IL-4 so works to decrease the TH2 inflammatory response
  - 380 patients with severe eczema in initial trial
  - 80% had improvement
  - 300 mg subcutaneously once a week

What's New in Pediatric Allergic Contact Dermatitis?

Allergic Contact Dermatitis-
Wet Wipes

Allergic Contact Dermatitis- Wet Wipes

- Due to preservative MCI/MI (Kathon CG)
- There are now 2 brands of wipes that don't contain the allergen
  - Honest Brand
  - Earth's Best Hypoallergenic

Allergic Contact Dermatitis- Easter Egg Hunt Dermatitis

- There is a small amount of nickel in some foods, including chocolate
- Typically not enough to cause a problem unless consumption of chocolate increases to extreme levels
- Can cause a widespread whole body dermatitis or sometimes presents as localized dermatitis in axilla and groin area

Allergic Contact Dermatitis- Easter Egg Hunt Dermatitis

What's New in Pediatric Psoriasis?

Psoriasis

- Topical steroids continue to be the mainstay for pediatric psoriasis
- Systemic therapy options have been largely limited to cyclosporine, acitretin, methotrexate
- Biologic therapy is difficult because of lack of FDA approval, lack of data
- Systemic effects of psoriasis are making it more advantageous to consider systemic therapy, even in children

Biologics in Kids

- Enbrel (etanercept)
  - Approved in Europe for psoriasis in kids >6 yrs old
  - Approved in US for JIA in kids >2 yrs old
  - 1 study in US in children- 2008- 211 patients age 4-17
    - 0.8 mg/kg/wk
    - 57% achieved PASI 75
- Humira (adalimumab)
  - Approved in US for kids with JIA (>2 yrs old) and Crohn's (>6 yrs old)
- Stelara (ustekinumab)
  - Several case reports of effectiveness and safety
  - 1 clinical trial- patients age 12-18
    - 80% reached PASI 75 at 12 wks
  - Large study outside US is in progress

Paradoxical Psoriasis in Kids on TNF Inhibitors

- Tends to be children with inflammatory bowel disease (Crohn's > Ulcerative Colitis)
- Most common with humira and infliximab

Molluscum

- Has actually been in the literature quite a bit this past year
- 170 kids with molluscum
- 50% of patients had their molluscum resolve by 1 yr
- 70% of patients had their molluscum resolve by 18 mos
- No difference between the "treated" and "untreated" groups


Molluscum Contagiosum: To Treat or Not to Treat? Experience with 170 Children in an Outpatient Clinic Setting in the Northeastern United States

Molluscum

- Does cantharidin work?
  - Study in SPD said no
  - Letter to the editor in response said yes
- Does imiquimod work?
  - Study in JAMA Derm said no
  - I think it does
- Does candida work?
  - Has become a good option for a lot of pediatric dermatologists, but no large studies yet

Pseudofurunculoid Molluscum

- Look like pimples/boils
- Due to body's immune system response
- BOTE sign- Beginning Of The End
- 2 patients with infected molluscum requiring admission (SPD March/April 2015)
  - Culture showed staph lugdunensis
  - Coag negative staph
  - Emerging pathogen
  - To culture or not to culture?

What's New in Acne?

Acne

- Happening younger and younger
- Used to be abnormal before age 9, now abnormal before age 7
- Most acne medicines are technically approved for age 12 and up (epiduo approved age 9 and older)
- Helpful to work through the mail order pharmacies in these situations
  - Philidor- Valeant products
  - Irmat- Galderma products

Mid Childhood Acne

- Acne in kids age 1-7
- Ask about inhaled steroid use- can be the cause
- Good idea to order labs and/or refer to peds endocrinology
  - Total/free testosterone
  - DHEA-S
  - LH/FSH
  - Bone age- plain film of left hand and left wrist

Food and Acne

- Diet with a low glycemic index can help (low carb)
- Dairy- still unclear
- Fish oil- might be helpful
- Probiotics- likely helpful
  - Probably works by decreasing inflammation

What's New with Moles?

Eclipse Nevi

Eclipse Nevi

- Very common on the scalp of children
- Frequently biopsied because of somewhat atypical coloring, large size, history of changing
- Often read out as atypical on pathology, but these are known to be completely benign
- Probably a "special site" that isn't currently recognized as a special site

Congenital Melanocytic Macules of the Tongue

- Probably underdiagnosed
- Presents as multiple asymptomatic dark brown macules on the dorsum of the tongue (often left side)
- Observing these is the right course of action
- Congenital melanoma has never been reported in the oral cavity

What's New in Alopecia Areata?

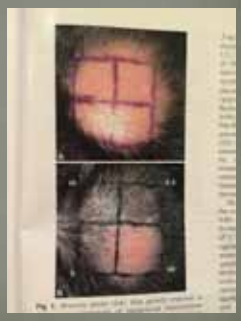

Alopecia areata: new hope for the hopeless

Alopecia Areata

- Pulse IV Methylprednisolone
  - IV pred for 3 days in a row every month for 2-3 mos
  - Good regrowth, but quick relapse
- Low Dose IL-2 (Pro-Leukin)
  - Used in high dose for metastatic renal cell carcinoma and metastatic melanoma
  - Study in France using it for alopecia areata
- Fexofenadine (Allegra)
  - Apparently used in Japan quite extensively
  - Both as adjunctive treatment and monotherapy

Alopecia Areata

- Treated 4 quadrants of same alopecia areata patch with no treatment, 2.5, 5, 10 mg/cc
- Results from 2.5=5=10



Alopecia Areata- Exciting Times!

- 2014- 2 Yale Researchers published a case report in JID
  - Male patient with h/o arthritis and alopecia totalis
  - Started on Tofacitinib (Xeljanz- JAK1/3 inhibitor) for arthritis
  - All his hair regrew
- 2 studies are underway investigating tofacitinib for alopecia areata
  - Yale (5 mg BID) and Europe
- Ruxolitinib (JAK 1 and 2 inhibitor) is also in trials for alopecia areata
- Topical tofacitinib is in studies for psoriasis and eczema and potentially could be studied for alopecia areata

What's New with Kid's Nails?

Pediatric Trachyonychia (aka Twenty Nail Dystrophy of Childhood)

- Causes dystrophy of all fingernails and toenails
- Appear "sanded down", lack of luster, sometimes pits
- 82% improved over time (can persist up to a decade)
- Some patients develop alopecia areata and psoriasis over time (5-15%)
- No real treatment
  - Some try topical steroids under occlusion
  - Products like Nu-Vail

Pediatric Onychomycosis

- It happens!
- Often there is family history
- Evaluate for tinea pedis
- Treat with terbinafine for 3 mos
  - <20 kg- 62.5 mg daily (1/4 pill)
  - 20-40 kg- 125 mg daily (1/2 pill)
  - >40 kg- 250 mg daily
- Itraconazole can be used in a pinch (comes in syrup)
- Liver function tests- to test or not to test
- Griseofulvin doesn't work

What's New in Vascular Lesions?

Port Wine Stains

- GNAQ gene mutation (same mutation for PWS and Sturge-Weber)
- Pulsed Dye Laser Treatment issues
  - Irreversible alopecia can develop after PDL treatment of hair bearing areas
  - Imiquimod + Pulsed Dye Laser
  - Topical rapamycin + Pulsed Dye Laser
    - Seems the most promising combination, but cost of topical preparation is still an issue

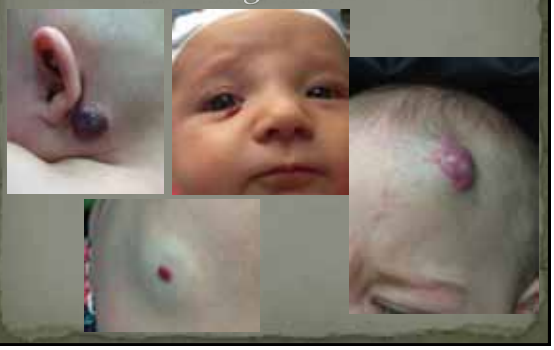
Port Wine Stains and Sturge Weber

- What port wine stains are most indicative of Sturge Weber?
- Hemifacial V1/V2 (#5)
- Median forehead (#6)
- Regardless, any child with a port wine stain that affects the upper eyelid should see ophthalmology

Capillary Malformation- Arterovenous Malformation Syndrome (CM-AVM)

- Newly described but probably not completely rare condition
- RASA1 gene mutation, Auto Dom
- Children will have multiple (>3) small capillary malformations on skin
- They are at risk for AVMs that can be cutaneous, subcutaneous, intramuscular, intraosseous, intracerebral or intraspinal
- Ultrasound any large, atypical, or growing capillary malformation
- Patients should see neurology, cardiology, orthopedic surgery for eval

Infantile Hemangiomas



Infantile Hemangiomas

- Propranolol is still great!
  - 2 mg/kg/day divided TID
  - Always give with food
  - Don't be afraid- if the hemangioma needs it, use it!
  - Typically used during growth period (1st 8-12 mos of life), but can work even beyond the proliferative phase
- Topical timolol 0.5% gel forming solution can work for superficial hemangiomas- applied BID

Pyogenic Granulomas

- Initial study in March/April 2014 SPD journal using timolol 0.5% gel forming solution BID
- Great results with clearance after 2-3 mos
- Bleeding stopped relatively instantly
- Likely working by vasoconstriction
- Important to followup these patients to ensure improvement (spitz nevi, even melanoma in ddx)

Pyogenic Granulomas

What's New in Genodermatoses?

Genodermatoses- New Genes That Have Been Identified

- GNAQ- port wine stains/sturge-weber
- HRAS/KRAS- epidermal nevi, nevus sebaceus
- NRAS- giant congenital nevi

Genodermatoses- Neurofibromatosis I

- Nevus anemicus is a newly discovered feature of NF-1
- Tends to be on the chest, often multiple
- Often not visible at first- rub the chest and then you should see it as the surrounding skin becomes pinker
- As high as 50% of patients with NF-1 have a nevus anemicus

Genodermatoses- Rapamycin

- Rapamycin (sirolimus) is an mTOR inhibitor
- It has immunosuppressant, antiproliferative, and antiangiogenic properties
- Lots of potential to treat cutaneous lesions of Tuberous Sclerosis, Birt-Hogg-Dube, PTEN Syndromes (Cowden's, etc)
- Seems to really augment treatment response using it in combination with Pulsed Dye Laser for port wine stains
- Cost is still the biggest issue

What's New with Vitiligo?

Vitiligo

- Rapidly progressive vitiligo
  - Either presents as regular vitiligo spreading rapidly or can take on a "confetti like" depigmentation pattern
  - Can treat with 3 wks of oral prednisone to stop the flare
  - Start topical treatment for the affected areas
- Segmental vitiligo
  - Good news, bad news
  - Excimer laser + protopic + short term oral steroids yielded best results (JAAD July 2015)
  - Pts over 19 yrs old- 20 mg pred for 3 wks
  - Pts under 19 yrs old- 0.3 mg/kg/day pred for 3 wks

Vitiligo- Excimer Laser

Vitiligo- Excimer Laser

- Works really well, doesn't hurt
- Can see better results if patients take Heliocare (Polypodium Leucotomos) on the day of the treatment

What's New with Pediatric Rashes?

Pediatric Rashes- Lichen Sclerosus

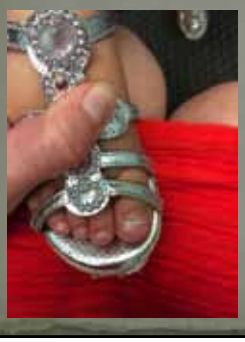
- Probably doesn't go away for most prepubertal girls
- Maintenance treatment is better than as needed treatment (SPD July/Aug 2015)
- My regimen:
  - Clobetasol ointment bid for 2 wks, then once daily for 2 wks, then followup
  - Repeat that course if needed until clear
  - Then clobetasol MWF once daily or elidel once daily for maintenance
  - I see the girls every month until they are clear and then at minimum every 6 mos on maintenance

Pediatric Rashes- Hand Foot and Mouth Disease

- Previously coxsackie A16 and enterovirus 71 were the most common causes
- Coxsackie A6 has emerged over the past 2-3 yrs as primary causative agent
- Produces more severe rash with prominent diaper area involvement
- Adults have been getting it

Pediatric Rashes- Hand, Foot and Mouth Disease

Pediatric Rashes- HFMD and Onychomadesis



Pediatric Rashes- Morphea

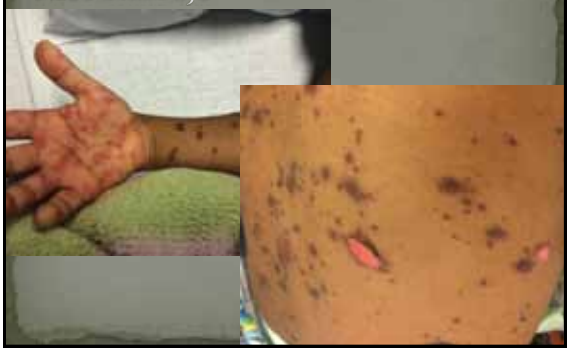
- Early morphea (especially en coup de sabre morphea) can mimic an acquired port wine stain
- Acquired port wine stains are very rare, suspicion should be high for early morphea

Pediatric Rashes- Mycoplasma Associated SJS/ EM Major

- Erythema Multiforme consists of targetoid rash with some oral involvement and is due to a virus
- SJS consists of a blistering, eroded rash with extensive mucosal involvement and is due to medications
- Erythema Multiforme Major described a rash that had some features of EM with some features of SJS
- Typically associated with Mycoplasma
- New name proposed- Mycoplasma Associated SJS
- Treatment: oral steroids better than IVIG (SPD Nov/Dec 2014)

Pediatric Rashes- Mycoplasma Associated SJS

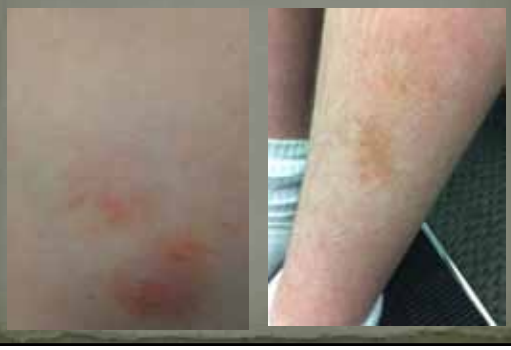
Pediatric Rashes- Mycoplasma Associated SJS



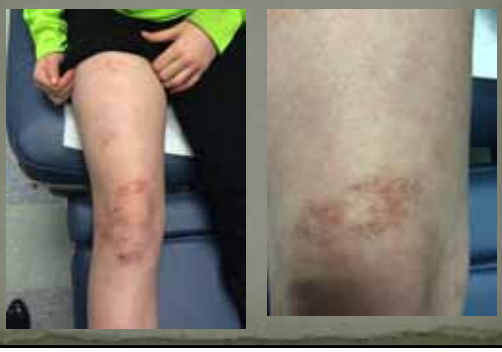
Pediatric Rashes- Pigmented Purpuric Dermatoses

- 5 types of pigmented purpuric dermatoses
- Most common type in kids in studies appears to be Schamberg's Purpura
- In my clinic, most common type is definitely Lichen Aureus
- Idiopathic
- Treatment is difficult, but it resolves on its own eventually
- Topical steroids and UV light might help (SPD May/June 2015)

Pediatric Rashes- Lichen Aureus



Pediatric Rashes- Lichen Aureus

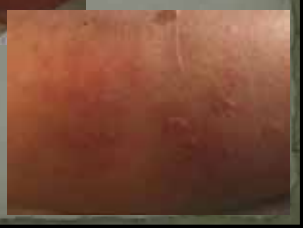


Pediatric Rashes- Herpes Zoster

- Since the chicken pox vaccine has been more regularly administered to children, cases of herpes zoster in children have been on the rise
- We don't know why immunity seems different with the vaccine vs having the chicken pox
- Patient is contagious to people who have not had the chicken pox (can't catch shingles from shingles)
  - Need to avoid unimmunized kids and pregnant women
- Treatment with Acyclovir 30-50 mg/kg/day divided TID (valtrex if old enough to take pills)

Pediatric Rashes- Herpes Zoster

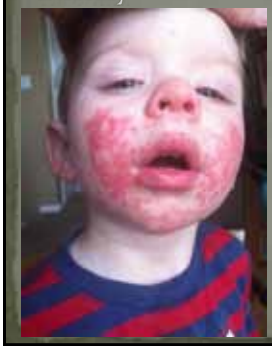
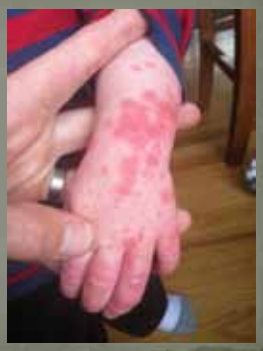

Pediatric Rashes- Herpes Zoster

Pediatric Rashes- Hemorrhagic Edema of Infancy

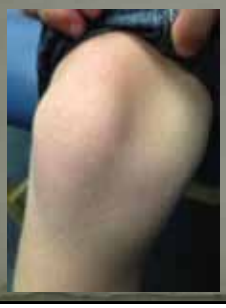
- Impressive rash, but not serious
- Likely virus triggered
- Children often feel sick, febrile, not themselves
- Characteristic distribution of juicy red papules and plaques on face, extremities
- On biopsy- vasculitis
- Treatment: observation or prednisone 1-1.5 mg/kg/day

Pediatric Rashes- Hemorrhagic Edema of Infancy

Pediatric Rashes- Hemorrhagic Edema of Infancy


Pediatric Rashes- Hyperkeratotic Lichenoid Papules of the Elbows and Knees




Pediatric Rashes- Hyperkeratotic Lichenoid Papules of the Elbows and Knees

- Very common in kids age 4-12, boys > girls
- Misdiagnosed as flat warts, molluscum, KP
- Probably a variant of KP
- Kids outgrow it
- Could treat with AmLactin, Cerave SA, etc

What's New with Pediatric Spots?

Pediatric Spots- Pilomatricomas

- Very common calcifying cysts
- Present as plate like firm subcutaneous growth
- Sometimes skin colored, sometimes bluish hue
- Positive teeter-totter sign
- Due to gene mutation in CTNNB1 which encodes beta-catenin

Pediatric Spots- Pilomatricomas

- Some kids have multiple pilomatricomas
- Can be associated with myotonic dystrophy and familial adenomatous polyposis
- But more often associated with no underlying disease or syndrome

Pediatric Spots- Cranial Dysraphism

- Any subcutaneous growth on the head of an infant can raise concerns for cranial dysraphism
- 3 main issues to evaluate for:
  - Cephaloceles- enlarge with crying, valsalva
  - Ectopic nests of meningeal tissue
  - Dermoid cysts/sinuses- entrapment of cutaneous tissues along embryonal fusion lines
    - Lateral eyebrow most common location- no imaging needed
    - If in midline (esp nasal root)- get MRI
- CT is best to look for bony defects of the skull
- MRI is more sensitive to detect intracranial connections
  - No ionizing radiation but does require general anesthesia

Pediatric Spots- Lumbosacral Dysraphism- HIGH RISK

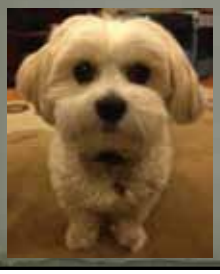
- Lesions overlying lumbosacral spinal cord can indicate a problem underneath- tethered cord, meningocele, tumor
- >2 cutaneous stigmata
- Lipoma
- Acrochordon/pseudotail/tail
- Aplasia cutis
- Dermoid cyst or dermal sinus
- Infantile hemangioma > 2.5 cm in size
- Must do an MRI

Pediatric Spots- Lumbosacral Dysraphism- Intermediate and Low Risk

- Intermediate
  - Atypical dimple (> 5 mm)
  - Hemangioma less than 2.5 cm in size
  - Hypertrichosis
  - Can do ultrasound if child < 3mos old, MRI if older than 3 mos old
- Low
  - Simple dimple
  - Hyperpigmentation/hypopigmentation
  - Congenital nevus
  - Port wine stain
  - No imaging needed

The End!

- Feel free to contact me with any questions
- lisaswansonmd@gmail.com



Sunday, October 18

Sunday lectures will be held at OMED with the AOA at Orange County Convention Center in W230 A/B/C of West Building, Level 2

7:30 a.m. - 8:30 a.m.	*What is an Osteopathic Dermatologist Anyway?* **Reagan Anderson, DO, FAOCD & Teodor Huzij, DO, FACN**

Rapid Fire Dermatologic Updates

8:30 a.m. - 8:45 a.m.	*Benign Epidermal and Dermal Tumors* **RMOPTI/Colorado Dermatology Institute**
8:45 a.m. - 9:00 a.m.	*Premalignant and Malignant Tumors* **OPTI-West/College Medical Center**
9:00 a.m. - 9:15 a.m.	*Cysts* **OPTI-West/Aspen Dermatology**
9:15 a.m. - 9:30 a.m.	*Acne and Related Conditions* **OPTI-West/Silver Falls Dermatology**
9:30 a.m. - 9:45 a.m.	*Psoriasis: A Therapeutic Update* **LECOM/Alta Dermatology**
9:45 a.m. - 10:00 a.m.	*Review of Granulomatous, Metabolic and Depositional Diseases* **Advanced Desert Dermatology**
10:00 a.m. - 10:15 a.m.	Break
10:15 a.m. - 10:30 a.m.	*Erythemas and Purpuras* **Affiliated Dermatology**
10:30 a.m. - 10:45 a.m.	*Vesiculobullous Diseases* **South Texas Osteopathic Dermatology**
10:45 a.m. - 11:00 a.m.	*Pregnancy Dermatoses* **UNTHSC/TCOM**
11:00 a.m. - 11:15 a.m.	*Vasculitides and Vaso-Occlusive Disease* **Oakwood Southshore Medical Center**
11:15 a.m. - 11:30 a.m.	*Eosinophilic and Neutrophilic Dermatoses* **MSUCOM/Lakeland Regional Medical Center**
11:30 a.m. - 11:45 a.m.	*Cutaneous Manifestations of Systemic Disease* **Botsford Hospital**
11:45 a.m. - 12:00 p.m.	*An Update on Alopecia* **St. Joseph Mercy Health System**
12:00 p.m. - 1:30 p.m.	Lunch on your own
1:30 p.m. - 1:45 p.m.	*Neuropsychocutaneous Disorders* **Still OPTI/Northeast Regional Medical Center**
1:45 p.m. - 2:00 p.m.	*Oral Diseases in Dermatology* **LECOM/Tri-County Dermatology**

2:00 p.m. - 2:15 p.m.	*Nails: Tales, Fails and What Prevails in Treating Onychomycosis* **O'Bleness Memorial Hospital**
2:15 p.m. - 2:30 p.m.	*Photodermatoses* **University Hospitals Regional Hospital**
2:30 p.m. - 2:45 p.m.	*Infectious Disease: Viral Infections* **Lewis Gale Hospital - Montgomery**
2:45 p.m. - 3:00 p.m.	Break
3:00 p.m. - 3:15 p.m.	*Infectious Diseases: Bacterial Infections* **OMNEE/Sampson Regional Medical Center**
3:15 p.m. - 3:30 p.m.	*Infectious Disease: Fungal Infections* **PCOM/North Fulton Hospital Medical Campus**
3:30 p.m. - 3:45 p.m.	*Pediatric Dermatology: Neonatal Dermatology* **Palisades Medical Center**
3:45 p.m. - 4:00 p.m.	*Pediatric Dermatology: Papulosquamous and Eczematous Dermatoses* **St. John's Episcopal Hospital**
4:00 p.m. - 4:15 p.m.	*Pediatric Dermatology: Pigmented Lesions* **St. Barnabas Hospital**
4:15 p.m. - 4:30 p.m.	*Pediatric Bullous Disease: Update and Current Treatment Strategies* **Lehigh Valley Health Network**
4:30 p.m. - 4:45 p.m.	*Goltz Syndrome* **NSUCOM/Larkin Community Hospital**
4:45 p.m. - 5:00 p.m.	*Pediatric Dermatology: Tumors of Fat, Muscle and Bone* **NSUCOM/Broward Health Medical Center**
5:00 p.m. - 5:15 p.m.	*Pediatric Vascular Disorders* **West Palm Hospital**
5:15 p.m. - 5:30 p.m.	*Pediatric Melanocytic Lesions of the Skin and Nails* **NSUCOM/Largo Medical Center**
5:30 p.m.	End of Conference

Osteopathic Dermatology

- Teodor Huzij, DO, FACN
- Reagan Anderson, DO, FAOCD, FASMS, Certificate of Added Qualification for Mohs Surgery, MPH, MCS, Program Director for RVU/CDI Dermatology Residency Program

Osteopathic Principles

Human being is a dynamic unit of function (body, mind, spirit)

Self-regulatory mechanisms that are self-healing in nature

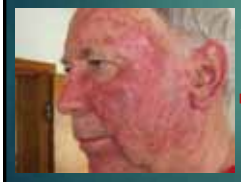
Structure and Function are interrelated at all levels

Rational treatment is based on these principles

Glossary of Osteopathic Terminology, 2011. FOM, 2nd ed, p10.

Actinic Keratosis

The body is a unit; the person is a unit of body, mind, and spirit



Appearance affects spirit

Consider whole region/unit affected for treatment

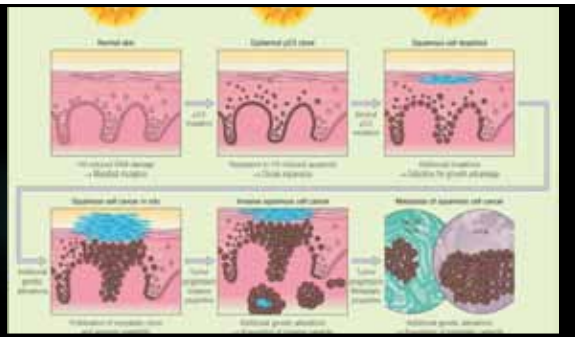
Actinic keratosis

Structure and function are reciprocally interrelated

Sun-damaged skin

P53 mutation

http://www.skincancercare.com/actinic-keratosis-pictures.html



Actinic keratosis

Actinic keratosis

The body is capable of self-regulation, self-healing, and health maintenance

Observe

Field Therapy

Cryotherapy

Light Therapy

Actinic keratosis Treatment

Cryotherapy

- Low 1-year clearance rate- 28%
- Isolated lesions vs. diffuse involvement

Krawtchenko N, Roewert-Huber I, Ulrich M, et al. A randomized study of topical 5% imiquimod vs. topical 5-flurouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. British Journal of Dermatology. 2007;157(2):34-40

Actinic keratosis Treatment

Imiquimod

- 73% 1-year clearance rate

5-FU

- 54% 1-year clearance rate

Krawtchenko N, Roewert-Huber I, Ulrich M, et al. A randomized study of topical 5% imiquimod vs. topical 5-flurouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. British Journal of Dermatology. 2007;157(2):34-40

Actinic Keratosis Treatment

Imiquimod

- Immunomodulator- best MOA for self-healing
  - Activator of Toll-like receptor 7
  - Induces TNF-alpha, INF-gamma,.....
- Minimal systemic absorption

Comprehensive Dermatologic Drug Therapy. Adams DR et al. Elsevier Saunders;2013:476.

Actinic Keratosis Treatment

5-FU

- Flourinated pyrimidine analog with cytotoxic effects
- 6% systemic absorption

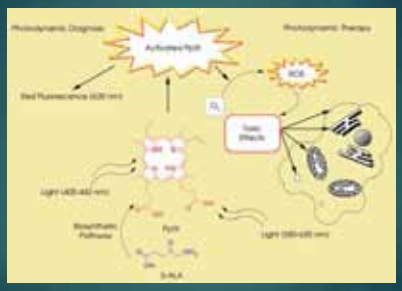
Comprehensive Dermatologic Drug Therapy. Adams DR et al. Elsevier Saunders;2013:518.

Actinic Keratosis Treatment

Diclofenac

- 64% 90 day clearance rate when combined with cryosurgery
- ↓ Prostaglandin synthesis
- Prostaglandins ↑ in sun damaged skin

Schmitt AR, et al. Photodynamic therapy, Cryotherapy, 5-flurouracil, imiquimod, diclofenac, or what? Facts and Controversies. Clinics in Dermatology. 2013;31:712-717.



http://www.photonics.com/Article.aspx?AID=34401

Actinic Keratoses Holistic Approach

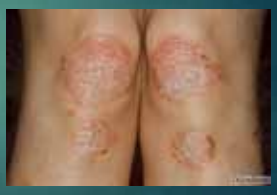
- Consider the whole patient
  - Isolated vs. broad area
  - Economics
  - Ability to self-heal
    - Immunomodulators

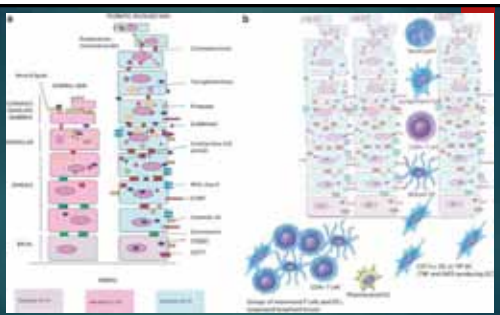
Psoriasis

Psoriasis

Structure and function are reciprocally interrelated.

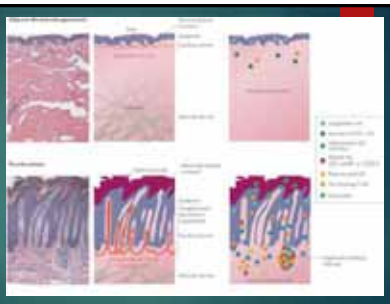
- Immune dysregulation
  - T-helper 1 cells
  - T-helper 17 cells





Liu Y, Kreuger JG, Bowcock AM. Psoriasis: genetic associations and immune system changes. Genes and Immunity. 2007:1–12

Psoriasis



Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 445: 866-873

Psoriasis

The body is a unit; the person is a unit of body, mind, and spirit.

Psoriasis Comorbidities

- Obesity
  - Leptin
    - Increased in psoriasis patients
    - Stimulates TNF-α and IL-6
- Weight loss

Chen YJ et al. Psoriasis is independently associated with hyperleptinemia contributing to metabolic syndrome. Arch Dermatol: 2008;Dec:144(12):1571-1575.

Psoriasis Comorbidities

- Cardiovascular
  - Hypertension
    - Increased renin and ACE levels
  - Adiponectin
    - Decreased in psoriasis patients
    - Anti-inflammatory and anti-atherogenic

Psoriasis

The body is capable of self-regulation, self-healing, and health maintenance.

- Stress
  - Activates HPA axis
  - Alters immune function
  - Impairs ability to self-regulate, self-heal
- Coping strategies

Cvitanović H, Jančić E. Influence of stressful life events on coping in psoriasis. Coll Antropol. 2014 Dec;38(4):1237-40

Osteopathic Treatment

The body is a unit; the person is a unit of body, mind, and spirit.

- Individualized
  - Extent of disease
  - Comorbidities
  - Lifestyle
  - Availability (distance from treatment facility)
- Comprehensive

Psoriasis Treatment

- Topical
  - Emollients
  - Keratolytics
  - Corticosteroids
  - Calcineurin inhibitors
  - Vitamin D analogs

Psoriasis Treatment

- Topical corticosteroids
  - ↓ number of antigen presenting cells and cellular receptors
  - ↓ neutrophil adhesion to vascular endothelium

Comprehensive Dermatologic Drug Therapy. Adams DR et al. Elsevier Saunders;2013.

Psoriasis Treatment

- Calcineurin inhibitors
  - FK506 binding protein
    - Binds calcineurin
    - Blocks IL-2
    - Inhibits T cell activation
- More appropriate for thin skin

https://www.dermquest.com/image-library/image/5044bfd0c97267166cd63d6b

Psoriasis Treatment

- Vitamin D analogs
  - Inhibits keratinocyte proliferation/differentiation
  - Inhibits IL-2, IL-6, IFN-γ
  - Inhibits cytotoxic T-cells and NK cells

Comprehensive Dermatologic Drug Therapy. Adams DR et al. Elsevier Saunders;2013.

Psoriasis Treatment

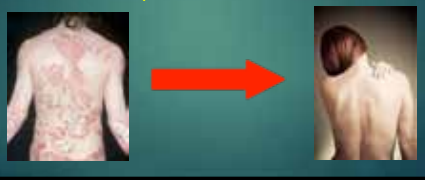
- Systemic
  - Steroids
  - Retinoids
  - TNF-α inhibitors
  - Other immune modulators

Psoriasis Treatment

- Oral Retinoids
  - Bind nuclear factor receptors
    - Stabilize inflammation
    - Cellular differentiation
    - Apoptosis
- Acitretin
  - Etretinate
  - Half life 80-160 days

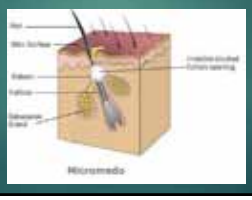
Psoriasis Treatment

Rational treatment is based upon an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function.



Acne- Pathophysiology

Structure and function are reciprocally interrelated



Follicular hyperkeratinization

Proliferation + ↓ desquamation

Microcomedone

Acne- Treatment

Structure and function are reciprocally interrelated

Treat the structural problem- microcomedone

Function will return to normal

Acne-Treatment

- Maintenance therapy with a topical agent
- Treats comedones (structural issue)
- Acne clears (normal function of skin returns)

Acne

The body is capable of self-regulation, self-healing, and health maintenance

Acne and Antibiotics

The body is capable of self-regulation, self-healing, and health maintenance.

Limit antibiotic use to 3-6 months

Ital

Narahari S, Gustafson CJ, Feldman SR. What's new in antibiotics in the management of acne? G Dermatol Venereol. 2012;147:227-238.

Acne and Diet

The body is a unit; the person is a unit of body, mind, and spirit.

- Low glycemic index
- Dairy has testosterone precursors that are converted to active forms when ingested and act on the pilosebaceous units
  - Stimulate insulin-like growth factors

Bowe WP et al. Acne and diet. Journal Am Acad Dermatol. 2009;63(1):1-18

Acne scarring

- Severe acne can result in deep pitting scars, which are cosmetically undesirable
- Significant psychological impact and decreased quality of life

Acne Scarring

The body is capable of self-regulation, self-healing, and health maintenance

- Many treatment option take advantage of the body's ability to self-heal to fill in the scars. Some examples are:
  - Chemical peels
  - Dermabrasion
  - Ablative modalities

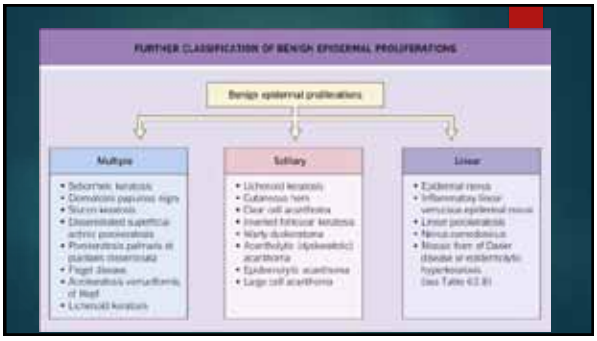
Acne Scarring

A comprehensive, Osteopathic approach to managing acne should not only include treating the acute presentation, but also long term sequelae such as disfiguring scarring. There are many treatment options available that take advantage of the bodies ability to self-heal in order to achieve results. In addition, treating patient as a whole person requires taking their psychological well-being into consideration.

Gozali MV, Zhou B. Effective treatments of atrophic acne scars. J Clin Aesthet Dermatol. 2015 May;8(5):33-40.

Benign Epidermal and Dermal Tumors

REAGAN ANDERSON, DO- PROGRAM DIRECTOR, COLORADO DERMATOLOGY INSTITUTE, RVU
PGY3 RESIDENTS- JONATHAN BIELFIELD, GEORGE BRANT
PGY2 RESIDENT- MICHELLE ELWAY



Seborrheic Keratosis

- Common benign growth seen after third/fourth decade of life
- Ubiquitous among older individuals
- Tan to black, macular, papular, or verrucous lesion
- Occur everywhere except palms, soles, and mucous membranes
  - Can simulate melanocytic neoplasms
- Pathogenesis: Sun exposure- Australian study found higher incidence in the head/neck
  - Alteration in distribution of epidermal growth factors
  - Somatic activating mutations in fibroblast growth factor receptor and phosphoinositide-3 kinase

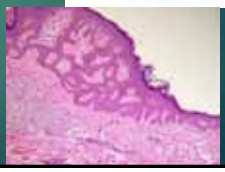
Seborrheic Keratosis

Sign of Leser-Trelat: Rare cutaneous marker of internal malignancy

- Gastric/colonic adenocarcinoma, breast carcinoma, and lymphoma m/c
- Abrupt increase in number/size of SKs that can occur before, during, or after an internal malignancy is detected
- 40% pruritus
- M/C location is the back
- Malignant acanthosis nigricans may also appear in 20% of patients
- Should resolve when primary tumor is treated, and reappear with recurrence/mets

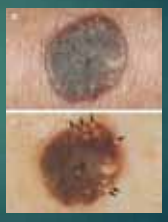
Seborrheic Keratosis

- 6 Histologic types
  - Acanthotic
  - Hyperkeratotic
  - Reticulated
  - Irritated
  - Clonal
  - Melanoacanthoma
- Borst-Jadassohn phenomenon
  - Well-demarcated nests of keratinocytes within the epidermis



Seborrheic Keratoses Treatment

- Reassurance
- Irritated SKs (itching, catching on clothes, inflamed)
  - Cryotherapy, curettage, shave excision
  - Pulsed CO2, erbium:YAG lasers
  - Electrodessication



Flegel Disease
Hyperkeratosis Lenticularis Perstans

- Multiple keratotic papules with a disc-like appearance in a symmetric distribution
  - Adults/Older
  - Attached scale may be prominent at peripheral margin
    - Bleed easily when removed
- Rare, possible AD
- Dorsal aspect of feet and distal extremities are preferred locations
  - Includes palms/soles (fine pits)
- Pruritus
- Absent/altered keratin granules (Odland bodies)
- May be a/w DM and hyperthyroidism

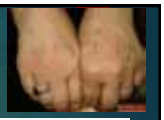
Flegel Disease
Hyperkeratosis Lenticularis Perstans

- DDx
  - Stucco Keratoses-
    - Do not bleed easily when removed
  - Perforating Disorders
    - Prominent central keratotic plugs
    - Transepidermal elimination of connective tissue
  - DSAP
    - Coronoid lamella
  - Lichenoid diseases
    - Use clinical criteria to differentiate

Flegel Disease
Hyperkeratosis Lenticularis Perstans

- Treatment
  - Problematic
  - 5-FU (irritation may limit utility)
  - PUVA + calcipotriol
  - Oral retinoids

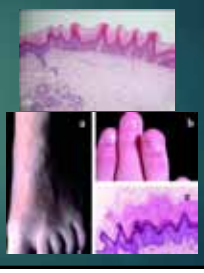
Acrokeratosis Verruciformis



- Multiple skin-colored, small, warty papules on the dorsal aspect of the hands and feet
- Often seen in patients with Darier disease
  - ATP2A2 gene mutation
- Small keratin-filled depressions on the palms/soles
  - Nail involvement
- Do not confuse with epidermodysplasia verruciformis
  - HPV 2, 3, 5, 8-10, 12, 14, 15, 17
  - Malignant transformation in 50%

Acrokeratosis Verruciformis

- Histology
  - "Church spire" hyperkeratosis similar to hyperkeratotic SK and stucco keratosis
- Treatment
  - Same as SKs and stucco keratoses



Clear Cell Acanthoma
Degos' Acanthoma

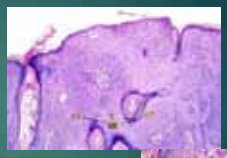
- Solitary erythematous papule/plaque m/c on lower extremity
- May look "stuck on" like SK
- Blanchable, erythematous, "wafer-like" scale at periphery
- Dermoscopy shows red dots in lines
  - Looped vessels within dermal papillae
- Histology- regular psoriasiform hyperplasia w/ enlarged pale keratinocytes that is well demarcated
  - Glycogen- PAS diastase-sensitive stains keratinocyte cytoplasm red

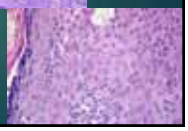
Clear Cell Acanthoma
Degos' Acanthoma

- DDx
  - Pyogenic granuloma
  - Trichilemmomas
    - On the face, inward growing lobule of pale keratinocytes
  - Sebaceous neoplasm
    - Cytoplasm has lipid, stain w/ oil Red O, epithelial membrane antigen, or adipophilin
  - Dermatofibroma
  - Inflamed SK
  - Amelanotic melanoma
- Tx- Shave excision/curettage with electrofulguration

Inverted Follicular Keratosis

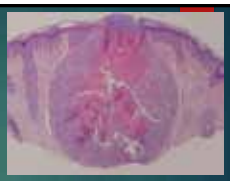
- Benign endophytic variant of irritated SK
- Firm white-tan to pink papule m/c on the face in older men
- DDx
  - Verruca
  - SK
  - Trichilemmoma
    - Clear cells, palisade of basal cells
  - NMSC
    - Overt cellular atypia absent in IFK





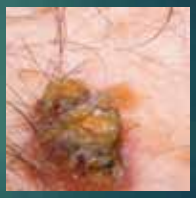
Warty Dyskeratoma

- Solitary verrucous crusted skin-colored to red-brown papule/nodule
  - Central pore and keratotic plug
  - Head and neck
- Histology- central cup-like invagination lined with epithelium displaying acantholysis
  - Research ongoing, probably a related entity to Darier disease
- Treatment- Excision



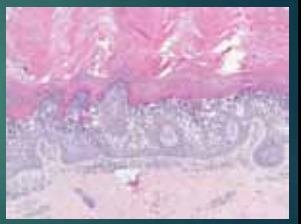
Epidermolytic Acanthoma

- Pigmented keratotic papules that can resemble verrucae or SKs
- Isolated vs. disseminated
  - Disseminated form predilection for the back
- Histology- epidermolytic hyperkeratosis
  - Typically more papillomatosis than in other conditions with this pattern
  - Pattern seen in epidermolytic ichthyosis, epidermal nevi, Vorner's palmoplantar keratoderma, SKs, AKs, cutaneous horns



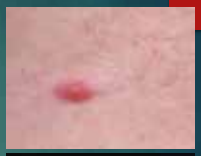
Epidermolytic Acanthoma

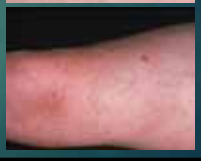
- Clear spaces surrounding nuclei in the stratum spinosum/granulosoum
- Compact hyperkeratosis
- Normal basal layer
- Treatment- observe, destruction, shave excision, linear excision
  - Can recur with superficial removal



Cutaneous leiomyoma

- Reddish-brown, pink or skin colored papules
- Solitary or multiple
- Can be painful
- Adolescents and young adults
- DDx:
  - Dermatofibroma
  - Neurofibroma (solitary)
  - Glomangioma



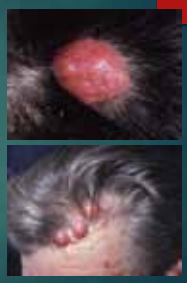


Cutaneous Leiomyoma

- Histology
  - Bland appearing myocytes with eosinophilic cytoplasm
  - "cigar shaped" nuclei
- Reed's Syndrome (Multiple cutaneous and uterine leiomyoma syndrome)
  - Increased risk of renal malignancy
  - Mutation: fumarate hydratase

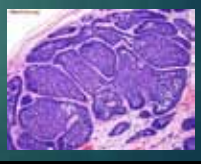
Cylindroma

- Single or multiple erythematous to bluish nodules
- Firm to rubbery
- +/- pain
- Typically on the scalp and face
- Middle-age to elderly



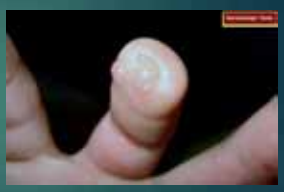
Cylindroma

- Multiple cylindromas seen in CYLD gene mutation
  - Cylindromatosis
  - Brooke-Spiegler Syndrome
- Histology:
  - Basaloid proliferation of "jigsaw" pattern lobules of cells
  - Hyalinized droplets within lobules



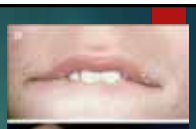
Neuroma

- Two subtypes
  - Traumatic neuroma (amputation neuroma)
  - Palisaded encapsulated neuroma
- Skin-colored to erythematous papules
- +/- pain



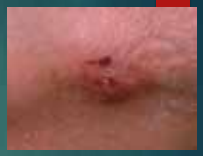
Neuroma

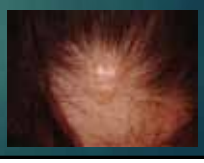
- Multiple mucocutaneous neuromas are associated with MEN2B
- Recently described in sybdromes associated with mutations of the PTEN tumor suppressor gene
  - Cowden Syndrome
  - Bannayan-Riley-Ruvalcaba Syndrome
  - Lhermitte-Duclos Syndrome
  - Proteus Syndrome
- Schaffer JV, Kamino H, Witkiewicz A, et al. Mucocutaneous neuromas: an underecognized manifestation of PTEN hamartoma-tumor syndrome. Arch Dermatol. 2006;142(5):625-632.



Neurothekeoma

- Pink, red to brown papule or nodule
- Often on head, neck, upper extremities
- Twice as common in women
- Two subtypes:
  - Myxoid (classic)
    - AKA "nerve sheath myxoma"
    - Middle age adults
  - Cellular
    - Young adults





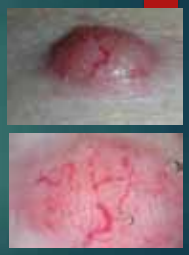
Neurothekeoma

- Histology
  - Myxoid (classic)
    - Nests of epithelioid and spindle cells arranged in a concentric whorling pattern
    - Abundant myxoid stroma
    - S100 positive
  - Cellular
    - Similar to myxoid variant, but myxoid stroma is sparse or absent
    - S100 negative

Neurothekeoma

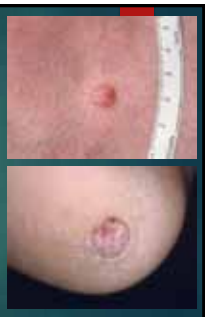
- 62 yo F with 5 month h/o enlarging nodule
- Dermoscopy revealed thick, arborizing vessels
- Pathology revealed cellular neurothekeoma
- Point: cellular variant may resemble BCC clinically and dermoscopically.

Aydingoz IE, Mansur AT, Dikicioglu-Cetin E. Arborizing vessels under dermoscopy: A case of cellular neurothekeoma instead of basal cell carcinoma. Dermatol Online J. 19 (3): 5. http://escholarship.org/uc/item/1nx5r21x



Eccrine Poroma

- Erythematous papule, plaque or nodule
- "Moat" surrounding lesion
- Palm, sole and scalp
- Ulceration may occur on points of pressure
- Eccrine poromatosis - >100 poromas, may be widely distributed or confined to palms and soles

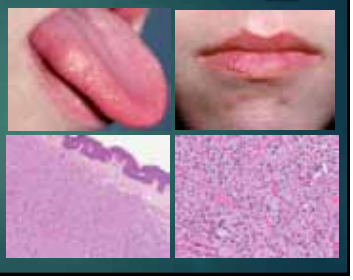


Eccrine poroma

- Well-circumscribed tumor in lower epidermis, extending into dermis
- Small, cuboidal epithelial cells
- Small sweat ducts
- Sharp demarcation between paler "poroid" cells and surrounding keratinocytes

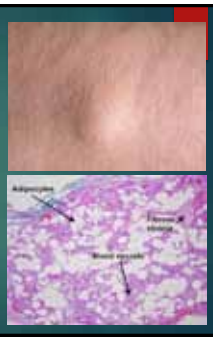
Granular Cell Tumor

- Skin-colored to red-brown papule or nodule (or yellowish on tongue)
- F>M
- Head and neck (esp tongue)
- Histology:
  - Poorly demarcated nodule in dermis
  - Pale cells with granular cytoplasm
  - Intracytoplasmic inclusions (pustulo-ovoid bodies of Milian)



Angiolipoma

- Looks like a lipoma
- Usually trunk, upper extremities
- 2nd and 3rd decade, rare in children and elderly
- Renal angiolipomas may be seen in tuberous sclerosis
- May be painful
- Histology:
  - Well –circumscribed
  - Mature lipocytes
  - Capillaries 5-50% of tumor
  - Scattered fibrin thrombi



Acquired Digital Fibrokeratoma

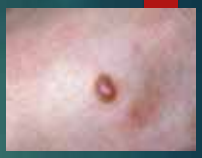
- Solitary exophytic papule with hyperkeratosis
- Acral skin, usually fingers
- Collarette of slightly raised skin may encircle the base of the lesion
- Middle aged adults

Acquired Digital Fibrokeratoma

- Histology:
  - Polypoid on low power
  - Hyperkeratosis and acanthosis
  - Coarse, vertically oriented collagen bundles
- Compare to supernumerary digit, which has increased number of nerves

Dermatofibroma

- Common, benign skin neoplasms composed of collagen, macrophages (histiocytes), capillaries, and fibroblasts
- Histology
  - Epidermal hyperplasia or atrophy
  - Spindle cells in loose, storiform pattern
  - Collagen trapping
- Multiple dermatofibromas seen in lupus erythematosus, atopic dermatitis and immunosuppression



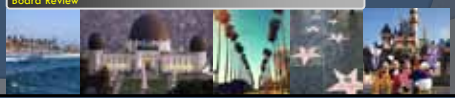
Syringocystadenoma Papilliferum

- Pink to red papule or plaque
- Head and neck
- About half present at birth and about a third arise from nevus sebaceous (most common tumor associated with a nevus sebaceous)
- Histology
  - Papillated fronds of apocrine epithelial cells associated with a cystic space
  - Basilar cuboidal cells and columnar cells compose epidermis
  - Epidermal connection
  - Plasma cells in the stroma

PREMALIGNANT AND MALIGNANT TUMORS

Western University of Health Sciences
Dermatology Department

Board Review



- I have no conflict of interest to report

Objectives

- Present board fodder on malignant tumors
- Discuss selected areas of importance or new information

The keratoacanthoma variant characterized by sudden appearance during childhood of multiple eruptive KAs that slowly resolve and reappear later on is called?

a) Grybowski variant
b) Ferguson-Smith variant
c) Keratoacanthoma centrifugum marginatum
d) Giant keratoacanthoma
e) Common solitary keratoacanthoma

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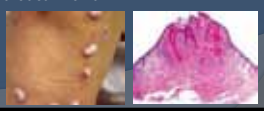
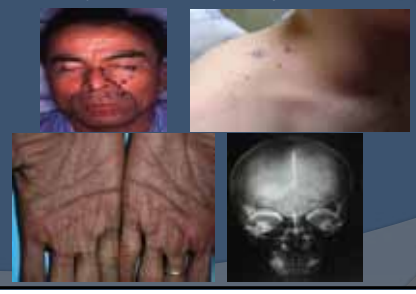


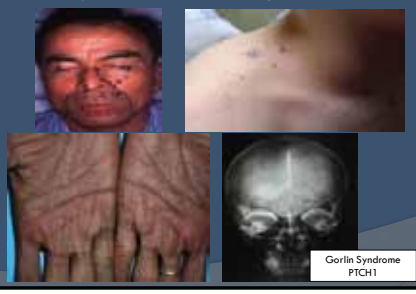
Keratoacanthoma

- well-differentiated SCC
- **KA Variants**
  - KA centrifugum marginatum: up to 20 cm with raised border and central involution
  - Giant KA: up to 9 cm with local destruction
  - Ferguson-Smith (AD): eruptive KAs in childhood with slow resolution
  - Grzybowski: hundreds of 1-3 mm KAs in adults
  - KA associated with **Muir Torre Syndrome**

What is gene mutated in this syndrome?



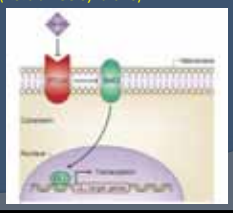
What is gene mutated in this syndrome?



Gorlin Syndrome
PTCH1

Sonic Hedgehog Signaling Pathway

- Mutations in PTCH1 gene on chromosome 9q, codes for sonic hedgehog receptor
  - Gorlin Syndrome (Nevoid BCC Syndrome)
  - Sporadic BCC



Hedgehog Pathway Inhibitors

- **Erivedge (vismodegib)**
  - FDA approved in 2012
  - Smoothened inhibitor
  - Adverse side effects (>30% incidence)
    - Muscle spasms
    - Alopecia
    - Dysguesia
    - Weight loss
    - Fatigue

- **Odomzo (sonidegib)**
  - Newly FDA approved in 2015
  - Smoothened inhibitor
  - In trials, led to shrinkage or disappearance of tumors in 58% of patients who took it
  - Black box warning: can cause fetal death
    - No blood donations!

The following syndromes have been associated with increased BCCs, except:

a) Bazex-Dupre-Christol Syndrome
b) Gardner Syndrome
c) Xeroderma Pigmentosum
d) Brooke-Spiegler Syndrome
e) Rombo Syndrome

The following syndromes have been associated with increased BCCs, except:

a) Bazex-Dupre-Christol Syndrome
b) **Gardner Syndrome**
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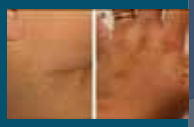
e) Rombo Syndrome

Rombo Syndrome

Basal cell carcinomas
Atrophoderma vermiculatum
Hypotrichosis
Milia
Acrocyanosis

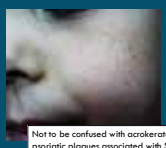
Bazex Syndrome

Basal cell carcinomas
Atrophoderma (follicular)
Zero Hair
Eccrine abnormalities - anhidrosis
X-linked dominant > AD



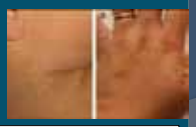
Rombo Syndrome

Basal cell carcinomas
Atrophoderma vermiculatum
Hypotrichosis
Milia
Acrocyanosis



Bazex Syndrome

Basal cell carcinomas
Atrophoderma (follicular)
Zero Hair
Eccrine abnormalities - anhidrosis
X-linked dominant > AD



Not to be confused with acrokeratosis paraneoplastica, also called Bazex - violaceous psoriatic plaques associated with SCC of aerodigestive

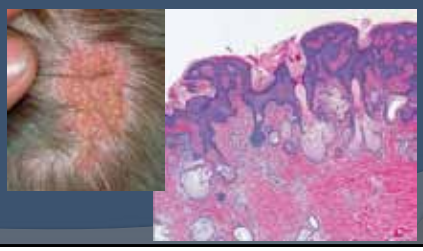
Brooke-Spiegler

CYLD mutation
Trichoepitheliomas
Cylindromas
Spiradenomas
Basal cell carcinomas

Xeroderma Pigmentosum

Autosomal recessive
Defect of DNA repair
Early skin cancers
Associated neurological abnormalities

What are the most common benign and malignant neoplasms found with this lesion?



What are the most common benign and malignant neoplasms found with this lesion?

Benign tumors: trichoblastoma, syringocystadenoma papilliferum
Malignant tumors: BCC

Which genetic bullous diseases predisposes patients to SCC?

a) Epidermolysis bullosa acquisita
b) Junctional epidermolysis bullosa
c) Dowling-Meara type of epidermolysis bullosa
d) Dominant dystrophic epidermolysis bullosa
e) Recessive dystrophic epidermolysis bullosa

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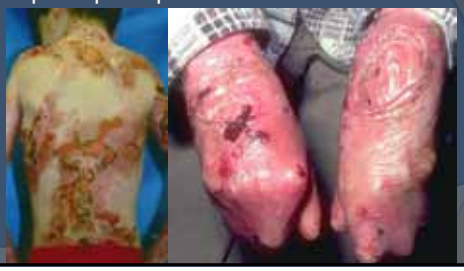
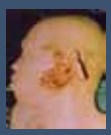


Conditions Predisposing to SCC

- Conditions with chronic wounds / sinuses
- Oculocutaneous albinism
- Transplant patients
- Patients on long-term voriconizole
- Patients on BRAF inhibitors
- Previous radiation therapy (20 years)
- Tanning bed use
- Many more..



Organ Transplant Recipients

- Substantial risk of NMSC
  - BCC 5-10x
  - SCC 40-250x
- Directly related to dose and length of immunosuppressive drug use
- Heart transplant, 27% died of skin cancer, most SCC (study was in Australia)
- Capcetabine or retinoids may decrease rate of NMSC in SOTR

The following are true regarding verrucous carcinoma, except

a) A low grade variant of SCC
b) Is successfully treated with radiation
c) May show perineural or vascular invasion
d) Located in the oral cavity, anogenital area or the sole of the foot
e) Associated with HPV

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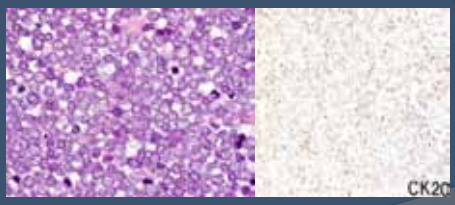
Verrucous Carcinoma

- Types
  - Oral florid papillomatosis: buccal mucosa
  - Giant condyloma of Bushke-Lowenstein: (HPV 6,11)
  - Epithelioma cuniculatum: plantar feet
- Deeply invasive but rarely metastasize
- Becomes more aggressive after radiation
- Treatment: excision (Mohs)

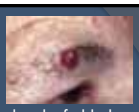
SCC High Risk

- Size >2 cm
- Depth of invasion >6mm
- Anatomic location
  - Ear / lip / mucosae
- Immunosuppression
- Etiology
  - Chronic ulcer / sinus tract /
  - Radiation / scar
- Aggressive histologic subtype

What virus is found in 80% of these tumors?



Merkel Cell Carcinoma



- Cutaneous neuroendocrine tumor
- Solitary, pink to red nodule on head and neck of elderly
- Aggressive with high rates of recurrence and metastasis
- Polyomovirus associated (80%)
- Three histologic patterns
  - Stains: CK20, NSE, chromogranin A/B, synaptophysin
- Treatment
  - WLE with 2-3.0 cm margins or Mohs
  - +/- adjuvant therapy

References

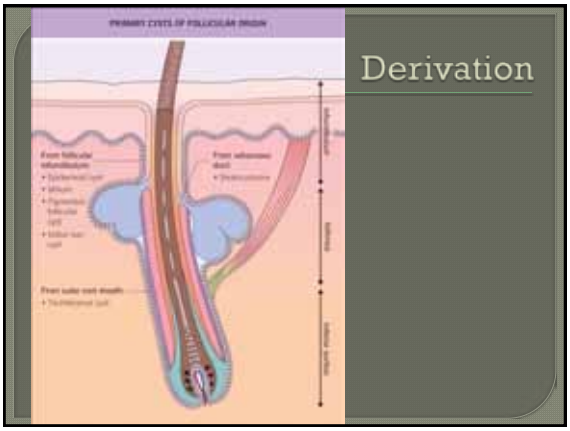
- Bolognia, Jean L. Dermatology. 3rd ed. S.l.: Elsevier Saunders, 2012.
- Elston, Dirk M. Dermatopathology. Edinburgh: Saunders/Elsevier, 2009.
- Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41:45-60
- Kunishge JH, Brodland DG, Zitelli JA. Surgical margins for melanoma in situ. J Am Acad Dermatol. 2012:438-44.
- Morton DL1, Thompson JF, Cochran AJ et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;599-609.
- Rapini, Ronald P. Practical Dermatopathology. 2nd ed. Edinburgh: Elsevier /Saunders, 2012.
- Schaelch S, et al. High risk tumors, clinical and histological considerations. Dermatologic Clinics of North American 1999;17:93-111.
- Schwartz RA. Keratoacanthoma. J Am Acad Dermatol 1994;30:1-19.
- Sladden M, Zagarella S, Popescu C, et al. No benefit for patients with melanoma undergoing sentinel lymph node biopsy: critical appraisal of the multicenter selective lymphadenectomy trial-I final report. Br J Dermatol. 2015;172:566-71.
- Yanofsky V, Mercer S, Phelps R. Histopathological variants of cutaneous squamous cell carcinoma: a review. J Skin Cancer. 2011;2011:210813.

Cysts

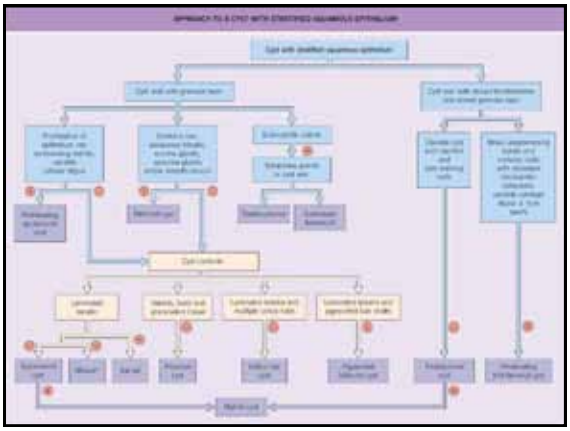
Aaron Peterson DO
Aspen Dermatology Residency
Spanish Fork, UT

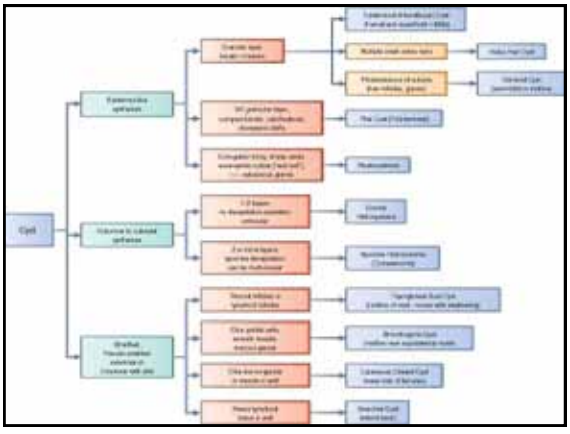
Cysts

- A cyst is a walled off subepidermal cavity filled with keratin, mucin or fluid.
- Cutaneous cysts can be classified by anatomic location, embryologic derivation or histologic features.
- Three main categories exist for classifying cutaneous cysts histologically:
  - Stratified Squamos Epithelium
  - Non-Stratified Squamos Epithelium
  - Absence of Epithelium



Derivation





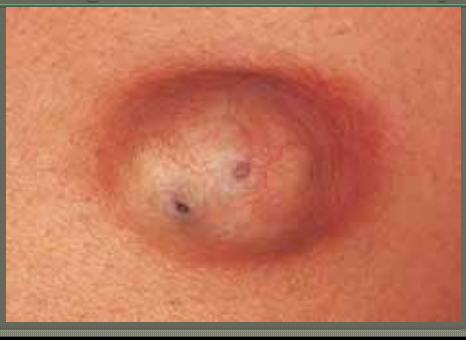
Cysts containing a stratified squamous epithelium

- Epidermal Inclusion Cyst
- Milium
- Pilar Cyst
- Proliferating Trichilemmal Cyst
- Proliferating EIC
- Vellus Hair Cyst
- Steatocystoma
- Cutaneous Keratocyst
- Pigmented Follicular Cyst
- Dermoid Cyst
- Verrucous Cyst
- Ear Pit Cyst
- Pilonidal Cyst

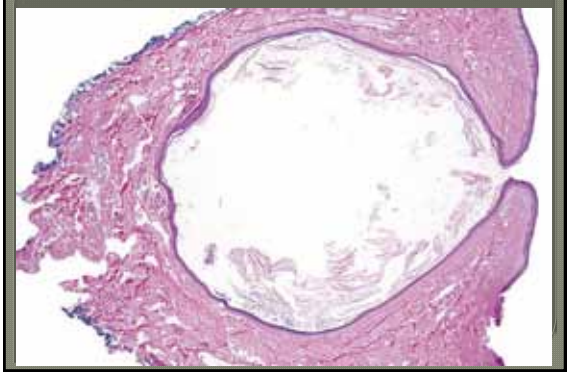
Epidermal Inclusion Cyst

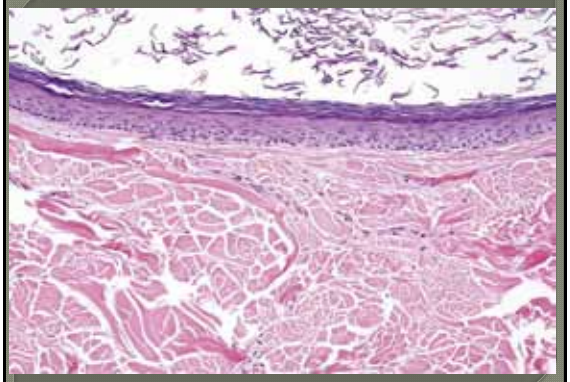
- Most common cyst, found most commonly on the upper trunk and face.
- Arise from the follicular infundibulum.
- May also arise from traumatically implanted epithelium.
- Some individuals seem to be genetically predisposed and association is documented in:
  - Gardner Syndrome
  - Nevoid Basal Cell Carcinoma Syndrome
  - Pachyonychia Congenita

Epidermal Inclusion Cyst



Epidermal Inclusion Cysts

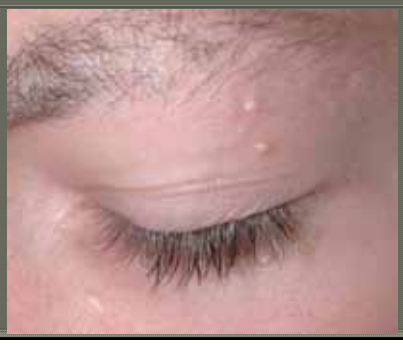


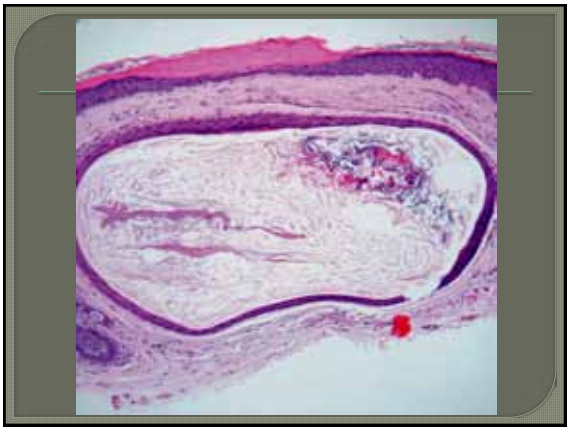


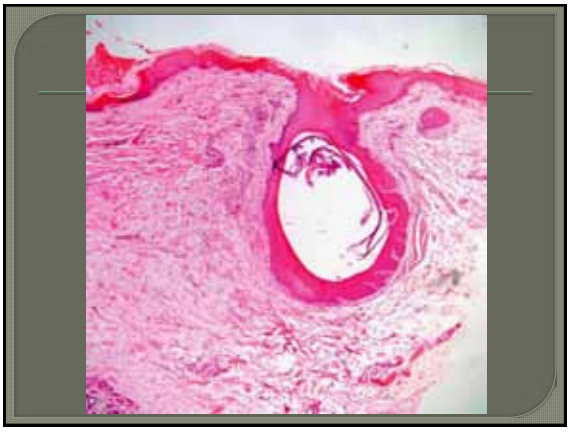
Milium

- Essentially just small EICs
- Extremely common in children and on the face
- Can be seen in widespread distribution in:
  - Hereditary Trichdysplasia
    - (Marie-Unna Hypotrichosis)
  - Oral-Facial-Digital Syndrome Type 1
  - Rombo Syndrome
  - Bazex Syndrome

Milium



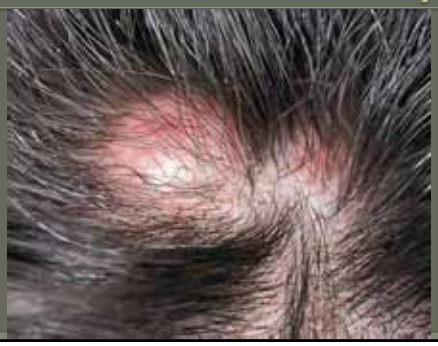


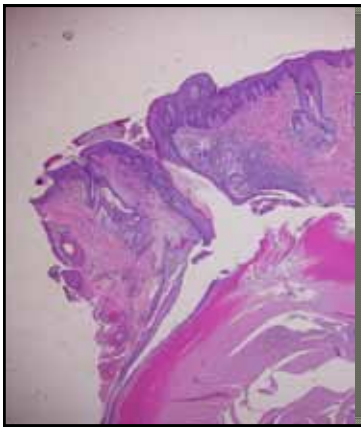


Pilar Cyst

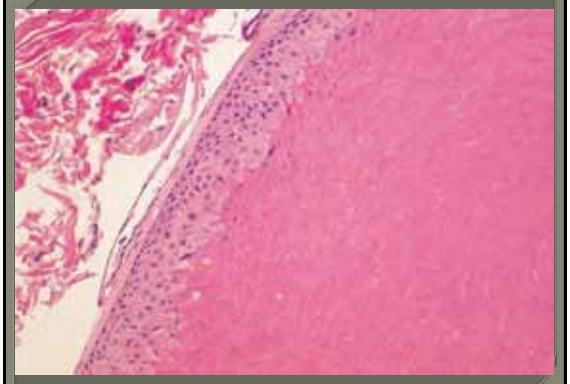
- Much less common than EICs
- 90% occur on the scalp
- Frequently are multiple and inherited as an autosomal dominant trait
- Have also been associated with Pachyonychia Congenita Type 2

Pilar Cyst





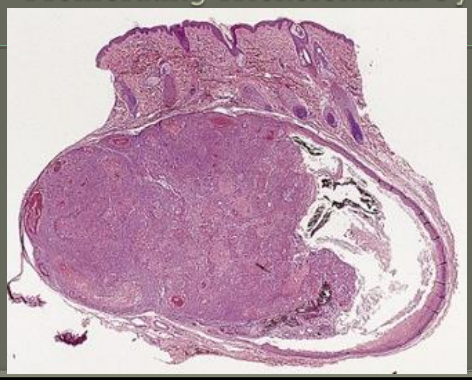
Pilar Cyst

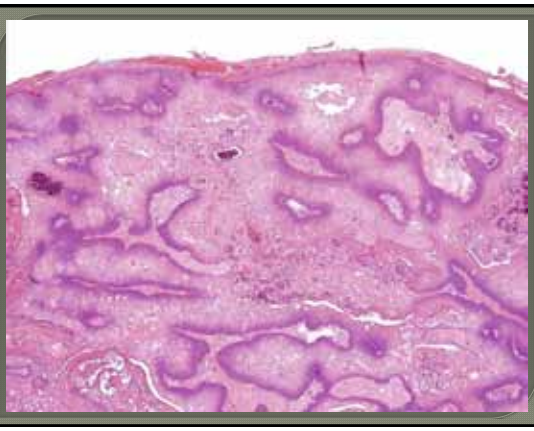


Proliferating Trichilemmal Cyst

- Usually found on the scalp of older women
- Can reach sizes of 20 cm or larger
- Are thought to be benign however, at least 30 cases of distant metastases have been reported

Proliferating Tricholemmal Cyst

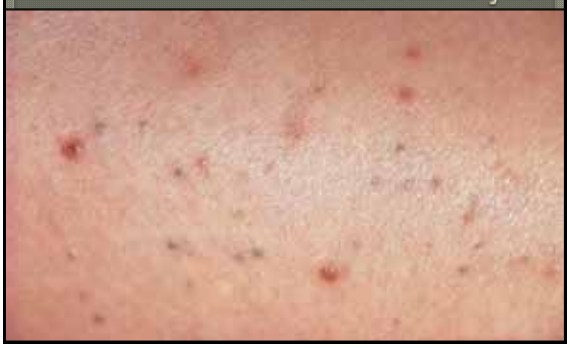


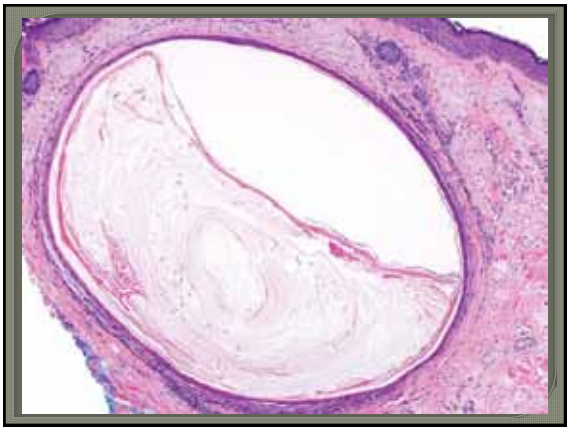


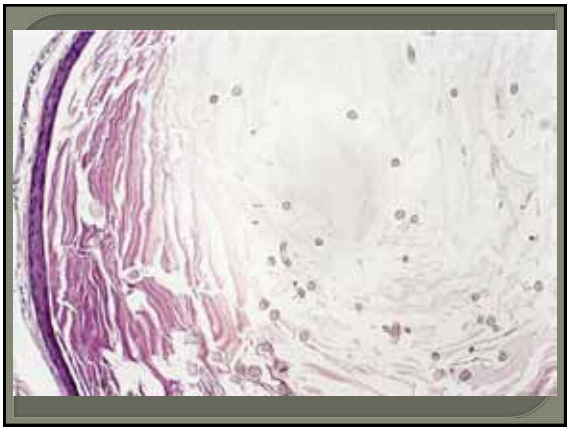
Vellus Hair Cyst

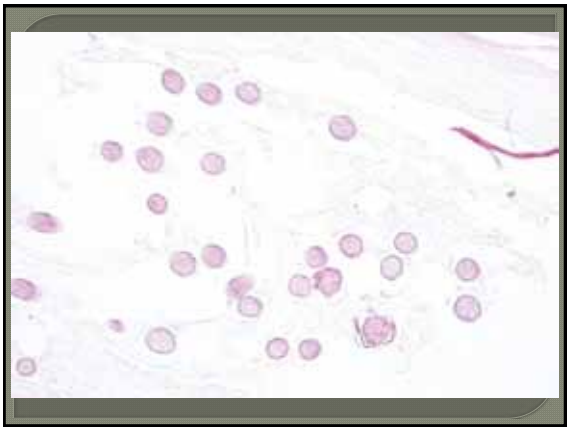
- Commonly located on the trunk
- May be inherited in an autosomal dominant fashion
- Can often be eruptive in nature presenting with hundreds of small papules on the chest
- Can also be seen in Pachyonychia Congenita Type 2

Vellus Hair Cyst

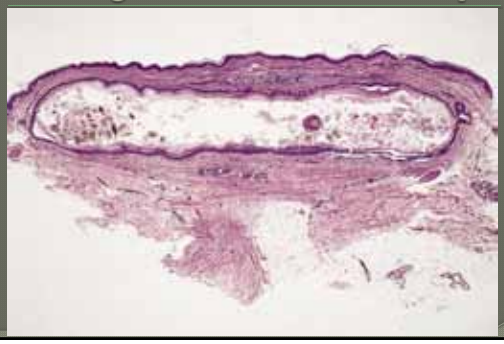


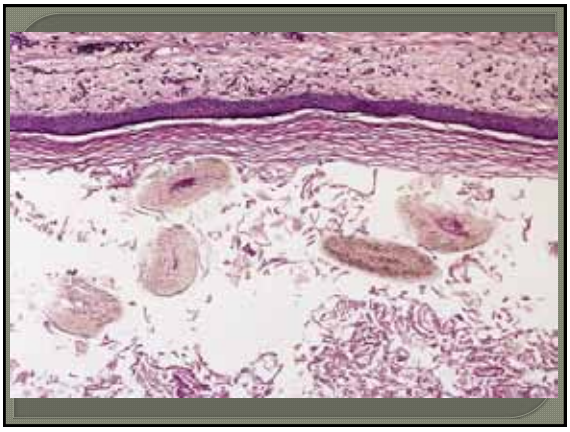






Pigmented Follicular Cyst

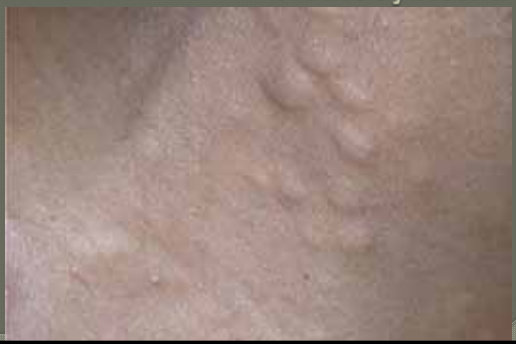




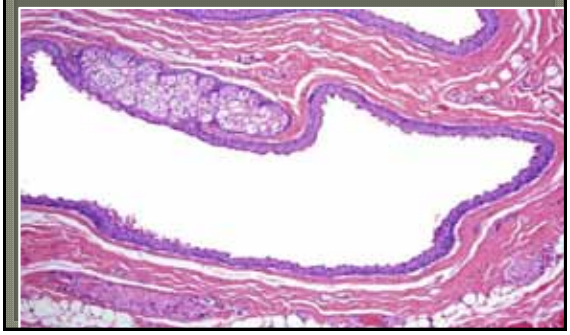
Steatocystoma

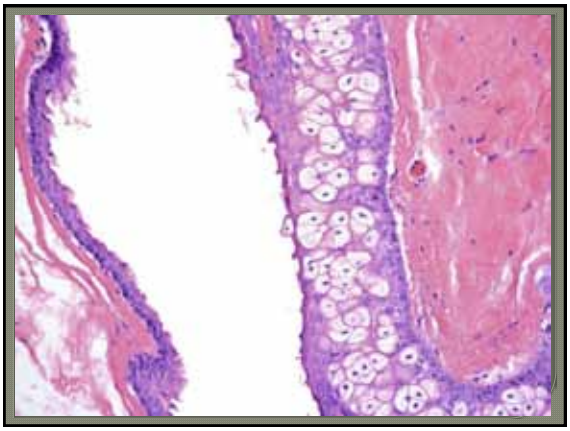
- Can be single or multiple
- Dermal cysts that drain oily fluid
- Usually found on the chest, axillae and groin
- Can be inherited as an autosomal dominant condition called Steatocystoma Multiplex and seen in conjunction with eruptive hair cysts and again in Pachyonychia Congenita

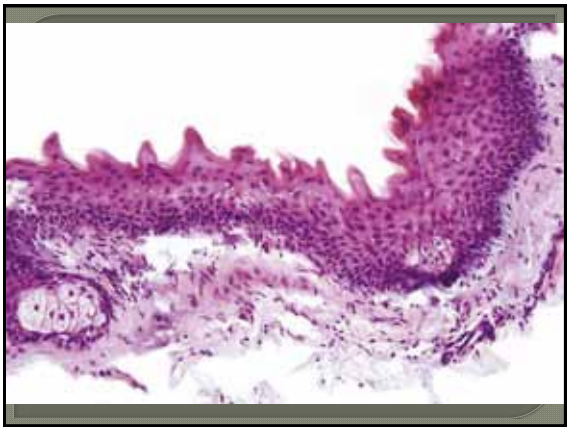
Steatocystoma



Steatocystoma



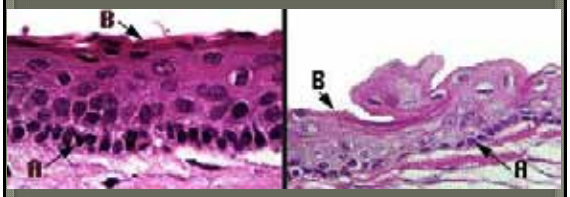


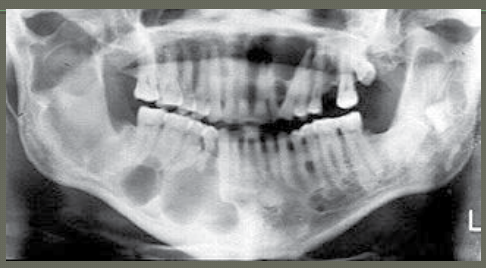


Cutaneous Keratocyst

- Clinically appear similar to EICs and have mainly been observed with Nevoid Basal Cell Carcinoma Syndrome
- Appear similar to a steatocystoma on pathology but without sebaceous lobules
- No granular layer

Cutaneous Keratocyst

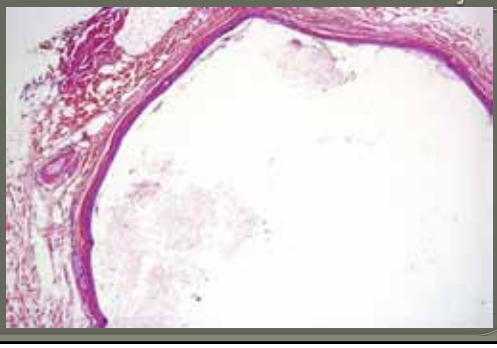




Dermoid Cyst

- Usually seen in an infant along an embryonic fusion plane with the most common location around the eyes
- Use caution if excision is desired since these may have connections to the central nervous system

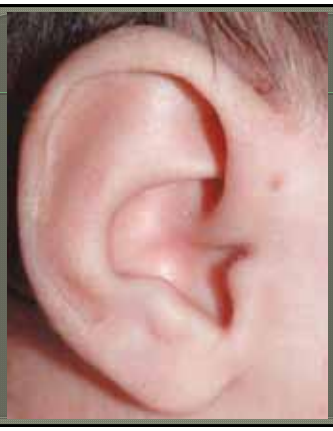
Dermoid Cyst



Ear Pit Cyst

- A congenital defect in embryologic fusion and epithelial entrapment
- About 1% of population is affected and can be inherited in an autosomal dominant fashion
- Associations Include:
  - Branchio-otic syndrome
  - Branchio-oto-renal dysplasia
  - Treacher Collins-Francschetti syndrome
  - Goldenhar sysndrome
  - Lowry-MacLean syndrome
  - Cat-eye syndrome

Ear Pit

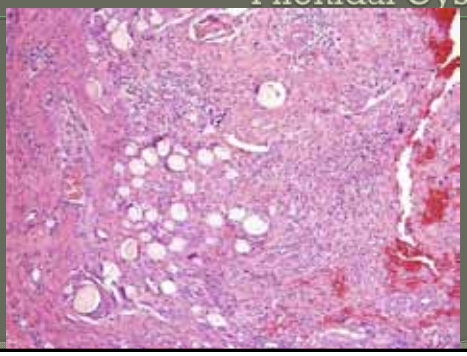


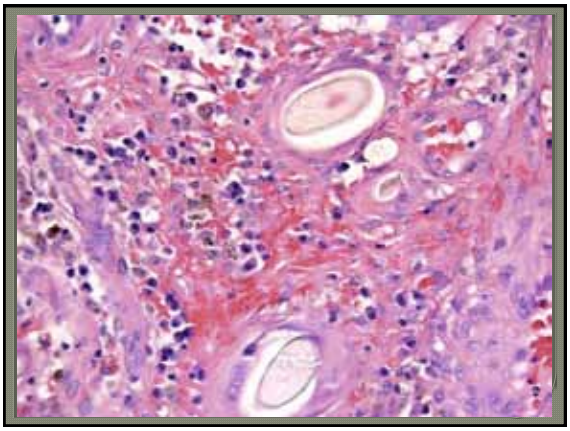
Pilonidal Cyst

- Usually present as a painful swelling of the upper gluteal cleft or sacrococcygeal area
- Often seen in hairy men

Pilonidal Cyst

Pilonidal Cyst





Cysts with a Non-Stratified Squamos Epithelium

- Hidrocystoma
- Bronchogenic Cyst
- Thyroglossal Duct Cyst
- Branchial Cleft Cyst
- Cutaneous Ciliated Cyst
- Ciliated Cyst of the Vulva
- Median Raphe Cyst
- Omphalomesenteric Duct Cyst

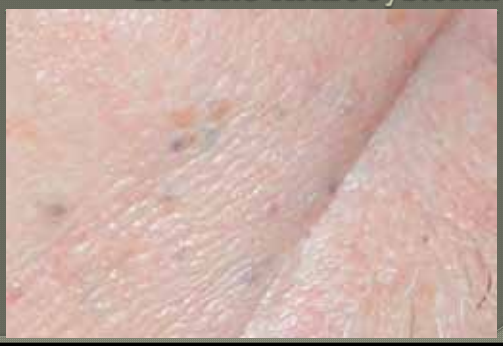
Hidrocystoma

- Skin colored to translucent or even blue cysts on the face
- Can be classified as Eccrine or Apocrine and each type behave differently
- Associated with:
  - Ectodermal Dysplasia
  - Schopf-Schulz-Passarge Syndrome

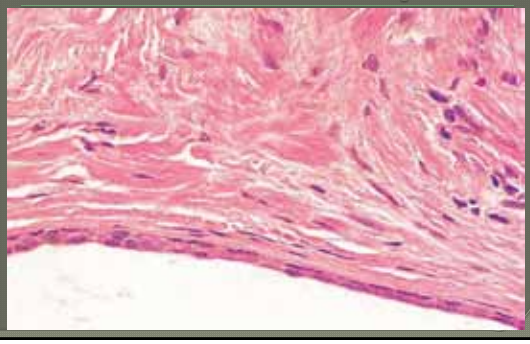
Apocrine Hidrocystoma

Apocrine Hidrocystoma

Eccrine Hidrocystoma



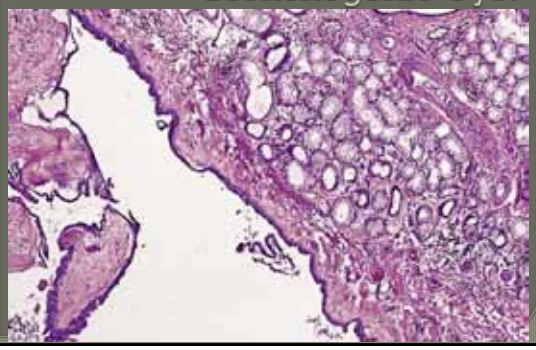
Eccrine Hidrocystoma

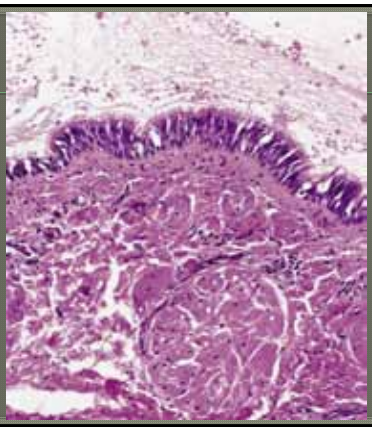


Bronchogenic Cyst

- Most commonly found in the suprasternal notch at birth
- Formed from trapped respiratory epithelium of the trachea during embryologic development

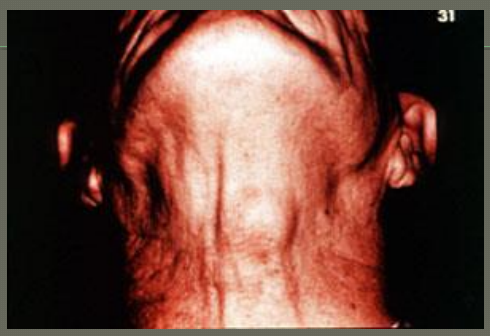
Bronchogenic Cyst



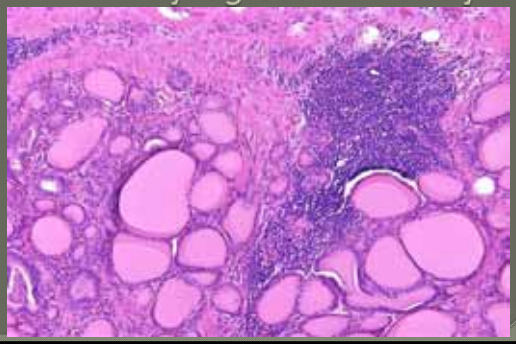


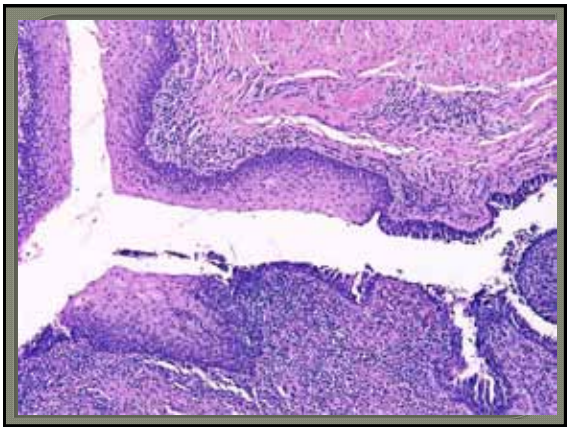
Thyroglossal Duct Cyst

- Seen in young adults or children as a midline cystic nodule on the anterior neck
- Form during development from remnants of the thyroglossal duct



Thyroglossal Duct Cyst

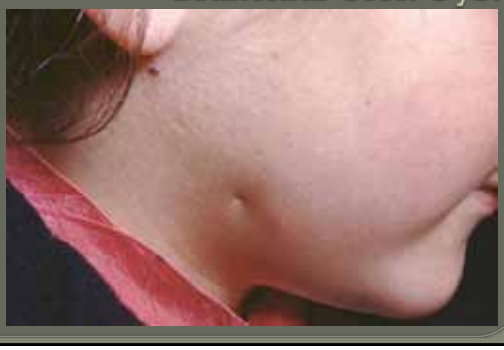


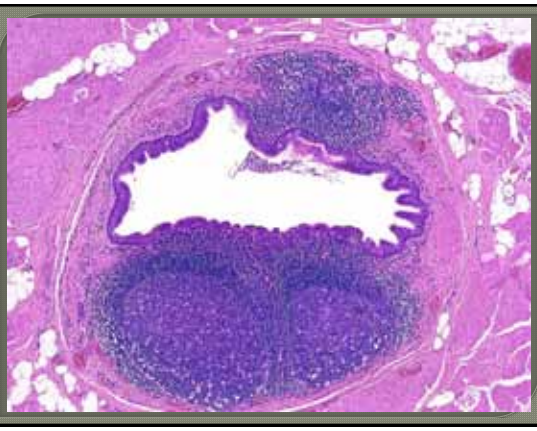


Branchial Cleft Cyst

- Often present in the second or third decades of life
- Occur along the SCM, pre-auricular area, or the mandible
- Thought to be remnants from the brachial cleft

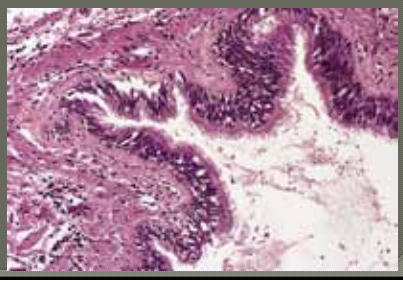
Branchial Cleft Cyst

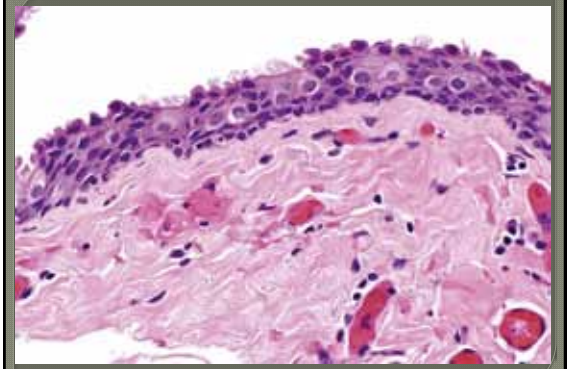




Cutaneous Ciliated Cyst

- Occur on lower extremities of young women

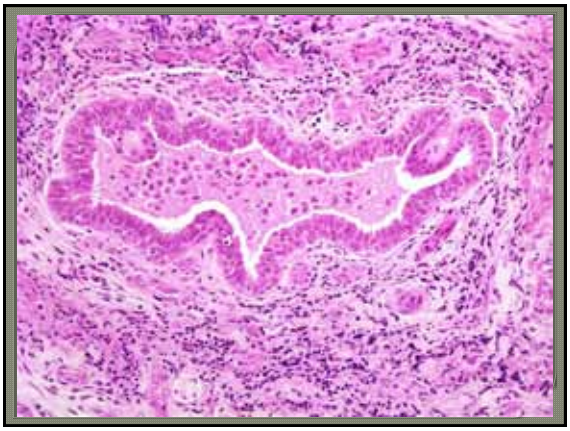




Median Raphe Cyst

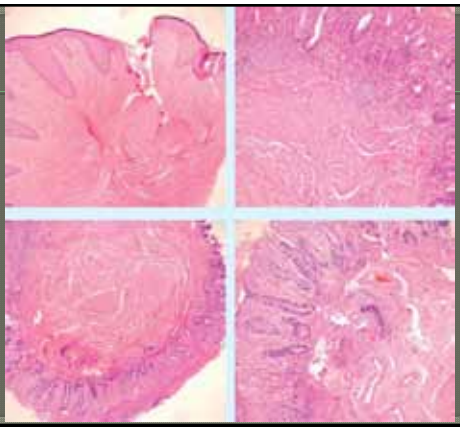
- Occur on the ventral penis near the glans in young men
- Are thought to be remnant urethral epithelium

Median Raphe Cyst



Omphalomesenteric Duct Cyst

- A closure defect of the omphalomesenteric duct which connects the midgut to the yolk sac



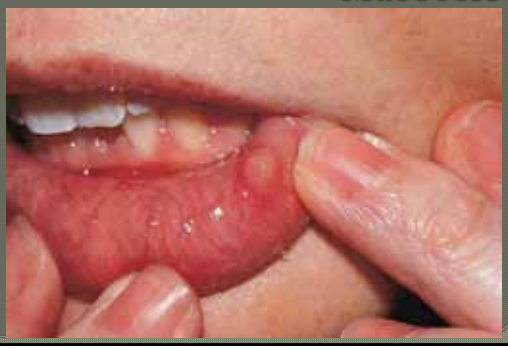
Pseudocysts—Those Without an Epithelial Lining

- Mucocele
- Digital Mucous Cyst
- Ganglion Cyst
- Pseudocyst of the Auricle
- Cutaneous Metaplastic Synovial Cyst

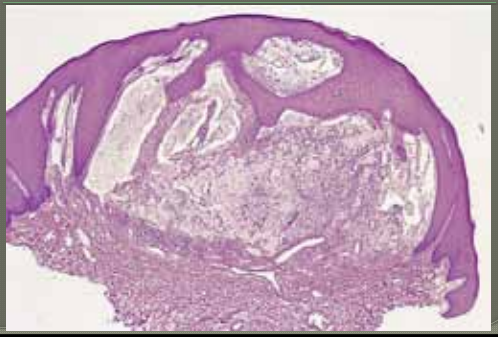
Mucocele

- Disruption of the minor salivary gland ducts
- Usually on the lower labial mucosa
- Accumulation of mucinous material can illicit inflammation and granulation to the area

Mucocele



Mucocele

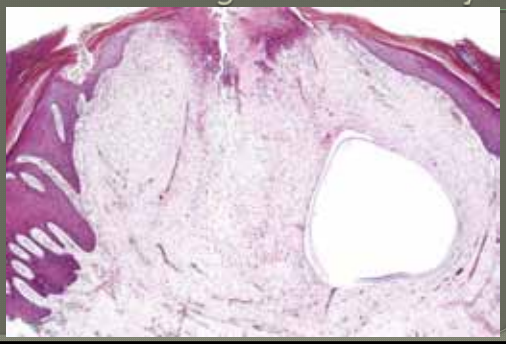


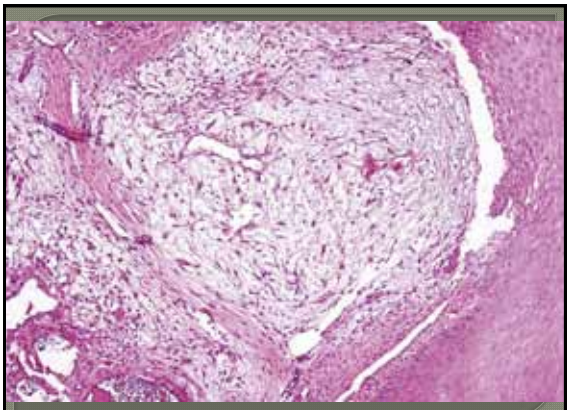
Digital Mucous Cyst

- Most commonly found on the dorsal distal phalanx of the finger
- Drain clear gelatinous material if punctured
- Usually have an underlying connection to a joint space
- Will often traumatize the nail matrix causing nail changes extending directly distal to the visible cyst

Digital Mucous Cyst

Digital Mucous Cyst

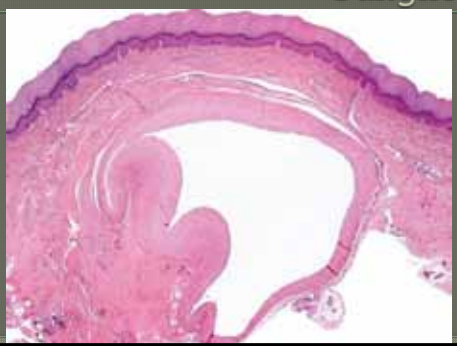




Ganglion

- Large mucinous filled cysts attached to a tendon sheath or joint capsule but not communicating with the joint space
- Mucin is thought to be produced from fibroblasts
- Found on volar wrists, dorsal wrist, fingers, feet or knees

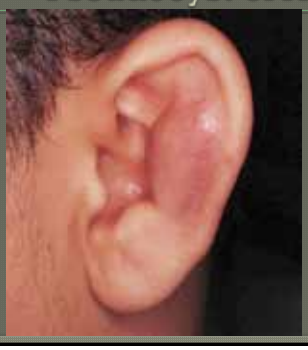
Ganglion



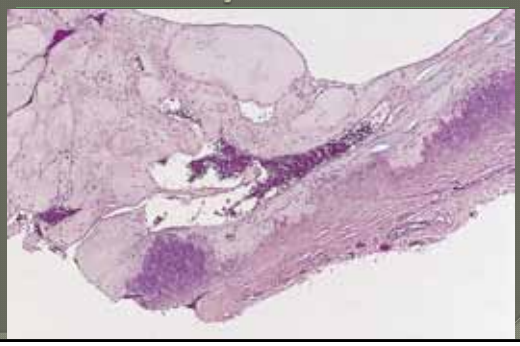
Pseudocyst of the Auricle

- Presents painless swelling of the scaphoid fossa in middle-aged men
- Trauma? or developmental defect?

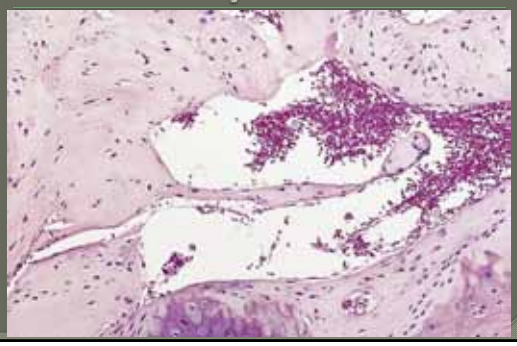
Pseudocyst of Auricle

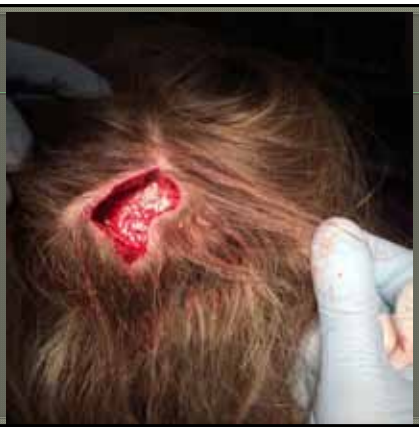


Pseudocyst of the Auricle



Pseudocyst of the Auricle





Cyst

References

- Bolognia, Jorizzo, Schafer. (2012) Dermatology 3rd edition. Saunders
- Weedon. (2010). Weedon's Skin Pathology, 3rd Edition, Churchill Livingston
- Spitz. (2005). Genodermatoses, a guide to genetic skin disorders, 2nd edition, Lippincott, Williams & Wilkins

ACNE

Western University of Health Sciences
Silver Falls Dermatology

Lauren Boudreaux, PGY2
Bryce Desmond, PGY3
Stephanie Howerter, PGY2
Ben Perry, PGY3
Karla Snider, PGY4
Scott Thomas, PGY4

EPIDEMIOLOGY

- 40-50 million individuals in the US affected each year
- Infants to adults
- Peaks in adolescence and affects 85% of people between age 12-24 years old
- 35% of women and 12% of men
- $2.5 billion in annual cost

THE FOUR MAIN PATHOGENIC FACTORS

1. **Microcomedo formation**
   - Alteration in the keratinization process/epidermal hyperproliferation
   - Secondary to androgens, decreased linoleic acid, increased IL-1 alpha
2. **Sebum production**
   - Androgens
3. ***P. acnes* follicular colonization**
   - Breaks down TGs, stimulates ab production, inflammatory response,
   - binds TLR2 → release of IL-1a, IL-8, IL-12, TNFa
   - Coproporphyrin III
4. **Release of inflammatory mediators**
   - Before or after microcomedo formation

DIETARY FACTORS

- Controversial
- High glycemic diets and dairy (especially milk) have been found to be associated with increased prevalance and severity
- High glycemic index foods and dairy consumption increase androgen levels and insulin-like growth factor-1 (IGF-1)
- IGF-1 controls signaling of the Fox01 nuclear transcription factor
- Fox01 in combination with nutrient-sensitive kinase mTOR complex 1 signaling currently hypothesized to be primary mediators of food-induced acne promotion

CLINICAL FEATURES OF ACNE

- Non-flammatory
  - Comedones (follicular)
  - Open (blackhead)
  - Closed (whitehead)
- Inflammatory
  - Papules
  - Pustules
  - Cysts
  - Nodules
  - Sinus tracts

Scarring can occur from all forms, including comedones

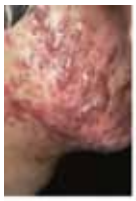
PIH and persistent erythema can be permanent

NEONATAL AND INFANTILE ACNE

- Neonatal: 2-3 weeks to 3 months, no comedones, Malassezia
- Infantile: 3-6 months, comedones presents, transient elevation of DHEA

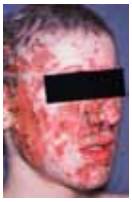
ACNE CONGLOBATA

- Severe nodulocystic acne WITHOUT systemic symptoms
- Follicular occlusion tetrad
  - Acne conglobata, dissecting cellulitis of the scalp, hidradenitis suppurativa, pilonidal cyst
- Treatment: Isotretinoin



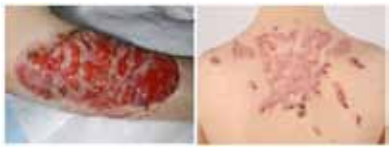
ACNE FULMINANS

- Most severe form of acne
- Abrupt onset in young men
- Systemic symptoms
  - Fever, arthralgias, myalgia, hepatosplenomegaly
  - Osteolytic bone lesions in the clavicle and sternum
- Painful, oozing, friable plaques with hemorrhagic crusts
- Labs: elevated ESR, leukocytosis, anemia, proteinuria
- Treatment: Isotretinoin + oral corticosteroids
- May be associated with SAPHO syndrome
  - **S**ynovitis, **A**cne, **P**ustulosis, **H**yperostosis, **O**steitis
  - Treatment: NSAIDS, sulfasalazine, infliximab



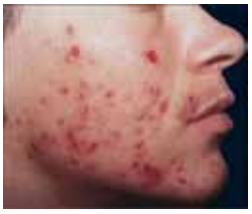
PAPA SYNDROME

- **P**yogenic **A**rthritis, **P**yoderma gangrenosum, **A**cne
  - PSTPIP1 gene encoding CD2 antigen-binding protein 1 (CD2BP1)
  - Tx: Infliximab, Anakinra



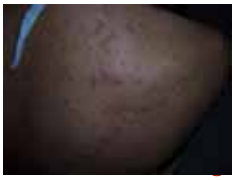
OTHERS

- Acne mechanica
- Acne excoriee des jeunes
- Acne with endocrine abnormality
  - PCOS/Stein-Leventhal syndrome
  - Congenital adrenal hyperplasia

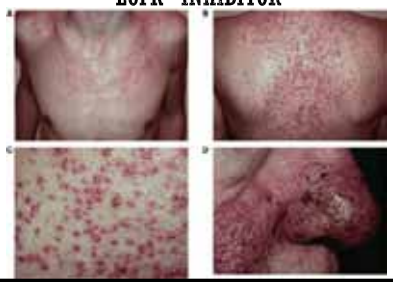


DRUG-INDUCED ACNE

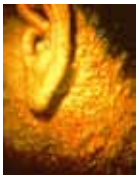
- Monomorphorous inflammatory papules
- Hormones
  - Anabolic steroids (danazol, testosterone)
  - Corticosteroids, Corticotropin
- Phenytoin
- Lithium
- Isoniazid
- Iodides, bromides
- EGFR inhibitors



ACNEIFORM ERUPTION WITH EGFR- INHIBITOR



CHLORACNE



- Exposure to chlorinated aromatic hydrocarbons
  - Chloracnegens – fat-soluble, persist in body fat
  - Insecticides, insulators, fungicides, herbicides, wood preservatives
- Malar, retroauricular, mandibular, axillae, scrotum
- Scarring, recurrent outbreaks for many years
- TREATMENT
  - Topical/oral retinoids and antibiotics

TREATMENT

- Topicals
- Systemics
- Light/Laser
- Surgery

TOPICAL THERAPIES

- Benzoyl peroxide (BPO), salicylic acid, glycolic acid, azelaic acid, lipohydroxy acid, sulfur, tea tree oil
- Antibiotics: Clindamycin, Dapsone
- Retinoids:
  - 1st gen – Tretinoin, isotretinoin
  - 2nd gen – Etretinate, alitretin
  - 3rd gen – Tazarotene, adapalene, bexarotene
    - Cornerstone of combination therapy
    - Bind nuclear retinoic acid receptors – RAR, RXR
    - Reverse abnormal keratinization; down regulating K6, K16
    - Comedolytic effect
    - Anti-inflammatory effect via inhibition of TLR-2

SYSTEMIC

- Antibiotics: doxycycline, cephalosporins, minocycline
- Isotretinoin:
  - Teratogenic → ipledge
  - Adverse effects: xerostomia/cheilitis, pseudotumor cerebri, hypertriglyceridemia
    - Hypertriglyceridemia: 150 – 499 → lifestyle changes >500 → first line = treatment
      - 1st line treatments: niacin, omega 3 fatty acids
      - 2nd line: fibrates, statins
- OCPs
- Spironolactone
- Zinc
- Probiotics

LASER AND LIGHT TREATMENTS

- P. acnes makes coproporphyrin III → light (blue) → reactive oxygen species
- Red light penetrates deeper
- PDT

Table 1

Mechanism of action of light-based therapies

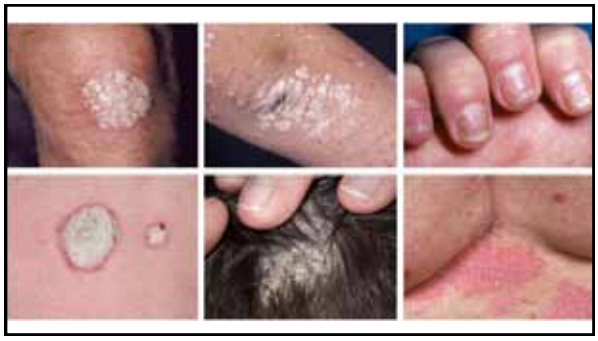
Therapy	Wavelength (nm)	Mechanism of action
Narrowband blue light	415	Bactericidal effects on Propionibacterium acnes
Narrowband red light	660	Bactericidal effects on P. acnes; disrupt sebaceous gland function; exert anti-inflammatory effects
Intense pulsed light	400-1200	Bactericidal effects on P. acnes; disrupt sebaceous gland function; exert anti-inflammatory effects
Pulsed dye laser	585	Bactericidal effects on P. acnes; disrupt sebaceous gland function; exert anti-inflammatory effects
Potassium titanyl phosphate laser	532	Bactericidal effects on P. acnes; disrupt sebaceous gland function
Infrared lasers	1320, 1450, 1540	Disrupt sebaceous gland function
Photodynamic therapy	630, 580-700 (variable depending on light source used, light-emitting diodes, fluorescent lamps, filtered incandescent or arc lamps)	Disrupt sebaceous gland function
Photopneumatic technology	400-1200	Negative pressure opens sebaceous gland, allowing for more effective evacuation of sebum, bacteria, and dead skin cells; increases efficiency of energy transmission from light source

LASERS FOR ACNE RESURFACING

- CO2
- Picosecond PDL
- Picosecond Alexandrite
- Histology suggest improvement in scarring from laser goes beyond remodeling of collagen

REFERENCES

- Bolognia J, Jorizzo JL, Rapini RP (eds). Dermatology. 2nd ed. Vol. 2. St. Louis: Mosby/Elsevier; 2008. Chapter 68 Alopecias; p.950-95.
- Bowe, Whitney P. et al. Diet and Acne, Journal of the American Academy of Dermatology , Volume 63 , Issue 1 , 124 – 141
- Bowe W, Logan A. Acne vulgaris, probiotics and the gut-brain-skin-axess – back to the future? *Gut Pathogens.* 2011;3(1):1-11
- Bowe, WP. Probiotics in acne and rosacea. Cutis 2013;92:6-7.
- Brauer, Jeremy A., Viktoryia Kazlouskaya, Hamad Alabdulrazzaq, Yoon Soo Bae, Leonard J. Bernstein, Robert Anolik, Patricia A. Heller, and Roy G. Geronemus. "Use of a Picosecond Pulse Duration Laser With Specialized Optic for Treatment of Facial Acne Scarring." *JAMA dermatology* 151, no. 3 (2015): 278-284.
- Eichenfield LF, Fowler JF Jr, et al. Perspectives on therapeutic options for acne: an update. *Skin All News.* 2010;41(8)S13-16
- Enshaieh S, Jooya A, et al. The efficacy of 5% tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo control trial. *Indian J Dermatol Venereol Leprol.* 2007;73(1):22-25.
- Kwon H, Yoon J, et al. Clinical and Histological Effect of a Low Glycemic Load Diet in Treatment of Acne Vulgaris in Korean Patients: A Randomized, Controlled Trial. *Acta Derm Venereol.* 2012;92(3) 241-246.
- Leyden JJ, Del Rosso JQral antibiotic therapy for acne vulgaris: pharmacokinetic and pharmacodynamic perspectives. J Clin Aesthet Dermatol. 2011 Feb;4(2):40-7. PubMed PMID: 21386959; PubMed Central PMCID: PMC3050614.
- Melnik BC, Schmitz G. Role of insulin, insulin-like growth factor-1, hyperglycemic food and milk consumption in the pathogenesis of acne vulgaris. *Exp Dermatol.* 2009;18(10):833-841.
- Melnik BC. Diet in acne: further evidence for the role of nutrient signaling in acne. *Acta Derm Venereol.* 2012;92(3)228-231
- Rai R, Natarajan K. Laser and light based treatments of acne. *Indian J Dermatol Venereol Leprol.* 2013 May-Jun;79(3):300-9.
- Seidler EM, Kimball AB. Meta-analysis of randomized controlled trials using 5% benzoyl peroxide and clindamycin versus 2.5% benzoyl peroxide and clindamycin topical treatments in ace. *J Am Acad Dermatol.* 2011;65(4):e117-e119.
- Smith R, Mann N, et al. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: A randomized, investigator-masked, controlled tria. *J Am Acad Dermatol.* 2007;57(2):247–256.
- Tanghetti E, Dhawan S, et al. Clinical evidence for the role of topical antiinflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. *J Drugs Dermatol.* 2011;10(7)783-792.
- Taylor MN, Gonzales ML. The practicalities of photodynamic therapy in acne vulgaris. *Br J Dermatol.* 2009;160(6):1140-1148.
- Tennacli, Khamurai A, et al. In vitro modulation of TLR-2, CD1d and IL-10 by adagalese on normal human skin and acne inflammatory lesions. *Exp Dermatol.* 2007 Jun;16(6):500-6
- Tennacli, Khamurai A, et al. In vitro modulation of TLR-2, CD1d and IL-10 by adagalese on normal human skin and acne inflammatory lesions. *Exp Dermatol.* 2007 Jun;16(6):500-6.
- Thiele A, Gollnick H. Recent therapeutic developments for acne. *Exp Rev Dermatol.* 2013;8(1):37-50.
- Williams H, Dellavalle R,et al. Acne Vulgaris. *Lancet* 2012;379:361–372.



Psoriasis: A Therapeutic Update

Presenter: Christine Moussa, PGY-4
Program Director: Stephen Kessler, D.O.
Alta Dermatology/LECOM

Disclosures

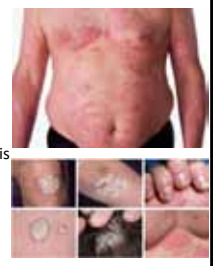
- I have no relevant financial or nonfinancial relationships to disclose.

Objectives

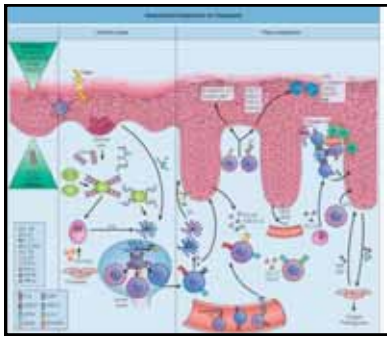
- Brief review of the pathogenesis of psoriasis
- Discuss traditional treatment options for psoriasis
- Introduce emerging therapeutic options for psoriasis
- Appreciate a "whole-person" approach to psoriasis

Psoriasis

- Chronic inflammatory disease
- Systemic inflammatory state
  - Obesity, diabetes mellitus, cardiovascular disease, dyslipidemia, etc…
  - Up to 30% of patients with psoriatic arthritis
  - Up to 60% with clinical depression
- Earlier onset associated with more severe disease
- Affects 2% of the population

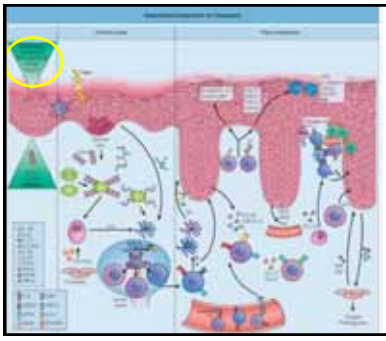


Pathogenesis of Psoriasis



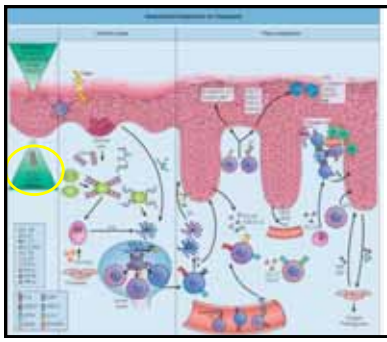
Board Review

Triggering factors
Genetic Predisposition
Chronic T cell activation



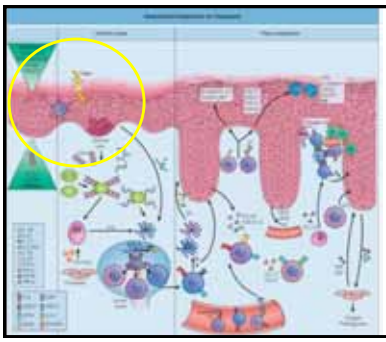
Board Review

Triggering factors
- Infection
- Trauma
- Stress
- Drugs
  - ACE inhibitors
  - Beta blockers
  - Lithium
  - Rapid steroid withdrawal



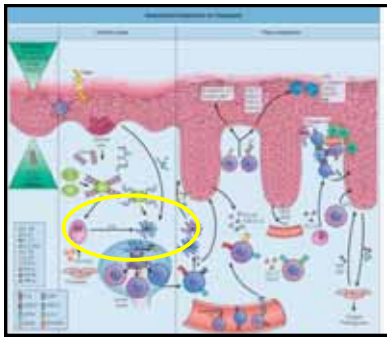
Board Review

Genetic Predisposition
- HLA-Cw6 & B17 → early onset disease
- HLA-B27→ arthritis
- HLA-B13 & B17→guttate



Board Review

Abnormal chronic T cell activation:
- **Stressed keratinocytes**
  - **TNFα, IL-1, IL-6**
- Dendritic cells activated
  - Present "antigen"
- Naïve T cells differentiate
- TH1, TH17, TH22 migrate to psoriatic dermis from the lymph and blood
- Psoriatic plaque develops



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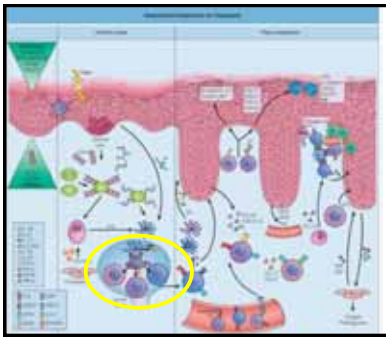

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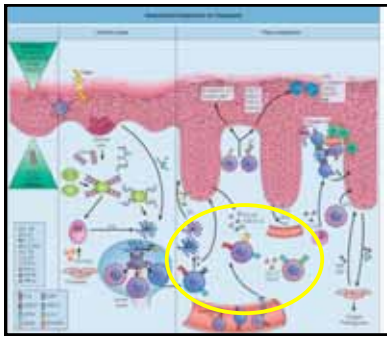

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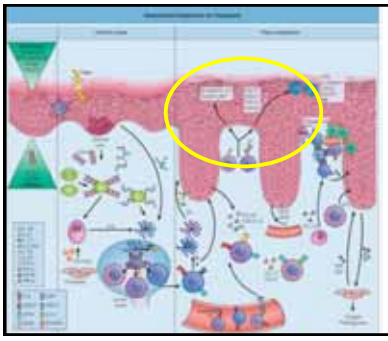

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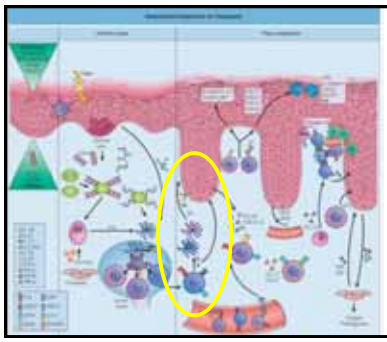
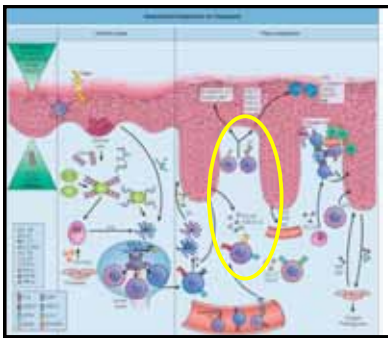


Board Review

Abnormal chronic T cell activation:

- **TH1 cells release TNFα amplifying inflammatory cascade**
  - IL-12 stimulates TH1
- TH17 cells secrete TNFα, IL-17 and IL-22
  - IL-23 and IL-17 stimulates TH17



Board Review

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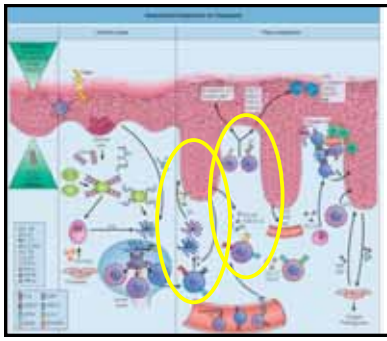

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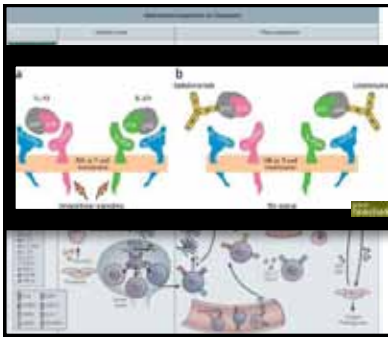
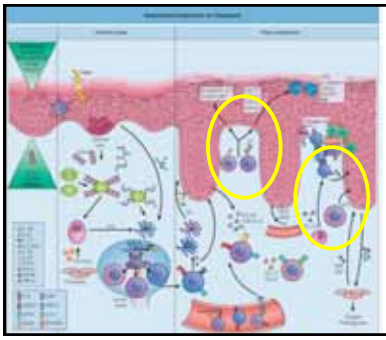


Board Review

Abnormal chronic T cell activation

- **IL-12 stimulates TH1**
- **IL-23 stimulates TH17**

- **Recall**:
  IL-12 and IL-23 have common subunit p40 (target of ustekinumab)



Board Review

Abnormal chronic T cell activation:

- TH22 cells secrete IL-22, inducing further recruitment of T cells
  - IL-22 levels correlate with disease severity

Traditional Therapies

To find health should be the object of the doctor. Anyone can find disease.
—A.T. Still

Topical Agents

- Majority of patients with mild to moderate disease can be treated with topical agents only
- Generally provide both high efficacy and safety
- Can also be used as an adjunct for resistant lesions or extensive disease

Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

Topical Agents

- **Topical Corticosteroids**
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Anti-inflammatory and antiproliferative
- 80% of patients experience clearance with high-potency topical corticosteroids
- Maximum improvement usually achieved within 2 weeks
- Decrease to alternate day dosing for prolonged courses
- Side effects: Tachyphylaxis and rebound can occur rapidly

Topical Agents

- Topical Corticosteroids
- **Vitamin D analogues**
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Antiproliferative
- ~60% reduction of PASI after 8 weeks
- Combination with a high-potency topical corticosteroid → greater efficacy and a more rapid onset of action than either agent alone
- Not to use >100 grams weekly
- Not for use on face or body folds
- Side effects: burning, irritation, hypercalcemia, hypercalciurea

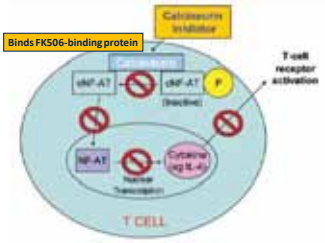
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- **Topical retinoids**
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Antiproliferative
- 50% improvement noted in half of patients using tazarotene gel twice daily after 6 weeks
- Up to 10-20% BSA
- Side effect: irritating

Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- **Calcineurin inhibitors**
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths



Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- **Calcineurin inhibitors**
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Facial and flexural areas
- 65% almost clear at 8 weeks
- Side effects: burning and itching that improves with usage
- Controversial black box warning

Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- **Keratolytics**
- Anthralin
- Coal Tar
- Salt-water baths

- Salicylic acid 5-10%
- Useful for thick scaling lesions of scalp or other localized areas
- Use 2-3 times weekly

Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- **Anthralin**
- Coal Tar
- Salt-water baths

- Antiproliferative
- Side effects: odor, staining, irritation

Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- **Coal Tar**
- Salt-water baths

- Anti-inflammatory, anti-proliferative
- Side effects: odor, staining, contact dermatitis

Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- **Salt-water baths**

Systemic Agents

Table 1
Selected patient considerations in systemic psoriasis therapy

Parameter	Consideration
Extent or severity of psoriasis	Typically >10% BSA, or involved areas significantly impede quality of life
Presence of psoriatic arthritis	Consider systemic, disease-modifying therapy regardless of level of skin involvement
Woman of childbearing potential	Not a good candidate for most oral psoriasis medications
Man attempting to conceive a child	Not a good candidate for methotrexate
Chronic or binge alcohol user	Avoid concomitant therapies with significant risk of hepatotoxicity
History of hepatitis	Avoid therapies with significant risk of hepatotoxicity
History of hematologic malignancy	Use immunosuppressants with caution
Immunodeficiency	Avoid immunosuppressants
Smoker	Counsel on quitting

Kelly R et al.

Systemic Agents

Table 2
Suggested baseline laboratory workup before systemic psoriasis therapy

Frequent	Less Frequent
Comprehensive metabolic panel	Magnesium, phosphate
Complete blood count	β-human chorionic gonadotropin
	HIV serology
	Lipid panel
	Hepatitis B serology
	Hepatitis C serology
	Interferon-gamma releasing assay for the detection of latent tuberculosis or purified protein derivative tuberculin

Kelly R et al.

Systemic Agents

- Phototherapy
- Methotrexate
- Cyclosporine
- Systemic retinoids

Systemic Agents

- **Phototherapy**
- Methotrexate
- Cyclosporine
- Systemic retinoids

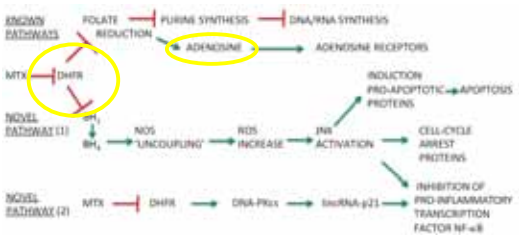
- Decreased cellular proliferation, apoptosis of T cells, suppression of Langerhans cells
- Narrow band UVB (311-313 nm) optimal
  - Remission rate up to 55% at 1 year
- Excimer laser (308 nm) for limited, localized plaques
- Side effects: erythema/blistering, photoaging, theoretical risk of photocarcinogenesis

Systemic Agents

- Phototherapy
- **Methotrexate**
- Cyclosporine
- Systemic retinoids

- Oldest systemic therapy for psoriasis (>40 years)
- Increases endogenous adenosine levels (potent anti-inflammatory)
- 40% achieve PASI 75 at week 16
- Monitoring for rare, severe side effects (liver, bone marrow, lung)
  - Psoriasis is an independent risk factor for liver disease

Systemic Agents



Systemic Agents

- Phototherapy
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Systemic Agents

- Phototherapy
- Methotrexate
- **Cyclosporine**
- Systemic retinoids

- Calcineurin inhibitor: inhibits T cell activation
- Used as bridge therapy, for severe flares or refractory disease
- Up to 88% achieve PASI 75
- Use for up to 1 year
- Monitoring
  - Hypertension, nephrotoxicity, ↓Mg ↑uric acid, ↑K, gingival hyperplasia

Systemic Agents

- Phototherapy
- Methotrexate
- Cyclosporine
- **Systemic retinoids**

- Anti-proliferative effects on keratinocytes
- Not immunosuppressive
- Up to 41% achieve PASI 75
- Poor tolerability
- Effective for pustular or erythrodermic psoriasis
- Side effects: abnormal LFTs, hyperlipidemia, pseudotumor cerebri, etc…

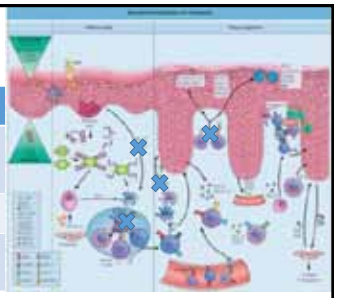
Systemic Agents

Phosphodiesterase 4 inhibitor (apremilast):

- Downregulates TNFα, IL-2,IL-12, IL-23
- FDA approved for psoriasis and psoriatic arthritis
- Side effects:
  - Diarrhea, nausea, headache, URI, weight loss, depression
  - Starter pack dosing and resolution of GI symptoms in first month
- 33% achieve PASI 75 at week 16
- No need for blood monitoring

Systemic Agents

Target	Biologic Agent(s)
TNFα	Etanercept Infliximab Adalimumab
p40 subunit of IL-12/23	Ustekinumab
IL-17	Secukinumab Brodalumab Ixekizumab



Systemic Agents

Target	Biologic Agent(s)	Efficacy	Safety
TNFα	Etanercept Infliximab Adalimumab	68-80% achieve PASI 75 20-57% achieve PASI 90	Concern for infection
p40 subunit of IL-12/23	Ustekinumab	Up to 70% achieve PASI 75 28% achieve PASI 100	Concern for infection
IL-17	Secukinumab	Up to 87% achieve PASI 75 54% achieved PASI 90 44% achieve PASI 100	Concerns for invasive candidiasis and Crohn's exacerbations

New and Emerging Therapies

My father was a progressive farmer, and was always ready to lay aside an old plough if he could replace it with one better constructed for its work. All through life, I have ever been ready to buy a better plough.

- A.T. Still

New and Emerging Therapies

JAK inhibitors (Tofacitinib and Ruxolitinib):

- FDA approved for rheumatoid arthritis
- Impedes a wide array of inflammatory cytokines, including IL-12 and IL-23
- Phase III trials (topical and systemic formulations)
- Side effects:
  - Risk of infection, theoretical increased risk of malignancy (interferes with anti-tumor responses), cytopenias, lipid abnormalities
- Up to 63% achieve PASI 75 at week 12

Other Emerging Therapies

- IL-23 inhibitors (Guzelkumab, Tildrakizumab)
  - Up to 81% achieve PASI 75 in phase II studies
- Adenosine A3 receptor antagonists
  - Decrease proinflammatory cytokines, including TNFα
- Oxidized phospholipids
  - Inhibits secretion of inflammatory markers, such as TNFα, IL-12 and IL-23
- Fumaric acid derivatives
  - Approved in Europe, not the US
  - Efficacy on par with methotrexate; requires lab monitoring
  - Shifts inflammatory infiltrate towards Th2 and away from Th1 and Th17
- Sphingosine 1-phosphate receptor-1 modulators
  - Inhibits migration of T lymphocytes into circulation
  - Concern with cardiac conduction abnormalities
- And others….

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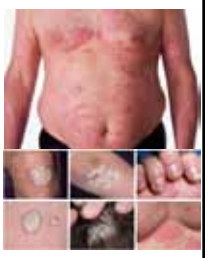
- And others….

A "Whole Person" Approach

We look at the body in health as meaning perfection and harmony, not in one part, but in the whole.
—A.T. Still

Obesity and Psoriasis

- Obesity = chronic inflammatory state
- Obese patients have higher risk of severe disease and reduced response to therapy
  - Adipocytes produce TNFα, IL-6, leptin
  - Obese patients have higher levels of IL-17 and IL-23 compared to lean patients
  - Inflammatory markers decrease with weight loss



Effect of Weight Loss in Psoriasis Management

CLINICAL AND LABORATORY INVESTIGATIONS — British Journal of Dermatology

Diet and physical exercise in psoriasis: a randomized controlled trial*

L. Naldi,[1,2] A. Conti,[3] S. Cazzaniga,[1] A. Parodi,[4] M. Pazzaglia,[4] A. Lanzoni,[5] L. Veneziano,[5] G. Pellacani[6] and the Psoriasis Emilia Romagna Study Group

Results:

- Median PASI reduction of 48% in intervention group (vs 25%)
- PASI 50 achieved by 49% of intervention group (vs 34%)

EatRight.org

- Unique patients with unique needs
  - Osteopathic manipulation?
  - Yoga?
  - Massage?
  - Mindfulness?
  - Prayer?
  - Diet?
- Team approach!

British Journal of Dermatology 2000; **142**: 857–861.

The usage of complementary therapies by dermatological patients: a systematic review

E. ERNST

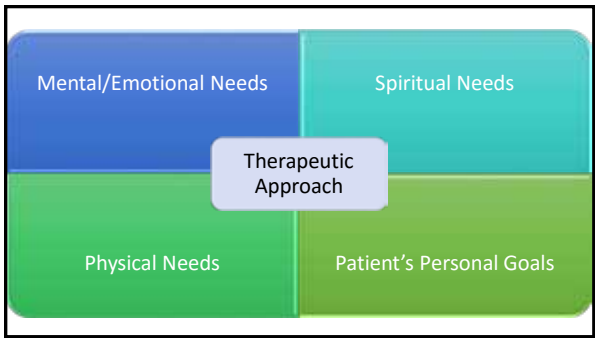
Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, U.K.

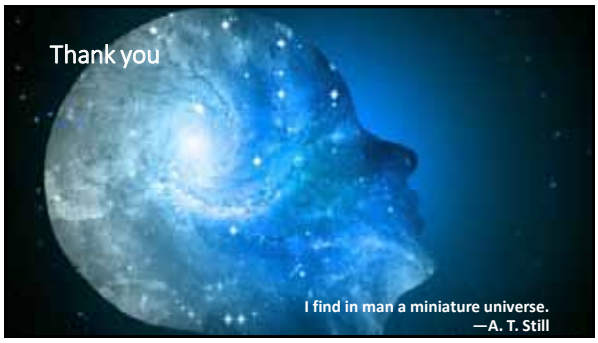
Accepted for publication: 30 Dec 1999

- Complementary medicine is more popular than ever before
- Lifetime prevalence ranged from 35-69%
- Only 40% of complementary therapy use is discussed with physicians
- Consider discussing complementary medicine openly with patients

Integrative Dermatology

- Quit smoking
- Limit alcohol intake
- Sleep 8 uninterrupted hours nightly
- Learn and practice daily a relaxing activity
- Eat a nutrient dense diet (consider working with a nutritionist)
- Exercise 5-7 days a week (ex. brisk walk 20 minutes daily)





Works Cited

Kelly, John B., Peter Foley, and Bruce E. Strober. "Current and Future Oral Systemic Therapies for Psoriasis." *Dermatologic Clinics* 33.1 (2015): 91-109. Web.

Yiu, Zenas Zn, and Richard B. Warren. "Efficacy and Safety of Emerging Immunotherapies in Psoriasis." *Immunotherapy* 7.2 (2015): 119-33. Web.

Bolognia, Jean, Joseph L. Jorizzo, and Julie V. Schaffer. "Psoriasis." *Dermatology*. 3rd ed. Vol. 1. Philadelphia: Elsevier Saunders, 2012. N. pag. Print.

"Psoriasis Guideline." American Academy of Dermatology, n.d. Web. 16 Aug. 2015.

Jain, Sima. *Dermatology: Illustrated Study Guide and Comprehensive Board Review*. New York: Springer, 2012. Print.

Benson, Jacqueline M., Clifford W. Sachs, George Treacy, Honghui Zhou, Charles E. Pendley, Carrie M. Brodmerkel, Gopi Shankar, and Mary A. Mascelli. "Therapeutic Targeting of the IL-12/23 Pathways: Generation and Characterization of Ustekinumab." *Nat Biotechnol Nature Biotechnology* 29.7 (2011): 615-24. Web.

Thaçi, Diamant, Andrew Blauvelt, Kristian Reich, Tsen-Fang Tsai, Francisco Vanaclocha, Küllli Kingo, Michael Ziv, Andreas Pinter, Sophie Hugot, Ruquan You, and Marina Milutinovic. "Secukinumab Is Superior to Ustekinumab in Clearing Skin of Subjects with Moderate to Severe Plaque Psoriasis: CLEAR, a Randomized Controlled Trial." *Journal of the American Academy of Dermatology* (2015): n. pag. Web.

Treloar, Valori. "Integrative Dermatology for Psoriasis: Facts and Controversies." *Clinics in Dermatology* 28.1 (2010): 93-99. Web.

Works Cited

Debbaneh M, Millsop JW, Bhatia BK, Koo J, Liao W. "Diet and psoriasis, part I: Impact of weight loss interventions." J Am Acad Dermatol. 2014 Apr 4.

Di Minno MN, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R, CaRRDs Study Group. "Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor blockersα" Ann Rheum Dis. 2014 Jun 1;73(6):1157-62.

Naldi, L., A. Conti, S. Cazzaniga, A. Patrizi, M. Pazzaglia, A. Lanzoni, L. Veneziano, and G. Pellacani. "Diet and Physical Exercise in Psoriasis: A Randomized Controlled Trial." British Journal of Dermatology 170.3 (2014): 634-42. Print.

Sumarac-Dumanovic M, Stevanovic D, Ljubic A, Jorga J, Simic M, Stamenkovic-Pejkovic D, Starcevic V, Trajkovic V, Micic D. "Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese women." Int J Obes (Lond). 2009 Jan;33(1):151-6.

CarrascosaJM, RocamoraV, Fernandez-TorresRM, etal. "Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications." Actas Dermosifiliogr. 2014;105(1):31-44.

Charles F. Spurlock III, Nancy J. Olsen and Thomas M. Aune (2015). Will Understanding Methotrexate Modes of Action Teach us About Rheumatoid Arthritis?, Autoimmunity - Pathogenesis, Clinical Aspects and Therapy of Specific Autoimmune Diseases, Dr. Katerina Chatzidionysiou (Ed.), ISBN: 978-953-51-2134-3, InTech, DOI: 10.5772/59901.

Ernst E. The usage of complementary therapies by dermatological patients: a systematic review. Br J Dermatol. 2000 May;142(5):857-61.

Kevin Svancara DO PGY$_3$
Jennifer Peterson DO PGY$_3$
Advanced Desert Dermatology
Midwestern University AZCOM

Review of Granulomatous, Metabolic and Depositional Disorders

http://www.aocd.org/?page=GranulomaAnnulare

Granuloma Annulare

- Benign
- Asymptomatic
- Self-limited granulomatous disease of the dermis
- Five common Variations
  - Localized
  - Generalized
  - Subcutaneous
  - Perforating
  - Patch

Granuloma Annulare

- Etiology/Pathogenesis- Unknown
  - Thought to be a delayed type hypersensitivity reaction
  - T_H-1 Response causing degradation of collagen
  - May be induced by
    - trauma
    - sun exposure
    - TB skin testing
    - vaccinations
    - viral infections
    - herpes zoster
    - genetic predisposition - HLA-B35 has had increased frequency in two studies

Granuloma Annulare - Localized

- Classic variant
- Skin colored, pink non scaly papules coalescing into annular or arciform plaques, moderately firm, ropelike border with central clearing. Most common locations on the distal extremities

Granuloma Annulare

- Generalized
  - 15% of cases
  - 10 or more lesions
  - **45% have lipid abnormalities**
  - More chronic and relapsing course
- Subcutaneous
  - **Most common form in children**
  - Scalp and extremities
  - Painless

Granuloma Annulare

- Rare variants include –Perforating, Patch
- Histology
  - Palisading Granuloma with a necrobiotic foci in the dermis
  - **Mucin** present
  - lymphocytic infiltrate

http://www.dermpedia.org/case-type/9?page=65

Granuloma Annulare

- Associated Disorders
- Diabetes Mellitus
  - The relationship between diabetes and GA is controversial
  - Earlier studies presented a relationship, more recent studies have failed to find the association previously reported
- Autoimmune Thyroiditis
- Hodgkin's and Non Hodgkin's Lymphoma
- Hyperlipidemia and Hypercholesterolemia
- HIV
- Hep B and C

Granuloma Annulare

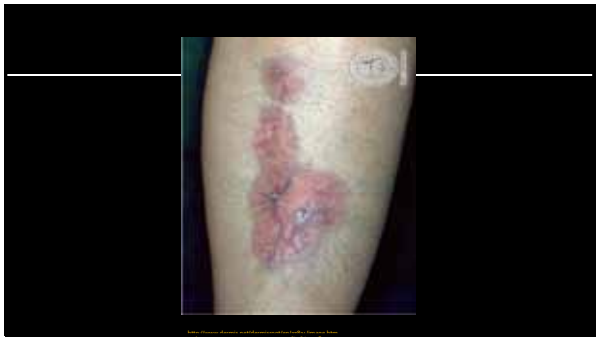
- Treatments
  - Often self-limited – 50% resolve within the first 2 years
  - First Line – High potency topical or intralesional steroids
  - Destructive
    - Cryotherapy: 25/31 patients had resolution with 1 treatment (10-60 sec)
    - Biopsy – controversial
  - Lasers – PDL, CO_2, Excimer

Granuloma Annulare

- Treatments
  - Oral antibiotics
    - Doxycycline 100mg bid
    - Dapsone
  - Antimalarials
    - Hydroxychloroquine, Chloroquine
  - Immunosuppressants
    - Methotrexate, Cyclosporine, TNF-a
  - Light Therapy
    - NBUVB, PUVA, PDT

Granuloma Annulare

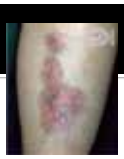
- Take home points
  - Benign – self limited in 50% of cases
  - Delayed type hypersensitivity reaction – T_H-1
  - Localized form – most common
  - Subcutaneous form – most common in children
  - Can be associated with autoimmune thyroiditis
  - Consider checking triglycerides in generalized GA



Necrobiosis Lipoidica

- Clinical
  - DM associated –65% of patient's have DM. Only found in 0.3% of DM patients
  - average age of 25 in patients with DM
  - Non-DM associated in mid 40s
  - Most commonly located on the anterior shins.
  - Red, brown or violaceous papules. Progress to yellow, brown, atrophic telangiectatic plaques.

Necrobiosis Lipoidica



- Pathogenesis
  - Exact etiology remains unknown.
  - One theory suggests that NL results from systemic microangiopathy associated with DM.
  - May precede diabetes

http://www.dermis.net/dermisroot/en/37834/image.htm

Necrobiosis Lipoidica

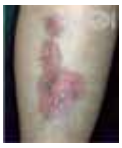
- Pathology
  - Histology – Layers of granuloma in between pale degenerated collagen. Plasma cells, **no mucin**

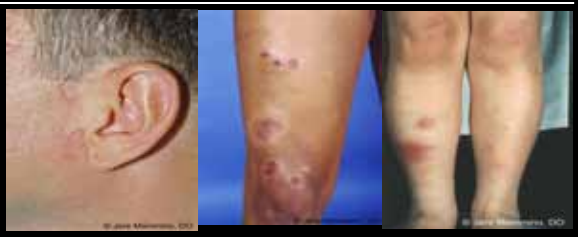
Necrobiosis Lipoidica

- Treatment
  - First Line – High potency (Class I) topical steroids under occlusion
  - Intralesional steroids – Use caution not to cause ulceration
  - Topical PUVA
  - Antimalarials – Hydroxychloroquine 200mg qd
  - Fumaric Acid Esters – Not approved by the FDA
  - Pentoxifylline

Necrobiosis Lipoidica

- Take home points
  - Only a small portion of patients with DMII (0.3%) will develop Necrobiosis Lipoidica
  - Histology: Palisading Granuloma **without mucin**
  - **Located on anterior shins**





http://www.aocd.org/?page=Sarcoidosis

Sarcoidosis

- Clinical - can affect multiple organs: Lungs most common
  - Skin manifestations occur in 17% of patients
  - **Cutaneous manifestations are the initial presentations in 1/3 of patients**
  - Multiple presentations exist
  - Macules, papules, nodules and plaques
    - red-brown, yellow-brown, violaceous, or hypopigmented
  - Erythema nodosum – most common non-specific cutaneous manifestation

Sarcoidosis

- Pathogenesis - Unknown
  - Thought to involve genetically influenced dysregulation of the T_h-1 immune response to one or more extrinsic antigens
  - May lead to over activation of inflammatory pathways and subsequent granuloma formation
  - Case control study of 700 patients was unable to find any single etiologic agent.

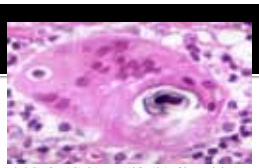
Sarcoidosis

- Histopathology
  - **Non-caseating granulomas**
  - Aggregates of epithelioid histiocytes
  - Giant cells
  - Macrophages
  - Minimal lymphocytic infiltrate

http://dermaamin.com/site/histopathology-of-the-skin/25-s2095-sarcoidosis-.html

Sarcoidosis

- Histology
  - Schaumann bodies
    - Basophilic laminated Inclusions in giant cells
  - Asteroid Bodies
    - Eosinophilic stellate inclusion bodies

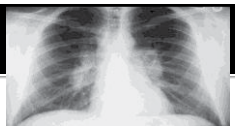


https://upload.wikimedia.org/wikipedia/commons/7/7b/Sarcoidosis_-_Schaumann_body_2.jpg

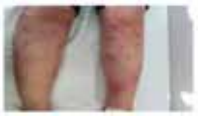
Sarcoidosis

- Variants
  - Lupus Pernio – violaceous infiltration of the nose, cheeks or earlobes, often associated with a **chronic course**
    - Can cause scarring after resolution
    - Often associated with **upper respiratory tract disease**

Sarcoidosis



- Lofgren's Syndrome
  - Triad
    - **Erythema nodosum** - Most common non-specific cutaneous finding, 25% of patients with sarcoidosis
    - **bilateral hilar adenopathy**
    - **migrating polyarthritis**

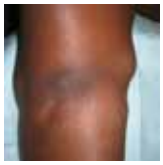


Sarcoidosis

- Heerfordt's syndrome –Uveoparotid fever
  - Fever
  - parotid gland enlargement
  - anterior uveitis
  - **facial nerve** palsy

Sarcoidosis

- Darier-Roussy disease - Sarcoidal panniculitis
  - painless subcutaneous mobile nodules without epidermal change.



Sarcoidosis

- Treatment – lack of high quality evidence to support efficacy
- Topicals - super potent steroids, mid potency for face.
- Intralesional injections
- systemic corticosteroids for severe disease
  - 20-40mg/kg/day with a slow taper
  - May add hydroxychloroquine 200-400mg/day or methotrexate 25mg/week, tapered to 5-15mg

Sarcoidosis

- minocycline – retrospective study of 27 patients, 14 had partial improvement while 6 had complete improvement on 1-6 months of minocycline
- Refractory treatments
  - Biologics - TNF – alphas – notably infliximab but data has been conflicting in larger studies

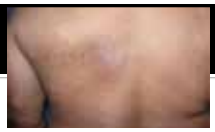
Sarcoidosis

- Take home points
  - Lesions that develop within a **scar** or **tattoo** should be ruled out for sarcoidosis
  - Erythema Nodosum – **positive prognosis**, associated with acute sarcoidosis
  - **TH1** response to unknown antigen

Amyloidosis

- Cutaneous
  - Macular
  - Lichen
  - Nodular
  - Secondary
- Systemic
  - Primary systemic
  - Secondary systemic
  - Hemodialysis- associated

Amyloidosis



- Macular
  - **Keratinocyte derived**
  - Hyperpigmented firm papules localized to the interscapular region
    - Asymptomatic or pruritic
    - Commonly associated with notalgia paresthetica

Amyloidosis

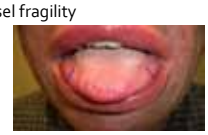
- Lichen amyloidosis
  - **Keratinocyte derived**
  - Flat topped shiny papules
  - Commonly over the shins
  - **Pruritic**
  - **Seen in MEN 2A**

Amyloidosis

- Nodular
  - Single or multiple waxy nodules
    - occasionally with purpura
  - AL –immunoglobin light chains
    - Frequently **Lambda** light chains
  - Long term follow up needed for potential to progress to systemic

Amyloidosis

- Systemic
  - Primary Systemic
    - Pinch Purpura - ecchymosis and vessel fragility
    - **Macroglossia** – indentation of teeth
    - Shoulder pad sign- deposition around periarticular soft tissue
    - **AL -light chain**
    - **May be associated with multiple myeloma**



Amyloidosis

- Hemodialysis associated amyloidosis
  - Long term hemodialysis
  - **Beta 2 microglobulin**
  - Deposition in synovial membranes
    - **Carpal Tunnel**
- Senile Systemic amyloidosis
  - Late onset in elderly patients
  - **ATTR - Transthyretin**

Amyloidosis

- Treatment
  - **Macular**
    - Capsaicin
    - Topical steroids
  - **Lichen**
    - Topical and intralesional steroids
    - NBUVB
    - CO_2 laser
    - Retinoids
  - **Nodular**
    - Excision or laser ablation

Scleromyxedema

- Clinical – Symmetric waxy firm papules, leonine facies, commonly involves the glabella with longitudinal furrowing
- Pathology
  - Associated with monoclonal gammopathy (debatable)
  - **IgG lambda light chain**
- Treatment –IVIG, Bortezomib, melphalan, thalidomide, stem cell transplant

http://images.rheumatology.org/image_dic/album7562/md_04-10-0056.jpg

Scleredema

http://images.rheumatology.org/image_dic/album7562/md_04-10-0056.jpg

- Clinical - Cutaneous brawny induration of the face, neck, scalp and upper extremities
- Three forms
  - **Infection related** – Streptococcal
  - **Gammopathy related** – Monoclonal gammopathy, **IgG Kappa**
  - **Diabetes** – IDDM
- Treatment – Phototherapy, cyclophosphamide, oral glucocorticoid, cyclosporine

http://www.dartmouth.edu/~thabif/weeklyclinics1990s/pictures/1990porphyriacthands.jpg

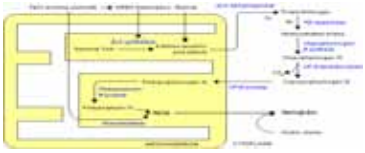
Porphyria Cutanea Tarda

- Blisters, erosions and milia on sun exposed skin

http://www.dartmouth.edu/~thabif/weeklyclinics1990s/pictures/1990porphyriacthands.jpg

- Most common type of porphyria world wide

Porphyria Cutanea Tarda



- Defect – Uroporphyrinogen Decarboxylase

Porphyria Cutanea Tarda

- Triggers
  - Alcohol
  - **HCV**
  - Estrogen
  - **Iron Over load**
  - **Hemochromatosis**
- Labs: Total plasma porphyrins with reflex
  - Then stool, plasma and RBC fractionation

Porphyria Cutanea Tarda

- Treatment - Phlebotomy every 2 weeks, may combine with antimalarials
- Hydroxychloroquine: 100mg BIW
  - Takes on average 6.5 months to reach therapeutic levels with hydroxychloroquine and phlebotomy
  - Better compliance than phlebotomy

http://dermaamin.com/site/images/clinical-pic/e/erythropoietic_protoporphyria/erythropoietic_protoporphyria5.jpg

Erythropoietic Protoporphyria

- **Most common porphyria in children**
- Clinical – erythema, edema, crust, purpura and skin thickening
- Labs – Total erythrocyte protoporphyrin
  - **Urine porphyrin levels normal**
- Complications
  - Protoporphyric hepatopathy
  - Gallstones

http://dermaamin.com/site/images/clinical-pic/e/erythropoietic_protoporphyria/erythropoietic_protoporphyrias.jpg

Erythropoietic Protoporphyria

- Treatment
  - Broad Spectrum Sunscreen, Photo protective Clothing
  - Avoidance of sunlight exposure from 11:00 AM – 3:00PM
  - Beta-Carotene 30-90mg/day in children
  - Cysteine supplements, 500mg bid
  - Afamelanotide

Works Cited

- 1. Kapoor R, Piris A, Saavedra AP, et al. Wolf isotopic response manifesting as postherpetic granuloma annulare: a case series. Arch Pathol Lab Med. 2013; 137(2):255-258.
- 2. Muhlemann MF, Williams DR. Localized granuloma annulare is associated with insulin-dependent diabetes mellitus. Br J Dermatol. 1984;111(3):325.
- 3. Li A, Hogan DJ, Sanusi ID, Smoller BR. Granuloma annulare and malignant neoplasms.. Am J Dermatopathol. 2003;25(2):113.
- 4. Keimig E, Louise E. Granuloma Annulare. Dermatol clin. 2015;33(3):315-329.
- 5. Kosaka S, Kowana S. Case of necrobiosis lipoidica diabeticorum successfully treated by photodynamic therapy. J Dermatol. 2012;39(5):497-499.
- 6.Lecha M, Puy G, Deybach JC. Erythropoietic Protoporphyria. Orphanet J Rare Dis. 2009; 4:19.
- 7. Thornsberry, L, English, A. Etiology, diagnosis, and therapeutic management of granuloma annulare: an update. AM J Clin Dermatol. 2013; 14(4):279-290.
- 8. Alexandrescu, Doru T; Kauffman, C Lisa; Ichim, Thomas E; Riordan, Neil H; Kabigting, Filamer; & Dasanu, Constantin A. (2011). Cutaneous sarcoidosis and malignancy: An association between sarcoidosis with skin manifestations and systemic neoplasia. Dermatology Online Journal, 17(1)
- 9. Steen, T, English JC, Oral Minocycline in Treatment of Cutaneous Sarcoidosis. Jama Dermatol. 2013. 149(6): 758-760.
- 10. Rose AS, Tielker MA, Knox KS. Hepatic, ocular, and cutaneous sarcoidosis. Clin Chest Med. 2008;29(3):509
- 11. Salas-Alanis JC, Martinez-Jaramillo B, Gomez-Flores M, et al. Scleromyxedema, a therapeutic dilemma. Indean J Dermatol. 2015; 60(2): 215.
- 12. Dereure O, Jumez N, Bessis D,e t al. Measurement of liver iron content by magnetic resonance imaging in 20 patients with overt porphyria cutanea tarda before phlebotomy therapy: a prospective study. Acta Derm Venereol. 2008;88(4):341.
- 13.. Harms JH, Lautenschlager S, Minder CE, et al. Photosensitivity of erythropoietic protoporphyria patients by an agonistic analog of alpha-melanocyte stimulating hormone. Photochem Photobiol. 2009 Nov;85(6):1434-9.
- 14. Mathews-Roth MM, Rosner B, Benfell K, et al. A double-blind study of cysteine photoprotection in erythropoietic
- protoporphyria. Photodermatol Photoimmunol Photomed. 1994 Dec;10(6):244-8.
- 15. Jain, S. 2012. Dermatology:Illustrated Study Guide and Comprehensive Review. New York, NY: Springer.
- 16. Sanchez M, Haimovic A, Prystowsky S. Sarcoidosis. Dermatol Clin. 2015; 33(3): 389-416.
- 17. Ladizinski B, Lee KC. Lichen Amyloidosis. CMAJ. 2014; 186(7): 532.

Figurative Erythemas

Michelle Goedken, DO
Affiliated Dermatology
Scottsdale, AZ

Figurative Erythemas

- Erythema annulare centrifugum
- Erythema marginatum
- Erythema migrans
- Erythema gyratum repens
- Erythema multiforme

Erythemas

- Erythemas represent a change in the color of the skin that is due to the dilation of blood vessels, especially those in the papillary and reticular dermis
- The color is blanchable and most last for days to months
- Figurative erythemas have an annular, arciform or polycyclic appearance

ERYTHEMA ANNULARE CENTRIFUGUM

ERYTHEMA ANNULARE CENTRIFUGUM

- Pathogenesis: EAC represents a reaction pattern or hypersensitivity to one of many antigens
  - IL-2 and TNF-alpha may have a role
  - Most patients do not have an underlying disease identified

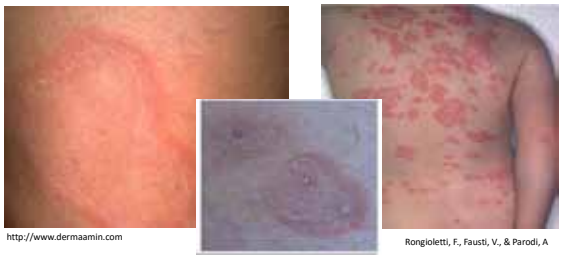
ERYTHEMA ANNULARE CENTRIFUGUM

- Associated with:
  - Infection
    - » Dermatophytes and other fungi (*Candida* and *Penicillium* in blue cheese)
    - » Viruses: poxvirus, EBV, VZV, HIV
    - » Parasites and ectoparasites
  - Drugs: diuretics, antimalarials, gold, NSAIDs, finasteride, amitriptyline, etizolam, Ustekinumab (2012)

ERYTHEMA ANNULARE CENTRIFUGUM

- Foods
- Autoimmune endocrinopathies
- Neoplasms (lymphomas and leukemias)
- Pregnancy
- Hypereosinophilic syndrome
- Lupus (2014)

ERYTHEMA ANNULARE CENTRIFUGUM



http://www.dermaamin.com

Rongioletti, F., Fausti, V., & Parodi, A

ERYTHEMA ANNULARE CENTRIFUGUM

- 2 major forms:
  - Superficial: classic **trailing scale**, may have associated pruritus
  - Deep: **infiltrated borders**, usually no scale, edges are elevated, usually not pruritic

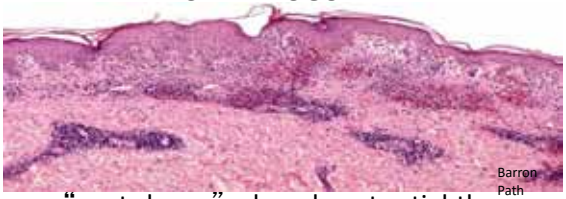
ERYTHEMA ANNULARE CENTRIFUGUM

- Pink papules expand outwards, develop central clearing
- Annular lesions with trailing scale; favor thighs, hips and trunk
- Desquamation is present at the inner margin=**"trailing scale"**
  - Lesions persist for weeks to months
  - Rarely involves palms/soles, scalp, mucous membranes
  - As lesions resolved: no scarring.

ERYTHEMA ANNULARE CENTRIFUGUM

- Histology:
  - Superficial form: nonspecific, mild spongiosis, microvesiculation, focal parakeratosis, **"coat sleeve"** superficial perivascular lymphohistiocytic infiltrate
    - Advancing edge is a result of dermal papillary edema
  - Deep form: normal epidermis, mononuclear infiltrate with a sharply demarcated perivascular arrangement in the mid and lower dermis

ERYTHEMA ANNULARE CENTRIFUGUM



Barron Path

"coat sleeve" = lymphocytes tightly associated with vessels

ERYTHEMA ANNULARE CENTRIFUGUM

- Treatment:
  - Treat underlying disorder
  - Topical steroids to advancing border, antihistamines, +/- empiric antibiotics and antifungals
  - Systemic treatment is rarely necessary

ERYTHEMA MARGINATUM

ERYTHEMA MARGINATUM

- Introduction:
  - Erythema marginatum is a cutaneous manifestation of acute rheumatic fever
  - Rheumatic fever is characterized by an abnormal immunologic response to a preceding infection with group A β-hemolytic streptococci
  - Triad of fever, arthritis and carditis

ERYTHEMA MARGINATUM

- Epidemiology: **3% of untreated** patients develop rheumatic fever, of that 3% the rash is seen in less than 10% of patients
- The peak age-related incidence is between 5 and 15 years

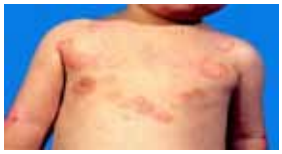
ERYTHEMA MARGINATUM

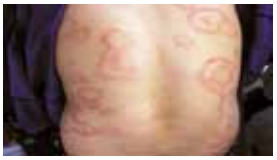
- Major criteria for acute rheumatic fever:
  - **J**oints (migratory polyarthritis)
  - ♥ (carditis)
  - **N**odules (subcutaneous nodules- painless, over bony prominences in long standing disease)
  - **E**rythema marginatum
  - **S**ydenham's chorea
- Minor criteria: fever, arthralgias, elevated ESR, elevated CRP, prolonged PR interval

ERYTHEMA MARGINATUM

- Clinical: **migratory annular and polycyclic** erythema**,** 2-5 week latency
  - **MC locations: trunk, axillae, proximal extremities**
  - New lesions last from a few hours to a few days, most noticeable in the afternoon
  - **Lack of scale** (helps to r/o EAC and other papulosquamous conditions)

ERYTHEMA MARGINATUM





http://www.patienthelp.org/diseases-conditions/erythema-marginatum.html

ERYTHEMA MARGINATUM

- Histology: Interstitial and perivascular infiltrate composed mostly of neutrophils w/o vasculitis, extravasated RBCs in later stages, DIF is negative
- Tx: no specific treatment, lesions resolve spontaneously

ERYTHEMA (CHRONICUM) MIGRANS

ERYTHEMA (CHRONICUM) MIGRANS

- **Borrelia burgdorferi** spirochetes by Ixodes tick (may transmit babesiosis, human anaplasmosis)
  - **Must be attached >48hrs for transmission**
- Seen mostly in US (northeast, midwest, west coast) and Europe
- Natural hosts for Borrelia are white-footed mice and white-tailed deer
- Not all patients who have had tick bites or positive serologic tests for **B. burgdorferi** develop Lyme

ERYTHEMA (CHRONICUM) MIGRANS

- Pathogenesis: *Ixodes* uses tick salivary protein (Salp 15) as a means of enhancing transmission
  - Once in the body it is thought to trigger innate and adaptive immunity
  - 45% of patients with erythema migrans have spirochetemia
  - Spirochetes can be found in the skin for long periods of time after tick bite

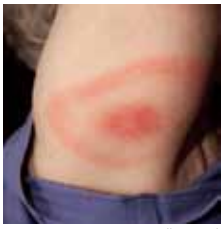
ERYTHEMA (CHRONICUM) MIGRANS

- Clinical: erythematous, expanding annular plaque appears on an **average of 7-15 days after** the tick bite, may have a **bull's eye appearance**
  - MC sites for primary erythema migrans is **trunk, axilla, groin, popliteal fossa**
  - Major organ manifestations of untreated patients: 60% monoarticular or oligoarticular arthritis (usually knees), 10% neurological (MC facial nerve palsy), 5% cardiac (AV block)

ERYTHEMA (CHRONICUM) MIGRANS

- The diagnosis of early Lyme disease can be made soley on clinical grounds when a characteristic erythema migrans lesion is present in patients who live in or have recently traveled to an endemic area.
  - Patients who present with an EM lesion will likely be seronegative, since the lesion often appears prior to the development of a diagnostic immune response. Serologic testing is neither necessary nor recommended in these patients.

ERYTHEMA (CHRONICUM) MIGRANS




http://hdjaguar.mobi/erythema-chronicum-migrans-photo/

ERYTHEMA (CHRONICUM) MIGRANS

- Southern tick-associated rash illness (STARI) has a rash that is indistinguishable from that of Lyme disease
- The etiologic agent is not known
- No serious systemic complications from STARI are currently recognized
- In the Southeast, STARI is much more prevalent than Lyme disease
- TX: Doxycycline

ERYTHEMA (CHRONICUM) MIGRANS

- Histology: Routine histology is nonspecific. Many specimens contain eosinophils and plasma cells; **Warthin-Starry stain** (silver stain) will occasionally reveal the organism
  - Decreased Langerhans cells in the dermis, multiple apoptotic cells in the epidermis
  - Inflammatory infiltrate contains macrophages, CD4+ helper T cells, CD45+ RO memory T cells

ERYTHEMA (CHRONICUM) MIGRANS

- Tx: only 1% of those bitten get Lyme disease, routine treatment not recommended unless:
  - If in an endemic area (>20% of ticks are infected) and bitten by a tick identified to be Ixodes and attached >36hrs: prophylaxis within 72hrs with single dose of Doxy 200mg

ERYTHEMA GYRATUM REPENS

ERYTHEMA GYRATUM REPENS

- Gammel's disease
- **Paraneoplastic** figurate erythema
- Pathogenesis: immune cross-reaction between tumor antigens and cutaneous antigens

ERYTHEMA GYRATUM REPENS

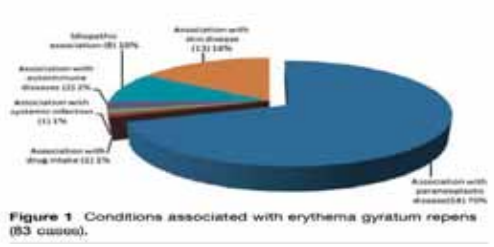


Figure 1 Conditions associated with erythema gyratum repens (83 cases).

Rongioletti, F., Fausti, V., & Parodi, A

ERYTHEMA GYRATUM REPENS

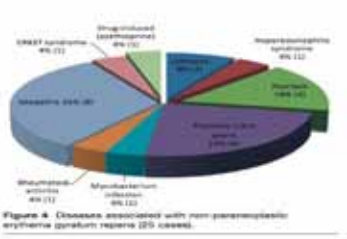


Figure 4 Diseases associated with non-paraneoplastic erythema gyratum repens (25 cases).

Rongioletti, F., Fausti, V., & Parodi, A

ERYTHEMA GYRATUM REPENS

- Figurate erythema that is migratory and composed of concentric rings with a **wood-grain** appearance.
- Lesions develop scale at edges and **advance at a rapid rate** = up to 1cm per day (much faster than EAC)
  - **85%** of patients have an **underlying neoplasm**; most commonly **lung,** breast, or esophagus/stomach, may coincide with pulmonary TB
  - Rash develops from 1yr prior to 1yr after the diagnosis of the neoplasm

ERYTHEMA GYRATUM REPENS

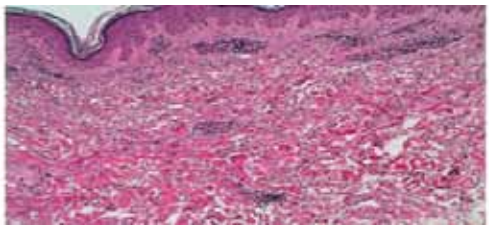
"WOOD GRAIN" APPEARANCE

Andrews disease of the skin and Rongioletti, F., Fausti, V., & Parodi, A

ERYTHEMA GYRATUM REPENS

- Histology: Non-specific; hyperkeratosis, focal parakeratosis, moderate patchy spongiosis, mild perivascular lymphohistiocytic infiltrate; eosinophils and melanophages may be seen
  - Accumulation of active Langerhan's cells in upper layers of epidermis
  - DIF: IgG and C3 in the floor of the blister cavity (only seen in some patients, not required for confirmation)

ERYTHEMA GYRATUM REPENS



Rongioletti,, F., Fausti, V., & Parodi, A

ERYTHEMA GYRATUM REPENS

- Tx: Resolves when underlying condition is treated.

ERYTHEMA MULTIFORME

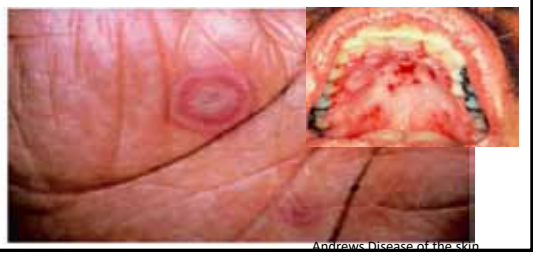
ERYTHEMA MULTIFORME

- Classified by etiology
  - Herpes Simplex
  - Mycoplasma
  - Contact Dermatitis
  - Drug induced
  - Radiation induced
  - Idiopathic
  - Tan et al (2015) *in press*: Case series of three infants with erythema multiforme following Hepatitis B Vaccination

ERYTHEMA MULTIFORME

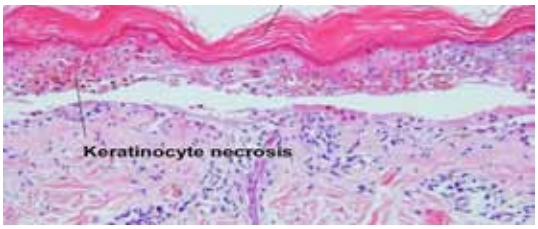
- EM minor
  - Self limited, recurrent
  - "target" lesions= peripheral erythema, edematous pale ring and central dusky purpura
- EM major
  - On a spectrum with SJS and TEN
  - More severe, most likely drug related
  - More mucosal involvement

ERYTHEMA MULTIFORME



Andrews Disease of the skin

ERYTHEMA MULTIFORME



ERYTHEMA MULTIFORME

- Histo: “basket weave” stratum corneum, cellular necrosis out of proportion to lymphocytes
- Tx: prevent HSV outbreaks, acyclovir

Resources

- James, William D., Timothy G. Berger, and Dirk M. Elston. *Andrews' Diseases of the Skin: Clinical Dermatology*. 11th ed. China: Elsevier, 2011. Print.
- Bolognia, J. L., Jorizzo, J. L., & Schaffer, J. V. (2012). *Dermatology: 2-Volume Set* (3rdrd ed., Vol. 1). New York: Elsevier.
- Chou, W., & Tsai, T. Recurrent Erythema Annulare Centrifugum During Ustekinumab Treatment in a Psoriatic Patient. *Acta Derm Venereol*, *93*, 208-209.
- Chander, R., Yadav, P., Singh, A., & Nangia, A. Systemic lupus erythematosus presenting as erythema annulare centrifugum. *Lupus*, *2014*(23), 1197-1200.
- Chu, C., Tuan, P., & Yang, S. (2015, August). Molluscum Contagiosum–Induced Erythema Annulare Centrifugum. *AMA Dermatology*.
- Rongioletti,, F., Fausti, V., & Parodi, A. Erythema gyratum repens is not an obligate paraneoplastic disease: a systematic review of the literature and personal experience. *Journal of the European Academy of Dermatology and Venereology*, *2014*(28), 112-115.
- Blanton, L., Keith, B., & Brzezinski, W. (2008). Southern Tick-Associated Rash Illness: Erythema Migrans Is Not Always Lyme Disease. *Southern Medical Journal*, *101*(7), 759-760.
- Batycka-Baran A, Zychowska M, Baran W, Szepietowski JC, Maj J.
- Erythema Annulare Centrifugum Associated with Ovarian Cancer. Acta Derm Venereol. 2015 May 27
- Forrester DM. Self-assembled multi-ring formations of glutamine and a possible link to erythemagyratum repens. Med Hypotheses. 2015 Jul;85(1):10-6
- Tan ZH, Thoon KC, Koh MJ. Case Series of Three Infants with Erythema Multiforme Following Hepatitis B Vaccination. Pediatr Neonatol. 2015 May 23. [Epub ahead of print]

UNT HEALTH SCIENCE CENTER

2015 AOCD Fall Meeting

October 18, 2015 - 10:30 – 10:45 AM

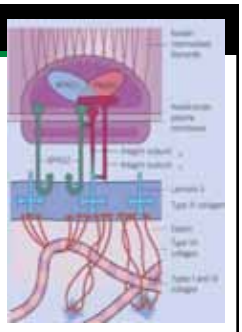
Vesiculobullous Diseases

Dylan Alston, DO Robert Lin, DO
Sarah Gracie, DO Gregory Polar, DO

Program Director: ***Alpesh Desai, DO FAOCD***
South Texas Osteopathic Dermatology
University of North Texas Health Science Center

Basic Science

- Keratin intermediate filaments
  - K5, 14
- Hemidesmosome
  - Plectin
  - BPAg I
  - BPAg II
  - Integrins
- Lamina lucida
  - Anchoring filaments
    - Laminin 5
    - Type XVII collagen (BPAg II)
- Lamina densa
  - Type IV collagen
- Sub-Lamina Dense
  - Type VII collagen



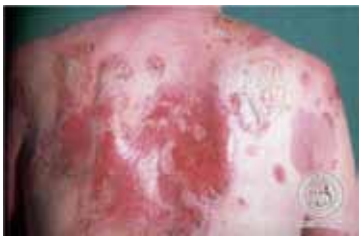
UNT HEALTH

Pemphigus Vulgaris

- Potentially fatal autoimmune bullous disease of the skin and mucous membranes
- Clinical Features:
  - Flaccid vesicles/bullae which rupture leaving large, painful erosions with bleeding and crusting
  - Erosions may also be in nose, mouth, larynx, pharynx, vagina
  - + Nikolsky sign, + Asboe-Hansen sign (pressure to surface of blister causes lateral spread)

UNT HEALTH

Pemphigus Vulgaris



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Pemphigus Vulgaris

- Autoantigen:
  - Cadherin family, desmosomal protein
    - Desmoglein 3 (mucosal)
    - Desmoglein 1 (mucocutaneous)
- Drug-induced:
  - Thiol drugs - penicillamine, captopril, enalapril, lisinopril, piroxicam
  - Pyrazolone derivatives - phenylbutazone, oxyphenylbutazone
  - Antibiotics - penicillin derivates, cephalosporin, rifampicin

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Pemphigus Vulgaris

- Histology:
  - Suprabasal cleavage with acantholytic keratinocytes
  - “Tombstone Row” of basal cells attached to basement membrane
  - perivascular lymphocytes and eosinophils
  - acantholysis may involve hair follicles

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Pemphigus Vulgaris

- Direct Immunofluorescence:
  - Intercellular IgG4 > C3 (net-like pattern in epidermis, more pronounced in lower epidermis)
- Indirect Immunofluorescence:
  - Monkey esophagus - Positive in 80–90% cases, titer correlates with disease activity
- Treatment:
  - Oral corticosteroid, methotrexate, azathioprine, mycophenolate mofetil, plasmapheresis, IVIG, rituximab

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IgA Pemphigus

- Blistering disease with intraepidermal IgA deposits
- Clinical Features:
  - Subcorneal pustular dermatosis:
    - Serpiginous vesicles or pustules, may be associated with underlying IgA gammopathy
  - Intraepidermal neutrophilic type:
    - Flaccid pustules and bullae involving intertriginous locations which enlarge forming annular or polycyclic arrangement

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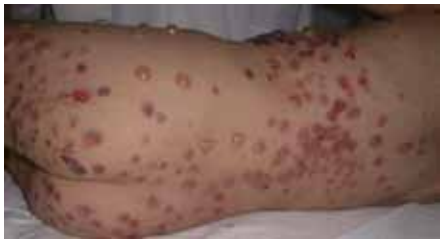
IgA Pemphigus



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IgA Pemphigus

- Histology:
  - Intraepidermal pustule or vesicles containing neutrophils, no acantholysis
- Direct Immunofluorescence:
  - Intercellular IgA deposition
- Indirect Immunofluorescence:
  - Positive in 50%, intercellular IgA
- Treatment:
  - Dapsone
  - Oral corticosteroid

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Bullous Pemphigoid

- Most common autoimmune bullous disorder with chronic nature, typically in patients over 60
- Clinical Features:
  - Presents with initial urticarial lesions which evolve into large, tense bullae over medial thighs, groin, abdomen, and legs
  - +/- pruritus initially with tenderness
  - No constitutional symptoms unless extensive disease
  - 10-35% with oral involvement

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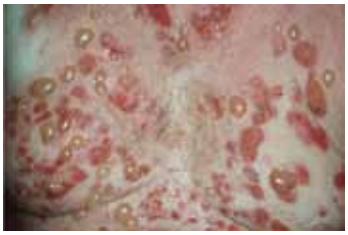
Bullous Pemphigoid



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Bullous Pemphigoid

- Autoantigen:
  - BPAG2: 180 kDa, transmembrane hemidesmosomal protein
  - BPAG1: 230 kDa, cytoplasmic plaque protein
- Drug Induced:
  - furosemide, NSAIDs, PCN derivates, gold, captopril, D-penicillamine, sulfasalazine

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Bullous Pemphigoid

- Histology:
  - Subepidermal bulla with increased eosinophils and lymphocytesin papillary dermis, +/- neutrophils
- Direct Immunofluorescence:
  - Linear C3 and IgG at BMZ
- Indirect Immunofluorescence:
  - Positive in 60-80%
  - IIF on salt split skin shows binding to epidermal side (roof)

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Bullous Pemphigoid

- Treatment: (Good Prognosis)
  - Oral corticosteroid
  - Steroid sparing agent (azathioprine, mycofenolate, etc)
  - Dapsone
  - TCN + nicotinamide

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Linear IgA Bullous Dermatosis

- Rare, subepidermal blistering disease with IgA deposition at BMZ; likely identical to chronic bullous disease of childhood
- Clinical Features:
  - Annular or grouped vesicles/bullae over extensor extremities and buttock typically in herpetic arrangement, mucosal involvement

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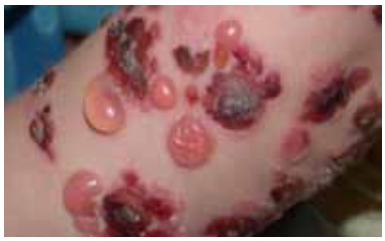
Linear IgA Bullous Dermatosis



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Linear IgA Bullous Dermatosis

- Autoantigen:
  - LAD-1 (120 kDa, part of BPAG2); LAD-1 cleavage results in second autoantigen, LABD97 (97 kDa)
- Drug Induced:
  - Vancomycin, captopril, cephalosporin, PCN, NSAIDs, phenytoin, sulfonamide
- Histology:
  - Subepidermal bullae with rich neutrophilic infiltratein papillary dermis (may resemble DH)

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Linear IgA Bullous Dermatosis

- Direct Immunofluorescence:
  - Linear IgA (+/- C3) deposition at BMZ
- Indirect Immunofluorescence:
  - Positive in 60% cases, IIF on (SSS) shows binding to epidermal side of split (roof)
- Treatment:
  - Dapsone or sulfapyridine
  - Low dose oral corticosteroid

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Dermatitis Herpetiformis

- Recurrent chronic pruritic disease associated with gluten sensitive enteropathy
- Clinical Presentation:
  - Erythematous grouped papules or vesicles over elbows, knees, buttocks, intensely pruritic, primary lesions not visible due to excoriations
- Associated with:
  - HLA-DQ2 (strongest)
  - HLA-B8

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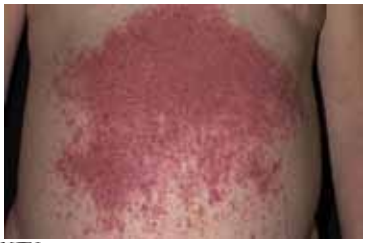
Dermatitis Herpetiformis



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Dermatitis Herpetiformis

- Autoantigen:
  - Epidermal Transglutaminase (TG-3)
  - Tissue Transglutaminase (Endomysial)
- Labs:
  - Anti-gliadin/antiendomysial antibodies in DH/celiac disease

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Dermatitis Herpetiformis

- Histology:
  - Neutrophilic microabscesses in dermal papillae
  - +/- subepidermal vesicles
- Direct Immunofluorescence:
  - Granular IgA>C3 deposition in dermal papillae
- Indirect Immunofluorescence:
  - Negative

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Dermatitis Herpetiformis

- Comorbidities:
  - Increased incidence thyroid disease (Hashimoto's thyroiditis)
  - Insulin Dependent Diabetes Mellitus
  - Enteropathy-associated T cell lymphoma
- Treatment:
  - Dapsone (immediate skin improvement)
  - Referral to GI (>90% with gluten sensitive enteropathy and risk of small bowel lymphoma)

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Biopsy Techniques

- Bullous Pemphigoid & Pemphigus Vulgaris
  - Biopsy the edge of an active blister or erythematous skin
  - Avoid having the epidermis come off, ulcers and distal extremities
- Dermatitis Herpetiformis
  - Biopsy normal appearing skin 3 mm from a blister
  - May require multiple biopsies
  - Avoid active lesions
- Specify to dermatopathologist whether biopsy comes from involved or uninvolved skin

UNT HEALTH

Pregnancy Dermatoses

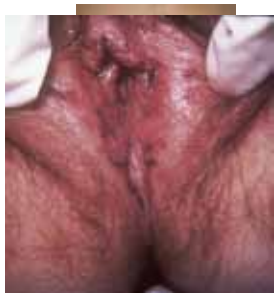
Christa Tomc, DO PGY-4
October 18, 2015 AOCD
Bridget McIlwee DO PGY-3
Heather Kelly DO PGY-2
Michael Carletti DO PGY-2

Outline

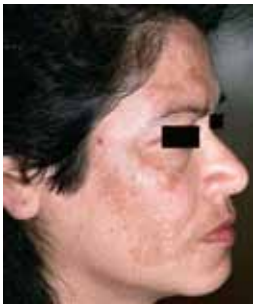
- Physiologic changes
- Atopic eruption of pregnancy
- Pemphigoid (herpes) gestationis
- Polymorphic eruption of pregnancy (PEP), (Pruritic Urticarial Papules and Plaques of Pregnancy)
- Intrahepatic cholestasis
- Impetigo herpetiformis

Dermatologic Changes during Pregnancy

- Hyperpigmentation: localized or generalized
  - Occurs in 90% of pregnant women
  - Increased α- and β-melanocyte-stimulating hormone (MSH), β-endorphin, estrogen, progesterone
- Common sites:
  - **Linea alba**
  - Nipples, areolae, external genitalia, axillae, neck
  - **Voigt (Futcher) lines**: congenital demarcations along posterior extremities



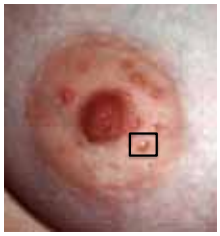
Dermatologic Changes during Pregnancy



- Melasma occurs in 75% of women during 2nd trimester
  - Centrofacial
  - Malar
  - Mandibular
- Histology shows excessive melanin deposition in epidermis or within melanophages
- UV avoidance and sunscreen are during pregnancy
- Resolves by one year postpartum or after discontinuation of OCPs
  - Persists in 30% of patients

Dermatologic Changes during Pregnancy

- Striae distensae commonly appear during 2nd or 3rd trimester and develop at right angles to skin tension lines
- Eccrine/apocrine changes
  - Eccrine activity **increased**
    - Worsening hyperhidrosis and dyshidrotic eczema
  - Apocrine activity **decreased**
    - Improvement in Fox-Fordyce disease, hidradenitis suppurativa
  - Sebaceous gland activity **increased**
    - Worsening of acne – most notable in 3rd trimester
    - **Montgomery's tubercles**
      - Brown to tan papules on the areolae
      - Hypertrophy of sebaceous glands
      - 30-50% of pregnant women



Dermatologic Changes during Pregnancy

- Vascular changes due to increase in maternal blood volume, vascular dilation, capillary permeability, and neovascularization
  - Varicosities
  - Pyogenic granulomas
  - Spider angiomas
  - Erythema palmare

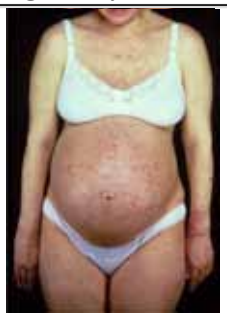
Atopic Eruption of Pregnancy (AEP)

- Most common dermatosis in pregnancy, accounts for 50% of pruritic rashes in gravid women, or 1 in 5 to 1 in 20 pregnancies
  - Includes eczema, prurigo, and pruritic folliculitis of pregnancy
- ¾ present prior to the last trimester
- In 80%, it is the first recognized manifestation of eczema, though often have a personal or family history of atopy
- To prevent an allograft-like rejection of fetus, the immune system switches from T_H1 (cell-mediated) to T_H2 (antibody mediated), allowing it to survive despite its paternal MHCs
  - Decreased T_H1:T_H2 incites AEP and worsens existing atopic dermatitis

Introduction | Physiologic changes | Atopic Eruption | Herpes gestationis | PEP | Intrahepatic cholestasis | Impetigo herpetiformis | Conclusions

Atopic Eruption of Pregnancy (AEP)

- Characteristic patterns
  - **E**-type: patchy, **e**czematous
  - **P**-type: **p**apular or **p**rurigo
- Recurrence in subsequent pregancies
- Management for mild disease same as that for mild eczema
- Severe disease may require UVB or systemic steroids
- Fetal prognosis unchanged



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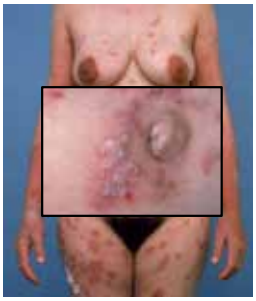
Herpes (Pemphigoid) Gestationis

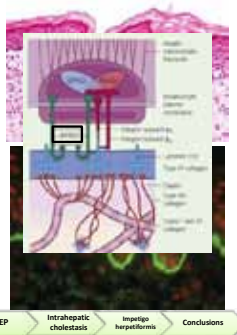


- Occurs in 1:40,000 to 1:60,000, 18% in 1st trimester, 34% in 2nd, and 34% in 3rd
  - Mean onset 21 to 28 weeks
- Associated with maternal MHC II antigens HLA-DR3 and DR4
  - 61-80% express DR3
  - 52-53% express DR4
- Begins as periumbilical, pruritic urticarial papules and plaques that can become targetoid, annular or polycyclic
- Clustered vesicles develop days to weeks later

Introduction | Physiologic changes | Atopic eruption | Herpes gestationis | PEP | Intrahepatic cholestasis | Impetigo herpetiformis | Conclusions

Herpes (Pemphigoid) Gestationis

- Patients produce anti-hemidesmosome antibodies to the transmembrane NC16A region of BPAG2 antigen [180kDa]
- Biopsy imperative to distinguish from polymorphic eruption of pregnancy (PEP)
- Eosinophilic spongiosis, papillary dermal edema, and mixed perivascular infiltrate at the basement membrane
- Linear deposition of C3 in 100% cases ± IgG_1 (25%) on DIF
- BP180 antibody serum immunoassay available



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Herpes (Pemphigoid) Gestationis

- Progesterone suppresses antibody production, most patients improve the few weeks before delivery when levels are high and flare in the post-partum and premenstrual periods
- Increased risk for SGA infants and preterm delivery due to antibodies attacking placental tissue, neonatal PG occurs in 3-5% and is typically more mild
- Recurs and more severe in subsequent pregnancies
- Topical or systemic steroids, increasing dose after 3 days if vesicles continue to develop
- Plasmapheresis in recalcitrant cases

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Polymorphic Eruption of Pregnancy (PEP)

- Pruritic urticarial papules and plaques of pregnancy (PUPP)
- Most common pregnancy dermatosis
  - 1 in 160 pregnancies
- 75% occur late in 3rd trimester (36-39 weeks)
- 57.6% cases occur in primagravidae, increased incidence in multibirths and high maternal weight gain
- Start as pruritic urticarial papules in abdominal stretch marks with periumbilical sparing
- 51% go on to develop polymorphous lesions—vesicles, targetoid or polycyclic wheals
- In 70% eruption becomes confluent and widespread, usually spares the face
- Koebnerization is common

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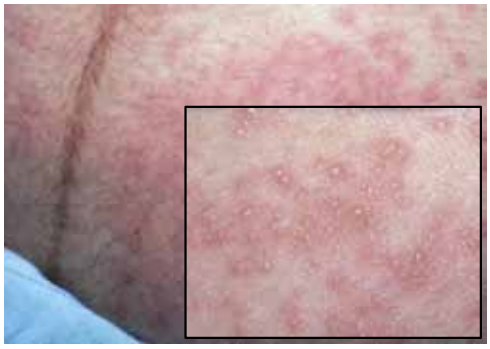

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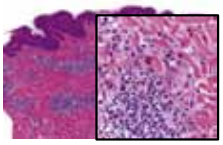
Polymorphic Eruption of Pregnancy (PEP)

- Rapid abdominal wall distention leads to connective tissue damage, eliciting allergic-type reaction
- No specific HLAs and no circulating autoantibodies have been identified
- Superficial and mid-dermal lymphohistiocytic infiltrate with spongiosis and papillary dermal edema with eosinophils
  - DIF negative



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Polymorphic Eruption of Pregnancy (PEP)

- Mean duration of 4-6 weeks, usually not severe for more tan 1 week
- Normal fetal prognosis, however 1 study found increase incidence of cesarean section (40% of cases)
- 15% cases present postpartum, no impact on presentation, disease course, or obstetric findings
- Does not occur in subsequent pregnancies
- Menthol or urea-containing emollients and mid-potency topical steroids for mild cases. Oral prednisolone x7-14 days in severe cases.
- Biopsy for DIF to rule out Herpes gestationis

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Intrahepatic Cholestasis of Pregnancy

- Multifactorial – genetic and hormonal factors play a role
  - More common in South American and Scandinavian patients (prevalence of 0.5-1.5%)
    - 50% have + family history
  - Mild malfunction of hepatic canalicular transport
  - Metabolites of progesterone and estrogen (17β-estradiol glucoronide) effect bile acid secretion
- Presents in latter half of pregnancy
  - **Intense pruritus with no primary lesions**
  - Begins as itching of palms and soles and is localized to the extremities
  - Pruritus worse at night

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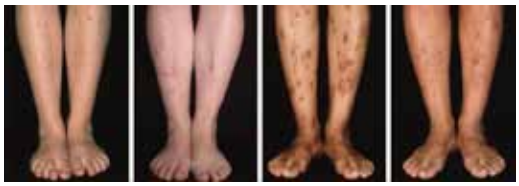
Intrahepatic Cholestasis of Pregnancy

- Skin findings range in severity from excoriations to prurigo nodules and secondary infection
- Jaundice seen in only 10%
- **Total serum bile acids > 11.0µmol/L**, more sensitive than liver function test or bilirubin



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Intrahepatic Cholestasis of Pregnancy

- Significant **fetal risk**, correlated to disease severity and causes placental anoxia and fetal cardiomyocyte dysfunction.
  - Premature birth (19-60%)
  - Intrapartum fetal distress (22-33%)
  - Stillbirth (1-2%)—majority of intrauterine deaths occur after **37 weeks**
- Fetal monitoring especially after 34 weeks and elective delivery at 37 weeks
- Ursodeoxycholic acid (15mg/kg/d) corrects maternal bile acid by stimulating excretion of bile acids

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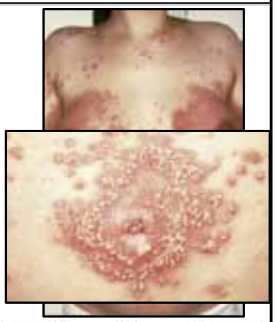
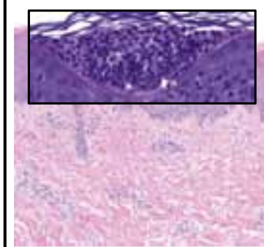
Impetigo Herpetiformis

- Pustular psoriasis of pregnancy
- Rare, occurs in 3rd trimester in women ± history of psoriasis
- Has been associated with hypoparathyroidism/ hypocalcemia, which may incite flare
- Acutely inflamed skin erupts with superficial sterile pustules in skin folds, spreading centrifugally on trunk and periumbilical skin
- May involve mucosa
- Constitutional symptoms
- Risk of cardiac and renal failure



Impetigo Herpetiformis



- Dermatologic emergency—prompt diagnosis key
  - Characteristic features of pustular psoriasis on H&E
- Placental insufficiency leads to fetal abnormalities, stillbirth, and neonatal death
- Treat with systemic corticosteroids with slow taper to avoid flare
  - Topical treatment alone is ineffective
  - Cyclosporine in refractory cases
- Typically, there is abrupt resolution after delivery
- Recurs with subsequent pregnancy with earlier onset and higher severity

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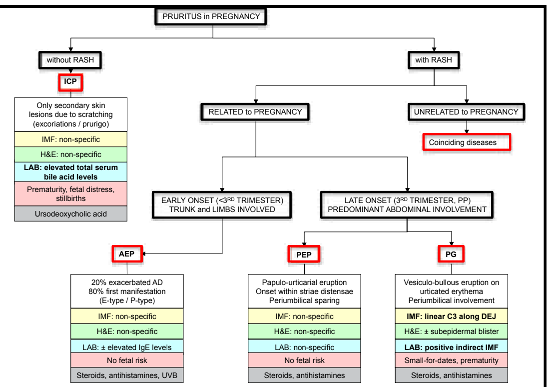

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Resources

- Black M, Ambros-Rudolph C, Jones S. *Obstetric And Gynecologic Dermatology*. 3rd ed. Mosby/Elsevier; 2008:65-72.
- Bolognia J, Jorizzo JL, Schaffer JV. Dermatology: Sect. 27. Pregnancy Dermatoses. Saunders; 2012.
- Calonje E. McKee's Pathology of the Skin, With Clinical Correlations. Saunders; 2012.
- James WD, Elston DM, Berger TG. Andrews' Diseases of the Skin, Clinical Dermatology. Saunders; 2011.
- Elling S.V., and Powell F.C.: Physiological skin changes in the skin during pregnancy. Clin. Dermatol. 1997; 15: pp. 35-43Wong R.C., and Ellis C.N.: Physiologic skin changes in pregnancy. J. Am. Acad. Dermatol. 1984; 10: pp. 929-940
- Sanchez N.P., Pathak M.A., Sato S., et al: Melasma: A clinical, light microscopic, ultrastructural and immunofluorescent study. J. Am. Acad. Dermatol. 1981; 4: pp. 698-710
- Chang A.L.S., Agredano Y.Z., and Kimball A.B.: Risk factors associated with striae gravidarum. J. Am. Acad. Dermatol. 2004; 51: pp. 881-885
- Elson M.L.: Treatment of striae distensae with topical tretinoin. Dermatol. Surg. Oncol. 1990; 16: pp. 267-270
- Pribanich S., Simpson F.G., Held B., et al: Low dose tretinoin does not improve striae distensae: a double blind, placebo-controlled study. Cutis 1994; 54: pp. 121-124
- Winton G.B.: Skin diseases aggravated by pregnancy. J. Am. Acad. Dermatol. 1989; 20: pp. 1-13
- Fryer J.M., and Werth V.P.: Pregnancy-associated hyperpigmentation: longitudinal melanonychia. J. Am. Acad. Dermatol. 1992; 26: pp. 493-494
- Chanco Turner M.L.: The skin in pregnancy. In Burrow G.N., and Duffy T.P. (eds): Medical Complications During Pregnancy, 5th edn. Philadelphia: W. B. Saunders, 1999. pp. 453-468
- Woollons A., and Darley C.R.: Unilateral naevoid telangiectasia syndrome in pregnancy. Clin. Exp. Dermatol. 1996; 21: pp. 459-460
- Wilkin J.K., Smith J.G., Cullison D.A., et al: Unilateral dermatomal superficial telangiectasia. Nine new cases and a review of unilateral dermatomal superficial telangiectasia. J. Am. Acad. Dermatol. 1983; 8: pp. 468-477
- Graham-Brown R.A.C.: Pregnancy, childbirth and the puerperium. In Rook A., Wilkinson D.S., and Ebling F.J.G. (eds): Textbook of Dermatology, 6th edn. Oxford: Blackwells, 1998. pp. 3268-3275
- Visualdx.com
- Ambros-Rudolph C, Müllegger R, Vaughan-Jones S, Kerl H, Black M. The specific dermatoses of pregnancy revisited and reclassified: Results of a retrospective two-center study on 505 pregnant patients. *Journal of the American Academy of Dermatology*. 2006;54(3):395-404. doi:10.1016/j.jaad.2005.12.012.
- Lehrhoff S, Pomeranz M. Specific dermatoses of pregnancy and their treatment.*Dermatologic Therapy*. 2013;26(4):274-284. doi:10.1111/dth.12078.
- Tani N, Kimura Y, Koga H et al. Clinical and immunological profiles of 25 patients with pemphigoid gestationis. *Br J Dermatol*. 2014;172(1):120-129. doi:10.1111/bjd.13374.
- Seidel R, Lavi N, Chipps L. Pemphigoid Gestationis: A Case Report and Review of Management. J Drugs Dermatol. 2015;14(8):904-7.
- Lotem M, Katzenelson V, Rotem A, Hod M, Sandbank M. Impetigo herpetiformis: a variant of pustular psoriasis or a separate entity?. J Am Acad Dermatol. 1989;20(2 Pt 2):338-41.
- Kondo RN, Araújo FM, Pereira AM, Lopes VC, Martins LM. Pustular psoriasis of pregnancy (impetigo herpetiformis)--case report. An Bras Dermatol. 2013;88(6 Suppl 1):186-9.
- Imai N, Watanabe R, Fujiwara H, Ito M, Nakamura A. Successful treatment of impetigo herpetiformis with oral cyclosporine during pregnancy. Arch Dermatol. 2002;138(1):128-9.
- Ahmadi S, Powell FC. Pruritic urticarial papules and plaques of pregnancy: current status. Australas J Dermatol. 2005;46(2):53-8.
- Rudolph CM, Al-fares S, Vaughan-jones SA, Müllegger RR, Kerl H, Black MM. Polymorphic eruption of pregnancy: clinicopathology and potential trigger factors in 181
- Lee RH, et al.: Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol. 25 (6):341-345 2008 Jun
- Roncaglia N, et al.: A randomised controlled trial of ursodeoxycholic acid and S-adenosyl-l-methionine in the treatment of gestational cholestasis. Br J Obstet Gynaecol. 111:17 2004
- Lammert F., Marschall H.U., Glantz A., et al: Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J. Hepatol. 2000; 33: pp. 1012-1021
- Reyes H., and Sjövall J.: Bile acids and progesterone metabolites in intrahepatic cholestasis of pregnancy. Ann. Med. 2000; 32: pp. 94-106
- patients. Br J Dermatol. 2006;154(1):54-60.

Introduction | Physiologic changes | Atopic eruption | Herpes gestationis | PEP | Intrahepatic cholestasis | Impetigo herpetiformis | Conclusions

Thanks!

Introduction | Physiologic changes | Atopic eruption | Herpes gestationis | PEP | Intrahepatic cholestasis | Impetigo herpetiformis | Conclusions

Vasculitides and Vaso-Occlusive Disease

Oakwood Southshore Medical Center/Beaumont Health
Dermatology Residency Program

Alexandra Grob, DO, PGY-IV
Kristi Hawley, DO, PGY-IV

Overview

- Vasculitides
  - LCV
  - Urticarial vasculitis
  - HSP
  - EED
  - Granuloma faciale
  - Cryoglubulinemia
  - Churg-Strauss
  - Wegener's
  - PAN
- Vaso-Occlusive Disease
  - Heparin necrosis
  - Warfarin necrosis
  - Calciphylaxis
  - Cholesterol emboli
  - Antiphospholipid syndrome
  - Sneddon syndrome
  - Livedoid vasculopathy
  - Malignant atrophic papulosis

Vasculitides

- The classification and cutaneous signs of vasculitis are a reflection of the size of vessels involved
  - Small vessel
  - Small to medium vessel "mixed"
  - Medium vessel
  - Large vessel

Cutaneous Small Vessel Vasculitis

Leukocytoclastic Vasculitis (LCV)

- General term describing the histopathologic features of LCV involving only small cutaneous blood vessels (post-capillary venules of the dermis), irrespective of the etiology
- Initiated by the deposition of circulating immune complexes within and around vessel walls

LCV

- Etiology
  - **Idiopathic (50%)**
  - Post Infectious (15-20%)
  - Underlying Connective Tissue Diseases (15-20%)
  - Drug Induced (10-15%)
  - Hematologic or Solid Organ malignancies (2-5%)

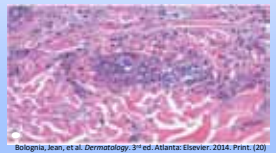
LCV

- Clinically presents as **palpable purpura**, with erythematous macules, papules, and vescicles over the lower extremities and other dependent areas.
- Prognosis depends on the severity of systemic involvement.

http://www.hindawi.com/journals/criid/2011/356370/fig1/

LCV

- Pathology
  - **Perivascular and interstitial infiltrate of neutrophils with nuclear dust (leukocytoclasia)**
  - Fibrin within the vessel wall and extravasation of erythrocytes



Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print. (20)

LCV

- Treatment
  - **Rule out systemic vasculitis**
  - Remove any suspected triggers
  - Supportive care for skin-limited disease (90% spontaneous resolution)
  - Chronic (>4 weeks)
    - Colchicine and dapsone may be useful for skin and joint disease
    - 1mg/kg/day prednisone for severe or progressive disease

Urticarial Vasculitis

- Synopsis:
  - Condition that **clinically resembles urticaria** but also demonstrates features of LCV histologically

Epidemiology:

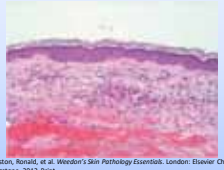
- Peak incidence is in the fifth decade with a predilection for females
- Two Forms
  - Normocomplementemic (70-80%): benign course, ~3 year duration
  - Hypocomplementemic (~25%): almost exclusively in women
    - ↓ complement, anti-C1q antibody

Urticarial Vasculitis

- Pathogenesis:
  - Complement activation triggers mast cell release of inflammatory mediators, such as TNF-α
- Associated with:
  - Sjögren's syndrome, SLE, serum sickness cryoglobulinemia, infections, medications, and hematologic malignancies

Urticarial Vasculitis

- Clinically: Urticarial papules and plaques with associated **burning or pain**, lasting **>24 hours**



Johnston, Ronald, et al. *Weedon's Skin Pathology Essentials*. London: Elsevier Churchill Livingstone. 2012. Print

Hai Long, et al. Eosinophilic Skin Diseases: A Comprehensive Review. *Clinical Reviews In Allergy And Immunology*. Apr 2015

Pathology: Prominent edema in upper dermis; mild infiltrate; similar to LCV

Urticarial Vasculitis

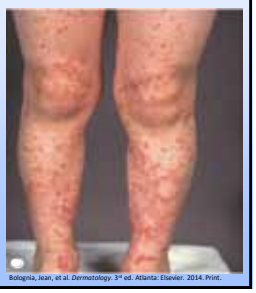
- Treatment
  - Workup for any associated systemic disease
  - Antihistamines may reduce swelling and pain of cutaneous lesions
  - Oral corticosteroids, NSAIDs, Colchicine, Dapsone, Antimalarials

Henoch-Schönlein Purpura (HSP)

- Synopsis
  - Specific type of cutaneous small vessel vasculitis (CSVV) with **vascular IgA deposition** that typically affects children (M>F) after a respiratory tract infection
- Pathogenesis
  - HSP frequently presents 1 to 2 weeks following a URI, especially in children
  - Associated with positive antistreptolysin O titers, but no causal role has been demonstrated
  - IgA deposits in the postcapillary venules of the skin and mesangium
  - Circulating IgA-containing immune complexes with increased serum levels of IgA

HSP

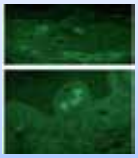
- Clinical Presentation:
  - Erythematous macules or urticarial papules that evolve into **palpable purpura** with a predilection for the lower extremities and buttocks.
  - **Classic "tetrad"**: palpable purpura, arthritis, abdominal pain, and hematuria.
- Pathology:
  - Leukocytoclastic vasculitis of the small dermal blood vessels
  - DIF demonstrates **perivascular IgA**, C3 and fibrin deposits.



Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print.

HSP

- Indistinguishable from LCV histologically
- **DIF = perivascular IgA**



Johnston, Ronald, et al. *Weedon's Skin Pathology Essentials*. London: Elsevier Churchill Livingstone. 2012. Print.

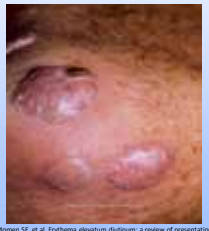
- Treatment:
  - HSP is commonly self-limited, resolving over the course of weeks to months
  - Don't forget UA to evaluate renal involvement!

Erythema Elevatum Diutinum (EED)

- Synopsis:
  - Rare chronic dermatosis, favoring the extensor surfaces, usually found in middle-aged and older adults
- Pathogenesis:
  - Due to circulating immune complexes, with repeated deposition, associated inflammation and partial healing
  - Associations
    - Autoimmune diseases, infections, inflammatory bowel disease, and hematologic disorders

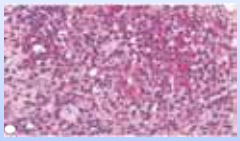
EED

- Clinical Presentation:
  - Violaceous, red–brown or yellowish papules, plaques or nodules that are symmetrically distributed
  - Favor acral and periarticular sites, specifically the extensor surfaces of the elbows, knees, ankles, hands and fingers

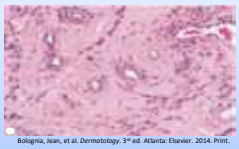


Momen SE, et al. Erythema elevatum diutinum: a review of presentation and treatment. *J Eur Acad Dermatol Venereol*. 2014 Dec; 28(12): 1594-602

EED



Early lesion: LCV with neutrophilic infiltrate



Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print.

Late Lesion: marked perivascular fibrous thickening

- Treatment
  - **Dapsone** shows excellent improvement, however, relapses are common

Granuloma Faciale

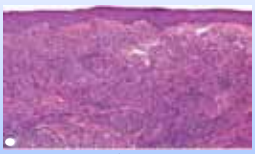
- Synopsis:
  - An idiopathic cutaneous disorder, characterized by red–brown plaques on the face, which occurs predominately in middle-aged white males
- Pathogenesis:
  - A role for interferon-γ as an important proinflammatory mediator in this disorder has been suggested, as has elevated local IL-5 production

Granuloma Faciale

- Clinical Presentation:
  - Presents as a solitary, asymptomatic, smooth red–brown to violaceous plaque on the face
  - Very rare to have extra-facial sites of involvement

Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print.

Granuloma Faciale



Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print.

- Pathology
  - LCV
  - Normal epidermis, **grenz zone** above diffuse infiltrate of neutrophils, histiocytes, and lymphocytes
  - Often hemosiderin deposition within the dermis
- Treatment
  - Often resistant to treatment
  - IL/topical corticosteroids, **dapsone**, clofazamine, topical tacrolimus
  - Excision, cryosurgery, dermabrasion, electrosurgery, CO_2 or pulsed dye lasers

Mixed Vessel Vasculitis

Cryoglobulinemia

- Synopsis:
  - Cold-precipitable immunoglobulins (single or mixed), divided into three types

Type	Molecular Composition	Associations	Clinical Findings
I	*Monoclonal IgM>IgG*	*Plasma cell dyscrasias, Lymphoproliferative disorders (LPD)*	*Raynaud's phenomenon, retiform purpura, gangrene, acrocyanosis, arterial thrombosis*
II (Mixed)	*Monoclonal IgM (or IgG) wth polyclonal IgG*	*HCV, HIV, autoimmune connective tissue diseases, LPD*	*Vasculitis with palpable purpura, arthralgias, peripheral neuropathy, glomerulonephritis*
III (Mixed)	*Polyclonal IgM complexed with polyclonal IgG*		

Cacoub P, et al. Cryoglobulinemia Vasculitis. *American Journal of Medicine*. 2015 Mar 30.

Cryoglobulinemia

- Pathogenesis:
  - Cryoglobulinemic vasculitis occurs when immune complexes form from circulating cryoglobulins and then deposit within the walls of small vessels
- Treatment
  - Treat the underlying cause (ex: HCV: IFNα + ribavarin)

Churg-Strauss Syndrome

- Synopsis:
  - ANCA associated, granulomatous, necrotizing vasculitis of small vessels, that affects multiple organ systems. Distinguished by **asthma and eosinophilia**
- Pathogenesis:
  - Triggering factors for the onset of symptoms include, vaccination, desensitization therapy, leukotriene inhibitors and rapid discontinuation of corticosteroids
  - T lymphocytes, **eosinophils** and ANCA all play a role
  - Th2 cells are implicated in granuloma formation

Churg-Strauss Syndrome

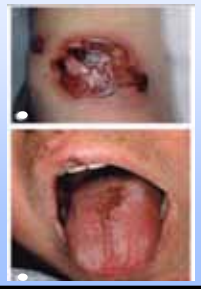
Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print

- Clinical Presentation:
  - Palpable purpura (typically lower extremities), SubQ nodules (scalp or extremities), urticaria, and livedo reticularis
  - Labs: ↑IgE, **p-ANCA** (anti-myeloperoxidase {MPO})
- Treatment
  - Oral corticosteroids +/- cytotoxic agents

Granulomatosis with Polyangitis (Wegener's)

- Synopsis
  - **Triad** of granulomatous inflammation of the upper and lower respiratory tracts, systemic necrotizing small vessel vasculitis, and pauci-immune **glomerulonephritis**
- Pathogenesis
  - Th1 mediated granuloma formation, and small-medium vessel vasculitis.
- Clincally
  - May present with mucocutaneous findings including palpable purpura, oral ulcers, red friable gingiva, painful ulcers or nodules (mimicking pyoderma gangrenosum).
  - Labs: ↑ESR, WBC, **c-ANCA** (anti-proteinase-3 {PR-3})

Granulomatosis with Polyangitis



- Treatment
  - Systemic corticosteroids in conjunction with oral cyclophosphamide

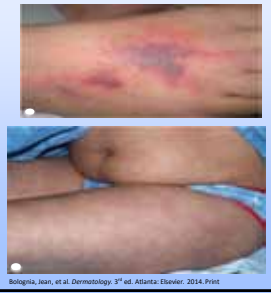
Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print

Medium Vessel Vasculitis

Polyarteritis Nodosa (PAN)

- Synopsis:
  - A multisystem vasculitis characterized by segmental necrotizing vasculitis that involves predominantly medium sized blood vessels.
    - **Cutaneous PAN**: skin limited variant, usually benign but chronic (10% of all cases)
- Pathogenesis
  - Associated with infections, inflammatory diseases, malignancies (especially hairy cell leukemia), and medications.
    - IBD, SLE, **HBV**, & strep

PAN



Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print

- Clinically
  - Palpable purpura, livedo reticularis, retiform purpura, "punched out" ulcers, SubQ nodules, acral gangrene
- Treatment
  - Classic PAN: systemic corticosteroids
  - **Cutaneous PAN**: topical or intralesional steroids, occasionally oral

Diagnostic Approach to Vasculitis

- History and Physical
  - Antecedent illnesses or exposures
  - Autoimmune connective tissue disease or malignancy
  - Systemic symptoms in ROS
  - Complete head and neck, cardiopulmonary, abdominal, musculoskeletal and neurologic examination should be performed

Diagnostic Approach to Vasculitis

- Histological Examination:
  - Tissue biopsy from affected areas for possible diagnosis
  - H/E and DIF samples
- Laboratory Examination:
  - CBC with Diff, LFT, BUN/Cr
  - ANCA, Cryoglobulin, Complement levels, RF, HBV/HCV serologies
  - ANA if signs of CTD
  - Urine dipstick and microscopy, stool guaiac
  - Consider blood cultures, imaging as indicated

Treatment

- Rule out any obvious infection, inflammatory, or neoplastic etiology
  - A treatable etiology exists in 50%
- **Systemic disease should always be ruled out**, or followed up as appropriate
- Treatment as appropriate for type of vasculitis

Vaso-Occlusive Diseases

Vaso-Occlusive Disease

- The differential diagnosis can be extensive and the evaluation can be trying
- Distinguish between inflammatory versus non-inflammatory
- Telltale finding of retiform purpura, macular, violaceous, connecting rings that form a netlike pattern
- Accurate diagnosis is critical to appropriate therapy, as treatment for inflammatory disease is vastly different than occlusive diseases

Heparin Necrosis

Synopsis:

-Iatrogenic syndrome causing necrosis **5-10 days** after exposure to SubQ or IV heparin

-Heparin necrosis can happen with low molecular weight heparin (lower risk) or unfractionated heparin

Epidemiology:

-Heparin-induced thrombocytopenia (HIT) occurs in 1-5% of adults; thrombosis percentages range from 30 - 90% of patients

Pathogenesis:

-Secondary to **antibody binding of heparin plus platelet factor 4 complexes**

-Leads to platelet aggregation & consumption

Heparin Necrosis

- Clinical:

-Lesions are tender, non-inflammatory, purpuric/necrotic with a retiform morphology at or distant to the site of administration

Christiaens L, Nieuwenhuis K. Heparin-Induced Skin Necrosis. N Engl J Med 1996; 335:715.

Heparin Necrosis

- Pathology:
  - Pathology often shows non-inflammatory occlusion of vessels involving either the microvasculature, arterial, or venous system
  - **Platelet plugs are "white"** vs usual "red" clot of fibrin thrombi

Heparin Necrosis

- Treatment:
  - Discontinue heparin
  - Argatroban, danaparoid, or lepirudin
  - Do not begin warfarin in this setting as initial decrease in protein C may cause further thrombosis or necrosis

41

Warfarin Necrosis

- Epidemiology:

- Relatively rare

- 4x more common in women, specifically in 70s-80s

- Pathogenesis:

-Necrosis occurs within **2-5 days** of starting therapy (> w/loading dose)

-Vitamin K sensitive factors include II, VII, IX, X, protein C (VII and protein C shortest half life)

-Occurs more commonly in patients with i**nherited defects in protein C**

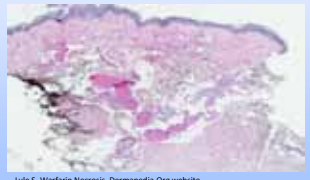
Warfarin Necrosis

- Clinical:
  - Prefers fatty areas of the body (butt, hip, thigh, breast).
  - Presents with pain —> erythema —> hemorrhage and necrosis

Clinical cases.org 1024 x 768 - jpegCoumadin Induced Skin Necrosis

Warfarin Necrosis

- Pathology:
  - Fibrin-platelet thrombi are present in venules and arterioles in the deep dermis and subcutis
- Treatment:
  - Discontinue warfarin, administer vitamin K and heparin



Lyle S. Warfarin Necrosis. Dermapedia Org website. http://www.dermpedia.org/dermpedia-textbook/warfarin-necrosis. Accessed Aug 25, 2015.

Calciphylaxis

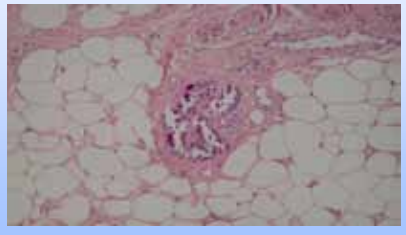
Synopsis:
- Progressive vascular calcification and ischemic necrosis of the skin and soft tissues

Epidemiology:
- Female predominance
- Associated with diabetes mellitus, obesity, and poor nutritional status

Pathogenesis:
- Protein C dysfunctional in some patients
- End-stage renal failure common, but may be associated with primary hyperparathyroidism
- No known trigger in some instances
- Mortality is HIGH (~85%) with proximal involvement having worse prognosis

Calciphylaxis

Pathology:
Intravascular calcium deposits, chiefly within small and medium-sized venules and arterioles



Nunley J. Calciphylaxis. Epathologies website. Accessed Aug 24, 2015.

Calciphylaxis

- Clinical:

-Lesions present as painful, violaceous, reticulated patches with the progression to bullae; gray color signifies impending tissue necrosis

Pliquett RU, Schwock J, Paschke R, Achenbach H: Calciphylaxis in chronic, non-dialysis-dependent renal disease. BMC Nephrol 2003, 4(1):8.

Calciphylaxis

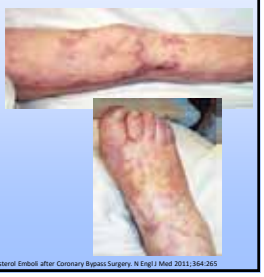
- Treatment
  - Normalizing calcium-phosphate product (medication and low phosphate diet vs parathyroidectomy)
  - Restoring tissue perfusion and good wound care
  - Other proposed treatment modalities include sodium thiosulfate, pamidronate, cinacalcet, hyperbaric oxygen, and low dose tissue plasminogen activator

Cholesterol Emboli

- Synopsis:
  - Fragmentation of ulcerated atheromatous plaques
  - Three settings that prompt embolization: arterial or coronary catheterization (emboli within hours-days), prolonged anticoagulation (1-2 months after therapy), acute thrombolytic therapy (hours to days)
- Epidemiology:
  - Men 50 years of age or older

Cholesterol Emboli

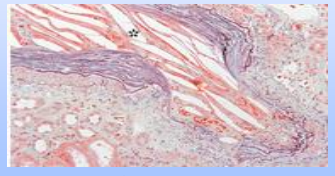
- Clinical:
  - Fever, weight loss, altered mental status, new-onset hypertension
  - Cutaneous manifestations, (most to least common): livedo reticularis, peripheral gangrene, cyanosis, ulceration, nodules, and purpura
  - Laboratory values: peripheral eosinophilia; decreased complement; leukocytosis; pyuria; increased ESR, BUN, and serum creatinine



Frank R, Veldon J. Cholesterol Emboli after Coronary Bypass Surgery. N Engl J Med 2011;364:265

Cholesterol Emboli

- Pathology:
  - **Elongated clefts** within small vessels and thrombi, usually at dermal-subcutaneous junction
  - Frozen section demonstrates **doubly refractile crystals**
  - (Biopsy specimens should be an elliptical incision and include subcutaneous fat)



Frank R, Veldon J. Cholesterol Emboli after Coronary Bypass Surgery. N Engl J Med 2011;364:265

Antiphospholipid Syndrome

- Synopsis:
  - Characterized by the presence of autoantibodies directed against phospholipids
  - Associated with repeated episodes of thrombosis, fetal loss, and thrombocytopenia
- Epidemiology:
  - Female predominance and common in 3rd to 5th decade

Antiphospholipid Syndrome

- Clinical:
  - Livedo reticularis +/- retiform purpura, leg ulcers, pseudovasculitis, digital gangrene, cutaneous necrosis, splinter hemorrhage
  - Most common extracutaneous findings are DVT/PE and CNS disease

Bhattacharya D. Antiphospholipid Syndrome. Hx Benefit Website. Accessed 26 Aug 2014

Antiphospholipid Syndrome

Clinical Criteria:

- Vascular thrombosis
  - One or more clinical episodes of arterial, venous or small vessel thrombosis
- Complications of pregnancy
  - One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of pregnancy; or
  - One or more premature births of morphologically normal neonates at or before the 34th week of gestation; or
  - Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

Antiphospholipid Syndrome

Laboratory Criteria:

- Anticardiolipin antibodies*, IgG or IgM, present at moderate or high levels† on two or more occasions at least 12 weeks apart
- Lupus anticoagulant antibodies on two or more occasions at least 12 weeks apart
- Anti-β2-glycoprotein I antibodies, IgG or IgM (in titer >99th percentile) on two or more occasions at least 12 weeks apart

*β2-glycoprotein I-dependent.
†Several thresholds exist for low versus moderate-to-high: (1) >40 international "phospholipid" units; (2) 2–2.5× the median level of anticardiolipin antibodies (ACA)

Antiphospholipid Syndrome

- Treatment:
  - Initially heparin, followed by long term warfarin therapy
  - Target INR 2-3

Sneddon Syndrome

- Synopsis:
  - AKA: **idiopathic livedo reticularis with cerebrovascular accidents**
- Pathogenesis:
  - Persistent livedo reticularis associated with systemic arterial thrombi, labile hypertension, and recurrent neurologic symptoms
  - May appear as a manifestation of antiphospholipid syndrome or may represent a distinctive vasculopathy affecting smaller arteries and larger arterioles, especially in the skin and the brain

Sneddon Syndrome

- Epidemiology:
  - Most commonly affects **young women**
  - Onset in **3rd to 4th decade** of life
  - Mortality rate of ~10%

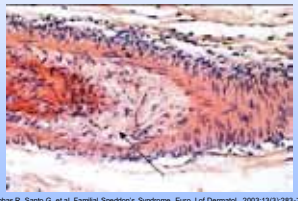
Sneddon Syndrome

- Clinical:
  - Persistent and widespread livedo reticularis which may precede the onset of neurologic disease by several years
  - CNS disease usually presents as TIAs, stroke, or dementia
  - Patient may have a history of fetal loss

Mascarenhas R, Santo G, et al. Familial Sneddon's Syndrome. Euro J of Dermatol. 2003:13(3):283-7.

Sneddon Syndrome

- Pathology:
  - Endothelial inflammation, followed by subendothelial myointimal hyperplasia, with partial and complete occlusion of the involved arterioles
  - **White areas, rather than red areas should be biopsied (center of livedo)**
  - 4mm punch biopsy has 27% sensitivity, but increases to 80% if three biopsies are performed



Mascarenhas R, Santo G, et al. Familial Sneddon's Syndrome. Euro J of Dermatol. 2003:13(3):283-7.

Sneddon Syndrome

- Treatment:
  - Warfarin, however may not be completely effective
  - If patient has antiphospholipid antibodies a target INR of 2-3 should be achieved
  - Corticosteroids and immunosuppressive agents do not prevent cerebrovascular disease

Livedoid Vasculopathy
(Atrophie Blanche)

- Synopsis:
  -Chronic cutaneous disease favoring distal lower extremities, predominantly in females
- Pathogenesis:
  -May be primary (idiopathic) or secondary to chronic venous hypertension, varicosities, or hypercoagulable states (eg. APLS)
  -Occlusion of small dermal vessels by fibrin thrombi is a primary event

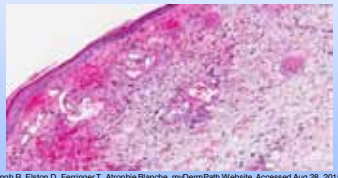
Livedoid Vasculopathy
(Atrophie Blanche)

- Clinical:
  -Painful punched out ulcers on a background of livedo reticularis
  -Ulcers may heal as stellate atrophic hypopigmented scars with peripheral telangiectasia

Singh R, Elston D, Ferringer T. Atrophie Blanche. myDermPath Website. Accessed Aug 28, 2015.

Livedoid Vasculopathy
(Atrophie Blanche)

- Pathology:
  - Atrophic or ulcerated epidermis
  - Thrombi in dermal vessels surrounded by hyalinization of walls
  - Dermal fibrosis and extravasated RBC



Singh R, Elston D, Ferringer T. Atrophie Blanche. myDermPath Website. Accessed Aug 28, 2015.

Livedoid Vasculopathy
(Atrophie Blanche)

- Treatment
  - No treatment consistently effective
  - Smoking cessation
  - Antiplatelet agents: low dose aspirin, dipyrimadole, pentoxyfyline
  - Anticoagulants: warfarin (depending on underlying etiology
  - Other clinical scenarios may support the use of anabolic steroids, hydroxychloroquine, folic acid

Malignant Atrophic Papulosis
(Degos Disease)

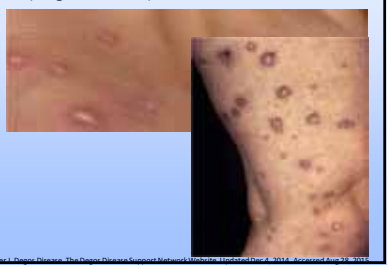
- Synopsis:
  - Rare, often fatal, multisystem vaso-occlusive disorder
- Pathogenesis:
  - Unknown but assumed to be a vasculopathy

Malignant Atrophic Papulosis
(Degos Disease)

- Epidemiology:
  - Occurs between the 2nd to 4th decade of life
  - Women and men affected equally
- Clinical:
  - Cutaneous features precede systemic features
    - Crops of small 2-5mm erythematous papules on trunk or extremities
    - Papules evolve over 2-4 weeks developing a central depression, ending in an atrophic scar with surrounding telangiectasia

Malignant Atrophic Papulosis
(Degos Disease)

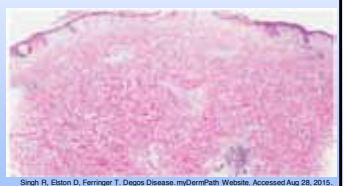
- Clinical cont:
  - Systemic symptoms can include CNS lesions leading to cerebrovascular accidents
  - Infarctive GI lesions may lead to bowel perforation



Calder I. Degos Disease. The Degos Disease Support Network Website. Updated Dec 4, 2014. Accessed Aug 28, 2015.

Malignant Atrophic Papulosis
(Degos Disease)

- Pathology
  - Epidermal atrophy with overlying hyperkeratosis
  - Underlying wedge shaped area of ischemia extending to the deep dermis
  - Acid mucopolysaccharides are present in abundance in the dermis
  - Late stages resemble lichen sclerosis et atrophicus



Singh R, Elston D, Ferringer T. Degos Disease. myDermPath Website. Accessed Aug 28, 2015.

Malignant Atrophic Papulosis
(Degos Disease)

- Treatment
  - No consistently proven treatment
  - Aspirin +/- pentoxifylline
  - IVIg

Thank you!

- Dr. Matt Laffer, PGY-3
- Dr. Dustin Portela, PGY-3
- Dr. Chelsea Duggan, PGY-2
- Dr. Peter Jajou, PGY-2
- Dr. Steven Grekin
  - Program Director

References

- Micheletti R, Werth V. Small Vessel Vasculitis of the Skin. *Rheum Dis Clin North Am*. 2015; 41 (1): 21-32
- Bolognia, Jean, et al. *Dermatology*. 3rd ed. Atlanta: Elsevier. 2014. Print.
- Hai Long, et al. Eosinophilic Skin Diseases: A Comprehensive Review. *Clinical Reviews In Allergy And Immunology*. Apr 2015
- Johnston, Ronald, et al. *Weedon's Skin Pathology Essentials*. London: Elsevier Churchill Livingstone. 2012. Print.
- Yang YH. et al. The diagnosis and classification of Henoch–Schönlein purpura: An updated review. *Autoimmun Rev*. 2014 Apr-May;13(4-5):355-8
- Momen SE. et al. Erythema elevatum diutinum: a review of presentation and treatment. *J Eur Acad Dermatol Venereol*. 2014 Dec; 28(12): 1594-602.
- Cacoub P. et al. Cryoglobulinemia Vasculitis. *American Journal of Medicine*. 2015 Mar 30.
- Greco A. et al. Churg-Strauss syndrome. Autoimmunity Reviews. 2015 Apr; 14(4): 341-8.
- Guidelli GM. et al. Granulomatosis with polyangiitis and intravenous immunoglobulins: A case series and review of the literature. *Autoimmunity Reviews*. 2015 Aug; 14(8): 659-664.
- Suresh. Diagnostic approach to patients with suspected vasculitis. Postgrad Med J. 2006 Aug; 82(970): 483–488.

References

- Robinson-Bostom L, DiGiovanna JJ. Cutaneous manifestations of end-stage renal disease. *J Am Acad Dermatol.* 43:975-986 2000
- Baker BL, Fitzgibbons CA, Buescher LS. Calciphylaxis responding to sodium thiosulfate therapy. *Arch Dermatol.* 143:269-270 2007
- Da Costa JB, Da Costa AG, Gomes MM. Pamidronate as a treatment option in calciphylaxis. *J Eur Acad Dermatol Venereol.* 22:1128-1130 2008
- Sewell LD, Weenig RH, Davis MDP, et al. Low-dose tissue plasminogen activator for calciphylaxis. *Arch Dermatol.* 140:1045-1048 2004
- Jucgla A, Moreso F, Muniesa C, et al. Cholesterol embolism: Still an unrecognized entity with a high mortality rate. *J Am Acad Dermatol.* 55:786-793 2006
- Kang K, Botella R, White CR Jr. Subtle clues to the diagnosis of cholesterol embolism. *Am J Dermatopathol.* 18:380-384 1996
- Manganoni AM, Venturini M, Scolari F, et al. The importance of skin biopsy in the diverse clinical manifestations of cholesterol embolism. *Br J Dermatol.* 150:1230-1232 2004
- Sepp N, Zelger B, Schuler G, et al. Sneddon's syndrome – an inflammatory disorder of small arteries followed by smooth muscle proliferation. *Am J Surg Pathol.* 19:448-

References

- Bauer KA. Coumarin-induced skin necrosis. *Arch Dermatol.* 129:766-768 1993
- Nahass GT. Antiphospholipid antibodies and the antiphospholipid antibody syndrome. *J Am Acad Dermatol.* 36:149-168 1997
- Wandroo FA, Rose P, Sinha B. Cutaneous necrosis in a young woman. *Clin Exp Dermatol.* 32:231-232 2007
- Alegre VA, Winkelmann RK. Histopathologic and immunofluorescence study of skin lesions associated with circulating lupus anticoagulant. *J Am Acad Dermatol.* 19:117-124 1988
- Wohlrab J, Fischer M, Wolter M, Marsch WC. Diagnostic impact and sensitivity of skin biopsies in Sneddon's syndrome. A report of 15 cases. *Br J Dermatol.* 145:285-288 2001
- McCalmont CS, McCalmont TH, Jorizzo JL, et al. Livedo vasculitis: vasculitis or thrombotic vasculopathy?. *Clin Exp Dermatol.* 17:4-8 1992
- Kreuter A, Sommer A, Stücker M, Altmeyer P. Painful unusual ulcers of the ankle. *Clin Exp Dermatol.* 33:377-379 2008

References

- Hsiao G-H, Chiu H-C: Livedoid vasculitis. Response to low-dose danazol. *Arch Dermatol.* 132:749-751 1996
- Browning CE, Callen JP. Warfarin therapy for livedoid vasculopathy associated with cryofibrinogenemia and hyperhomocysteinemia. *Arch Dermatol.* 142:75-78 2006
- Magrinat G, Kerwin KS, Gabriel DA. The clinical manifestations of Degos' syndrome. *Arch Pathol Lab Med.* 113:354-362 1989
- Degos R. Malignant atrophic papulosis. *Br J Dermatol.* 100:21-35 1979
- Scheinfeld N. Malignant atrophic papulosis. *Clin Exp Dermatol.* 32:483-487 2007
- Subramaniam K, Debinski H, Heenan P. Degos' disease with delayed involvement of the gastrointestinal tract. *Australas J Dermatol.* 49:86-90 2008
- Soter NA, Murphy GF, Mihm MC. Lymphocytes and necrosis of the cutaneous microvasculature in malignant atrophic papulosis: a refined light microscope study. *J Am Acad Dermatol.* 7:620-630 1982
- Zhu KJ, Zhou Q, Lin AH, et al. The use of intravenous immunoglobulin in cutaneous and recurrent perforating intestinal Degos disease (malignant atrophic papulosis). *Br J Dermatol.* 157:206-207 2007

References

- Wysong, A. and Venkatesan, P. (2011), An approach to the patient with retiform purpura. *Dermatologic Therapy*, 24: 151–172.
- Drew PJ, Smith, MJ, Milling MA. Heparin-induced skin necrosis and low molecular weight heparins. *Ann R Coll Surg Engl*. 1999 Jul; 81(4):266-9
- Oh DH, Eulau D, Tokugawa DA, et al.: Five cases of calciphylaxis and a review of the literature. *J Am Acad Dermatol.* 40:979-987 1999

Neutrophilic and Eosinophilic Dermatoses

Shannon McKeen, DO, PGY-3
Rapid Fire Dermatologic Updates
Orange County Convention Center – Orlando, FL
Sunday October 18, 2015
Program Director: Mark A. Kuriata, DO, FAOCD
Dermatology Residents: Riddhi Shah, DO, PGY-4;
Kiran Mian, DO, PGY-2

MICHIGAN STATE UNIVERSITY | Lakeland HealthCare

Neutrophilic Dermatoses

Neutrophils

- Originate in the bone marrow from pluripotent stem cells
- Take 7-10 days to differentiate
  - Stages: myeloblast, promyelocyte, myelocyte, metamyelocyte, band, segmented neutrophil
- During maturation, they acquire intracellular granules
  - 1° - i.e. myeloperoxidase, lysozyme, neutrophil elastase
  - 2° - i.e. lactoferrin, neutrophil collagenase
  - 3° - i.e. neutrophil gelatinase
- Produced at a rate of 5-10 x 10^{10} daily
- Generally circulate in peripheral blood for 3-12 hours, then migrate to tissues and stay there for 2-3 days
- 1st cell to arrive during infection
- Fastest moving cell in body- 30 microns/min

Sweet's Syndrome

Sweet's Syndrome

Epidemiology

- Occurs in all age groups
- Average age of onset is 30-60
- Female predominance (4:1)
  - Especially in drug-induced variant

Variants

- Classic presentation:
  - URI or GI infection
  - IBD
  - Pregnancy
  - Autoimmune disorder
- Malignancy-associated:
  - AML or MDS
- Drug- induced presentation:
  - G-CSF

Clinical Presentation

- Tender papules or nodules coalescing into plaques favoring the head & neck
  - Often with vesicular, bullous or pustular appearance
  - May have a mammilated surface
- Constitutional symptoms
- Elevated CRP/ESR
- Leukocytosis
- Oral ulcers
- Extracutaneous manifestations
- Exhibit pathergy

Diagnostic Criteria

- Major criteria
  - Abrupt onset of cutaneous lesions consistent with Sweet's syndrome
  - Histopathology compatible/consistent with Sweet's syndrome
- Minor criteria
  - Preceded by associated systemic findings, such as infection, pregnancy, drugs, malignancy, or other inflammatory conditions
  - Fever and constitutional signs and symptoms
  - Excellent response to corticosteroids
  - Laboratory abnormalities:
    - Elevated white blood cell count (of which 70 % are neutrophils)
    - Elevated erythrocyte sedimentation rate or C-reactive protein levels

Clinical Image and Pathology

Alavi A, Sajobi O, Cerci FB, Ghazarian D, Rosenbach M, Jordan J. Neutrophilic dermatoses: an update. Am J Clin Dermatol. 2014 Oct;15(5):413-33.

Treatment

- 1st line therapy:
  - *Systemic corticosteroids
  - Intralesional or topical corticosteroids
  - Potassium iodide
  - Colchicine
- 2nd line therapy:
  - Dapsone
  - Indomethacin
  - Clofazimine
  - Cyclosporine
- Alternate therapy:
  - Interferon- α
  - Immunoglobulin
  - Thalidomide
  - TNF-α inhibitors
  - Anakinra

Pyoderma Gangrenosum

Pyoderma Gangrenosum

- Rare, recurring, chronic and painful disease of unknown etiology
- Commonly affects women 20-50 years of age
- 4% of cases occur in infants and children
- 50% of cases are associated with an underlying systemic disease
- All variants of the disease exhibit pathergy

Clinical Presentation - Variants

- **Classic PG**
  - Tender papulopustule that evolves into ulcer with purulent base and violaceous borders
  - Pretibial areas
  - Frequently occur with IBD and RA
- **Peristomal PG**
  - Occurs around ileostomy/colostomy sites
  - Associated with intestinal cancers or IBD
- **Pustular PG**
  - Multiple, discrete pustules surrounded by erythematous halo
  - Extensor extremities and trunk
  - Frequently occurs with IBD

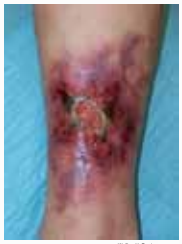
Clinical Presentation- Variants

- **Bullous PG**
  - Vesicles→ Bullae→Superficial ulcers/erosions
  - Face and upper extremities, especially dorsal hands
  - Frequently occurs with AML, MDS, IgA gammopathy
- **Vegetative PG**
  - Sterile pyoderma; possible sinus tracts
  - Labial and buccal mucosa
  - Frequently occurs with IBD
- **Drug-induced PG**
  - EGFRI, G-CSF, PTU

Clinical Presentation

Brooklyn T, Dunnill G, Probert C. Diagnosis and treatment of pyoderma gangrenosum. BMJ. 2006 Jul 22;333(7560):181-4.

Clinical Presentation

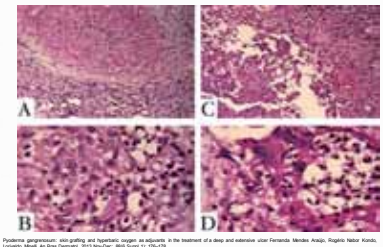


Wollina U. Pyoderma gangrenosum--a review. Orphanet J Rare Dis. 2007 Apr 16;2:19.

Histology

- **Early Findings**
  - Perivascular lymphocytic infiltrate with endothelial swelling (biopsy taken from the edge of lesion)
- **Late findings**
  - Dense neutrophilic infiltrate, leukocytoclasia without evidence of vasculitis (area of ulceration)
  - Fibrosing inflammation at edge of ulcer with thrombosis of vessels and extravasated RBCs

Histology



Pyoderma gangrenosum: skin grafting and hyperbaric oxygen as adjuvants in the treatment of a deep and extensive ulcer Fernanda Mendes Araújo, Rogério Nebor Kondo, Lorisaldo Mineli An Bras Dermatol. 2013 Nov-Dec; 88(6 Suppl 1): 176–178.

Treatment

- Corticosteroids:
  - Systemic, topical or intralesional corticosteroids
- TNF-α inhibitors:
  - Infliximab, Adalimumab, Etanercept
  - Thalidomide
- Calcineurin inhibitors
  - Cyclosporine
  - Oral or Topical Tacrolimus
  - Topical Pimecrolimus
- Antimetabolites/ Cytotoxic Chemotherapies
  - Azathioprine
  - Cyclophosphamide
  - Mycophenolate mofetil

Treatment

- Other systemic agents:
  - Clofazimine
  - Colchicine
  - Dapsone
  - Chlorambucil
  - Tetracyclines
  - Alefacept
  - IVIG
- Wound care agents:
  - Avoid debriding tissue
  - Hyperbaric oxygen
  - Biologic dressings
  - Skin grafts
  - Topical corticosteroids
  - Topical calcineurin inhibitors

Behcet's Disease

Overview

- A rare, multisystem, polysymptomatic inflammatory disorder of unknown etiology
- Classic triad of oral ulcers, genital ulcers, and ocular inflammation
- Peak age of onset 20-35 years, with a relapsing remitting nature
- Diagnostic Criterion:
  - At least 3 episodes of oral ulcerations within 12 months
  - 2 of the following: genital ulcers, eye lesions, skin lesions, positive pathergy test

Clinical Features

- Recurrent aphthous stomatitis and genital aphthae
- Anterior and posterior uveitis, hypopyon, retinal vasculitis
- Erythema nodosum-like lesions, pseudofolliculitis, sterile papulopustular lesions, palpable purpura
- Superficial thrombophlebitis, pulmonary arterial aneurysms
- Arthritis, arthralgias
- Neurologic: memory, behavioral changes, brainstem lesions

Histopathology

- Cutaneous lesions: angiocentric neutrophilic infiltrates with leukocytoclasia and erythrocyte extravasation
- May see a leukocytoclastic vasculitis
- Thrombi and necrosis
- Acneiform lesions: sterile neutrophilic vasculopathy

Clinical Image and Pathology

Seyahi E, Yurdakul S. Behcet's Syndrome and Thrombosis. Mediterr J Hematol Infect Dis. 2011;3(1):e2011026

Treatment

- Difficult secondary to variable nature and multi-organ involvement
- Cutaneous lesions:
  - Topical and intralesional corticosteroids
  - Methotrexate
- Systemic Disease:
  - Cyclophosphamide
  - Prednisone
  - Mycophenolate mofetil

SAPHO

Synovitis-Acne-Pustulosis-HyperOsteitis

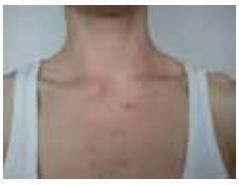
Overview

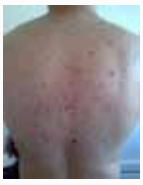
- A clinicoradiologic entity that involves skin, bone, and joints
- Rare in the US; more prevalent in Japan, Scandinavian countries, Germany, and France
- Affects children and young to middle aged adults
- Characterized by osteoarticular lesions and pustular dermatosis

Clinical Presentation

- Osteoarticular lesions: axial skeleton and chest wall
  - Osteitis, hyperostosis, synovitis, aseptic osteomyelitis
    - Pain, tenderness, swelling over affected areas
- Dermatoses:
  - Palmoplantar pustulosis, pustular psoriasis, severe acne

Clinical Photos





Coelho C, Souza M. The Dark Side of SAPHO syndrome. BMJ Case Report. 2011 Dec; bcr1120115197

Pathogenesis

- Some classify SAPHO under seronegative spondyloarthropathies due to its association with HLA-B27
- Other hypotheses include infectious causes:
  - S. aureus, H.parainfluenza, P. acnes isolated from bone lesions
- Bone Scintigraphy shows increased uptake, supporting increased osteoblast activity causing hyperostosis and osteitis

Treatment

- NSAIDS
- Antimicrobial therapies in those with positive biopsy cultures: azithromycin, doxycycline
- Immunomodulators: methotrexate
- Bisphosphonates for bone lesions
- Oral corticosteroids for skin and bone lesions

Bowel-Associated Dermatosis-Arthritis Syndrome

Overview

- Occurs 3 months to 5 years post-surgery in 20% of individuals
- Most commonly associated with:
  - Gastric resection
  - Jejunoileal bypass
  - Blind loops of bowel
  - Biliopancreatic diversion
- MOA- microbial overgrowth in blind loops of bowel which result in immune complex deposition in skin and synovium containing bacterial antigens

Clinical Presentation

- Flu-like symptoms
- Macules→ Papules→Purpuric Vesiculopustules
  - Favor the proximal extremities and trunk
- Erythema nodosum-like lesions
- Tenosynovitis
- Non-erosive, migratory, episodic polyarthritis
- Diarrhea and malabsorption
- Other systemic complications: renal stones, gallstones, hepatic dysfunction, vitamin deficiency

Treatment

- Mild Disease
  - Antibiotics:
    - Tetracyclines
    - Clindamycin
    - Metronidazole
  - Anti-neutrophilic agents:
    - Colchicine
    - Dapsone
    - Thalidomide
- Severe Disease
  - Immunomodulators:
    - Prednisone
    - Cyclosporine
    - Azathioprine
    - Mycophenolate mofetil
  - TNF-α inhibitors:
    - Infliximab
    - Etanercept
    - Adalimumab
  - Surgical restoration

Eosinophilic Dermatoses

Eosinophils

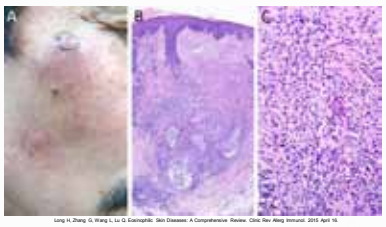
- Granulocytes that have a major function in allergic reactions and parasitic infections
- Migration and Chemotaxis
  - Through vascular endothelium: VLA-4 binds to VCAM-1
  - Through peripheral tissues: CCR3 binds eotaxin 1-3 and RANTES
- Cytokines
  - Activity from Th2 subset of T cells
  - IL-5, IL-3, GM-CSF
- Autocrine Effects: eosinophils produce IL-3, IL-5, GM-CSF
- Eosinophil Granules
  - Major Basic Protein – stimulates histamine release and activates neutrophils
  - Eosinophilic Cationic Protein, Eosinophil Peroxidase, Eosinophil-Derived Neurotoxin

Granuloma Faciale

Overview

- Benign condition with unknown etiology
- Classic presentation: long-standing asymptomatic red-brown to violaceous solitary smooth plaque with prominent follicular openings on the face
- Most commonly seen in middle-aged Caucasian males
- No associations with systemic diseases
- Histopathology:
  - Prominent Grenz Zone
  - Dense, dermal infiltrate consisting of lymphocytes, neutrophils and characteristic eosinophils

Clinical Image and Pathology



Long H, Zhang G, Wang L, Lu Q. Eosinophilic Skin Diseases: A Comprehensive Review. Clin Rev Allerg Immunol. 2016 April 16.

Treatment

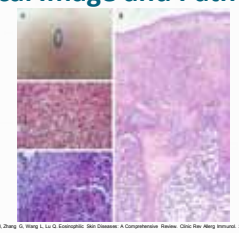
- Often resistant to therapy
- Intralesional triamcinolone 2.5-5.0 mg/mL
- Dapsone 50-150 mg by mouth daily
- Clofazimine 300 mg by mouth daily
- Topical PUVA
- Topical Calcineurin Inhibitors
- Pulsed Dye Laser
- Physical modalities: dermabrasion, surgical excision, cryotherapy

Wells' Syndrome

Overview

- Also known as eosinophilic cellulitis
- No predilection for age, sex or race
- Exact etiology unknown
  - Debated as its own entity verses a local hypersensitivity reaction that activates eosinophils
- Recurrent Episodes:
  - Prodrome of itching and burning → multiple areas of large, well-circumscribed edematous erythema in an annular or arcuate pattern → indurated red-brown to violaceous plaques and nodules
- Pathology: dense dermal infiltrate with lymphocytes, eosinophils and histiocytes, superficial dermal edema, flame figures

Clinical Image and Pathology



Long H, Zhang G, Wang L, Lu Q. Eosinophilic Skin Diseases: A Comprehensive Review. Clinic Rev Allerg Immunol. 2015 April 16.

Treatment

- Prednisone 20-30 mg by mouth daily until clear
  - Frequently recurring lesions controlled with maintenance 5mg every other day
- Oral antihistamines
- Topical or intralesional corticosteroids
- Resistant cases or for those intolerant to oral Corticosteroids
  - Dapsone, tacrolimus, cyclosporine
- Case report with successful response to adalimumab
- If present, treat underlying disease

Hypereosinophilic Syndrome

Overview

- Disorder characterized by peripheral blood eosinophilia with evidence of organ damage due to eosinophil infiltration and degranulation
  - Skin involvement in 50% of cases
- Three diagnostic criterion
  - Peripheral blood eosinophilia (>1,500 cells/μL) for > 6 months
    - >1,500 cells/μL on 2 separate occasions separated by 1 month
    - Can be expanded to include tissue hypereosinophilia
  - Evidence of eosinophil-related end organ damage
  - Exclusion of all other etiologies (allergic, parasitic, etc.)

Subtypes of HES

- There are two subtypes of Hypereosinophilic Syndrome
  - Myeloproliferative (Primary): molecular defect leading to abnormal eosinophil proliferation and activation
    - Due to FIP1L1-PDGFRA fusion gene which leads to unregulated tyrosine kinase activity
  - Lymphocytic (Secondary): secondary disease process releases cytokines (IL-5) that in turn expands and activates eosinophils
    - Associations: solid tumors, B-cell and T-cell lymphoproliferative diseases

Myeloproliferative HES

- Male predominance (9:1 ratio of males:females)
- Typical presentation: Fever, weight loss, fatigue, malaise
  - Skin lesions: range from pruritic erythematous maculopapules to urticarial lesions to angioedema to mucosal ulcerations (poor prognostic sign)
- Labs: elevated serum B12 and serum tryptase
- Associated with endocardial fibrosis/restrictive cardiomyopathy → monitor with echocardiogram
  - Concern for progression to leukemia
- Treatment: imatinib mesylate (Gleevec)

Lymphocytic HES

- Approximately 25% of HES cases
- Equal incidence in males and females
- Typical presentation: fever, weight loss, fatigue, malaise
  - Skin lesions (more prominent than myeloproliferative HES): severe pruritus, eczematous lesions, erythroderma, urticarial, angioedema
- Labs: elevated serum IgE levels
- Concern for transformation to lymphoma
- Treatment: prednisone 1 mg/kg/day in combination with steroid sparing agent
  - Hydroxyurea
  - IFNα2b: 12-50 x 10^6 U/week

HES Investigational Therapies

- Monoclonal Antibodies against IL-5
  - Mepolizumab
  - Reslizumab

Eosinophilic Fasciitis

Overview

- A rare fibrosing disorder of unclear etiology, often classified as a scleroderma-like syndrome
- Characterized by fibrosis of the skin and subcutaneous tissues, thickening of fascia, peripheral eosinophilia
- May have history of strenuous physical activity preceding onset
- Also seen in chronic GVHD.
- Reported in one case of Mycoplasma arginini infection

Presentation

- Severe pain and edema of extremities, which can quickly progress to fibrosis, causing a woody induration to the skin
- "Groove sign" – linear depressions where veins appear sunken in within indurated skin

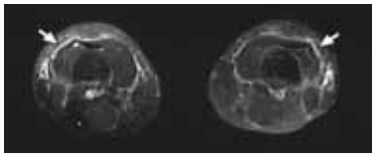
Clinical Photo

Sillo P, Pinter D, Ostorhazi E. Eosinophilic Fasciitis Associated with Mycoplasma Arginini infection. J Clin Microbiol. 2012 Mar;50(3): 1113-1117.

Eosinophilic Fasciitis

- Diagnosis: biopsy of fascia or thickening seen on MRI
- Laboratory values: eosinophilia, hypergammaglobulinemia, elevated ESR, pancytopenia. Normal ANA and complement levels
- Histology: Deep fascia 10-50 times normal width, with a patchy lymphocytic infiltrate and plasma cells

MRI Photo



Sillo P, Pinter D, Ostorhazi E. Eosinophilic Fasciitis Associated with Mycoplasma Arginini infection. J Clin Microbiol. 2012 Mar;50(3): 1113-1117.

Eosinophilic Fasciitis

- Differential diagnosis: systemic sclerosis, nephrogenic systemic fibrosis, eosinophilia-myalgia syndrome, scleromyxedema, Churg-Strauss syndrome
- Treatment: immediate treatment necessary to preserve function
  - Prolonged course of prednisone for 6-12 months
  - Hydroxychloroquine, cyclosporine or dapsone may also be used

References

- Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. Am J Clin Dermatol. 2012 Jun 1;13(3):191-211.
- Alavi A, Sajic D, Cenci FB, Ghazarian D, Rosenbach M, Jorizzo J. Neutrophilic dermatoses: an update. Am J Clin Dermatol. 2014 Oct;15(5):413-23.
- Anzaikou CL, Cohen PR. Acute febrile neutrophilic dermatosis (Sweet's syndrome). Curr Opin Hematol. 2013 Jan;20(1):26-35.
- Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology: Third Edition. Elsevier Limited: 2012.
- Brooklyn T, Dunnill G, Probert C. Diagnosis and treatment of pyoderma gangrenosum. BMJ. 2006 Jul 22;333(7560):181-4.
- Callen JP, Jackson JM. Pyoderma gangrenosum: an update. Rheum Dis Clin North Am. 2007 Nov;33(4):787-802.
- Coelho C, Souza M. The Dark Side of SAPHO syndrome. BMJ Case Report. 2011 Dec; bcr1120115997
- Cohen PR, Kurzrock R. Sweet's syndrome: a review of current treatment options. Am J Clin Dermatol. 2000;1(2):117-31.
- Cohen PR. Sweet's syndrome--a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis. 2007 Jul 26;2:34.
- Cohen PR. Neutrophilic dermatoses: a review of current treatment options. Am J Clin Dermatol. 2009;10(5):301-12.
- Hee Seon Lee, Chang Seo Jin. A Case of Eosinophilic Fasciitis presenting as Pitting Edema in Lower Extremities. Allergy Asthma Immunol Res. 2014 Mar; 6(2): 179-182.
- Hsieh FH. Hypereosinophilic Syndrome. Ann Allergy Asthma Immunol. 2014; 112:484-488.
- Jain S. Dermatology. First Edition. Springer Science + Business Media. 2012.
- Long H, Zhang G, Wang L, Lu Q. Eosinophilic Skin Diseases: A Comprehensive Review. Clinic Rev Allerg Immunol. 2015 April 16.
- Marzano AV, Ishak RS, Saibeni S, Crosti C, Meroni PL, Cugno M. Autoinflammatory skin disorders in inflammatory bowel diseases, pyoderma gangrenosum and Sweet's syndrome: a comprehensive review and disease classification criteria. Clin Rev Allergy Immunol. 2013 Oct;45(2):202-10.
- Powell FC, Collins S. Pyoderma gangrenosum. Clin Dermatol. 2000 May-Jun;18(3):285-93.
- Rochet NM, Chavan RN, Cappel MA, Wada DA, Gibson LE. Sweet syndrome: clinical presentation, associations, and response to treatment in 77 patients. J Am Acad Dermatol. 2013 Oct;69(4):557-64.
- Seyahi E, Yurdakul S. Behcet's Syndrome and Thrombosis. Mediterr J Hematol Infect Dis. 2011;3(1):e2010026
- Sillo P, Pinter D, Ostorhazi E. Eosinophilic Fasciitis Associated with Mycoplasma Arginini infection. J Clin Microbiol. 2012 Mar;50(3): 1113-1117.
- Wollina U. Pyoderma gangrenosum--a review. Orphanet J Rare Dis. 2007 Apr 15;2:19.

Cutaneous Manifestations of Systemic Disease

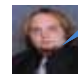
Beaumont Health - Botsford Hospital
Dermatology

Alexander Dane DO, Ivy DeRosa DO, Megan Furniss DO,
Summer Moon DO, Bryan Gray DO, Nichelle Arnold DO
Program Director: Annette LaCasse, DO

Beaumont Health

- Acrodermatitis enteropathica
  Acrodynia
  Acute febrile neutrophilic dermatosis
  Amyloidosis
  Angioedema
  Annular erythema
  Antiphospholipid syndrome
  Argyria
  Autoinflammatory syndromes
  Behçet disease
  Biotin-responsive dermatoses
  Blau syndrome
  Bloom syndrome
  Bowel bypass syndrome
  Calciphylaxis
  Carotenaemia
  Chilblains
  Chloracne
  Churg Strauss syndrome
  CINCA
  Compulsive skin picking
  Congenital adrenal hyperplasia
  Congenital erythropoeitic porphyria
  Connective tissue diseases
  Costello syndrome
  Crohn disease
  Cryoglobulinaemia
  Cushing syndrome
  Cutaneous markers of malignancy
  Cryopyrin-associated periodic syndromes
  Degos disease
  Dermatitis herpetiformis
  Dermatomyositis
  Diabetes
  Diabetic foot ulcers
  Down syndrome
  Drug eruptions
  Dysmorphophobia
  Ehler Danlos syndrome
  Eosinophilic fasciitis
  Erythema multiforme
  Erythema nodosum
  Erythropoeitic protoporphyria
  Familial cold autoinflammatory syndrome
  Familial Mediterranean fever
- Flushing
  Focal dermal hypoplasia
  Genital Crohn disease
  Glucagonoma
  Goltz syndrome
  Gorlin syndrome
  Gout
- Livedo reticularis
  Lupus erythematosus
  Lyme disease
  Majeed syndrome
  Marfan syndrome
  Mastocytosis
  McCune-Albright syndrome
  Menopause
  Metabolic syndrome
  Mevalonic aciduria
  Monogenic autoinflammatory syndromes
  Morphoea
  Mucinoses
  Muckle-Wells syndrome
  Myxoma syndrome
  Necrobiosis lipoidica
  Necrolytic migratory erythema
  Neurotic excoriations
  NOMID
  Orofacial Crohn disease
  Orofacialdigital syndrome type 1
  Orofacial manifestations of inflammatory bowel disease
  Panniculitis
  PAPA syndrome
  Periodic fever syndromes
  PFAPA syndrome
- Photosensitivity
  POEMS syndrome
  Polyarteritis nodosa
  Polymorphous eruption of pregnancy
  Porphyria cutanea tarda
  Pretibial myxoedema
  Prolidase deficiency
  Prurigo nodularis
  Proteus syndrome
  Pruritus
  Pseudoxanthoma elasticum
  Pyoderma gangrenosum
  Pyodermatitis-Pyostomatitis vegetans
  Reiter syndrome
  Reticular erythematous mucinosis
  Rheumatoid arthritis
  Rothmund-Thomson syndrome
  SAPHO syndrome
  Sarcoidosis
  Schnitzler syndrome
  Scleroderma (localised)
  Scleredema
  Scleromyxoedema
  Scurvy
  Sézary syndrome
  Sjögren syndrome
- Variegate porphyria
  Vasculitis
  Waldenström macroglobulinaema
  Wegener granulomatosis
  Wells syndrome
  Whipple disease
  Wilson disease
  Xanthomas
  Xeroderma pigmentosum

Wow! That's sure a lot of diseases!

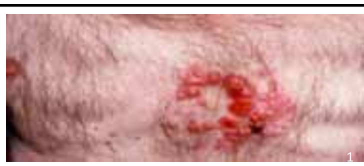


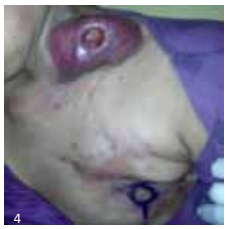
B. Gray

Cutaneous Manifestations of Systemic Disease

- Internal Malignancies
- Cardiovascular
- Pulmonary
- Rheumatic
- Gastrointestinal
- Renal
- Metabolic/Endocrine

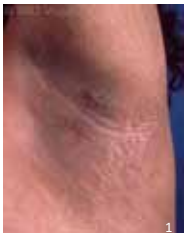
Internal Malignancies

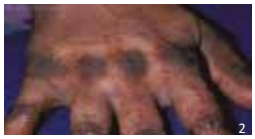




Metastatic Carcinoma

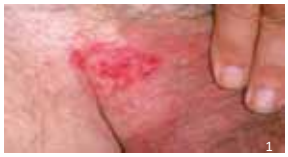
- Direct extensions or distant metastasis via lymphatic or hematogenous dissemination
- The most frequent primary tumors are carcinomas of the breasts, stomach, lungs, uterus, kidneys, ovaries, colon, or bladder.
- Approximately **1.0% to 4.5% of internal cancers metastasize to the skin.**
- Metastases from the **breast, lung, and genitourinary** system have a propensity for the **scalp**
- GI tract cancers often manifest on the skin of the **abdominal wall.**

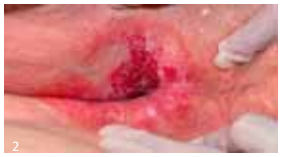




Acanthosis Nigricans

- Acanthosis nigricans has various subtypes relating to cause and/or location: obesity-associated, syndromic, acral, unilateral, familial, drug-induced, and malignant.
- Three common types: AN with maligancy, familial, insulin-resistant states/syndromes
- Assoc. conditions include: obesity, diabetes, polycystic ovarian syndrome (**PCOS**), **Cushing syndrome**, **HAIR-AN**, Atypical (palmar or mucosal) distributions or acute onset acanthosis nigricans may also be associated with malignancy (usually **gastrointestinal** adenocarcinoma).
- Tripe palms: (Lung CA); Tripe palms + AN: (Gastric CA)
- Associated drugs: Niacin, insulin, folate, estrogens, protease inhibitors

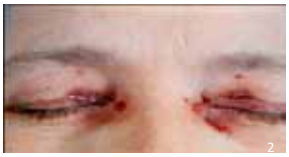




Extramammary Paget's (EMPD)

- Approximately a quarter of cases are associated with an underlying neoplasm, usually **adnexal apocrine carcinoma**, but cases of carcinoma of the prostate, urethra, cervix, vagina, endometrium, bladder, and Bartholin's glands have been described.
- **Perianal disease** is more frequently associated with an underlying carcinoma of the **rectum**.
- In **vulvar** EMPD 4–17% have an associated adnexal neoplasm, and some have a distant carcinoma of the breast, cervix, vagina, bladder, colon, rectum, ovary, liver, gallbladder, or skin.
- In **perianal** EMPD an underlying adnexal carcinoma occurs in 7–10% of cases, and a distant carcinoma of the rectum, stomach, breast, or ureter in 15–45%.
- In **penile/scrotal** EMPD has an associated carcinoma of the prostate, bladder, testicles, ureter, or kidney in 11% of cases.


1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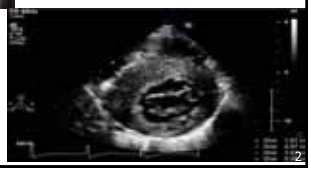
Primary Systemic Amyloidosis (PSA)

- **Multiple myeloma** is the most common association, but it is also seen with **Waldenstrom macroglobulinemia** and other **paraproteinemias**.
- Neurologic symptoms include a **sensory peripheral neuropathy**, presenting in a **stocking and glove distribution**. An "idiopathic" **carpal tunnel syndrome** can also occur.
- Cardiac **arrhythmias** and right sided **congestive heart failure** are common causes of death
- The diagnosis is confirmed by evaluation of the patient's serum and urine for immunoglobulin fragments and by amyloid stains or electron microscopy of the skin biopsies

Cardiovascular


1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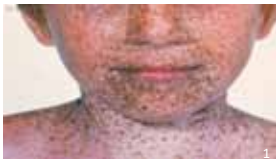
Leopard Syndrome

- Multiple Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth, sensorineural Deafness
- AD; **PTPN11** gene mutation leads to abnormal RAS/MAPK activation
- Most common cardiac abnormality is **hypertrophic cardiomyopathy**
  - Important to identify early as HOCM is most common cause of sudden cardiac death in young persons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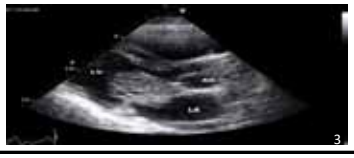
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Carney Complex

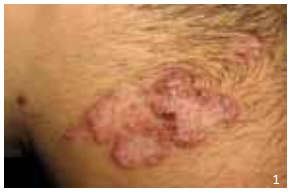
- Multiple neoplasia syndrome including skin findings (lentigines, blue nevi, café-au-lait spots, cutaneous fibromas/myxomas), endocrine overactivity/tumors (primary pigmented nodular adrenal hyperplasia), and visceral myxomas (cardiac)
- AD; **PRKAR1A** gene causes dysfunction of regulatory subunit of Protein Kinase A
- 80% of patients with **atrial myxoma** will present with co-existant or preceding **cutaneous myxoma**
- Early echocardiogram recommended to detect valvular obstruction and prevent stroke


1


2

Pseudoxanthoma Elasticum

- Hereditary disorder marked by abnormal calcification of elastic fibers. Findings include "**plucked chicken**" skin at flexural sites, retinal (**angioid streaks**), GI (**gastric artery aneurysm**), and CV (HTN, accelerated CAD, MVP) manifestations.
- AR; mutation in **ABCC6** gene
- Typically skin changes precede all other
- Important to control/eliminate cardiac r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Marfan's Syndrome

- AD: Caused by mutation in **fibrillin-1**, a component of extracellular matrices causing characteristic body habitus, hyperextensible joints, skeletal abnormalities, **upward** lens dislocation, and **aortic aneurysm**
- Skin findings include distensible skin, striae densa, and **elastosis perforans serpiginosa**
- Most commonly affected with **MVP** and **aortic root dilation**: at risk for AR, dissection, and rupture.

Pulmonary

Sarcoidosis

- Multi-organ granulomatous disease attributed to overactivity of cell mediated immunity
- Eitiology proposed to be autoimmune, environmental vs infectious
- Up to 1/3 of patients with systemic sarcoid will have skin lesions; typical lesions are red to brown papules and plaques on lips, nose, neck, upper trunk and extremities.
- **90% of patients WILL have lung involvement**.

Sarcoidosis

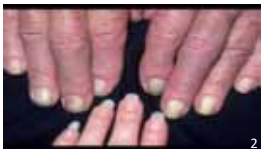
- Aveolitis and granulomatous infiltration of vessels, bronchioles.
- **Hilar lymphadenopathy** is commonly present though often **asymptomatic**
- End stage results in **honeycombing fibrosis**

Sarcoidosis

- Diagnosis is made with clinical and histological findings
- **Chest X-ray** recommended to allow for baseline and follow up
- High resolution **CT scans** differentiate fibrosis from inflammation
- **Pulmonary function tests** are helpful if patient becomes symptomatic

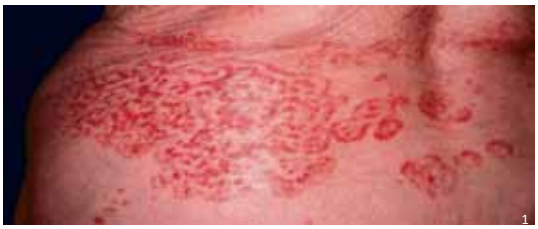
Yellow Nail Syndrome

- Pathogensis unknown, rare
- Triad includes **lymphedema, nail changes** and **respiratory tract involvement**
- Nails become hyperkeratotic, color from pale to dark yellow to green



Yellow Nail Syndrome

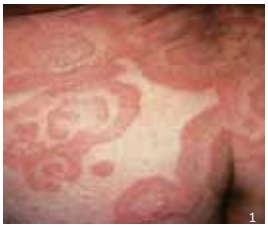
- Condition is associated with **chronic bronchitis, pleural effusions, bronchiectasis, sinusitis**
- Often involves all 20 nails
- Lunulae may be absent, inc longitudinal and transverse curvature
- Any patient you suspect needs Chest Xray and ENT eval
- TX: Treat the underlying disease! (Also Vit E and antifungals are helpful)



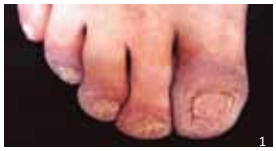
Erythema Gyratum Repens

- Figurate erythema with "Rings with in rings" pattern
- Migrates up to a **1 cm/day**
- Lesions are typically itchy and scaly
- Possible cross reactivity between tumor and cutaneous antigens

Erythema Gyratum Repens

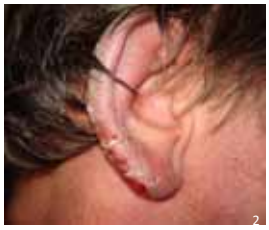


- **Paraneoplastic**
- Most commonly **associated with lung cancer**
- May occur 1 year before or following diagnosis.
- Thorough workup with chest Xray/CT scans are warranted!
- Tx underlying neoplasm



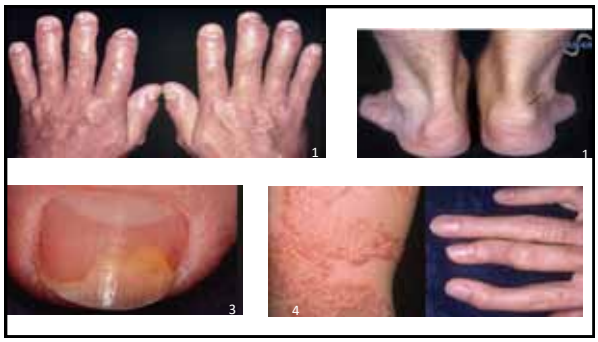
Acrokeratosis Paraneoplastica

- 'Bazex Syndrome'
- Nails most commonly present first. Brittle, hyper-keratotic and deform nail plate.
- Also noted are erythematous papules and plaques on acral areas, nose or **helices of ears**



- **Paraneoplastic** phenomenon most commonly **for upper aerodigestive tract cancers,** commonly **squamous cell cancer**.
- Detailed workup for neoplasms in larynx, pharynx and esophagus.

Rheumatic

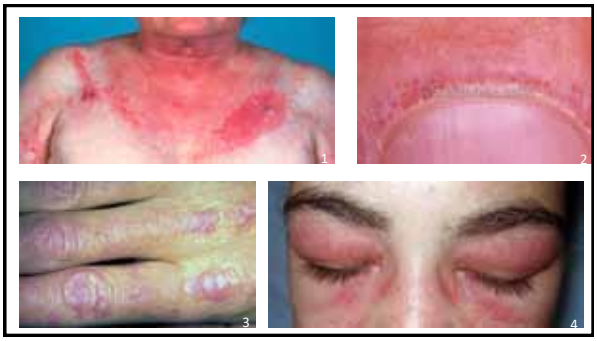


Psoriatic Arthritis

- Psoriatic Arthritis occurs in **5-30%** of patients with cutaneous psoriasis.
- In **10-15%** of patients symptoms of psoriatic arthritis appear before skin involvement.
- **Risk Factors** include early age of onset, female, polyarticular involvement, genetic predisposition, and radiographic signs of disease early on.
- Most commonly patients present with **rheumatoid factor negative, mono- and asymmetric oligoarthritis**
  - Affecting the small joints of the hands

Psoriatic Arthritis

- **Onycholysis** is more frequently associated with psoriatic disease.
- Associated with obesity, T2DM, HTN, dyslipidemia, non-alcoholic steatohepatitis, CVD and lymphoma
  - **CRP** is a predictor of CVD as well as joint inflammation.
- **HLA-B27** associated **spondylitis** and **sacroilitis** may have associated **IBD** and/or **uveitis**.
- **Early diagnosis** of psoriatic arthritis is important, as disease progression may result in loss of dextertity.

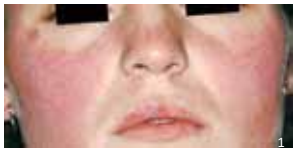


Dermatomyositis

- **Diagnose** with **triceps muscle biopsy,** EMG, MRI or U/S.
- **Internal disease** associations include:
  - **Interstitial fibrosis** occurs in **15-30%** of patients and is associated with **Anti-aminoacyl-tRNA synthetase** antibodies.
    - Amyopathic DM with rapidly progressive **interstitial lung disease** is associated with **Anti-CADM-140** antibodies.
  - **Cardiac disease** presents with **arrhythmia** or **conduction** defects and is associated **with Anti-SRP** antibodies

Dermatomyositis

- Risk of **malignancy** varies from **10-50%** and is highest within the first few years of disease.
  - Occurs most commonly in the **adult** and **amyopathic** subtypes.
  - **Anti-155/140** antibodies are associated with internal malignancy risk.
  - Lung and GI cancer are more common in men.
  - Ovarian and breast cancer are more common in women
- Recommendations: Evaluate for malignancy (chest/abdomen/pelvis CT) at baseline and at regular intervals for 2-3 yrs post diagnosis.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4

Systemic Lupus Erythematosus

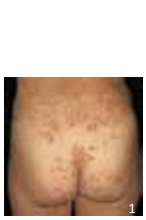
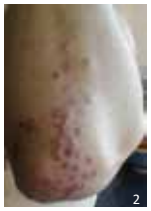
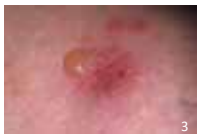
Need 4/11 for diagnosis

- **S**erositis (Pleuritis, Pericarditis)
- **O**ral Ulcers
- **A**NA
- **P**hotosensitivity
- **B**lood (Hemolytic anemia, leukopenia, lymphoma, thrombocytopenia)
- **R**enal (Proteinuria or cellular casts)
- **A**rthritis (non-erosisve)
- **I**mmunology abnormality ((anti-dsDNA, anti-sm, antiphopholipid)
- **N**eurological disorder (seizures or psyc
- **M**alar Rash
- **D**iscoid lesions.

Systemic Lupus Erythematosus

- **Associations**: HLA-DR2, HLA-DR3
- **Labs**: ANA with profile (anti-dsDNA, anti-sm), urinalysis, CBC with diff, platelet count, CMP, ESR, C3, C4.
- Must **exclude drug** induced systemic lupus erythematosis
  - Usually lacks renal disease or CNS symptoms
  - Hydralazine, procainamide, chlorpromazine, INH, quinidine, practolol, d-penicillamine, PUVA, minocycline

Gastrointestinal

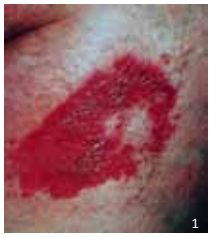
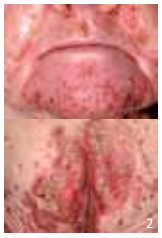





Dermatitis Herpetiformis, a.k.a. Duhrings Disease

- Strongly associated with celiac disease, **> 90% of those with DH have CD**
- HLA-DQ2 > HLA-DQ8
- Test of serum IgA **anti-tissue transglutaminase-2** and anti-gliadin antibodies, total serum IgA
- **Small bowel biopsy** is gold diagnostic standard, reveals **blunting** of the papillae
- Direct Immunoflorescence reveals **granular IgA in the dermal papillae**
- Increased risk of developing **Hashimoto's thyroiditis, non-Hodgkin's lymphoma and GI lymphomas**.


Acrodermatitis Enteropathica

- Congenital zinc deficiency
- **SLC39A4** zinc uptake protein defect
- Erosive, **recalcitrant**, seborrheic dermatitis-like rash in a periorificial, acral and **diaper region**, as well as **alopecia** and **diarrhea**
- Labs: **serum zinc** and **alkaline phosphatase**
- Acquired form has similar presentation, which is often precipitated by **weaning**

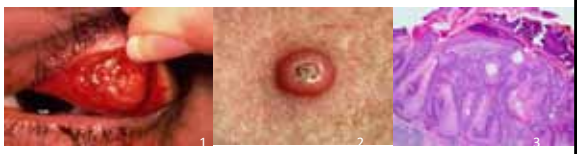



Necrolytic Migratory Erythema

- **Paraneoplastic**
- Affects skin around the mouth and extremities; but may also be found on the lower abdomen, buttocks, perineum, and groin
- Strongly associated with **glucagonoma** – syndrome includes: NME, weight loss, glossitis, and DM
- Other assoc: liver disease and intestinal malabsorption
- Work-up: glucagon levels, serum glucose, chromogranin A, LFTs, CBC
- Imaging: **CT/MRI/US abdomen** and **PET scan** as indicated by labs and symptoms

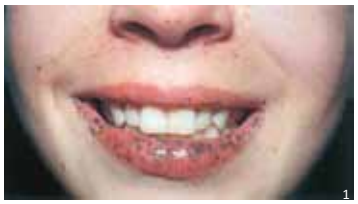
Lichen Planus

- May be the presenting sign of **Hepatitis C** infection
  - Erosive mucosal LP is MC in HCV
- Typically more difficult to treat than non-mucosal LP
- Associated with HBV immunization, primary biliary cirrhosis, medications and dental amalgams
- Oncogenic role of HCV driving oral LP → SCC debated, evidence is country specific



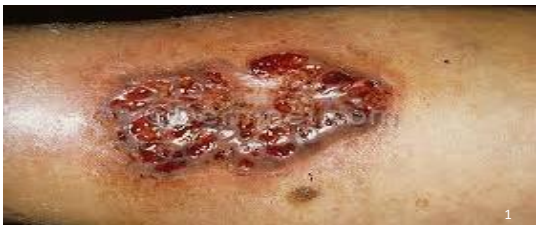
Muir-Torre Syndrome

- AD: DNA mismatch repair gene defect in **MSH2**, (MC) MLH1, also MLH3, PMS2, or MSH6.
- Characterized by **sebaceous adenomas, epitheliomas, and carcinomas** as well as **keratoacanthomas**
- Strongly associated with **GI carcinoma**
- Also associated with GU, breast, hematologic, and head & neck malignancies
- Sebaceous tumors can present prior to, concurrently with, or after the diagnosis of a visceral malignancy
- **Negative stains for MSH2 and/or MLH1** on histopathology
- Current recommendation for **colonoscopy q1-2 years**, monitor 1st degree relatives



Peutz-Jeghers a.k.a. Hereditary Intestinal Polyposis Syndrome

- AD, STK 11 gene → **GI polyposis and GI adenocarcinoma**
- Characterized by mucocutaneous lentigines with perioral, oral mucosal and acral distribution
- Screening for internal malignancy based on FHx
- Annual CBC, hemoccult, CA-125 (starting at 18yo) and CA-19-9 (starting at 25)
- Begin mammography in 3rd decade
- Other associated malignancies include ovarian, cervical, testicular, breast, and pancreatic



Pyoderma Gangrenosum

- **Inflammatory bowel disease: (MC)**
  - Ulcerative colitis
  - Crohn's Disease
- Arthritides:
  - Rheumatoid arthritis
  - Seronegative arthritis
- Hematological disease:
  - Myelocytic leukemia
  - Hairy cell leukemia
  - Myelofibrosis
  - Myeloid metaplasia
  - Monoclonal gammopathy
- Autoinflammatory Disease:
  - Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome)

- Other Autoimmune Disease:
  - SLE
  - Sjogren's Syndrome
  - Primary Biliary Cirrhosis
- Physiologic stress such as surgery
- Treatment may require systemic immunosuppression

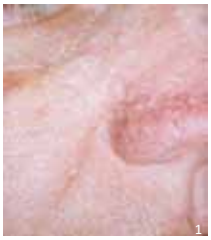
Renal




CD 34+

Nephrogenic Systemic Fibrosis

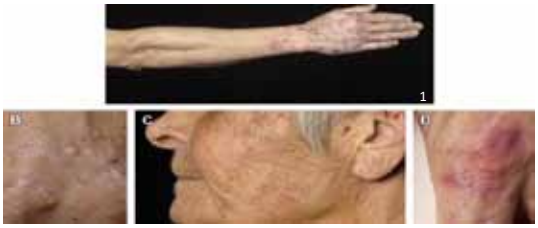
- **Renal injury** and exposure to a **gadolinium** based contrast agent → activation of circulating fibrocytes and creation of a highly active immune state
- Sleroderma-like skin changes including patterned erythematous plaques**, "cobblestoning,"** joint contractures, and marked induration/**Peau d'orange**
- Histopath demonstrates thickened collagen bundles, **"tram track"** arrangement, **CD34+**



Birt-Hogg-Dubé Syndrome

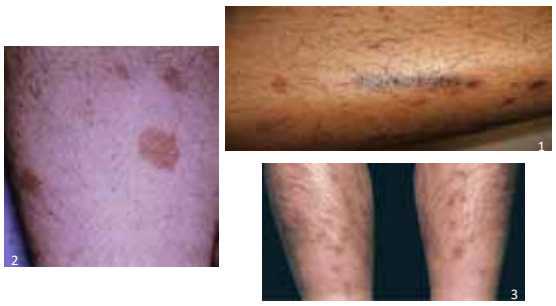
- AD, **BHD gene** encoding **folliculin** on 17p11.
- Growth of fibrofolliculomas, (acrochordons/trichodiscomas) and susceptibility to **malignant renal tumors** (chromophobe) as well as lung disease
  - Recurrent **spontaneous pneumothoraces**, bullous emphysema, lung cysts
- **Chest x-ray and abdominal CT,** screening of first degree relatives.

Metabolic/Endocrine



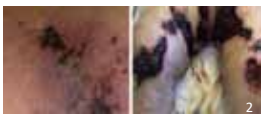
Porphyria Cutanea Tarda

- 75%-PCT-S, (sporadic variant) linked to liver disease
- Hepatic associations include: **Hep C, alcoholic liver disease, and hemochromatosis**
- Hepatic impairment of **uroprphyrinogen decarboxylase** (UROD) → photoreactive porphyrins
  - Porphyrins absorb at **400 – 410nm (Soret band)**
- Associated with DM, HIV, estrogen therapy, and exposure to polyhalogenated hydrocarbons, and hemodialysis
- Dx: **24 hour urine** for porphyrins and fecal studies
  - Ratio of Uroporphyrin:coproporphyrin is 3:1-5:1
  - Isocoproporphyrin in feces (pathognomonic)



Diabetic Dermopathy

- ↑ risk of neuropathy, retinopathy and nephropathy.
- **53% of patients also have CAD**
- Presents with multiple (> 4), well demarcated, atrophic, depressed, hyperpigmented macules on the shin of a patient with diabetes
- Must attempt to establish a diagnosis of diabetes or evaluate for complications of pre-existing illness



Calciphylaxis

- 1-4% of dialysis patients annually
- Mortality rate up to 80%
- Risk factors include: female sex, **ESRD**, hypophosphatemia, secondary hyperparathyroidism, hypercalcemia, calcium-based phosphate binders, obesity, diabetes, protein C and S deficiency, warfarin, liver disease, and systemic steroid use.
- Diagnosed by **full thickness biopsy adjacent to necrosis**
- Multidisciplinary approach: nephrology, endocrinology, dermatology, wound care, pain management, and nutrition.

Overview

- Internal Malignancies (cutaneous metastases, Paget's Dz., acanthosis nigricans, amyloidosis, paraneoplastic pemphigus, tripe palms)
- Cardiovascular disease (LEOPARD syndrome, Carney complex, PXE, Ehlers Danlos)
- Pulmonary disease (Sarcoidosis, Bazex Sign (acrokeratosis neoplastica), erythema gyratum repens, Yellow Nail Syndrome)
- Rheumatic disease (Psoriatic Arthritis, Lupus erythematosus, dermatomysositis)
- Gastrointestinal disease (DH, acrodermatitis enteropathica, necrolytic migratory erythema, Lichen planus, Muir-Torre, Peutz-Jeghers, pyoderma gangrenosum)
- Renal (NSF, Birt-Hogg-Dube)
- Metabolic/Endocrine (Porphyrias, Diabetic dermopathy, calcichylaxis)

Thank you!

References

- **Metastatic Carcinoma**
  Alcaraz I, Cerroni L, Rütten A, Kutzner H, Requena L. Cutaneous metastases from internal malignancies: a clinicopathologic and immunohistochemical review. *Am J Dermatopathol*. 2012 Jun;34(4):347-93
  (1), (2) http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do? moduleId=11&diagnosisId=51257
  (3), (4) Dane, A. Medical Mission, Iquitos, Peru. 2013
- **Acanthosis Nigricans**
  Braverman IM. Skin manifestations of internal malignancy. *Clin Geriatr Med*. 2002 Feb;18(1):1-19
  (1), (2), (3) http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do? moduleId=7&diagnosisId=51010
- **Extramammary Paget's Disease**
  Mengjun B, Zheng-Qiang W, Tasleem MM. Extramammary Paget's disease of the perianal region: a review of the literature emphasizing management. *Dermatol Surg*. 2013 Jan;39(1 Pt 1):69-75
  Ibrahim SF, Grekin RC, Neuhaus IM. Mammary and extramammary Paget's Disease. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York, NY: McGraw-Hill; 2012:1372-1376.
  (1), (2) http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do?moduleId=7&diagnosisId=52100
- **Primary Systemic Amyloidosis**
  Lachmann HJ, Hawkins PN. Amyloidosis and the skin. In: Fitzpatrick TB, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York, NY: McGraw-Hill; 2008:1257-1265
  Xavier SD, Bussoloti IF, Müller H. Macroglossia secondary to systemic amyloidosis: case report and literature review. *Ear Nose Throat J*. 2005 Jun;84(6):358-61.
  (1), (2) http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do?moduleId=7&diagnosisId=52988
- **LEOPARD Syndrome**
  Sei-Ichiro M, Yoko Y, Sachiko O, et al. Pathogenesis of Multiple Lentigines in LEOPARD syndrome with PTPN11 Gene Mutation. *Acta Derm Venerol*. 2015
  Tidyman WE, Rauen KA. Noonan, Costello and cardio-facio-cutaneous syndromes: dysregulation of the Ras-MAPK pathway. Expert Rev Mol Med 2008; 10: e37.
  (1) http://www.scielo.br/scielo.php?pid=S0365-05962006000600014&script=sci_arttext&tlng=en
  (2) http://www.bsecho.org/hypertropic-cardiomyopathy/
- **Carney Syndrome**
  Kaltsas G, Kanakis G, Chrousos G. Carney's Complex. [Updated 2013 Jul 31]. In: De Groot LJ, Beck-Peccoz P, Chrousos G, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279117/
  Espiard S, Bertherat J. Carney complex. Front Horm Res, 2013. 41: p. 50-62.
  (1) http://www.visualdx.com/visualdx/visualdx6/getZoomImage.do moduleId=10&diagnosisId=50724&imageIndex=1
  (2) http://emedicine.medscape.com/article/160000-clinical
  (3) http://ehjcimaging.oxfordjournals.org/content/9/3/430
- **Pseudoxanthoma Elasticum**
  Li Y, Cui Y, Zhao H, Wang C, Liu X, Han J. Pseudoxanthoma elasticum: A review of 86 cases in China. *Intractable & Rare Diseases Research*. 2014;3(3):75-78. doi:10.5582/irdr.2014.01011.
  Li Q, Jiang Q, Pfendner E, Váradi A, Uitto J. Pseudoxanthoma elasticum: Clinical phenotypes., molecular genetics and putative pathomechanisms. Exp Dermatol. 2009; 18:1-11
  (1) http://www.aocd.org/?page=PseudoxanthomaElast
  (2) http://www.ohiolionseyeresearch.com/eye-center/glossary/angioid_streaks/
- **Marfan's Syndrome**
  Frydman M. The Marfan syndrome. *Isr Med Assoc J*. 2008 Mar;10(3):175-8. PubMed ID: 18494226
  Ammash NM, Sundt TM, Connolly HM. Marfan syndrome-diagnosis and management. *Curr Probl Cardiol*. 2008 Jan;33(1):7-39. PubMed ID: 18155514
  (1) http://escholarship.org/uc/item/5ts1v967
  (2) http://80.36.73.149/almacen/medicina/oftalmologia/enciclopedias/duane/pages/v1/v1c073.html

- **Sarcoidosis**

  Bolognia, J. Sarcoidosis, Bolognia, 3rd Edition. 2012.

  (1) http://www.visualdx.com/visualdx/visualdx6/getZoomImage.do?moduleId=7&diagnosisId=52292&imageIndex=35

  (2) https://expertconsult.inkling.com/read/dermatology-bolognia-jorizzo-schaffer-3rd/chapter-100/erythema-nodosum

  (3) http://www.gpnotebook.co.uk/simplepage.cfm?ID=93978694

- **Yellow Nail Syndrome**

  Kurin M, Wiesen J, Mehta AC2. Yellow nail syndrome: A case report and review of treatment options. Clin Respir J. 2015 Aug 10. doi: 10.1111/crj.12354.

  Lotfollahi L, Abedini A et al. Yellow Nail Syndrome: Report of a Case Successfully Treated with Octreotide. Tanaffos. 2015;14(1):67-71.

  (1) http://www.visualdx.com/visualdx/visualdx6/getZoomImage.do?moduleId=19&diagnosisId=52549&imageIndex=0

  (2-3) http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do?moduleId=19&diagnosisId=52549

- **Erythema Gyratum Repens**

  Bolognia, J. et al. Erythema Gyratum Repens. Bolognia, 3rd Edition. 2012.

- **Acrokeratosis Paraneoplastica**

  Robert M, Gilabert M, et al. Bazex syndrome revealing a gastric cancer. Case Rep Oncol. 2014 Apr 30;7(1):285-7. doi: 10.1159/000362787

  Rodriguez A jr, Gresta L, et al. Bazex syndrome. An Bras Dermatol. 2013 Nov-Dec;88(6 Suppl 1):209-11. doi: 10.1590/abd1806-4841.20132488.

  (1) https://expertconsult.inkling.com/read/dermatology-bolognia-jorizzo-schaffer-3rd/chapter-53/figure-53-7

  (2) http://www.vgrd.org/archive/cases/2008/bazex/bazex.htm

  (3) http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do?moduleId=19&diagnosisId=51170

- **Psoriatic Arthritis**

  Nestle FO, Kaplan DH, Barker J: Psoriasis. N Engle J Med. 2009;361;496-509.

  Tobin AM, Veale DJ, Fitxgerald O, et al: Cardiovascular Disease and Risk Factors in Patients with Psoriasis and Psoriatic Arthritis. The journal of Rheumatology 2010;37:7

  (1)http://www.physio-pedia.com/Psoriatic_Arthritis

  (2)http://www.medscape.com/viewarticle/750045_5

  (3)http://www.medicinenet.com/psoriatic_arthritis_pictures_slideshow/article.htm

  (4)http://www.medicinenet.com/psoriatic_arthritis/article.htm

- **Dermatomyositis**

  Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV: Interstitial lung disease in polymyositis and dermatomyositis. Clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis. 141:727-733 1990

  Askari AD, Huettner TL: Cardiac abnormalities in polymyositis/dermatomyositis. Semin Arthritis Rheum. 12:208-219 1982

  Chow WH, Gridley G, Mellemkjaer L, et al.: Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. Cancer Causes Control. 6:9-13 1995

  Hill CL, Zhang Y, Sigurgeirsson B, et al.: Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 357:96-100 2001.

  (1) http://images.rheumatology.org/viewphoto.php?imageId=2862868&albumId=75696

  (2) http://Dermnet.com

  (3) http://hardinmd.lib.uiowa.edu/dermnet/dermatomyositis6.html

  (4) http://www.dermrounds.com/photo/dermatomyositis-heliotrope-2/next?context=user

- **Systemic Lupus Erythematous**

  Callen JP: Collagen vascular diseases. J Am Acad Dermatol. 51:427-439 2004

  Englert HJ, Hawkes CH, Boey ML, et al.: Degos' disease: association with anticardiolipin antibodies and the lupus anticoagulant. Br Med J (Clin Res Ed). 289:576 1984

  Frances C,Piette JC: Cutaneous manifestations of Hughes syndrome occurring in the context of lupus erythematosus. Lupus. 6:139-144 1997

  (1) www.accessmedicine.com

  (2) http://www.hss.edu/professional-conditions_in-depth-topic-review-systemic-lupus-erythematosus.asp

  (3) http://ddline.info/diseases/raynauds-phenomenon

  (4) http://medicalpicturesinfo.com/discoid-lupus-erythematosus/

- **Dermatitis Herpetiformis**

  Bolognia J, J Jorizzo, J Shaffer, *et al.*, Dermatology, 3rd edition, Chapter 31
  (1) http://www.derm101.com/therapeutic/dermatitis-herpetiformis-2/clinical-case/
  (2) http://www.doctortipster.com/1999-dermatitis-herpetiformis.html
  (3) http://www.derm101.com/therapeutic/dermatitis-herpetiformis-2/clinical-case/

- **Acrodermatitis Enteropathica**

  Bolognia J, J Jorizzo, J Shaffer, *et al.*, Dermatology, 3rd edition, Chapter 51
  Küry, S; Dréno, B; Bézieau, S; Giraudet, *et al.* Jp (July 2002). "Identification of SLC39A4, a gene involved in acrodermatitis enteropathica". *Nature Genetics* **31** (3): 239–40. doi:10.1038/ng913. PMID 12068297.
  (1) http://www.riversideonline.com/health_reference/articles/dg00023.cfm

- **Necrolytic Migratory Erythema**

  James W, T Berger, D Elston, Andrews' Diseases of the Skin: Clinical Dermatology, 11th edition, Chapter 22
  (1) http://www.medscape.com/viewarticle/487806
  (2)http://dermnetnz.org/systemic/img/s/glucagon1-s.jpg

- **Lichen Planus**

  Nagao Y, Kameyama T, Sata M: Hepatitis C virus RNA detection in orallichen planus tissue [letter]. *Am J Gastroenterol.* 93:850 1998
  Carrozzo M[1], Scally K[1]. World J Gastroenterol. Oral manifestations of hepatitis C virus infection.
  http://www.uptodate.com/contents/lichen-planus
  (1) http://www.ijdr.in/article.asp?issn=0970-9290;year=2011;volume=22;issue=6;spage=827;epage=834;aulast=Hiremath

- **Muir-Torre Syndrome**

  Bolognia J, J Jorizzo, J Shaffer, *et al.*, Dermatology, 3rd edition, Chapter 63
  Curry ML, Eng W, Lund K, *et al.*, Muir-Torre syndrome: role of the dermatopathologist in diagnosis. *Am J Dermatopathol.* 26:217-221 2004
  (1) http://www.eyeplastics.com/sebaceous-cell-carcinoma-malignant-eyelid-lesions-eyelid-tumors-cancer.html
  (2) https://www.dermquest.com/image-library/image/5044bfcfc9726716cd621f0
  (3)http://skinpathologyatlas.com/tumors/sebaceousglands/sebaceous-adenoma.htm

- **Peutz-Jeghers**

  Bolognia J, J Jorizzo, J Shaffer, *et al.*, Dermatology, 3rd edition, Chapter 53
  https://raradiseases.org/rare-diseases/peutz-jeghers-syndrome
  (1) http://www.anatomybox.com/peutz-jeghers-syndrome/
  (2) https://www.studyblue.com/notes/note/n/e1-dermatology-pt-ii/deck/3719025

- **Pyoderma Grangrenosum**

  Brooklyn, Trevor; Giles Dunnill; Chris Probert (2006). "Diagnosis and treatment of pyoderma gangrenosum". *British Medical Journal* **333**: 181–184.
  http://www.ncbi.nlm.nih.gov/pubmed/26253362
  (1) http://www.dermnet.com/images/Pyoderma-Gangrenosum

- **Nephrogenic Systemic Fibrosis**

  Kribben A, Witzke O, Hillen U, Barkhausen J, Dual AE, Erbel R, Nephrogenic systemic fibrosis. J Am Coll Cardiol 2009;53:1621-8.
  Tammaro A, Narcisi A, Tuchinda P, Sina B, Nephrogenic systemic fibrosis following gadolinium administration. Cutis 2015;96:E23-25.
  (1) Girardi M, Kay J, Elston D, LeBoit PE, Abdu-Affa A, Cowper SE, Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. J Am Acad Dermatol 2011;65:1095-106.

- **Birt-Hogg-Dubé**

  Alvaz O, Berkman S, Middelton L, Linehan MW, DiGiovanna JJ, Cowen EW, Comedonam and cystic fibrofolliculomas in Birt-Hogg-Dube Syndrome. JAMA dermatol. 2015;151:770-74.
  Vernooij M, Claessens T, Luijten M, van Steensel MAM, Coull BJ, Birth-Hogg-Dube syndrome and the skin. Familial cancer 2013;12:381-85.
  (1) Vincent A, Farley M, Chan E, James WD, Birt-Hogg-Dube syndrome: a review of the literature and the differential diagnosis for firm facial papules. J Am Acad Dermatol 2003;49:698-705.
  (2) Lebar EM, Koopmans AK, Gille JJ, van Os TA, Vittoz GG, David EF, et al, Birt-Hogg-Dubé Syndrome: Clinical and Genetic Studies of 20 Families. Journal of investigative Dermatology 2008;128:45-49.

- **Porphyria cutanea tarda**

  Robles-Mendez JC, et al. Skin manifestations of chronic kidney disease. Actas Dermosi- filiogr. 2015. http://dx.doi.org/10.1016/j.ad.2015.05.007 - Article in Press.
  Andersen J, Gjengedal E, Sandberg S, Råheim M. A skin disease, a blood disease or something in between? An exploratory focus group study of patients' experiences with porphyria cutanea tarda. The British Journal of Dermatology. 2015;172(1):223-229.
  (1)Danja Schulenburg-Brand, Ruwani Katugampola, Alexander V. Anstey, Michael N. Badminton, The Cutaneous Porphyrias. Dermatologic Clinics 2014;32(3):369-84.

- **Diabetic dermopathy**

  (1) Morgan AJ, Schwartz RA, Diabetic dermopathy: A subtle sign with grave implications. J Am Acad Dermatol. 2008;58:447-51.
  (2) McCash S, Emanuel PO, Defining diabetic dermopathy. J. Dermatol 2011;38 (10): 988-92
  (3) Duff M, Demidova O, Blackburn S, Shubrook J. Cutaneous Manifestations of Diabetes Mellitus. *Clinicall Diabetes* [serial online]. 2015 Winter 2015;33(1):40-48.

- **Calciphylaxis**

  (1) Arseculeratne G, Evans AT, Morley SM. Calciphylaxis--a topical overview. *J Eur Acad Dermatol Venereol*. 2006 May; 20(5):493-502
  (2) Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, Calciphylaxis: Risk factors, diagnosis, and treatment, Am J Kidney Dis 2015;66(1):133-46.
  (3) Auriemma M, Carbone A, Liberato DL, Cupaiolo A, Caponio C, De Simone C, et al, Treatment of cutaneous calciphylaxis with sodium thiosulfate: two case reports and a review of the literature. Am J Clin Dermatol. 2011;12(5):339-46

October 18, 2015

A Review of Alopecia

Saint Joseph Mercy Hospital, Ann Arbor, Michigan

Disclosures

No financial relationships exist with commercial interests

Saint Joseph Mercy Dermatology Residency

Outline

1. Non-cicatricial alopecia
   - Androgenic alopecia
   - Telogen effluvium
   - Trichotillomania
   - Alopecia areata
2. Cicatricial alopecia
   - Central centrifugal cicatricial alopecia
   - Lichen planopilaris
   - Discoid lupus
   - Acne keloidalis
   - Dissecting cellulitis
   - Folliculitis decalvans
   - Pseudopelade of Brocq
3. Comparative Review of Dermatopathology

NON-CICATRICIAL ALOPECIA

Androgenic Alopecia (Male/Female Pattern Hair Loss)

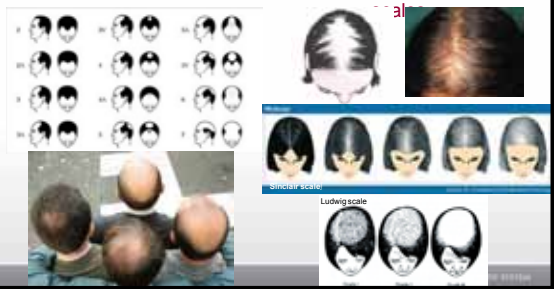
- Epidemiology: 80% of Caucasian men and 50% of women affected by age 70
- Hereditary
- Pathogenesis:
  - Testosterone ---(**5α-reductase**)---> Dihydrotestosterone (DHT)
  - **Type I 5α-reductase**: sebaceous glands and liver
  - **Type II 5α-reductase**: scalp, beard, and chest hair follicles, liver, prostate

– DHT leads to miniaturized hair follicles and hair shafts (terminal → vellus)

Clinical Presentation and Staging

Men: Hamilton-Norwood scale

Women: Sinclair/Ludwig/Olsen scale

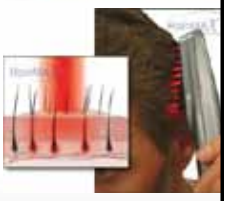


Androgenic Alopecia Treatment

- Topical minoxidil (2% or 5%)
- Finasteride
  - **Type II 5α-reductase inhibitor**
  - 1 mg daily
  - Pregnancy Category X
  - Stops hair loss in 90% of men for at least 5 years; hair regrows in 65% of cases
- Dutasteride
  - **Type I and II 5α-reductase inhibitor**
  - 0.5mg/day
  - More effective than Finasteride
  - Pregnancy Category X
- Women
  - Topical minoxidil
  - OCPs
  - Spironolactone
  - Finasteride 2.5 or 5mg daily (extreme caution if child bearing potential)
- Surgical Treatment options
  - Hair transplantation
  - Scalp reduction

Androgenic Alopecia Treatment

- Camouflage techniques
  - Hair pieces
  - Wigs
  - Creative styling
  - Hair dyes/Spray on hair/Hair fibers
- New and emerging treatments
  - Platelet rich plasma (PRP)
    - More studies needed to evaluate mechanism
  - Laser combs
    - 655 nm
    - Promising results in literature
    - Safe with few adverse side effects

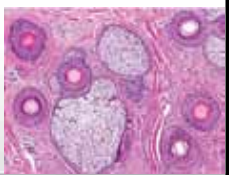


Telogen Effluvium

- Pathogenesis:
  - Premature conversion of anagen hairs to telogen hairs secondary to a precipitating event/trigger
- Common triggers:
  - Surgery, fever, medications
  - Crash dieting, iron deficiency
  - Papulosquamous disease affecting scalp
  - Thyroid disease
  - Pregnancy (2-3 months after delivery)
  - Severe emotional distress
- Chronic form with no precipitating factors
- Clinical Presentation:
  - Increased shedding of entire scalp (150-400 hairs/day)
  - Positive hair pull test (>10% club hairs)
  - Physician may not appreciate a decrease in hair density, while patient may complain of noticeably thinner hair

Telogen Effluvium

- Trichoscopy:
  - Empty follicles, short regrowing hairs of normal thickness
- Diagnosis:
  - Confirmed by >20% telogen hairs on biopsy
- Treatment:
  - Identify and avoid trigger
  - Check TSH, ferritin level
  - If drug induced, d/c drug
  - Reassurance, usually remits in 3-6 mos



Trichotillomania

- Classified under American psychiatric association's DSM-V as an "obsessive-compulsive disorder"
- Epidemiology
  - MC in girls <10
- Etiology
  - Habitual hair pulling
- Clinical presentation
  - Irregular patches of alopecia with hairs of varying lengths
  - Scalp, eyebrows, eyelashes or pubic hair
  - Uninvolved areas of scalp appearing completely normal
  - Trichophagia: chewing & swallowing of hairs →trichobezoars

Trichotillomania

- Diagnosis made clinically
- Treatment
  - Behavior modification
  - Psychotherapy
  - SSRIs
  - N-acetylcysteine
    - Increases glutamate concentration → reduced compulsive behavior

Alopecia Areata

- Epidemiology
  - Most common in children and young adults
- Etiology/pathophysiology
  - Th1-mediated autoimmune condition
    - IL-2, IFN-γ and TNF-α
  - Early onset/familial clustering
    - HLA-DR4, -DR11, -DQ7
- Associations
  - Thyroid disease, vitiligo, type 1 diabetes mellitus, pernicious anemia, systemic lupus
- Clinical presentation
  - Smooth round patches (1-5 cm) of hair loss
  - Exclamation point hairs

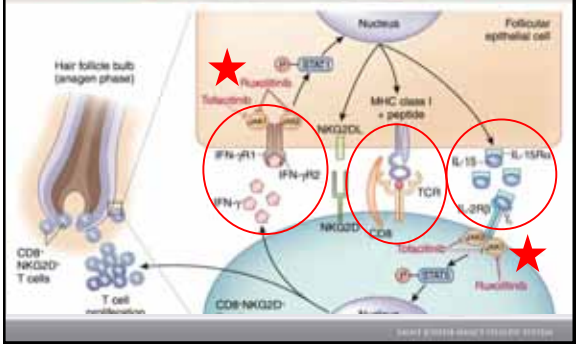
Alopecia Areata Subtypes

- Extent of involvement
  - Alopecia patchy (transient/persistent)
    - Hair loss in patches for < or > 6 months respectively
  - Alopecia totalis
    - Complete loss of scalp hair
  - Alopecia universalis
    - Complete loss of scalp & body hair
- Pattern of hair loss
  - Ophiasis
    - Band like hair loss on peripheral temple/occiput
  - Sisaipho
    - Inverse ophiasis
  - Diffuse
    - Generalized thinning
  - Linear

Alopecia Areata

- Treatment
  - First line
    - Intralesional steroids
    - Topical immunotherapy
  - Second line
    - Topical sensitizers, corticosteroids, prostaglandin analogues, minoxidil and retinoic acid
    - Camouflage
    - PUVA
  - New and emerging therapies
    - Janus kinase inhibitors (ruxolitinib, tofacitinib)

Inhibition of Janus Kinases in Alopecia Areata



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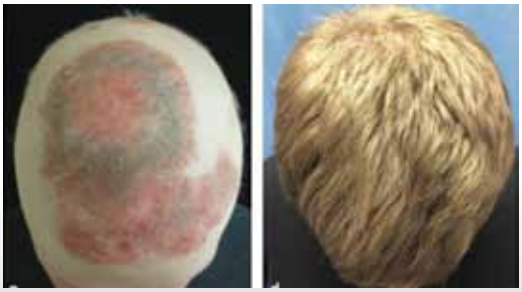


CICATRICIAL ALOPECIA

Central Centrifugal Cicatricial Alopecia (CCCA)

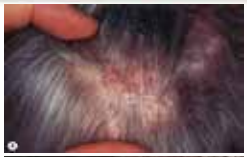
- Epidemiology
  - 3:1 female to male ratio
  - Most common form of scarring alopecia in African-Americans
- Pathogenesis
  - Hypothesized secondary to premature desquamation of the inner root sheath
  - Exacerbated by chemical hair relaxers
- Clinical presentation
  - Pruritus and tenderness
  - Centered on the vertex of the scalp, gradually expands centrifugally
  - Polytrichia: Multiple hair shafts emerging from one ostia
  - Inflammation in peripheral zone

Central Centrifugal Cicatricial Alopecia (CCCA)

- Treatment
  - Discontinuation of traumatic hairstyling
  - Corticosteroids
    - Topical and intralesional
  - Oral antibiotics
    - Tetracycline family
- New and emerging therapy
  - Hair transplantation

Lichen Planopilaris

- Epidemiology
  - F > M
  - Caucasian > African
- Pathogenesis
  - Unknown
- Clinical presentation
  - Variable pattern
  - Pruritus and tenderness often present
  - Scattered foci of partial hair loss w/ perifollicular erythema, follicular spines and scarring
  - >50% associated with cutaneous or oral lichen planus



Lichen Planopilaris

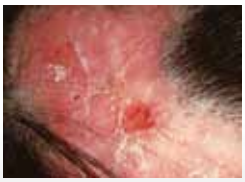
- LPP clinical patterns
  - Frontal fibrosing alopecia
  - Graham Little Piccardi syndrome

Lichen Planopilaris

- Treatment
  - Often resistant to therapy
  - Corticosteroids
    - Topical, intralesional and oral
  - Antimalarials
  - Anecdotal
    - Cyclosporine, mycophenolate mofetil, systemic retinoids, or low-dose methotrexate
- New and emerging treatment
  - Pioglitazone 15mg daily
    - PPAR gamma agonist

Discoid Lupus

- Epidemiology
  - Discoid lesions may be isolated or in association with systemic lupus
- Pathogenesis
  - Photosensitive disorder → cytotoxic keratinocyte damage
- Clinical Presentation
  - Follicular plugging
  - Central atrophic scarring
  - Peripheral hyperpigmentation and erythema
- Trichoscopy
  - Follicular red dots
    - Corresponds to dilated vessels, extravasated RBCs, and keratin plugs



Discoid Lupus

- Treatment
  - Photoprotection
  - Corticosteroids
    - Topical, intralesional and oral
  - Antimalarials
  - Anecdotal
    - Cyclosporine, mycophenolate mofetil, systemic retinoids, or low-dose methotrexate
- New and emerging treatments
  - Tacrolimus lotion 0.3%
    - Used as adjunct to antimalarials
    - Hair regrowth was seen over 3 month period
  - Imiquimod cream 0.5%
    - Applied 3x a week every other week for 2 months

Acne Keloidalis Nuchae

- Most common in African American men, Hispanics, Asians
  - 20:1 male to female
- Etiology unknown
  - No genetic factors identified
  - Bacterial infection, ingrown hairs not implicated
- Clinical
  - Posterior scalp and neck
  - Follicular pustules→ firm, dome shaped papules → smooth keloidal plaques

Acne Keloidalis Nuchae

- Treatment
  - Prevention
    - Avoidance of mechanical irritation to the posterior hairline
  - Tretinoin gel
  - Topical and/or systemic antibiotics
  - ILS corticosteroids
- New and Emerging
  - Targeted UVB therapy
    - Decreased mean lesion count from 14.8 to 7.0 after 16 weeks

Dissecting Cellulitis

Perifollicullitis capitis abscedens et suffodiens

- Epidemiology
  - Black males ages 20-40
- Pathogenesis
  - Follicular occlusion
- Clinical Presentation
  - Pustules, nodules, abscesses and sinuses on the scalp
  - Evolves into cicatricial alopecia
  - Secondary *Staph aureus* infection

Dissecting Cellulitis

- Treatment
  - Incision/excision and drainage
    - No effect on disease progression
  - Topical antibiotics
  - Intralesional corticosteroids
  - Oral antibiotics: doxycycline and rifampin
    - Moderate improvement with relapse upon discontinuation
  - Isotretinoin (0.5-0.8 mg/kg/day)
    - Complete remission within 3 months in 92%, but frequent relapses after discontinuation
- New and emerging treatment
  - Adalimumab 40 mg every 2 weeks
    - Symptoms relieved within 8 weeks, frequent relapses

Folliculitis Decalvans

- Epidemiology
  - Young male adults
- Pathogenesis
  - Altered host response to *Staph aureus*
- Clinical
  - Pain, itching, burning
  - Early: follicular papules
  - Late: crops of pustules with central scarring
- Treatment
  - Topical clindamycin, mupirocin
  - Tetracyclines
  - Oral clindamycin + rifampin

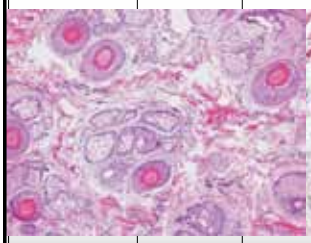
Pseudopelade of Brocq

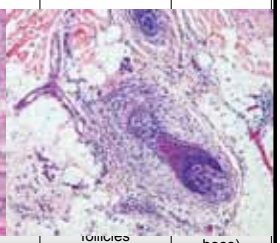
- Epidemiology
  - Rare; typically Caucasian adults
- Etiology
  - Likely represents the end-stage scarring alopecia (LPP, DLE, etc)
  - Diagnosis of exclusion!
- Clinical presentation
  - "Footprints in the snow"
  - Irregularly shaped, widely distributed patches
  - Hypopigmentation, atrophy
  - No follicular hyperkeratosis or perifollicular inflammation

DERMATOPATHOLOGY

Dermatopathology: Non-Scarring Alopecias

	Androgenic	Telogen Effluvium	Trichotillomania	Alopecia Areata

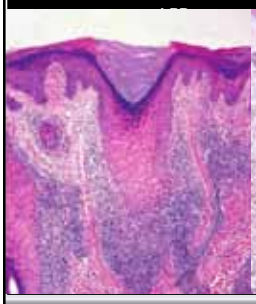




			follicles	bees)

Dermatopathology: Scarring Alopecias

		Dissecting



Summary

1. Non-cicatricial alopecia
   - Androgenic alopecia
   - Telogen effluvium
   - Trichotillomania
   - Alopecia areata
2. Cicatricial alopecia
   - Central centrifugal cicatricial alopecia
   - Lichen planopilaris
   - Discoid lupus
   - Acne keloidalis
   - Dissecting cellulitis
   - Folliculitis decalvans
   - Pseudopelade of Brocq
3. Comparative Review of Dermatopathology

References

- Amato L, Mei S, Massi D. Cicatricial alopecia; a dermatopathologic and immunopathologic study of 33 patients (pseudopelade of brocq is not a specific clinico-pathologic entity). Int J Dermatol. 2002;41:8-15.
- Bolduc, C. Alopecia Areata treatment-Corticosteroid injection. *Medscape*. 2015. Retrieved from: http://img.medscapestatic.com/pi/meds/ckb/89/27989tn.jpg.
- Bolognia, J. "Alopecias." Dermatology. 3rd ed. Vol. 1. Philadelphia: Elsevier Saunders, 2012. 1105-07.
- Blume-Peytavi, U, Hillmann K, Dietz E, et al. A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenic alopecia in women. *J Am Acad Dermatol* 2011 Dec;65(6):1126-1134.e2.
- Callender VD, Lawson CN, Onwudiwe OC. Hair transplantation in the surgical treatment of central centrifugal cicatricial alopecia. *Dermatol Surg*. 2014;40(10):1125-1130.
- Divito, S. and T. Kupper. Inhibiting Janus kinases to treat alopecia areata. *Nature*. 2014;20:9:989-990.
- Elder, D. Lever's Histopathology of the Skin. 11th ed. Philadelphia: Wolters Kluwer, 2015. 329-33.
- Gkini MA, Kouskoukis AE, Tripsianis G, et al. Study of platelet-rich plasma injections in the treatment of androgenetic alopecia through an one-year period. *J Cutan Aesthet Surg*. 2014 Oct-Dec;7(4):213-9
- Gubelin H, Barboza M, Tsai TF, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. *J Am Acad Dermatol*. 2014 Mar;70(3):489-498.e3
- Ioffreda M. Inflammatory diseases of hair follicles, sweat glands, and cartilage. In: Elder D, Elenitsas R, Johnson B, et al, eds. Lever's Histopathology of the Skin. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
- James, W. Berger, T. and D. Elston. Diseases of the Skin Appendages. *Andrews Disease of the Skin Clinical Dermatology*. 2011;11:741-743.
- Madu P, Kundu RV. Follicular and Scarring Disorders in Skin of Color: Presentation and Management. *Am J Clin Dermatol*. 2014;15:307-321.
- Mahadevia, B. Images of Alopecia areata-totalis and universalis. *Goodbyehairloss*. Retrieved from: http://goodbyehairloss.blogspot.com/2010/03/alopecia-areata.html.

References

- Mesinkovska NA, Tellez A, Dawes D, Piliang M, Bergfeld W. The use of oral pioglitazone in the treatment of lichen planopilaris. J Am Acad Dermatol. 2015. 72(2):355-6.
- Milam E, Ramachandran S, Franks A. Treatment of Scarring Alopecia in Discoid Variant of Chronic Cutaneous Lupus Erythematosus with Tacrolimus Lotion, 0.3%. JAMA Dermatol. 2015. Web. 29 July 2015.
- Leavitt M, Charles G, Heyman E, et al. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: A randomized, double-blind, sham device-controlled, multicentre trial. *Clin Drug Investig*. 2009;29(5):283-92.
- Mirmirani P, Willey A, Headington J. Primary cicatricial alopecia: Histopathologic findings do not distinguish clinical variants. J Am Acad Dermatol. 2005;52:637-643.
- Rapini, R. Adenexal Inflammatory Diseases. *Practical Dermatopathology*. 2012;10:157.
- Rodney I, Onwudiwe O, Callendar V, et al. Hair and scalp disorders in ethnic populations. *Journal of Drugs and Dermatology*. 2013 Apr;12(4):420-7.
- Rodríguez-Garcia C, Gonzalez-Hernandez S, Hernandez-Martin A. Aplasia cutis congenita and other anomalies associated with methimazole exposure during pregnancy. *Pediatr Dermatol*. 2011;28(6)743-6.
- Seetharam, K. Alopecia areata: An update. *Indian J Dermatol Venereol Leprol*. 2013;79:563-575.
- Sperling L, Solomon A, Whiting D. A new look at scarring alopecia. Arch Dermatol. 2000;136:235-242.
- Turan E, Sinem B, Turgut E, et al. "Successful treatment of generalized discoid lupus erythematosus with imiquimod cream 5%: a case report and review of the literature." *Acta Dermatovenerol Croat*. (2014);22(2): 150-9.
- Vivehanantha, S. and J. Berth-Jones. Alopecia areata. *Lebwohl Treatment of Skin Disease: Comprehensive Therapeutic Strategies*. 2014;10:29.
- Zhao, Y. Zhang, B. Caulloo, S. et. al. Diffuse alopecia areata is associated with intense inflammatory infiltration and CD8+ T cells in hair loss regions and an increase in serum IgE level. *Indian J Dermatol Venereol Leprol*. 2012;78:709-714.

Thank You

REMARKABLE MEDICINE.
REMARKABLE CARE

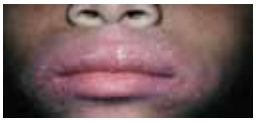
Neuropsychological Cutaneous Disorders

Doug Richley, PGY-4
Northeast Regional Medical Center
Kirksville, MO

Cutaneous Signs of Psychiatric Illness

- Skin is frequent target for emotional stress
  - Compulsive or repetitive hand washing
  - Lip lickers dermatitis
  - Bulimia
    - Russell's sign – lichenified papules on the dorsum of the hand from repetitive rubbing by teeth
  - Onychophagia (nail biting) or skin biting






Delusions of Parasitosis

- Patient may pick small pieces of epithelial debris from skin and bring them to be examined
  - "Matchbox" or "Ziplock" sign
- No objective evidence
  - Must r/o organic conditions, neurologic conditions, malignancies, endocrine disorders, infectious etiology

Delusions of Parasitosis

- Etiology
  - Fixed and false belief that patient suffers from parasitic infestation
  - Close contacts may share delusion
  - Other mental capabilities intact
- Symptoms
  - Formication
    - Cutaneous sensation of crawling, stinging, biting
  - Pruritus
- Epidemiology
  - Women:Men, 2:1
  - 50-60's
  - Paranoid tendencies

Delusions of Parasitosis

- Diagnosis
  - Skin biopsy
    - Assure patient - counseling
    - Exclude occult disease
  - Screening tests
    - CBC, CMP, LFT, UA, Thyroid function, Iron studies, Vitamin B 12
- Treatment
  - Pimozide: antipyschotic drug-blocks dopaminergic receptors
    - Side effects: prolongs QT interval, extrapyramidal reactions, tardive dyskinesia
  - Risperidone
  - Olanzapine

Neurotic Excoriations

- Etiology
  - Uncontrollable desire to pick or scratch
  - Lesions tend to be found on non-dominant side of the body
- Epidemiology
  - Middle aged
  - Female > male
  - Closely related to Obsessive Compulsive Disorder (OCD)

Neurotic Excoriations

- Clinical:
  - All stages of evolution
    - Erosions
    - Deep circular or linear ulcerations
    - Hypo or hyperpigmented scars
    - Well-healed scars
  - Favors
    - Scalp
    - Face
    - Upper back
    - Forearms
    - Shins
    - Buttocks

Neurotic Excoriations

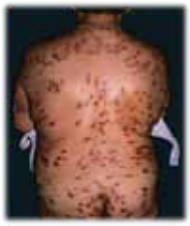
- Treatment
  - Control pruritus
  - Doxepin
    - Antipruritic, antidepressant, H1/H2 antihistamine
    - Side effects: May prolong QT interval, seizure disorder, urinary retention
  - OCD
    - Serotonin Selective Reuptake Inhibitors (SSRIs) or Tricyclic Antidepressants (TCAs)

Prurigo Nodularis

- Presentation
  - Chronic, hyperpigmented, scaly nodules
  - Pruritus is severe
    - Limited to lesions
  - Mainly on the extremities
    - Anterior thighs and legs

Prurigo Nodularis

- Etiology
  - Unknown
- Organic factors may contribute:
  - Atopic dermatitis
  - Hep C
  - HIV
  - Renal disease
  - Pregnancy
  - Stress
  - Lymphoproliferative diseases



Prurigo Nodularis

- Histopathology
  - Compact hyperkeratosis
  - Irregular acanthosis
  - Hypergranulosis
  - Perivascular lymphocytic infiltrate in the dermis
  - Increased vertical streaking of dermal collagen (especially in the dermal papillae)

Prurigo Nodularis

- Treatment
  - Super potent topical steroids
  - Intralesional steroids
  - PUVA
  - NB-UVB
  - Vitamin D3 ointment
  - Tacrolimus
  - Isotretinoin
  - Thalidomide
  - Pregabalin
  - SSRIs, TCAs, Doxepin
  - Cyclosporin
  - Cryotherapy

Lichen Simplex Chronicus

- Presentation
  - Thickened lichenified skin
  - Exaggerated normal skin lines
    - Striae form a crisscross pattern
  - Predilection
    - Back
    - Sides of the neck
    - Wrist and ankle flexures
    - Vulva, scrotum, anal area

Lichen Simplex Chronicus

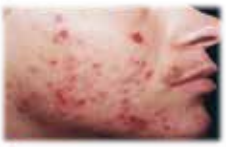
- Etiology
  - Long term chronic rubbing and scratching
  - May result in dermal deposits of amyloid
  - Predisposing factors
    - Xerosis, atopy, stasis dermatitis, anxiety, obsessive–compulsive disorder, and pruritus related to systemic disease
- Histopathology
  - Hyperkeratosis
  - Irregular acanthosis
  - Hypergranulosis
  - +/- vertical collagen bundles in the papillary dermis

Lichen Simplex Chronicus

- Treatment
  - Cessation of pruritus
  - High-potency topical steroid
    - Occlusion with medium-potency topical steroids
  - Adjunctive tx
    - Topical doxepin
    - Topical capsaicin
    - Topical pimecrolimus or tacrolimus

Acne Excoriee

- Scratching and picking acne lesions
- Young women
- Associated with OCD
- Management
  - Doxepin
  - SSRI



Dermatitis Artefacta

- AKA *facticial dermatitis*
- Etiology
  - Self-inflicted cutaneous lesions
  - With the intent to
    1. Illicit sympathy
    2. Escape reality or
    3. Collect disability insurance
  - Patient denial
- Epidemiology:
  - Middle aged women 3x > men
  - Correlation with borderline personality disorder

Dermatitis Artefacta

- Clinical
  - Usually within reach of hands
  - Unusual shapes
  - If chemical is used-red streaks/guttate marks seen beneath the principle patch where the chemical accidentally fell off skin
  - The only sign may be non-healing wound
- Common agents for destruction:
  - Fingernails, pointed instruments, hot metals, chemicals
- Chronic course, waxes and wanes

Dermatitis Artefacta

- Pathology
  - Not diagnostic
  - Erosion, ulceration, hyperkeratosis, vascular proliferation, fibroplasia
- Management
  - Occlusive dressing - to prevent patient from reaching the wound
  - SSRIs, TCAs, antipsychotics

Trichotillomania

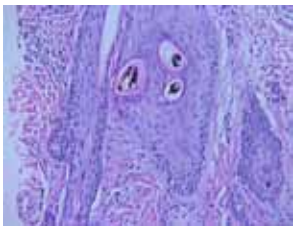
- Etiology
  - Non-scarring alopecia, due to habitual hair pulling
  - Most commonly seen in young girls
  - Associated with OCD
- Clinically
  - Areas of alopecia, with varying lengths of broken hairs within the localized area
  - Common locations:
    - Scalp
    - Eyebrows
    - Eyelashes

Trichotillomania

Trichotillomania

- Histology
  - Deformed hair shafts (trichomalacia)
  - Pigmented hair casts within the follicles
  - Empty follicles

Trichotillomania



Trichotillomania

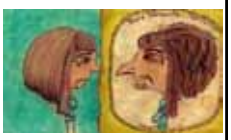
- Treatment
  - Behavior modification
  - TCAs, SSRIs
  - Hypnosis

Body Dysmorphic Disorder

- A preoccupation with a non-existent defect in appearance
- Presentation
  - Socially isolated
  - Adopt compulsive or ritualistic behaviors
  - Olfactory reference syndrome - preoccupied with the notion that they emit an unpleasant odor
    - Engage in compulsive behaviors such as repetitive showering

Body Dysmorphic Disorder

- Epidemiology
  - 1% of the population or 10-14% of those screened in a dermatology office
  - Mean age of onset is 34
  - Males and females equally affected
- Treatment
  - Obsessions category which falls within the OCD spectrum
    - SSRIs – 10-12 week trial then continue treatment for at least 6 months
  - Delusions category which falls within the psychotic spectrum
    - Antipsychotics



Gardner-Diamond Syndrome

- Synonyms: *Psychogenic purpura* or *autoerythrocyte sensitization*
- Etiology
  - Factitial disorder associated with abnormal response to bruising
  - Predominantly seen in women
  - Accompanies psychiatric illness

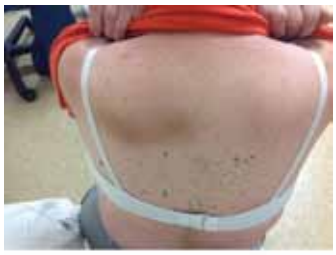
Gardner-Diamond Syndrome

- Clinically
  - Sudden onset of painful, swollen bruises
  - Characteristic atypical lesions with abnormal morphologies
  - Patients induce their own lesions by:
    - Injuring previously traumatized skin
    - Injecting own blood or other agents
- Treatment
  - Confronting patient is typically not useful
  - Gentle probing of underlying psychiatric cause
  - Treat underlying psychiatric illness

Notalgia Paresthetica

- Etiology
  - Focal pruritus over the medial scapular region
  - Occasionally accompanied by pain, paresthesias, or hyperesthesias
  - Often described as a deep sensation
  - Thought to be a sensory neuropathy, with underlying spinal nerve impingement
- Clinically
  - Well circumscribed hyperpigmented patch
  - Normal skin

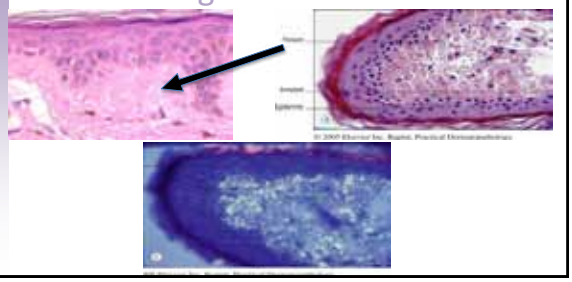
Notalgia Paresthetica



Notalgia Paresthetica

- Histology
  - Melanophages in the papillary dermis, induced by chronic rubbing
  - Overlap with macular amyloidosis (keratin)
    - Will stain positive with:
      - Congo Red (apple green birefringence on polarization)
      - Thioflavin T
      - Crystal Violet

Notalgia Paresthetica



Notalgia Paresthetica

- Treatment
  - Topical capsaicin 5 times per day for 1 week, then 3 times per day for 3-6 weeks
  - Topical corticosteroids
  - Topical anesthetics (pramoxine, lidocaine)
  - Gabapentin
  - Acupuncture
  - Osteopathic manipulation

Trigeminal Trophic Syndrome

- Self-induced ulcerative condition of the central face
- Generally involves the nasal ala
- Presentation
  - Small crust that develops into a crescentic ulcer
  - Often mistaken for basal cell carcinoma (BCC)
- Etiology
  - Triggered by paresthesias and dysesthesias
    - Occur secondary to impingement of or damage to the sensory portion of the trigeminal nerve, the Gasserian ganglion
  - Other causes include infection, stroke and CNS tumors

Trigeminal Trophic Syndrome

Trigeminal Trophic Syndrome

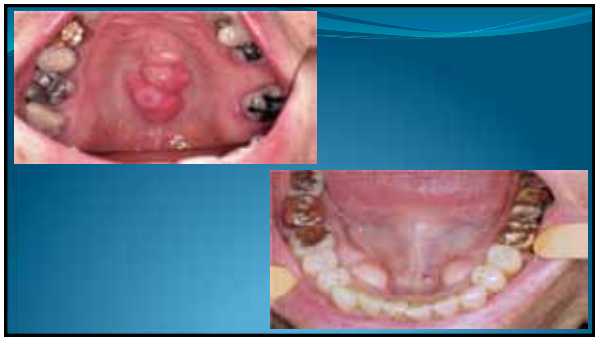
- Histology
  - Ulceration with signs of chronic trauma
    - Scarring, lichenification, and/or pseudoepitheliomatous hyperplasia
- Treatment
  - Medications: carbamazepine, diazepam, amitriptyline and pimozide
  - Physical barriers and patient education

Thank You

Diseases of the Oral Cavity

Tri-Country Dermatology
Cuyahoga Falls, Ohio
AOCD-Oct 2015

Anatomy



Pigmented Lesions

Melanocytic Macule

- **Presentation**: A slowly appearing solitary, brown or grayish brown macule, uniform in color and typically 2-15mm. *lower lip, vermillion border, gingiva or palate.
- **Pathogenesis**: Benign hyperpigmentation. Occurring in approximately 3% of the general population. Common in patients of color, women, ~ 40 y/o.
- **Histo**: Increased melanin in melanocytes and keratinocytes of the basal layer; melanophages in the dermal papillae, indicating pigmentary incontinence, mild acanthosis without elongation of the rete ridges.
- **Treatment**: Serial photography to track any changes. When on the vermillion border is often a cosmetic concern. Biopsy or excision if any fear of melanoma or family history. The pigmentation is epidermal and will respond to laser treatments including ruby, alexandrite, pulsed dye and Q-switched Nd:YAG lasers

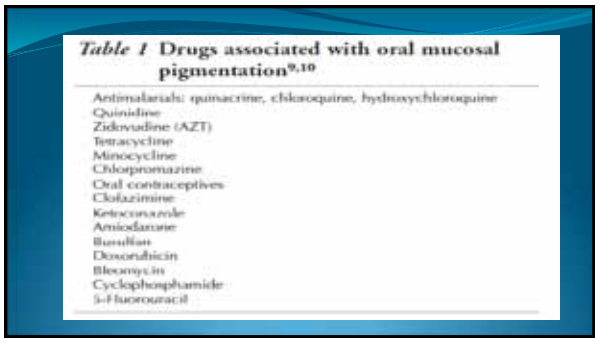
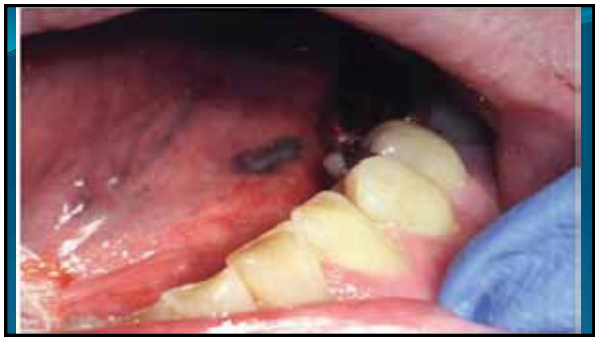


Table 1 **Drugs associated with oral mucosal pigmentation[9,10]**

Antimalarials: quinacrine, chloroquine, hydroxychloroquine
Quinidine
Zidovudine (AZT)
Tetracycline
Minocycline
Chlorpromazine
Oral contraceptives
Clofazimine
Ketoconazole
Amiodarone
Busulfan
Doxorubicin
Bleomycin
Cyclophosphamide
5-Fluorouracil



Amalgam Tatatoo

- **Presentation**: 0.5-1cm poorly defined or diffuse, solitary, slate-grey or blue-black macule. *gingiva, alveolar ridge mucosa and buccal mucosa. *adjacent to fillings or dental work containing silver filling material.
- **Pathogenesis**: Benign tattoo, present after dental work with silver filling material.
- **Histo**: Dark granules mainly along collagen bundles and around blood vessels.
- **Treatment**: No treatment is necessary unless for cosmetic reasons.

Buchner A, and Hansen LS. Amalgam pigmentation of the oral mucosa. A clinicalpathologic study of 268 cases. Oral Surg Oral Med Oral Pathol. 1980 Feb; 49(2): 139-47

Melanoma

- **Presentation**: Enlarging or spreading irregular plaque, darkly pigmented with multiple color variations, irregular borders, possible nodularity and ulceration. Typically on the hard palate or maxillary gingiva.
- **Pathogenesis**: rare in the oral cavity, <1% of all melanomas, men: 2:1, typically 5-6 decade or older. Very aggressive, vertical growth phase. Five year survival only 15%, average post diagnosis survival 2 years.
- **Histo**: Infiltration of connective tissue by atypical melanocytes, with or without melanin production. Confirmed by staining S100, HMB45, MART-1/Melan-A or MITF.
- **Treatment**: Wide excision, sentinel lymph node biopsy. Targeted therapies tyrosine kinase inhibitors may improve survival. Chemotherapy and radiation have little impact of course of disease.

Wushou A, and Zhao YJ. The management and site-specific prognostic factors of primary oral mucosal malignant melanoma. J. Craniofac Surg. 2015. Marl 26(2): 430-4.

Hyperpigmentation of Oral Mucosa - Assoc Syndromes

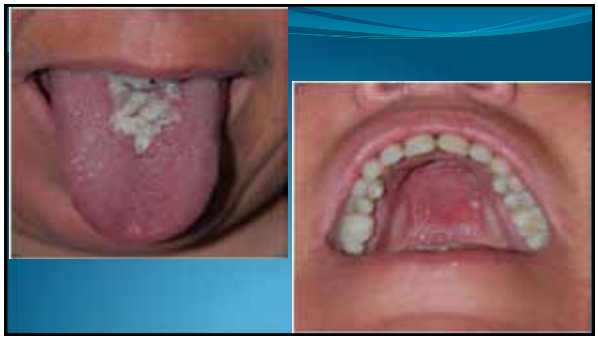
- **McCune- Albright Syndrome**:
  - Sporadic somatic mutation , GNAS1 Gs subunit of adenylate cyclase, precocious puberty, café-au-lait pigmentation , endocrine abnormalities, pathologic fractures, skull sclerosis
- **Peutz-Jeghers Syndrome**:
  - AD, STK11/LKB1 gene mutation, encodes serine-threonine kinase tumor suppressor. Hyperpigmented macules on lip, fingers (starts infancy/childhood) , intussusceptions, intestinal polyposis. GI Malignancies
- **Carney Complex** (LAMB or NAME Syndrome)
  - AD, PRKAR1A (protein kinase A regulatory subunit 1-alpha). Cardiac myxomas, endocrine abnormalities, pigmented skin lesions, psammomatous melanotic schwannoma
- **Laugier-Hunziker disease**:
  - Hyperpigmented macules of lips, oral cavity, genitals and longitudinal melanonychia
- **Addison's disease**:
  - Diffuse hyperpigmentation predominately over sun exposed regions. Weight loss, fatigue, vomiting and hypotension. Destruction of adrenocortical tissue via autoantibodies, trauma or infection

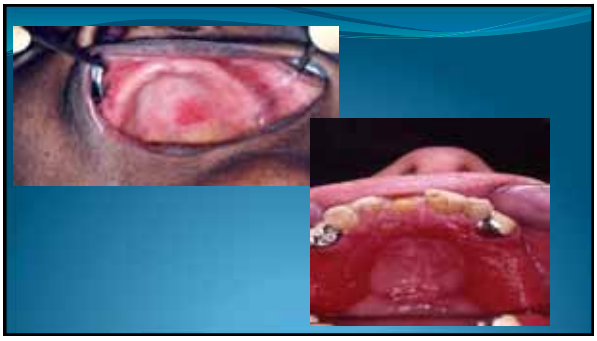
Infections

Angular Chelitis (Perlèche)

- **Presentation**: moist maceration, erythema, crusts or ulcers at the corners of the mouth; tenderness, burning, pruritus.
- **Pathogenesis:** ICD: anatomic-abnormal anatomy leading to exposure of irritant (loss of vertical dimension, improper fit of dental appliances; mechanical- eg, tobacco use, lip licking or drooling, dryness from mouth breathing; chemical factors- excessive saliva, burn, dental cleaning product. ACD (sunscreen, metals, fragrances, preservatives. Infection: (secondary syphilis, *C. albicans*, *S. aureus*, strep, HSV): Nutritional deficiencies (iron, vitamin B2, B3, B6, B12, folic acid, Zn). Systemic causes (DM, HIV, SLE, secondary syphilis Downs syndrome, xerostomia causes: Sjogrens syndrome or medication induced xerostomia.
- **Histo**: ulcerations, spongiosis, infiltration of plasma cells and lymphocytes.
- **Treatment:** topical antifungals, abx, avoidance of irritation/allergen. If failed therapy, consider investigating systemic cause or nutritional deficiency.

Park KK, Brodell RT, Helms SE. Angular cheilitis, part 2: nutritional, systemic, and drug-related causes and treatment. Cutis. 2011 Jul;88(1):27-32.
Park KK, Brodell RT, Helms SE. Angular cheilitis, part 1: local etiologies. Cutis. 2011 Jun;87(6):289-95.
Sharon V, Fazel N. Oral candidiasis and angular cheilitis. Dermatol Ther. 2010 May-Jun;23(3):230-42.

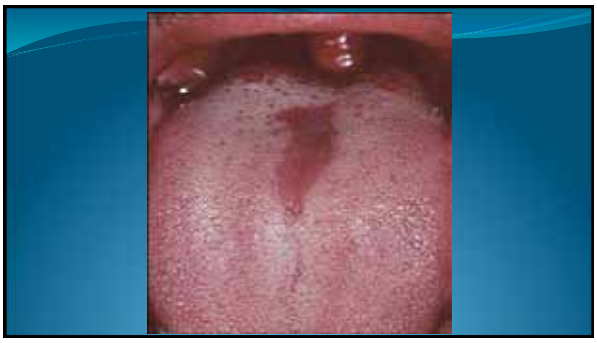




Oral Candidiasis (Thrush)

- **Presentation**: Creamy white lesions on the oral mucosa → gentle scraping shows erythematous mucosal surface.
  - acute pseudomembranous candidiasis; chronic erythematous candidiasis; acute erythematous candidiasis; and chronic hyperplastic candidiasis. Dx mostly clinical but may be confirmed through microscopic identification of *Candida* in the oral samples and/or isolation in culture.
- **Pathogenesis**: is normal flora but broad spectrum antibiotics may trigger thrush, diabetes, malnourishment, debilitation in elderly is common, -immunosuppressed individuals
- **Histo**: + *Candida* hyphae, an inflammatory cell infiltrate is invariably present within the lamina propria together with marked variations in epithelial thickness
- **Treatment**: single dose of fluconazole 150mg is effective for many adults. Immunosuppressed pts: 200mg/day starting dose, itraconazole 200mg/day for 5-10 days, or terbinafine 250mg/day. Oral antiseptic and antibacterial rinses such as Chlorhexidine or Hexetidine. Nystatin at doses of 100 000 IU/ml [5ml 4 times daily] and amphotericin b at 50mg [5ml 3 times per day]. Miconazole gel or buccal mucosal tablet.

Coronado-Castellote L, Jiménez-Soriano Y. Clinical and microbiologicaldiagnosis of oral candidiasis. J Clin Exp Dent. 2013 Dec 1;5(5):e279-86. García-Cuesta C, Sarrion-Pérez MG, Bagán JV. Current treatment of oralcandidiasis: A literature review. J Clin Exp Dent. 2014 Dec 1;6(5):e576-82.
Williams D, Lewis M. Pathogenesis and treatment of oral candidosis. J Oral Microbiol. 2011 Jan 28;3. **Presentation**:Creamy white lesions on the oral mucosa



Median Rhomboid Glossitis (MRG)

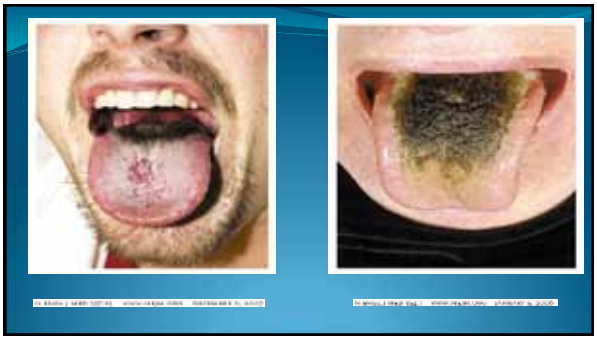
- **Presentation**- Shiny, smooth, red, diamond shaped or oval shaped elevation on midline dorsal aspect of tongue. Sessile appearance consistent with denuded papillae; w/ focal areas of residual papillae. Classic rhomboid appearance is most common.
  - AKA central papillary atrophy; happens in 1% of adults, with M > F 3:1
- **Pathogenesis**: abnormal fusion of posterior portion of the tongue; infection w/ *C. albicans*.
- **Histo**: absence of papillae with epithelium that can range from atrophic to hyperplastic. The underlying stroma usually contains an inflammatory infiltrate. Fungal stains, such as Gomori's methenamine silver, may be used to demonstrate *Candida*, but they are often unnecessary, as the organisms can frequently be seen with H&E.
- **Treatment**- Same as for thrush: Topical antifungals, such as nystatin (Mycostatin, generics) or clotrimazole (Mycelex, generics).

Fowler JC, White P. A classic case of median rhomboid glossitis. JAAPA. 2009 Jun;22(6):70

Chronic Mucocutaneous Candidiasis (CMC)

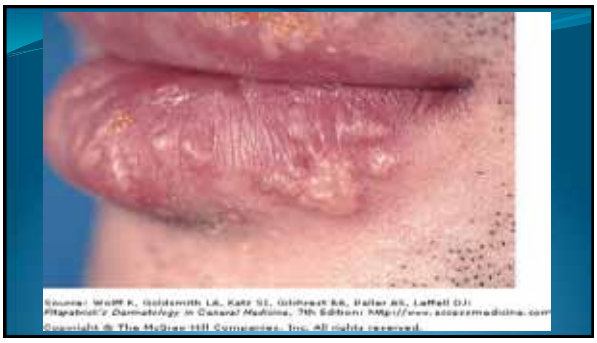
- **Presentation:** chronic mucosal, skin and nails - Candida. < 6 years old. Oral lesions are diffuse, and palate and lip fissures. Dystrophic nails, and may or may not be accompanied by endocrinopathy, hyper IgM, HIV infection.
- **Pathogenesis:** familial or sporadic, early or adult onset (especially with thymoma). The mechanism of CMC is unclear.
  - CMC with endocrinopathy →APECED (Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dysplasia) syndrome, a familial recessive inheritance gene defect associated with the autoimmune regulator, *AIRE* found on locus 21q22.3.
  - Iron deficiency and/or a selective defect in the ability of the cellular immune response to clear *C. albicans* infection is usually thought to be associated with CMC.
- **Histo**: The most important histological findings showed: (1) epithelial hyperplasia (acanthosis) with thick layer of keratinization; (2) superficial micro-abscesses, intraepithelial; (3) inflammatory cells (mainly neutrophils) throughout the layer of the epithelium; (4) intracellular edema adjacent to the micro-abscesses; and (5) large amounts of hyphae of *C. albicans* in the upper layer of the epithelium under the PAS staining.
- **Treatment**: PO fluconazole, itraconazole or ketoconazole, or nystatin.

Liu, X. and Hua, H. (2007), Oral manifestation of chronic mucocutaneous candidiasis: seven case reports. Journal of Oral Pathology & Medicine, 36: 528–532.



Black Tongue (Lingua Villosa Nigra)

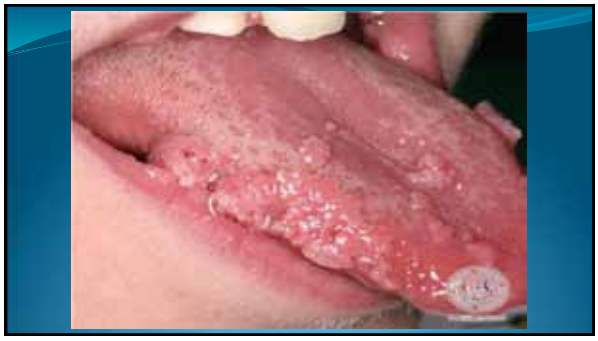
- **Presentation:** Black, brown, green, or yellow patches on dorsum of tongue w/ hairlike filaments.
- **Pathogenesis:** smoking, oral Abx use or psychotropic drug use and presence of *C. albicans* on the tongue.
- **Histo:** Hairs are benign hyperplasia of filiform papilla from retention of long conical filaments of orthokeratotic and parakeratotic cells.
  - Acanthosis, parakeratosis, irregular projections of keratin and vacuolated keratinocytes with Epstein- Barr present within them
- **Treatment:** Toothbrush to scrub off projections with 1-2% hydrogen peroxide
  - Application of Retin-A gel or 40% aqueous solution of urea or papain (meat tenderizer) then brush off projections.
  - Eliminate causative agent if known.



Herpes Simplex

- **Presentation:** numerous discrete, small vesicles in clusters (primary) or singly (secondary) on palate, gingiva or tongue or lips on one ½ of body (following a dermatome). Grouped vesicles rupture rapidly and form punctate erosions with a red base. Will be cyclical in immunocompetent individual: outbreak lasts approx 2 weeks then resolves; can get new outbreak with trigger as frequently as Qmonth.
  - **Ddx**: oral VZV, herpangina and oral aphthosis. The latter two involve nonattached mucosa whereas VSV typically involves mucosa fixed to bone.
- **Pathogenesis:** Herpes labialis is usually due to HSV1>HSV2.
  - Dx is usually mainly clinical and w/ hx. Smears from base with Wright stain will show multinucleate giant cells. Immunofluorescent tests and viral cx are confirmatory.
- **Histo:** acantholysis w/ solitary keratinocytes within the blister cavity. Nuclear changes of viral infection: *margination* of the nuclear chromatin, *multinucleation* and *moulding*.
- **Treatment:** Valacyclovir, 2 g twice in 1 day taken during the prodromal stage of herpes labialis, reduces the episode duration and time to healing. Acyclovir, 400 mg, taken 5 times a day for 5 days, decreases the pain duration and healing time to loss of crust. Both PO Valacyclovir and Acyclovir reduce outbreak by 1 day.
  - New buccal tablet Sitavig (Oral acyclovir 50mg x 1 PO) also reduces outbreaks by 1 day & decreased freq of outbreaks.
  - Topical penciclovir 1%, acyclovir 5% decrease the duration of pain and healing time.
  - The best prophylaxis for herpes labialis is PO valacyclovir 500 mg daily; it reduces the frequency and severity of attacks. SPF may be effective in sunlight-induced recurrence

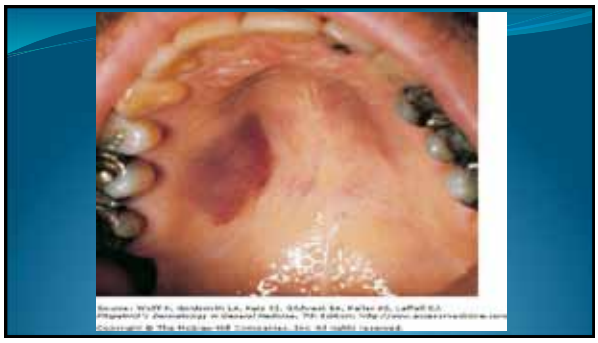
Chon, T, and Nguyen, L. What are the best treatments for herpes labialis? *J Fam Pract. 2007 July;56(7):576-578.*
Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Mar;103 Suppl:S12.e1-18.
Bieber et al. Efficacy and safety of aciclovir mucoadhesive buccal tablet in immunocompetent patients with labial herpes (LIP Trial): a double-blind, placebo-controlled, self-initiated trial. J Drugs Dermatol. 2014 Jul 1;13(7):791-8



Heck's Disease

- **Presentation:** ++ pinkish plaques on the oral mucosa & lower lip, gingiva, tongue or buccal mucosa
  - HPV 13, 32 (in adults)
- **Pathogenesis:** HPV induced focal epithelial hyperplasia (FEH).
  - Assoc to malnutrition, poor hygiene genetic factors.
- **Histo:** Mitosoid cells: virus-altered keratinocytes w/ nuclei resembling mitotic figures (pathognomonic for Heck's); also see focal parakeratosis, hyperkeratosis, acanthosis, verrucous proliferation and marked papillomatosis, hyperplasia of basal cells, and isolated perinuclear cellular vacuolization (koilocytosis).
- **Treatment:** Treatment of FEH is not always indicated as the lesions are asymptomatic and often regress spontaneously, but can be removed if are being traumatized.

Ozden, B. et al. A Case Report of Focal Epithelial Hyperplasia (Heck's disease) with PCR Detection of Human Papillomavirus. J Maxillofac Oral Surg. 2011 Dec; 10(4): 357–360.



Kaposi's Sarcoma

- **Presentation:** Oral KS (OKS) most often affects the hard and soft palate, gingiva, and dorsal tongue with plaques or tumors that can be non-pigmented, brownish-red, or violaceous. It may develop anywhere in the oral cavity, including the masseter muscle, uvula, and oropharynx. Tongue KS → mid-dorsal aspect of the tongue at the junction of the anterior two-thirds and posterior third.
  - Progression from patches of OKS to plaque or nodular forms is associated with worsening of immunosuppression.
  - Exophytic KS can become superinfected by oral microflora, present w/ problems w/tooth mobility and disfigurement if it is visible, and may interfere with mastication, the placement of oral prostheses, and oral hygiene
    - DDX: OKS needs to be distinguished clinically from other entities, including pyogenic granuloma, hemangioma, bacillary angiomatosis, and gingival enlargement caused by CsA, a drug frequently used in recipients of organ transplantation.
    - 4 known variants of KS: epidemic or AIDS-associated KS, endemic or African KS, iatrogenic post-transplantation KS, and Mediterranean or classic KS (CKS). CKS mostly affects elderly Eastern European Jewish or Mediterranean men (male/female ratio: 10-15:1). Lesions occur mostly on the skin of the lower limbs and, more rarely, in internal organs.
- **Pathogenesis:** Involvement of the oral cavity may be seen in all variants but is most common with AIDS-KS. HHV8, a herpesvirus associated with neoplastic diseases, which is postulated to be transmitted via the saliva, has been found in all pts with KS.
- **Histo:** depending on the stage (patch, plaque or nodular), but in general: spindle cell proliferation, lymphocytes and plasma cells, incomplete vascular slits, and extravasated erythrocytes and hemosiderin-ladin macrophages.These microscopic features may not be as evident in early patches,but develop with clinical progression into nodules.

Kaposi's Sarcoma

- **Treatment:** KS is an opportunistic tumor and the restoration of immunity is the best way to treat sarcoma in organ transplant recipients and in AIDS-associated KS (anti-retroviral therapy). In CKS, immunosenescence is not controllable and cannot therefore be targeted by treatment
  - Focal OKS may be surgically excised when lesions are accessible; however, large or diffuse lesions are best managed by debulking rather than full excision because of the potential for extensive residual defects and poor healing.
  - Radiotherapy, chemotherapy, interferon alfa, and surgery: in HIV-positive patients →HAART or with a combination of this therapeutic approach
  - Intralesional vincristine, intralesional interferon alfa-2, imiquimod, and nicotine patches
  - Systemic cytotoxic agents are usually prescribed to patients not responding to HAART and/or with widespread mucocutaneous and visceral disease. Several drugs, such as vincristine, vinblastine, etoposide, bleomycin, docetaxel, and paclitaxel, can be administered

Treatments for classic Kaposi sarcoma: A systematic review of the literature. Régnier-Rosencher, Elodie et al. Journal of the American Academy of Dermatology , Volume 68 , Issue 2 , 313 - 331

Oral HIV-associated Kaposi sarcoma: A case report. Journal of the American Academy of Dermatology , Volume 72 , Issue 5 , AB55
Pittore B, Pelagatti CL, Deiana F, et al. Isolated Kaposi Sarcoma of the Tonsil: A Case Report and Review of the Scientific Literature. Case Reports in Otolaryngology. 2015;2015:874548.
Grayson W, Pantanowitz L. Histological variants of cutaneous Kaposi sarcoma. Diagnostic Pathology. 2008;3:31
Fatahzadeh M, Schwartz RA. Oral Kaposi's sarcoma: a review and update. Int J Dermatol. 2013 Jun;52(6):666-72

Atypia

Actinic Chelitis

- **Presentation:** Lower lip → scaly, fissured, atrophic sometimes eroded and swollen.
- **Pathogenesis:** Inflammatory reaction of the lips due to chronic excessive sun exposure over many years. Propensity for development of leukoplakia or SCC.
- **Histo:** hyperplasia, acanthosis or atrophy of the epithelium, thickening of the keratin layer, and/or dysplasia, which may range from mild to severe, + solar elastosis
- **Treatment:** Avoid sun exposure and use of SPF. Cryosurgery may be effective. If diffuse, may use topical 5-FU, imiquimod or photodynamic therapy. Treatment with CO_2 or Er: YAG laser, dermabrasion or electeodessication may be needed for severe disease.

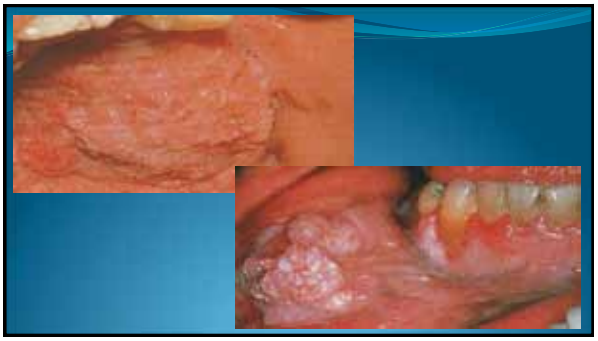
de Santana Sarmento DJ, da Costa Miguel MC, Queiroz LM, Godoy GP, da Silveira EJ. Actinic cheilitis: clinicopathologic profile and association with degree of dysplasia. Int J Dermatol. 2014 Apr;53(4):466-72

Leukoplakia

- **Presentation:** Whitish thickening of the epithelium of the mucous membranes. Attempts to remove → bleeding. It can also be thick rough and elevated plaque. Lips, gums, cheeks and edges of the tongue. Mostly common in males over age 40.
- **Pathogenesis:** From chronic irritation with little chance of conversion into precancerous form (smoking, smokeless tobacco, alcohol, poorly fitted dentures). Premalignant leukoplakia presents in 10-20% of leukoplakia. Viral induced variant called oral hairy leukoplakia occurs primarily in pts with AIDS.
  - High-grade dysplasia had significantly higher malignant incidence than low-grade dysplasia. Four factors including patient aged >60 years, lesion located at lateral/ventral tongue, non-homogenous lesion, high-grade dysplasia were independent significant indicators for Oral Leukoplakia malignant transformation
- **Histo:** orthokeratosis or parakeratosis with minimal inflammation or varying degrees of dysplasia; loss of polarity, increase # mit figures, nuclear pleomorphism, loss of differentiation.
- **Treatment:** Recommend complete removal if dysplastic via surgery or destruction. Fulguration, simple excision, cryotherapy and CO2 laser ablation are all effective methods of treatment. Elimination of irritant if known.

Park MW, Cho YA, Kim SM, Myoung H, Lee JH, Lee SK. Focal epithelial hyperplasia arising after delivery of metal-ceramic fixed dental prosthesis. J Adv Prosthodont. 2014 Dec;6(6):555-8

Liu W, Shi LJ, Wu L, Feng JQ, Yang X, Li J, Zhou ZT, Zhang CP. Oral cancer development in patients with leukoplakia--clinicopathological factors affecting

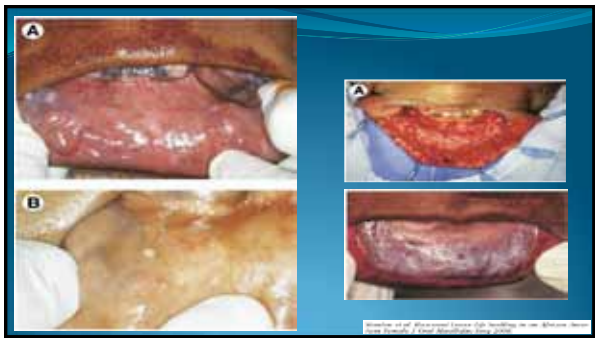


Condyloma Accuminata (CA)

- **Presentation:** any size, can be sessile, papillomatous, exophytic, hemorhagic, pedunculated
  - **Ddx:** VV, oral bowenoid papulosis and oral mucosal lesions of Cowden's (multiple hamartoma) syndrome.
- **Pathogenesis:** sexual transmission of HPV types 6, 11, and 32.
- **Histo:** benign acanthoma w/ papillomatous projections has a parakerotic surface w/ a compact stratum corneum, coarse hypergranulosis, and vaculoated keratinocytes; w/ rare koilocytosis.
- **Treatment**: For oral mucosa: surgical excision, which may be cryosurgery, scalpel excision, ED&C, or laser ablation. There are other treatments for CA when non-mucosal sites are involved (5-fu, TCA, imiquimod, etc).

Breen, E, et al. Condylomata acuminata (anogenital warts) in adults. UpToDate. Last updated Apr 30, 2015. Accessed Aug 2, 2015.
Ozdamar SS, Ozdamar O, Kucukodaci Z. Giant intraoral condyloma accuminatum lesion coexisting with genital condyloma. Pak J Med Sci. 2014 Sep;30(5):1143-6.
Gupta RR, Puri UP, Mahajan BB, Sahni SS, Garg G. Intraoral giant condyloma acuminatum. Indian J Dermatol Venereol Leprol. 2001 Sep-

Miscellaneous diseases of the lips



Cheilitis Glandularis

- **Presentation**: Pinpoint red macules, Macrocheilia due to mucous gland swelling +/- purulent discharge from the ducts.
  - Rare inflammatory condition of the minor salivary glands, usually affecting the lower lip.
  - It carries a risk of (18% to 35%) malignant transformation to squamous cell carcinoma.
- **Histo**: Salivary duct ectasia, mucous accumulation, chronic inflammation and fibrosis
- **Treatment**: Vermilionectomy (lip shave) is the treatment of choice. Intralesional steroids, minocycline and tacrolimus ointment are the other treatment modalities.

Reiter, S., Vered, M., Yarom, N., Goldsmith, C. and Gorsky, M. (2011), Cheilitis glandularis: clinico-histopathological diagnostic criteria. Oral Diseases, 17: 335–339. doi: 10.1111/j.1601-0825.2010.01762.x

Cheilitis Granulomatosa

- **Presentation**: Persistent, non-tender lip swelling progressing to chronic enlargement
- **Pathology**: Subepithelial non-caseating granulomas
  - Melkersson-Rosenthal Syndrome: triad of recurrent/chronic orofacial edema, facial nerve palsy, and fissured tongue
  - Evaluation for dental/sinus inflammation, Crohn's disease, sarcoidosis, leprosy, tuberculosis, chronic granulomatous disease, and possibly deep fungal infections should be considered
- **Treatment**: IL corticosteroids 10mg/cc, alternatively oral prednisone, hydroxychloroquine or minocycline

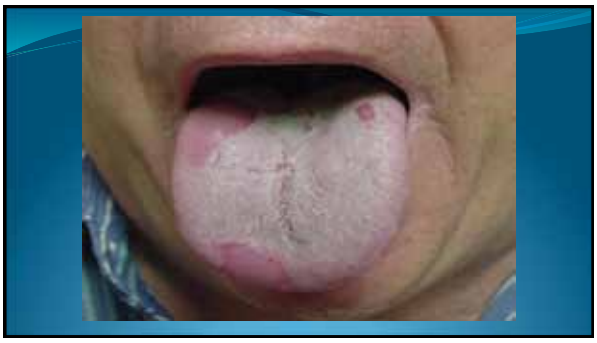
Al-Hamad, Arwa et al. Dermatologic Clinics , Volume 33 , Issue 3 , 433 – 446. Derm101

Diseases of the tongue

Atrophic Glossitis

- **Presentation**: Smooth, red glistening tongue that is often painful w/ loss of filiform papillae
- **Pathogenesis**: May be caused by:
  - Nutritional deficiencies (vitamin E, riboflavin, niacin, vitamin B 12 , iron) – Hunter Glossitis if B12
  - Infections (viral, candidiasis, tuberculosis, syphilis)
  - Trauma (poorly fitting dentures)
  - Irritation of the tongue from toothpaste, medications, alcohol, tobacco, citrus
  - Lichen planus, pemphigus vulgaris, erythema multiforme
- Obtain CBC, B12 level and KOH scraping
- **Treatment** directed at underlying disease. Biopsy may be needed to rule out neoplasm. Also, emphasize avoidance of primary irritants such as hot foods, spices, tobacco, and alcohol.

Glossitis with linear lesions: An early sign of vitamin B12 deficiency Graells, Jordi et al. Journal of the American Academy of Dermatology , Volume 60 , Issue 3 , 498 - 500

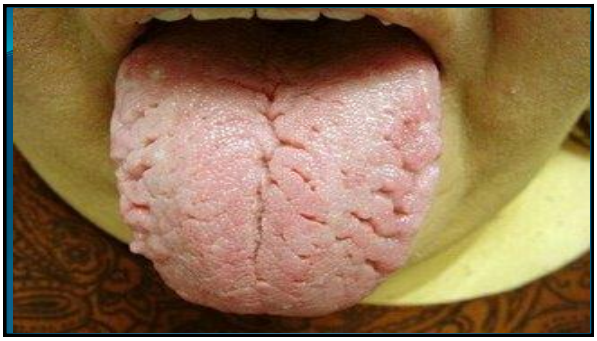


Geographic Tongue

- **Presentation**: Well-demarcated ringed or gyrate erythema with whitish rim typically involving dorsal and lateral tongue; usually asymptomatic
  - benign migratory glossitis
  - Irregular shaped swollen patches often look like maps
  - Noted in increased frequency in psoriasis
  - May be a manifestation of pustular psoriasis, allergy, hormonal disturbance, juvenile diabetes, Reiter syndrome, Down syndrome, nutritional deficiencies, and psychological stress, fissured tongue and LP.
  - ? genetic predisposition has also been suggested
  - A geographic tongue in an otherwise healthy person may indicate a propensity to develop generalized pustular psoriasis
- **Histo**: shows marked transepidermal neutrophil migration with the formation of spongiform pustules in the epidermis and an upper dermal mononuclear infiltrate.
- **Treatment**: Tretinoin 0.025% gel or 0.1% solution applied to the tongue twice daily, usually clears the lesions in less than 1 week.

Glossitis with linear lesions: An early sign of vitamin B12 deficiency Graells, Jordi et al. JAAD , Volume 60 , Issue 3 , 498 – 500

Assimakopoulos D, Patrikakos G, Fotika C, Elisaf M. Benign migratory glossitis or geographic tongue: an enigmatic oral lesion. Am J Med. 2002 Dec 15;113(9):757-9.



Fissured Tongue

- **Presentation**: Benign, non-painful furrows on dorsum of tongue with "corrugated appearance" (Scrotal tongue)
  - Also called lingua plicata
- May be associated with Melkersson-Rosenthal syndrome and Down Syndrome, pachyonychia congenita, pemphigus vegetans, Cowden syndrome. Usually occurs together with geographic tongue and more commonly present in patients with psoriasis
- **Treatment**: Maintenance of oral hygiene with mouthwashes

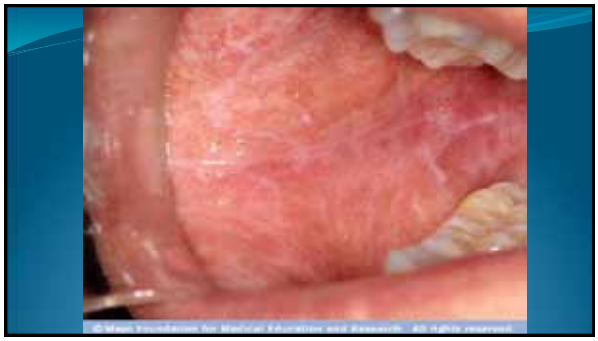
Nisa L, Giger R. Lingua plicata. CMAJ: Canadian Medical Association Journal [serial online]. March 6, 2012;184(4):E241. Available from: Academic Search Premier, Ipswich, MA. Accessed July 26, 2015

Amyloidosis

- **Presentation**: Macroglossia (firm, rubbery, smooth yellow-white nodules) may be the first manifestation with speech, chewing, and swallowing difficulties.
- **Pathogenesis**: Progressive extracellular deposition of amyloid within the suprahyoid muscles
  - Almost universally due to systemic disease
  - May be associated with blood dyscrasias, multiple myeloma or dialysis related lesions
  - Must rule out systemic disease with abdominal fat biopsy or rectal biopsy
- **Histo**: eosinophilic amorphous material on H&E with apple green birefringence under Congo Red staining and polarized light
- **Treatment**: dependent on overall organ involvement and presence of ROS element

Pentenero M, Davico Bonino L, Tomasini C, Conrotto D, Gandolfo S. Localized oral amyloidosis of the palate. Amyloid [serial online]. March 2006;13(1):42-46. Available from: Academic Search Premier, Ipswich, MA. Accessed July 26, 2015.
Xavier S, Filho I, Müller H. Macroglossia secondary to systemic amyloidosis: Case report and literature review. ENT: Ear, Nose & Throat Journal [serial online]. June 2005;84(6):358-361. Available from: Health Source - Consumer Edition, Ipswich, MA. Accessed July 26, 2015.

Inflammatory/reactive conditions



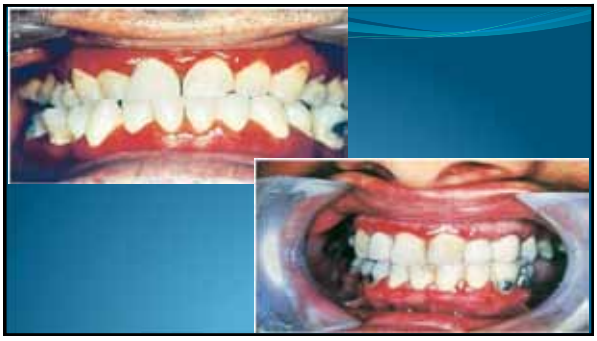
Oral Lichen Planus (LP)

- **Presentation**: "Classic" reticulate white lesions of the buccal mucosa
  - 80% in the buccal mucosa, 65% in the tongue, 20% lips, <10% seen in floor of mouth and palate
  - Malignant transformation → SCC
- **Pathogenesis**: T cell-mediated mucocutaneous disease of unknown etiology
- **Histo**: Band-like subepithelial mononuclear infiltrate consisting of (CD8+) T cells and histiocytes, increased numbers of intraepithelial T cells, and degenerating basal keratinocytes that form colloid bodies
  - Variable :parakeratosis, acanthosis, and sawtooth rete

Oral Lichen Planus

- **Treatment**: Eliminate local and exacerbating factors
  - Superpotent steroids in Orabase or gel form
  - Systemic therapy: Thalidomide, metronidazole, griseofulvin, and hydroxychloroquine, some retinoids, and corticosteroids
  - Surgical excision: Reserved to remove high risk dysplastic areas
  - Cryotherapy
  - CO2, ND:YAG laser, PUVA

Gupta S, Jawanda MK. Oral Lichen Planus: An Update on Etiology, Pathogenesis, Clinical Presentation, Diagnosis and Management. *Indian Journal of Dermatology*. 2015;60(3):222-229. doi:10.4103/0019-5154.156315.
Krupaa RJ, Sankari SL, Masthan KMK, Rajesh E. Oral lichen planus: An overview. *Journal of Pharmacy & Bioallied Sciences*. 2015;7(Suppl 1):S158-S161doi10.4103/0975-7406.155873



Erosive LP of the Gingiva

- **Presentation**: Diffuse erythematous areas that may or may not be interspersed with desquamative and ulcerated foci
  - hyperkeratotic radiating striae found at the periphery of the erosive regions
- **Pathogenesis**: T-cell–mediated autoimmune disease in which autocytotoxic $CD8^+$ T cells trigger apoptosis of oral epithelial cells
  - Malignant transformation: Higher rate of SCC seen in the non-reticular varieties (i.e. atrophic, plaque, and erosive forms)

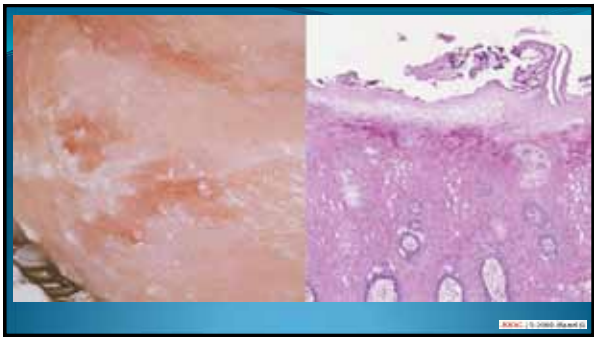
Erosive LP of the Gingiva

- **Histo**: H&E and DIF to exclude other autoimmune disease: Basal cells vacuolization, dense lymphocytic infiltrate at epithelium connective tissue junction with serrated rete ridge pattern
  - Ulcerative form of LP may not show the characteristic histological and DIF features of oral LP so a bx confined to an ulcerative lesion only r/o epithelial dysplasia or carcinoma
  - A bx of the ulcerative form should include adjacent areas featuring other forms of the disease

Erosive LP of the Gingiva

- **Treatment**: Aggressive oral hygiene
  - Topical steroids - Good environment for *C. albicans*
    - Fluocinonide, Clobetasol, Betamethasone, Triamcinolone acetonide 0.1%, mouthrinse or Orabase paste
  - Topical tacrolimus
  - Systemic therapies: Hydroxychloroquine, azathioprine, mycophenolate, dapsone, corticosteroids
  - Topical and systemic retinoids or PUVA

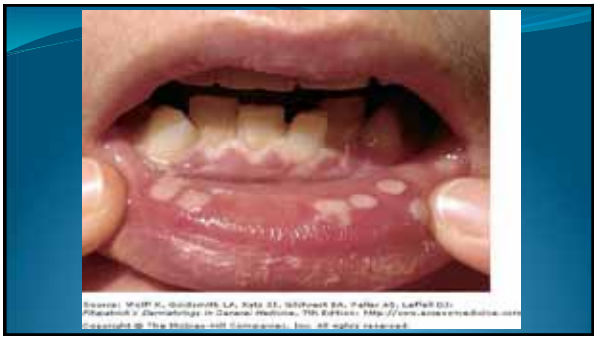
Sugerman PB, Satterwhite K, Bigby M. Autocytotoxic T-cell clones in lichen planus. *Br J Dermatol*. 2000 Mar. 142(3):449-56. [Medline].
Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med*. 2002. 13(4):350-65. [Medline].
Shan J, Ma JM, Wang R, Liu QL, Fan Y. Proliferation and Apoptosis of Peripheral Blood Mononuclear Cells in Patients with Oral Lichen Planus. *Inflammation*. 2012 Nov 8. [Medline].
Ambika Sharma, Chakshu Aggarwal, Vijay P. Mathur, and Divesh Sardana, "Severe Gingival Enlargement with Coexisting Erosive Lichen Planus in Severe Chronic Periodontitis Patient," Case Reports in Dentistry, vol. 2015, Article ID 538538, 6 pages, 2015. doi:10.1155/2015/538538
Al-Hashimi I, Schifter M, Lockhart PB, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Mar;103 Suppl:S25.e1-12
Kalmar JR. Diagnosis and management of oral lichen planus. J Calif Dent Assoc. 2007 Jun;35(6):405-11

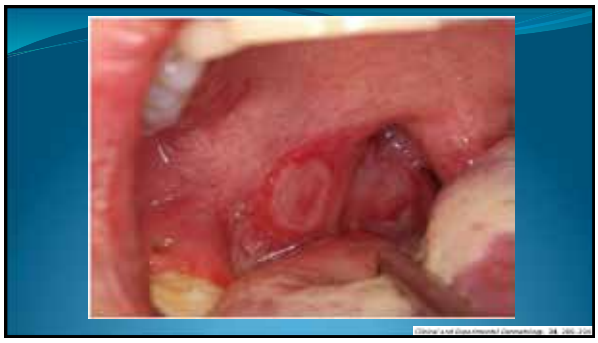


Morsicatio Buccarum, "Oral Frictional Hyperkeratosis

- **Presentation**: Shaggy white plaque on the buccal mucosa
- **Pathogenesis**: Chronic irritation from biting
- **Histo**: Hyperorthokeratosis and acanthosis with insignificant inflammation
- **Treatment**: Elimination of chronic trauma Cam K1,

Santoro A, Lee JB. Oral frictional hyperkeratosis (morsicatio buccarum): an entity to be considered in the differential diagnosis of white oral mucosal lesions. Skinmed. 2012 Mar-Apr ;10(2):11





Oral Aphthae/Recurrent Aphthous Stomatitis

- **Presentation**: most common lesion of the oral mucosa - affect up to 25% of the general population
  - Tender lesions involving the non-keratinized mucosa (not bound to underlying periosteum)
  - Multiple, small, or ovoid ulcers, having yellow floors and are surrounded by erythematous haloes
  - 3 forms (3-10 mm in size): Minor. Major – when larger. Herpetiform – small 1-3 mm lesions grouped into a coalescing larger plaque, taking 1-4 weeks to resolve

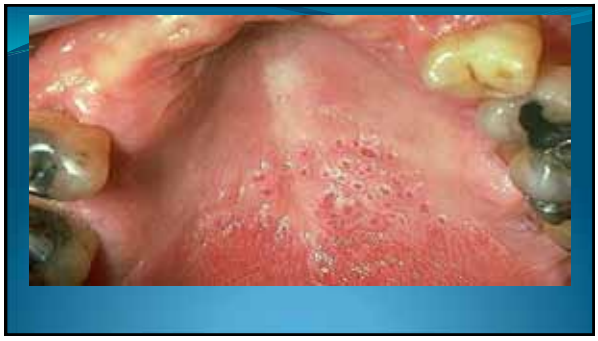
Oral Aphthae /Recurrent Aphthous Stomatitis

- **Pathogenesis** – true cause unknown, cell-mediated immune response, generation of T cells and production of TNF-α
  - Triggers: hormonal changes, trauma, drugs, food hypersensitivity, nutritional deficiency, stress, & tobacco, Associated with: Behcet's, celiac, Inflammatory bowel disease, HIV
- **Histo**: pre-ulcerative lesion demonstrates subepithelial inflammatory mononuclear cells with abundant mast cells, connective tissue edema and lining of the margins with neutrophils.

Oral Aphthae /Recurrent Aphthous Stomatitis

- **Treatment**
  - NO permanent cure is available
  - Topical analgesics
  - Topical steroids
  - Tetracycline mouth rinses
  - Short course of systemic corticosteroids
  - Systemics that reduce formation: Pentoxifylline, colchicine, dapsone and thalidomide

Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guideline for the Diagnosis and Treatment of Recurrent Aphthous Stomatitis for Dental Practitioners. *Journal of International Oral Health : JIOH*. 2015;7(5):74-80
Akintoye SO, Greenberg MS. Recurrent Aphthous Stomatitis. *Dental clinics of North America*. 2014;58(2):281-297. doi:10.1016/j.cden.2013.12.002

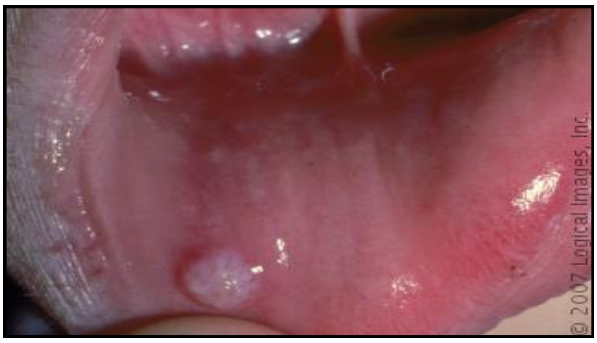


Stomatitis Nicotina

- **Presentation**: Umbilicated papules with central red depression affecting Hard palate/soft palate
- **Pathogenesis**: Inflamed palatal mucous salivary glands due to: Heavy smoking and Non-smokers who drink hot beverages
- **Histo**: Tissue biopsy not usually indicated
  - Acanthotic and hyperkeratotic
  - Mild to moderate chronic inflammation
- **Treatment**: Abstaining from tobacco and hot beverages

Reddy CRRM, Kameswari VR, Ramulu C, Reddy PG. Histopathological Study of Stomatitis Nicotina. *British Journal of Cancer*. 1971;25(3):403-410

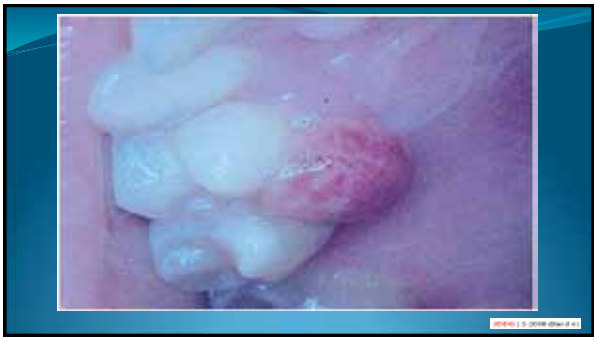
Benign growths



Mucocele

- **Presentation**: Soft, blue, translucent cyst (superficial) or mucosa-colored firm nodule (deep)
  - 2 to 10mm in diameter; Lower lip most commonly
  - Incision/compression releases sticky, straw colored or bluish fluid
- **Pathogenesis**: Obstruction or rupture of minor salivary glands; Trauma from biting
- **Histo**: One or more spaces filled with sialomucin; Lined by granulation tissue or a mixed infiltrate of fibroblasts, lymphocytes, and histiocytes
- **Treatment**: Excisional biopsy, Cryotherapy, Laser ablation

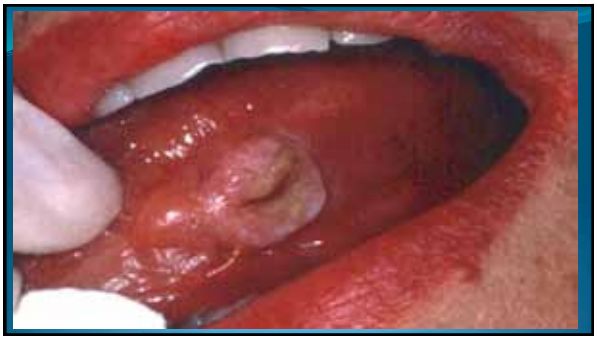
More CB, Bhavsar K, Varma S, Tailor M. Oral mucocele: A clinical and histopathological study. *Journal of Oral and Maxillofacial Pathology : JOMFP*. 2014;18(Suppl 1):S72-S77.



Pyogenic granuloma

- **Presentation**: Red to reddish-purple, soft, nodular mass; Bleeds easily, grows rapidly
- **Pathogenesis**: Response to injury; Hormonal factors
- **Histo**: lobular capillary hemangioma; Lobules separated by connective tissue septae
- **Treatment**: Surgical excision; Pulsed dye or Nd:YAG laser; Cryosurgery

Asha V, Dhanya M, Patil BA, Revanna G. An unusual presentation of pyogenic granuloma of the lower lip. *Contemporary Clinical Dentistry*. 2014;5(4):524-526.



Traumatic Ulcer

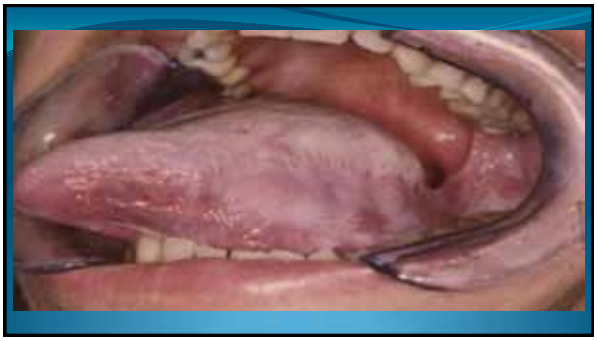
- **Presentation**: Painful ulceration
- **Pathogenesis**: accidentally biting oneself while talking, sleeping, or secondary to mastication
  - Also- Chemical, electrical, or thermal insults, may also be involved
- **Histo**: Surface ulceration covered by a fibrinopurulent membrane consisting of acute inflammatory cells intermixed with fibrin
  - Stratified squamous epithelium from the adjacent surface may be hyperplastic and exhibit areas of reactive squamous atypia
  - Ulcer bed is composed of a proliferation of granulation tissue with areas of edema and an infiltrate of acute and chronic inflammatory cells.
- DDx = SCC

Traumatic Ulcer

- **Treatment**
  - Removal of the irritants or cause
  - Soft mouth guard
  - Sedative mouth rinses
  - Consumption of a soft, bland diet
  - Warm sodium chloride rinses
  - Topical corticosteroids
  - Topical anesthetics

Houston, G. Traumatic Ulcers. http://emedicine.medscape.com/article/1079501-overview. Retrieved Aug 1, 2015.

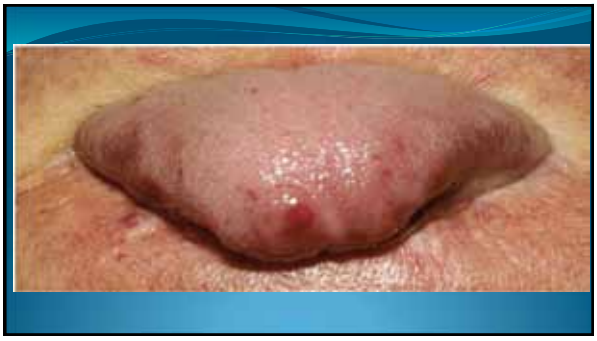
Hereditary diseases



White Sponge Nevus

- Benign, uncommon, AD disorder or sporadic; mutation in *KRT4 or KRT13 gene,* affecting non-keratinized stratified-squamous epithelia.
  - AKA familial white folded mucosal dysplasia, leukoderma exfoliativum mucosae oris, hereditary leukokeratosis
- **Presentation**: Onset in early childhood, 50% dx before age 20. White-to-gray, diffuse, painless, spongy folded plaques on the buccal mucosae > labial mucosae > tongue, floor of the mouth, and alveolar mucosae. Less frequently, the mucous membranes of the nose, esophagus, genitalia, and rectum are involved.
- **Pathogenesis**: attributed to an insertion, deletion, or substitution mutation in the helical domain of mucosal specific keratins, K4 and K13, causing an abnormal aggregation of tonofilaments and keratin filament instability.
- **Histo**: Parakeratosis, acanthosis with the formation of large, blunt rete ridges, spongiosis, and extensive vacuolation of suprabasal keratinocytes. Dyskeratotic cells exhibit dense peri-and paranuclear eosinophilic condensations, which correspond to tonofilament aggregates. Odland bodies are abundant within keratinocytes, but few are present in the intercellular spaces. This observation suggests a lack of acid phosphatase, which leads to retention rather than normal shedding of superficial cells.
- **Treatment**: No standard, reassurance only required. Generally, progression of the disorder stops at puberty and there is no malignant transformation. Oral abx can help.

Dyall-Smith, D. White Sponge Nevus. http://dermnetnz.org/site-age-specific/white-sponge-naevus.html. Accessed Aug 1, 2015.



Osler-Weber Rendu Hereditary Hemorrhagic Telangectasia

- **Presentation:** nosebleeds & telangectasia, normal life span. ~1/3 pts: chronic anemia, w/ GIB increasing with age. Asymptomatic AV malformations occur in pulmonary (~50%), hepatic (~30%), cerebral (~10%) and spinal (~1%) circulations.
- **Pathogenesis:** AD mutations in endoglin (HHT1) or ACVRL1 (HHT2). Rarely due to mutations in Smad4, or other genes. Known disease genes involved in TGF-β superfamily signaling. Marked intra-familial variation. Common AVM complications include stroke (ischemic and hemorrhagic) and brain abscess. Rarer HHT complications include DVT; symptomatic liver disease requiring liver transplantation; severe pulmonary HTN; pregnancy-related death; and spinovascular accidents.
- **Histo:** show focal dilatations of post capillary venules. Fully developed lesions have markedly dilated and convoluted venules extending through entire dermis with excessive layers of smooth muscle without elastic fibers, often connecting directly to dilated arterioles. Lymphocytes collect perivascularly.

Osler-Weber Rendu-HHT

- **Treatment:** repair Nasal telangectasia 90%
  - Sx: Nosebleeds & Iron deficiency anemia, Nasal humidification; packing in emergencies. ENT: laser; surgery; embolisation; Systemic: estrogen–progesterone, antifibrinolytics
  - Repair Mucocutaneous telangiectasia – 80%; repair Gastrointestinal telangiectasia – 20%; repair Pulmonary AVMs - 50%
  - Tx: Laser or other ablation therapies
  - Cerebral AVMs- 10%; Hepatic AVMs- 30%; Spinal AVMs <1%
  - Tx: Iron +/− transfusions for anemia in all cases.

Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. European Journal of Human Genetics. 2009;17(7):860-871.
Hereditary Hemorrhagic Telangiectasia. Alan E. Guttmacher, M.D., Douglas A. Marchuk, Ph.D., and Robert I. White, Jr., M.D. N Engl J Med 1995.

MEN2B: Multiple Endocrine Neoplasia

- **Presentation:** mucosal neuromas of the lips, tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the GI tract, and a 'marfanoid' habitus. Medullary thyroid carcinoma (MTC) typically occurs in early childhood in MEN 2B. **High risk for development of MTC, increased risk for pheochromocytoma,
- **Pathogenesis/Diagnosis:** AD. Molecular genetic testing to identify a heterozygous germline RET pathogenic variant is indicated in all individuals with a diagnosis of primary C-cell hyperplasia or MTC or a clinical diagnosis of MEN 2. Identification of a heterozygous germline RET pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.
- **Histo:** Unencapsulated masses of convoluted nerve fibers surrounded by a thickened perineurium. = plexiform neuromas.
- **Treatment**: thyroidectomy and lymph node dissection. External beam radiation therapy or intensity-modulated radiation therapy can be considered for advanced regional disease. Kinase inhibitors may be used in metastatic MTC. >>Pheos can be removed by adrenalectomy. Primary hyperparathyroidism is treated by parathyroidectomy, or more rarely, medications to reduce parathyroid hormone secretion. ALL PTS NEED YEARLY HORMONE MONITORING.
  - **Prevention of primary manifestations**: Prophylactic thyroidectomy for individuals with an identified germline RET pathogenic variant.

Marquard J, Eng C. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2015 Jun 25]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: **http://www.ncbi.nlm.nih.gov/books/NBK1257/**

Multiple idiopathic mucosal neuromas: A minor form of multiple endocrine neoplasia type 2B or a new entity? Pujol, Ramon M. et al. Journal of the American Academy of Dermatology, Volume 37, Issue 2, 349-352.

LEOPARD Syndrome

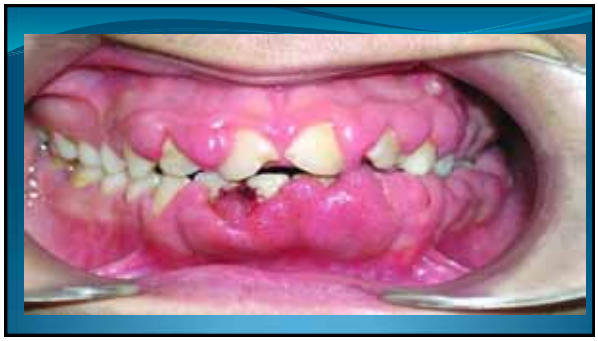
- **Presentation:** Lentigines, EKG defects, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retarded growth , Deafness (sensorineural).
  - Facial dysmorphism : ocular hypertelorism, palpebral ptosis and low-set ears. Stature is usually below the 25%. Cardiac defects hypertrophic cardiomyopathy - left ventricle. The lentigines may be congenital, although more frequently manifest by the age of 4–5 years and increase throughout puberty. Additional common features are café-au-lait spots (CLS), chest anomalies, cryptorchidism, delayed puberty, hypotonia, mild developmental delay, sensorineural deafness and learning difficulties.

LEOPARD Syndrome

- **Pathogenesis:** Missense mutations: exons 7, 12, or 13 of the PTPN11 gene in 90% of the cases. Others can be RAF 1 or de novo mutations. Mutations in PTPN11 affect RAS–MAPK pathway activity by up-regulating SHP-2 activation through impairing the switch between its active and inactive conformation without altering SHP-2's catalytic capability.
- **Histo:** Lentigines have increased number of melanocytes per unit skin and prominent rete ridges.
- **Treatment:** LS should be suspected in fetuses with severe cardiac hypertrophy (risk of sudden cardiac death) and prenatal DNA test may be performed.

Gorlin, R. J., Anderson, R. C. and Moller, J. H. (1971), The leopard (multiple lentigines) syndrome revisited. The Laryngoscope, 81: 1674–1681.
Delayed primary diagnosis of LEOPARD syndrome type 1. Staub, Janina et al.
Journal of the American Academy of Dermatology, Volume 68, Issue 2, e58 - e60

Systemic Disease



Hypertrophic gingivitis

- **Presentation**: increased size of the gingiva
- **Pathogenesis**: Inflammatory enlargement (from poor oral hygiene); Drug induced enlargement (anticonvulsants, CCB,CsA); Enlargement associated w/ systemic diseases or conditions (preg,puberty,vit c def,pyogenic granuloma); Neoplastic enlargement (carcinoma or melanoma); False enlargement (underlying bony or dental tissue lesion).
- **Histo**: Acanthosis, parakeratosis w/ pseudoepitheliomatous proliferation. Highly vascular connective tissue w/ focal accumulation of inflammatory cells, primarily plasma cells. IHC: increase in the number of Langerhans cells within the epithelium and adjacent to inflamed sites.
- **Treatment**: improved oral hygiene; change the offending drug, and/or correct/associated disease/malignancy, if applicable.

Mejia, LM. Drug-Induced Gingival hyperplasia. http://emedicine.medscape.com/article/1076264-workup#c7. Accessed Aug 1, 2015.
http://intranet.tdmu.edu.ua/data/kafedra/internal/stomat_ter_dt/classes_stud/en/stomat/ptn/child%20therapeutic%20dentistry/5/02.%20hypertrophyc%20gingivatis.htm

Pemphigus Vulgaris

- **Presentation – PV:** delicate, superficial labial & buccal mucosal ulcers. Desquamative gingivitis occurs (can also be seen in oral LP and mucous membrane pemphigoid)
  - Oropharynx, esophagus can be involved. 50% pts will have skin PV.
  - Nail dystrophy, paronychia, and subungual hematomas
- **Paraneoplastic pemphigus** (PNP) similar exam findings to PV and lichenoid, targetoid and tense blisters.
  - PNP - painful, progressive stomatitis of the tongue. In addition, the presence of blisters and targetoid lesions on the palms and soles can help differentiate PNP from PV. A biopsy with direct immunofluorescence (DIF) and a complete physical exam can further help differentiate PNP from PV.
- **Pathogenesis**: **PV**: IgG autoantibodies against desmoglein 1 → acantholysis. Mucocutaneous PV have detectable autoantibodies directed against Dsg-1 and Dsg-3 whereas patients with *only* mucosal disease have antibodies targeted against only Dsg-3. The triggering event leading to antibody formation is unknown.
  - Pts w/**PNP** also have autoantibodies against Dsg-1 and Dsg-3. In addition, PNP has antibodies targeted against proteins in the plakin family (plectin, desmoplakin I, desmoplakin II, bullous pemphigoid antigen I, envoplakin, and periplakin). These plakin proteins are also involved in cell-cell adhesion of keratinocytes.

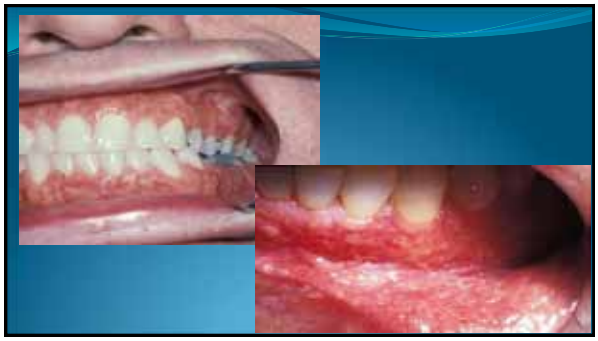
Pemphigus Vulgaris

- **Histo:** intraepithelial blister with few inflammatory cells (eos), some acantholytic cells and tombstoning at basal layer; w/ moderate perivascular chronic inflammation. DIF: intercellular deposition of IgG and C3 in a "chicken-wire" lattice pattern.
- **PNP -** variable presentation – similar to PV, LP, and EM; an intraepithelial blister with suprabasal acantholysis, interface dermatitis, dyskeratotic keratinocytes, and lymphocyte exocytosis. Spongiosis, chronic perivascular and lichenoid infiltrates and pigment incontinence can also be seen. DIF shows IgG deposition in all layers of the epidermis and C3 in the lower epidermis and basement membrane. In contrast to PV, intercellular staining is often focal and faint.

Pemphigus Vulgaris

- **Treatment PV:** Topicals: High-potency corticosteroids (rinses, gels, pastes), Tacrolimus ointment 0.1%. First line txs: Corticosteroids 1 mg/kg/day w/ clinical remission in 4–12 weeks,
  - Rituximab: 4 weekly infusions at 375 mg/m^2 of BSA (oncology dosing) or 1000 mg × 2 separated by 2 weeks (rheumatology dosing)
  - Others: IVIG (sometimes combined with rituximab), Azathioprine, Mycophenolate mofetil, Cyclophosphamide, MTX, gold, CsA, plasmapheresis, extracorporeal photochemotherapy, anti-TNF-α, thalidomide.
- **Treatment PNP:** Prednisone (0.5–1 mg/kg), CsA(5 mg/kg), sometimes combined w/ prednisone, Cyclophosphamide (2mg/kg), sometimes combined w/prednisone and CsA, Immunoablative cyclophosphamide without stem cell rescue, Immunoapheresis, IVIG, Rituximab, Alemtuzumab

Santoro FA, Stoopler ET, Werth VP. Pemphigus. Dental clinics of North America. 2013;57(4):10.1016/j.cden.2013.06.002.



Pyostomatitis Vegatans

- **Presentation:** chronic mucocutaneous ulcerative disorder associated with IBD and consisting of multiple miliary white or yellow pustules with an erythematous and edematous mucosal base. The pustules can rupture and coalesce to form linear or "snail-track" ulcers. The labial gingiva, labial, and buccal mucosa are most frequently involved.
  - Prevalent between 20 and 59 years, M > F (2:1-3:1).
  - Is oral equivalent of pyodermatitis vegetans on the skin.
  - Intestinal involvement usually predates its onset in IBD. Pts present w/ fever, enlarged and tender submandibular lymph nodes, and pain. Eosinophilia is seen in 90% of cases.
- **Pathogenesis:** unknown, a marker of disease severity in UC, associated with IBD (primarily UC)
  - **DDx**: PV, BP, EBA, bullous drug eruptions, herpetic infection, Behçet's disease, and EM, HSV
- **Histo:** intra-epithelial and/or sub-epithelial micro-abscesses w/ neutrophils and eosinophils w/ hyperkeratosis, acanthosis, and acantholysis. DIF is negative for deposits of IgA, IgG and C3 and this result is helpful in distinguishing it from pemphigus vulgaris.

Pyostomatitis Vegatans

- **Treatment:** tx underlying IBD.
  - Topical steroids & antiseptic mouthwashes are sometimes effective.
  - Systemic steroids = treatment of choice.
  - Azathioprine and sulfamethoxypyridazine can be used in parallel with steroids as sparing agents. Dapsone is another option, but should be used as a second line agent, especially in relapsing cases. CsA has been successfully used. Injections of infliximab followed by maintenance therapy w/ Mtx have been also effective, especially when this disease is associated with Crohn's. Humira has also proven effective in inducing remission of both oral and GI manifestations. Surgical colectomy produces promising results in this disease when associated with ulcerative colitis.

Lankarani KB, Sivandzadeh GR, Hassanpour S. Oral manifestation in inflammatory bowel disease: A review. World Journal of Gastroenterology : WJG. 2013;19(46):8571-8579.

The End

NAILS:
TALES, FAILS AND WHAT PREVAILS IN TREATING ONYCHOMYCOSIS

(AND OTHER BOARD RELEVANT INFORMATION)

J. Hibler, D.O.
OhioHealth - O'Bleness Memorial Hospital, Athens, Ohio

AOCD Annual Conference
Orlando, Florida
10.18.15

The image below represents:

A) Onychodystrophy
B) Onychogryphosis
C) Onychomycosis
D) All the above
E) None of the above

"Question dogma."
– Michael Conroy, MD

"Important" nail facts

- Nail development begins at 8-10 weeks EGA
  - Complete by 5th month
  - Keratinization ~11 weeks
  - No granular layer
- Nail plate growth:
  - Fingernails 3 mm/month, toenails 1 mm/month
  - Faster in summer or winter?
    - Summer!
  - Index finger or 5th digit nail grows faster?
    - Index finger!
  - Faster growth to middle or lateral edge of each nail?
    - Lateral!

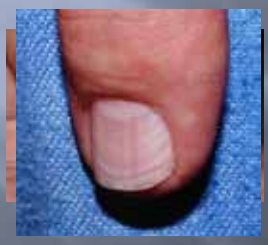
Nail anatomy

Pitting: psoriasis, eczema, aa

Nails and systemic disease

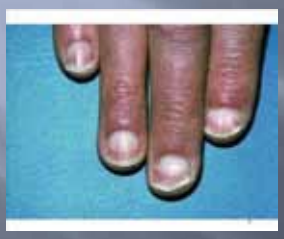
- Mee's lines
- Aka leukonychia striata
  - **Arsenic poisoning**
  - Trauma
  - Medications
  - Illness
  - Psoriasis flare

Nails and systemic disease



- Muerhrcke's bands
  - **Hypoalbuminemia**
  - Chemotherapy

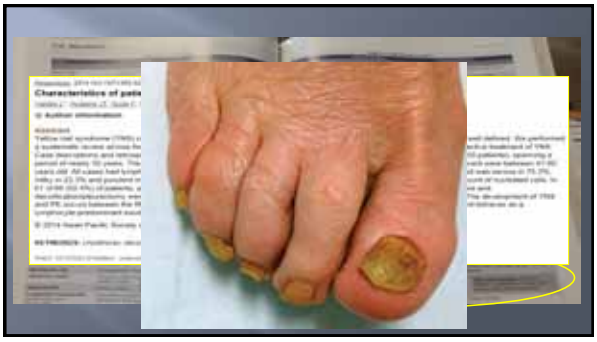
Nails and systemic disease



- Half & half nails
- Aka Lindsay's nails
  - **Chronic renal disease**

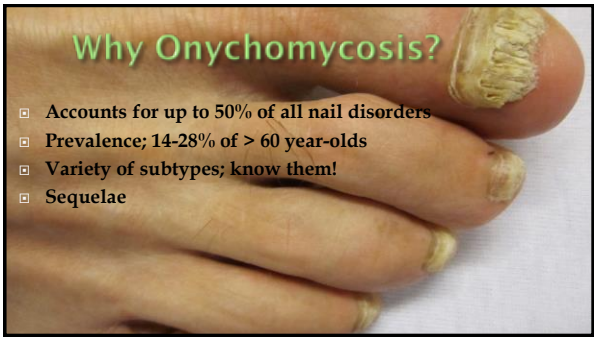
Nails and systemic disease

- Terry's nails
  - **Liver failure, Cirrhosis**
  - Malnutrition
  - Diabetes
  - Cardiovascular disease



Pertinent terminology

- True or False: Onychomycosis = Tinea Unguium?
  - FALSE.
- Onychomycosis:
  - A fungal disease of the nails (all causes)
    - Dermatophytes, yeasts, molds
- Tinea unguium:
  - A fungal disease of nail caused by **dermatophyte** fungi
- Onychodystrophy ≠ onychomycosis



Why Onychomycosis?

- **Accounts for up to 50% of all nail disorders**
- **Prevalence; 14-28% of > 60 year-olds**
- **Variety of subtypes; know them!**
- **Sequelae**

Onychomycosis quiz #1

- What is the most common cause of onychomycosis?
  - A) *Epidermophyton floccosum*
  - B) *Microsporum spp*
  - C) *Trichophyton mentagrophytes*
  - D) *Trichophyton rubrum*
  - -Account for ~90% of infections

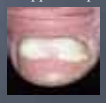
Onychomycosis usual suspects…

- Dermatophytes
  - *Trichophyton rubrum*
  - *Trichophyton mentagrophytes*
  - *Trichophyton tonsurans, Microsporum canis, Epidermophyton floccosum*
- Nondermatophyte molds
  - *Acremonium spp, Fusarium spp*
  - *Scopulariopsis spp, Sytalidium spp, Aspergillus spp*
- Yeast
  - *Candida parapsilosis*
  - *Candida albicans*
  - *Candida spp*

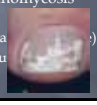
Onychomycosis subtypes

- Distal/lateral subungal onychomycosis (DLSO)
  - Most common; T. rubrum

- Proximal subungual onychomycosis (PSO)
  - Often in immunosuppressed patients
  - T. rubrum
  - T. Megninii



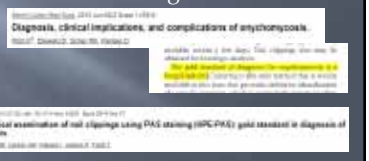
- Superficial white onychomycosis (SWO)
  - T. mentagrophytes (va
  - T. rubrum (immunosu



- Candidal onychomycosis

Onychomycosis quiz #2

- What is the gold standard for diagnosis?
  - A) Culture
  - B) Microscopy
  - C) HPE-PAS
  - D) PCR



Onychomycosis: current treatment options

- First line therapy
  - Terbinafine (250mg/day x 12 weeks)
- Second line
  - Itraconazole (200-400mg/day x 1 week for 3 months)
  - Fluconazole (300-450 mg/week x 9 months)
  - Posoconazole (200-400mg/day x 6 months)
- Third line
  - Terbinafine + amorolfine
  - Terbinafine + nail debridement
  - Photodynamic therapy
- Topical amorolfine, ciclopiroxolamine, terbinafine

ORAL THERAPY; TERBINIFINE, ITRACONAZOLE, FLUCONAZOLE, POSACONAZOLE, AND OTHERS

Jessica Vincent Hoy, DO

Terbinafine

- Fungicidal allylamine (inhibits fungal ergosterol)
- Standard dosing: 250mg daily x 6weeks for fingernails, x12 weeks for toenails
  - Pulse dosing: 250mg daily x 1 week a month for 3 months
- A meta-analysis of 18 studies showed a superior mycological cure rate of 76-78% when compared with pulse itraconazole and fluconazole (*Gupta, 2004*)
- After 5 years, 46% of patients remained disease-free vs. 13% treated with itraconazole (*Sigurgeirsson, 2002*)

Onychomycosis quiz #3

- How is "**mycological cure**" characterized?
  - Clinical appearance/observation
  - Microscopy/KOH
  - PAS staining
  - Culture
  - PCR

Itraconazole

- Fungistatic synthetic triazole
- Dosing: 200mg daily x 6 weeks for fingernails, x12 weeks for toenails
  - Pulse dose: 400mg daily x 1 week for 3 months
  - Pulse therapy advantages: adverse-effect profile, cost-effective and preferred by patients (*Gupta, 1998*)
- A meta-analysis showed a mycological cure rate for pulse itraconazole of 63-75% (*Gupta, 2004*)

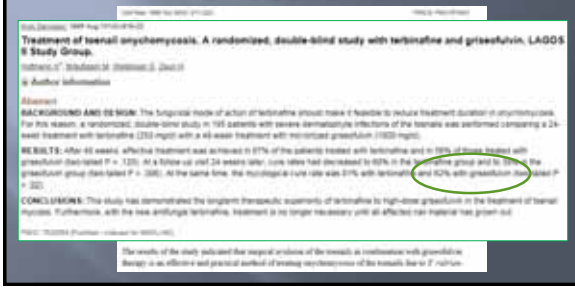
Fluconazole

- Fungistatic bis-triazole
- Dosed as pulse therapy
  - 150 to 450mg once weekly for 6 months (fingernails), 9 months (toenails)
- A meta-analysis of 3 studies on fluconazole showed a mycological cure rate of 48-53%
- A double-blind RCT showed terbinafine 250mg daily x 12 weeks to be significantly more effective than fluconazole 150mg once weekly for either 12 or 24 weeks (*Havu, 2000*)

Posaconazole

- Newer azole (inhibits fungal cell membrane ergosterol synthesis)
- Mycological cure rate 48%
- A randomized, placebo- and active-controlled, parallel-group, investigator blinded study compared 4 doses of posaconazole with placebo and terbinafine
  - At 48 weeks, cure rate was similar for posaconazole 200mg and 400mg for 24 weeks and terbinafine 250mg for 12 weeks
- "Use is likely to be limited to second-line treatment in terbinafine-refractory infections, those with non-dermatophyte mold infections or those sensitive to or intolerant of terbinafine" (*Elewski, 2011*)

Griseofulvin


Treatment of toenail onychomycosis. A randomized, double-blind study with terbinafine and griseofulvin. LAGOS II Study Group.

Combination therapy

Baran and Kaoukhov, 2005

TOPICALS FOR ONYCHOMYCOSIS; CICLOPIROX, AMOROLFINE NAIL LACQUER, EFINACONAZOLE (JUBLIA), TAVABOROLE (KERYDIN), AND OTHERS

Kylee Crittenden, DO

Topical treatment

- Adverse effects are site specific.
- No need for laboratory monitoring or concern about systemic adverse effects
- Efficacy affected by ability to penetrate nail unit

Ciclopirox lacquer, 8%

- Approved by FDA for onychomycosis in 1999
- Binds trivalent cations and blocks enzymatic co-factors; interferes with active membrane transport; disruption of cell membrane integrity, and inhibition of enzymes required for respiratory processes
- Requires frequent nail debridement
- 29-36% mycologic cure; 5.5% to 8.5% complete cure from once daily application
- Promising results of combination of ciclopirox and itraconazole for 3 months[3]. Needs further investigation.

(Baran, R. et al 2000)

Amorolfine lacquer, 5%

- Acts primarily by inhibiting ergosterol biosynthesis
- Fungistatic and fungicidal
- Used in combinations therapy with systemics; griseofulvin, terbinafine, itraconazole or fluconazole, against a number of dermatophytes implicated in superficial infections[5].

(Polak A. 1993)

Efinaconazole (Jublia) 10% solution

- Triazole antifungal; blocks ergosterol biosynthesis, presumably through inhibition of sterol 14α-demethylase, leading to degenerative changes
- First topical triazole to become available for dermatologic use
- No debridement of nails is required
- Applied daily x 48 weeks
- In trials, yielded a mycologic cure of about 50% and complete cure of about 15% to 18%

(Tatsumi, et al. 2013)

Tavaborole (Kerydin) 5% solution

- Broad-spectrum oxaborole antifungal agent with low molecular weight, permitting nail plate penetration
- Inhibits aminoacyl-tRNA synthetase; inhibits fungal protein synthesis
- Applied daily x 48 weeks
- Mycologic cure rate of 16%; complete cure rate of 6.5% vs. 5% cure rate for vehicle alone

(Elewski, et al. 2014)

Topical Treatment Regimens

Topical agent	Length of treatment in trials	Complete cure rate from once daily application
Ciclopirox 8%	Apply daily, up to 48 weeks	5.5% to 8.5%
Efinaconazole	Phase III clinical trials studied daily application for 48 weeks	15% to 18%
Tavaborole	Phase III clinical trial (data available on first of two recently completed) studied daily application for 52 weeks[3]	6.5%

OTHER TREATMENT OPTIONS FOR ONYCHOMYCOSIS

Rich Winkelmann, DO

Laser for onychomycosis

- Pros:
  - Minimal systemic side effects
  - No laboratory monitoring or black box warning
- Cons:
  - Expensive
  - Poor efficacy
  - Research is lacking in highly variable
    - Small case studies, limited # pts, significant COI

Nd:YAG Laser

- 37 patients
- One to three sessions four to six weeks apart
- **Cure rate**
  - 51% (complete cure)
  - 19% (significant improvement)
  - 11% (moderate improvement)

Kimura et al, J *Drugs Dermatol*, 2012

Dual-wavelength near-infrared laser (Noveon 870 and 930 nm)

- Treatment on days 1, 14, 42, and 120
- **Clinical cure rate:**
  - Mild cases: 65% (3 mm of nail clearance), 26% (4 mm of nail clearance)
  - Moderate to severe cases: 63% (3 mm of nail clearance)
- **Mycotic cure rate**:
  - 50-65% (mild to moderate cases)
  - 35% (severe cases)

Landsman et al, *J Am Podiatr Med Assoc* , 2010

Mentholated ointment


Novel treatment of onychomycosis using over-the-counter mentholated ointment: a clinical case series.

Derby et al, *J Am Board Fam Med*, 2011

Cyanoacrylate, undecylenic acid, and hydroquinone

- n = 154 patients


A new concept in the topical treatment of onychomycosis with cyanoacrylate, undecylenic acid, and hydroquinone.

- 50-65% (mild to moderate cases)
- 35% (severe cases)

Rehder et al, *Foot Ankle Spec*, 2008

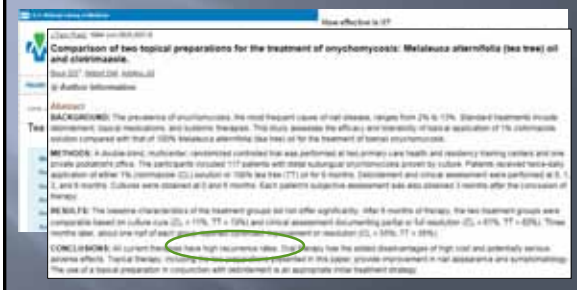
Argeratina pichinchensis (snakeroot extract)

- Applied every th… r the first month, twice per week f… ond month, then once per week fo… l month
- **Clinical cure rat…**
- **Mycotic cure rat…**
- Study of 110 pat… ctiveness was similar to that in the cicl… ntrol group

Romero-Cerecero et al, *Planta Med*, 2008

Onychomycosis; other treatment options

- Salicylic acid
  No current literature
- Tea tree oil
- Hydrogen peroxide
- Vinegar soaks
- Oil of Bitter Orange
- Bleach soaks

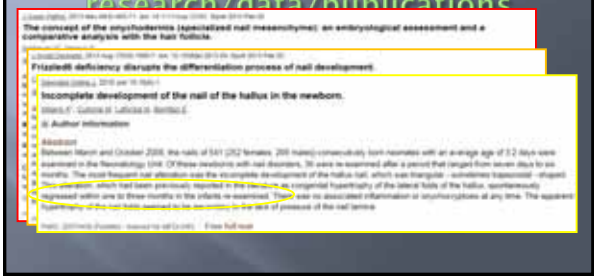

Comparison of two topical preparations for the treatment of onychomycosis: Melaleuca alternifolia (tea tree) oil and clotrimazole.

Onychomycosis quiz #4

- How is "**complete cure**" defined?
  - 0% involvement of target nail(s) PLUS
  - Mycological cure (Culture & KOH)

Therapy & Dose	Mycological cure rate
Itraconazole 400mg daily x 3 months + **Amorolfine** x 6 mo	>90%
Itraconazole 400mg daily x 1.5 months + **Amorolfine** x 6 mo	>90%
Terbinafine 250mg daily x 3 months + **Amorolfine** x 15 mo	~89%
Terbinafine 250mg daily x 3 months	~77%
Terbinafine 250mg daily x 1.5 months + **Amorolfine** x 15 mo	~73%
Itraconazole 400mg daily x 1 week for 3 months	~69%
Ageratina (snakeroot extract) applied q3rd night	~59%
Nd-YAG laser 1-3 sessions, 4-6 weeks apart	~61%
Efinaconazole 10% solution applied daily x 12 months	~50%
Cyanoacrylate, undecylenic acid, hydroquinone applied every 2 weeks x 3-4 visits	~50%
Griseofulvin 1g daily x 12 months	~50%
Fluconazole 450mg weekly x 9 months	~51%
Posaconazole 200mg daily x 6 months	~48%
Ciclopirox 8% lotion applied daily x 9 months	~33%
Mentholated ointment (Vicks) applied daily x 12 months	~28%
Tavaborole 5% solution applied daily x 12 months	~16%

Recent research/data/publications



Bonus:

Conclusions

- Onychomycosis..
  - Easy to diagnose
  - Easy to treat
  - Difficult to cure (without a lot of work)
- Many oral, topical and alternative options exist
- Tailor treatment to patient needs

References

1) Sigurgeirsson B, Olafsson JH, Steinsson JB, et al. Long-term effectiveness of treatment with terbinafine versus itraconazole in onychomycosis. Arch Dermatol. 2002;138:353–357.

2) Baran, Kaoukhov. Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy. JEADV (2005) 19 , 21–29

3) Gupta AK, ryder JE, Johnson, AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. Br J Dermatol. 2004;150:537–544.

4) Havu V, Heikkila H, Kuokkanen K, Nuutinen M, Rantenen T, Saari S, et al. A double-blind, randomized study to compare the efficacy and safety of terbinafine (Lamisil) with fluconazole (Diflucan) in the treatment of onychomycosis. Br J Dermatol 2000; 142: 97-102.

5) Nolting S. Open studies of ciclopirox nail lacquer in onychomycosis: a review. In: Shuster S, ed. Hydroxy-pyridones as Antifungal Agents with Special Emphasis on Onychomycosis. Springer-Verlag,Berlin,1999:75–80.

References

6) Elewski, B., Pariser, D., Rich, P., & Scher, R. K. (2013, June). Current and emerging options in the treatment of onychomycosis. In Seminars in cutaneous medicine and surgery (Vol. 32, No. 2 Suppl 1, pp. S9-12).

7) Baran, R., & Kaoukhov, A. (200%). Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy. Journal of the European Academy of Dermatology and Venereology, 19(1), 21-29.

8) Haria, M., & Bryson, H.M. (1995). Amorolfine. Drugs, 49(1), 103-120.

9) Polak A. Combination of amorolfine with various antifungal drugs in dermatophytosis. Mycoses 1993; 36: 43 – 49.

10) Tatsumi, Y., Nagashima, M., Shibanushi, T., Iwata, A., Kangawa, Y., Inui, F., ... & Nishiyama, Y. (2013). Mechanism of action of efinaconazole, a novel triazole antifungal agent. Antimicrobial agents and chemotherapy, 57(5), 2405-2409.

References

11) Elewski, B. E., & Tosti, A. (2014). Tavaborole for the treatment of onychomycosis. Expert opinion on pharmacotherapy, 15(10), 1439-1448.

12) Penlac (ciclopirox 8%) [package insert]. Bridgewater, NJ: Dermik Laboratories; 2006.

13) Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. J Am Acad Dermatol. 2013;68:600-608.

14) Tavaborole (AN2690). Available at: http://www.anacor.com/an2690.php.

Thank you:

- OhioHealth - O'Bleness Memorial Hospital
- Program director Dr. Dawn Sammons
- OhioHealth – O'Bleness residents
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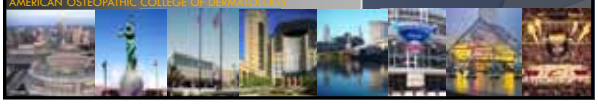
- The Ohio State University Dermatology Residency

PHOTODERMATOSES

Ashley Feneran, DO
Jenifer Lloyd, DO

University Hospitals Regional Hospitals

AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY



Objectives

- Review key points of several photodermatoses
- Update knowledge and treatment of photodermatoses
- Discuss vitamin D levels in photodermatoses

Types of photodermatoses

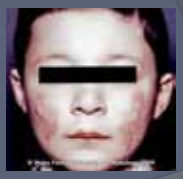
- Immunologically mediated disorders
- Defective DNA repair disorders
- Photoaggravated dermatoses
- Chemical- and drug-induced photosensitivity

Types of photodermatoses

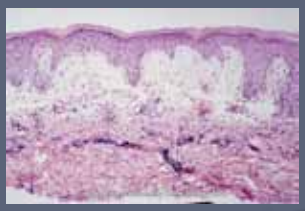
- Immunologically mediated disorders
  - Polymorphous light eruption
  - Actinic prurigo
  - Hydroa vacciniforme
  - Chronic actinic dermatitis
  - Solar urticaria

Polymorphous light eruption (PMLE)

- Most common form of idiopathic photodermatitis
- Possibly due to delayed-type hypersensitivity reaction to an endogenous cutaneous photo-induced antigen
- Presents within minutes to hours of UV exposure and lasts several days



Pathology



- Superficial and deep lymphocytic infiltrate
- Marked papillary dermal edema

PMLE Treatment

- Topical or oral corticosteroids
- High SPF
- Restriction of UV exposure
- Hardening – natural, NBUVB, PUVA
- Antimalarial

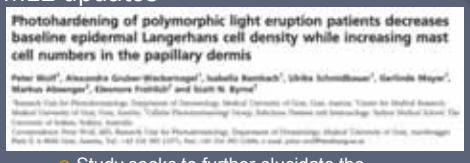
PMLE updates

Randomized double-blinded placebo-controlled intra-individual trial on topical treatment with a 1,25-di-hydroxyvitamin D_3 analogue in polymorphic light eruption

- Study suggests topical vitamin D analogue used prophylactically may provide therapeutic benefit in PMLE

Gruber-Wackernagel A, Bambach FJ, Legat A, et al. Br J Dermatol, 2011.

PMLE updates



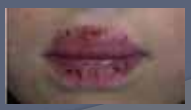
Photohardening of polymorphic light eruption patients decreases baseline epidermal Langerhans cell density while increasing mast cell numbers in the papillary dermis

- Study seeks to further elucidate the pathogenesis of PMLE
- Found a decrease in Langerhans cells and an increase in mast cell density in lesional skin

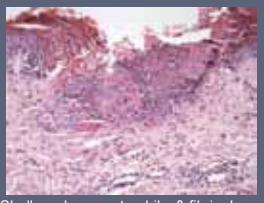
Wolf P, Gruber-Wackernagel A, Bambach I, et al. Exp Dermatol, 2014.

Actinic prurigo

- Similar to PMLE
- Common in native American children
- Strong association with HLA DR4 subtype DRB1*0407
- Heals with scarring



Pathology



- Shallow ulcer, neutrophils, & fibrin deposits
- Acanthosis, spongiosis, & superficial vessel telangiectasias
- Follicular chelitis

Actinic prurigo treatment

- Photoprotection
- UV protective film on windows
- Topical and oral steroids
- NBUVB
- Thalidomide
- Pentoxifylline
- Cyclosporine
- Azathioprine
- TNF-a inhibitors

Actinic prurigo updates

CASE SERIES

Thalidomide experience of a major Australian teaching hospital

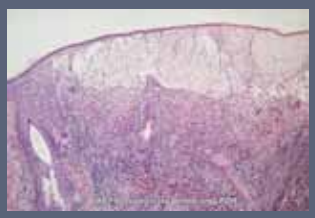
- Study describes successful use of thalidomide in 6 total adult and pediatric patients with actinic prurigo
- Regular nerve conduction studies performed

Crouch R, Foley P, Ng J, et al. Australas J Dermatol. 2002.

Hydroa vacciniforme (HV)

- Rare, scarring photodermatosis seen in early childhood
- Some cases are associated with latent EBV infection
- Hemorrhagic bullae heal with varioliform scars

Pathology



- Spongiosis & epidermal vesicles
- Epidermal and upper dermis necrosis
- Lymphocytic infiltrate of dermis

Hydroa vacciniforme treatment

- Refractory to treatment
- Close monitoring for atypical features
- Photoprotection
- NBUVB
- Oral antimalarials
- Azathioprine
- Thalidomide
- Cyclosporine
- Beta carotene
- Fish oil supplements

Hydroa vacciniforme updates


A patient with elderly-onset atypical hydroa vacciniforme with an indolent clinical course

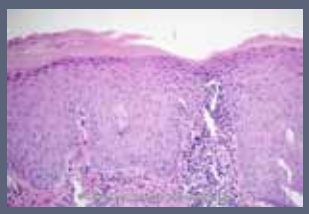
- Recent case report illustrates adult-onset HV with T-cell monoclonality with a favorable course

Nomura H, Suzuki H, Egami S, et al. Br J Dermatol. 2015.

Chronic actinic dermatitis

- Chronic eczema caused by UV radiation and visible light
- Tends to affect older men
- Likely a delayed-type hypersensitivity reaction
- Often a pre-existing allergic or photoallergic contact dermatitis

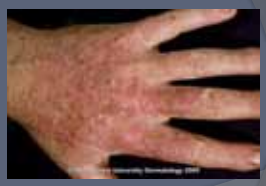
Pathology



- Spongiosis, acanthosis, superficial perivascular infiltrate
- Occasional apoptotic keratinocytes
- Exocytosis of inflammatory cells

Chronic actinic dermatitis treatment

- Photoprotection
- Topical steroids
- Topical calcineurin inhibitors
- NBUVB
- PUVA
- Azathioprine
- Cyclosporine
- Mycophenolate mofetil



Chronic actinic dermatitis updates

Loss-of-Function Mutations in the Gene Encoding Filaggrin Are Not Strongly Associated with Chronic Actinic Dermatitis

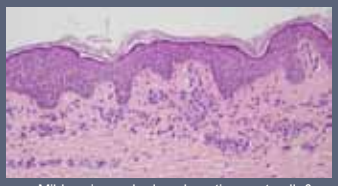
- This study disproved the hypothesis that the filaggrin gene plays a strong role in the pathogenesis of chronic actinic dermatitis

Harkins C, Waters A, Kerr A, et al. J Invest Dermatol. 2015.

Solar urticaria

- Urticaria induced by sun exposure
- Appears within 5-10 minutes of sun exposure & resolve over 1-2 hours
- Most cases do not resolve
- Risk of anaphylactic-type response

Pathology



- Mild perivascular lymphocytic, mast cell, & eosinophilic infiltrate
- Mild dermal edema
- Can see intraluminal neutrophils and eosinophils

Solar urticaria treatment

- Photoprotection
  - Sunscreen is not particularly helpful for those sensitive to visible light
- Anti-histamines
- Topical steroids
- Graduated UV exposure
- IVIG
- Omalizumab
- Plasmapheresis

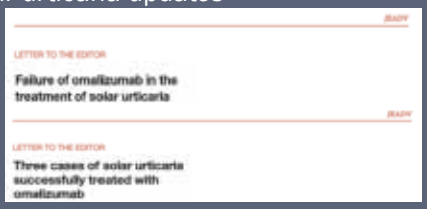
Solar urticaria updates

Severe and refractory solar urticaria treated with intravenous immunoglobulins: A phase II multicenter study

- This study showed promising results with IVIG to treat solar urticaria, however the duration of response was not prolonged and adverse effects were frequent

Aubin F, Porcher R, Jeanmougin M. J Am Acad Dermatol. 2014.

Solar urticaria updates



LETTER TO THE EDITOR

Failure of omalizumab in the treatment of solar urticaria

LETTER TO THE EDITOR

Three cases of solar urticaria successfully treated with omalizumab

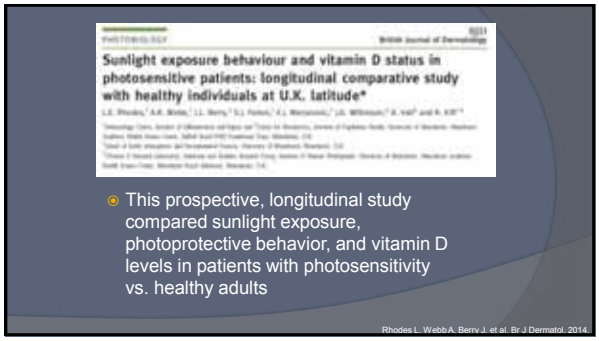
- Case studies are conflicting on efficacy of omalizumab in solar urticaria

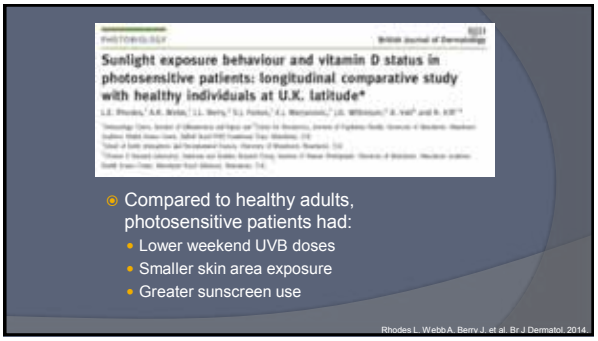
Baliu-Piqué C, Aquilera Peiró P. J Eur Acad Dermatol Venereol, 2015.
Müller S, Schempp C, Jakob T. J Eur Acad Dermatol Venereol, 2014.

Vitamin D levels in photodermatoses

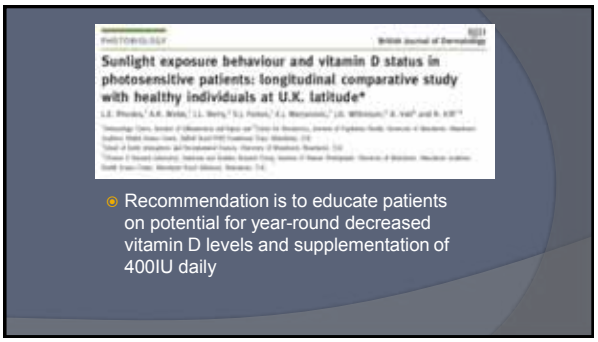
Vitamin D levels

- All of the discussed photodermatoses have the recommendation for photoprotection, but what effect, if any, does this have on vitamin D levels?


Sunlight exposure behaviour and vitamin D status in photosensitive patients: longitudinal comparative study with healthy individuals at U.K. latitude*
This prospective, longitudinal study compared sunlight exposure, photoprotective behavior, and vitamin D levels in patients with photosensitivity vs. healthy adults
Rhodes L, Webb A, Berry J, et al. Br J Dermatol. 2014.


Sunlight exposure behaviour and vitamin D status in photosensitive patients: longitudinal comparative study with healthy individuals at U.K. latitude*
Compared to healthy adults, photosensitive patients had:
Lower weekend UVB doses
Smaller skin area exposure
Greater sunscreen use
Rhodes L, Webb A, Berry J, et al. Br J Dermatol. 2014.


Sunlight exposure behaviour and vitamin D status in photosensitive patients: longitudinal comparative study with healthy individuals at U.K. latitude*
Compared to healthy adults, photosensitive patients had:
Lower vitamin D levels year-round
Year-round lows
Rhodes L, Webb A, Berry J, et al. Br J Dermatol. 2014.


Sunlight exposure behaviour and vitamin D status in photosensitive patients: longitudinal comparative study with healthy individuals at U.K. latitude*
Recommendation is to educate patients on potential for year-round decreased vitamin D levels and supplementation of 400IU daily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Program Director: Jenifer Lloyd, DO
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PGY-2
Mathew Loesch, DO, PhD
Miesha Merati, DO
AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY


QUESTIONS?
AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY

References

1. Aubin F, Porcher R, Jeanmougin M. Severe and refractory solar urticarial treated with intravenous immunoglobulins: A phase II multicenter study. J Am Acad Dermatol. 2014; 71(5): 948-953.
2. Ballu-Piqué C, Aquilera Peiró P. Three cases of solar urticaria successfully treated with omalizumab. J Eur Acad Dermatol Venereol. 2015. Epub ahead of print.
3. Bruderer P, Shahabpour M, Christoffersen S, Andre J, Ledoux M. Hydroa vacciniforme treated by a combination of beta-carotene and canthaxanthin. Dermatology. 1995;190:343-345.
4. Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. Br J Dermatol. 1995;132:956-963.
5. Crouch R, Foley P, Ng J, et al. Thalidomide experience of a major Australian teaching hospital. Australas J Dermatol. 2002; 43(4): 278-284.
6. Durbec F, Regulai Z, Leonard F, Pluot M, Bernard P. Efficacy of v-3 polyunsaturated fatty acids for the treatment of refractory hydroa vacciniforme. Pediatr Dermatol. 2012;29: 118-119.
7. Gruber-WackernagelA, Bambach I, Legat FJ. Randomized double-blinded placebo-controlled intra-individual trial on topical treatment with a 1,25-dihydroxyvitamin D_3 analogue in polymorphic light eruption. Br J Dermatol 2011; 165(1): 152-63.
8. Hall L, Eminger L, Hesterman K. Epstein-Barr virus, Dermatologic associations and implications: part I. Mucocutaneous manifestations of Epstein-Barr virus and nonmalignant disorders. J Am Acad Dermatol. 2015; 72(1): 1-19.
9. Harkins C, Waters A, Kerr A, et al. Loss-of-function mutations in the gene encoding filaggrin are not strongly associated with chronic actinic dermatitis. J Invest Dermatol. 2015; 135(7): 1919-1921.
10. Kutlubay, Z, Sevim A, Engin B, et al. Photodermatoses, including phototoxic and photoallergic reactions (internal and external). Clin Dermatol. 2014; 32: 73-79.
11. Lim H, Snauwaert J. Vitamin D and photodermatoses. Br J Dermatol. 2014; 171(6): 1297-1298.
12. Moller S, Schempp C, Jakob T. Failure of omalizumab in the treatment of solar urticarial. J Eur Acad Dermatol Venereol. 2014. Epub ahead of print.
13. Nityarom R, Wongsaparut C. Hydroa vacciniforme and solar urticaria. Dermatol Clin. 2014; 32(3): 345-353.
14. Nomura H, Suzuki H, Egami S, et al. A patient with elderly-onset atypical hydroa vacciniforme with an indolent clinical course. Br J Dermatol. 2015. Epub ahead of print.
15. Rhodes L, Durham B, Fraser W, et al. Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. J Invest Dermatol. 1995; 105: 532-535.
16. Rhodes L, Webb A, Berry J, et al. Sunlight exposure behaviour and vitamin D status in photosensitive patients: Longitudinal comparative study with healthy individuals at U.K. latitude. Br J Dermatol. 2014; 171(5): 1478-1486.
17. Rhodes L, White S. Dietary fish oil as a photoprotective agent in hydroa vacciniforme. Br J Dermatol. 1998; 138: 173-178.
18. Valbuena M, Muvdi S, Lim H. Actinic prurigo. Dermatol Clin. 2014; 32(3): 335-344.
19. Wolf P, Gruber-WackernagelA, Bambach I, et al. Photohardening of polymorphic light eruption patients decreases baseline epidermal Langerhans cell density while increasing mast cell numbers in the papillary dermis. Exp Dermatol. 2014; 23: 424-448.

Viral Infections

Chris Hixon DO, PGY4
Megan Joint DO, PGY 4

Lewis Gale Hospital Montgomery /VCOM
Program Director: Daniel S. Hurd DO, FAOCD

Review of Topics

- Human Herpes Virus 1-8
- Parvo Virus
- Molluscum Contagiousum
- Milker's Nodule
- Human Papilloma Virus
- Measles
- Rubella
- Hand-Foot-Mouth Disease
- Orf
- Vaccinia
- Cowpox

Human Herpesviruses

	Classification	Lytic Infection	Latent Infection
Herpes Simplex Virus type 1	Alphaherpesvirinae	Epithelial cells	Neuron
Herpes Simplex Virus type 2	Alphaherpesvirinae	Epithelial cells	Neuron
HHV 3 – Varicella Zoster virus	Alphaherpesvirinae	Epithelial cells	Neuron
HHV 4 - EBV	Gammaherpesvirinae	Epithelial cells and B – cells	B Lymphocytes
HHV 5 - CMV	Betaherpesvirinae	Lymphocytes, Macrophages and Endothelial cells	Macrophages, Lymphocytes
HHV 6	Betaherpesvirinae	CD_4 T cells	Lymphocytes
HHV 7	Betaherpesvirinae	T cells	T Lymphocytes
HHV8	Gammaherpesvirinae	Lymphocytes	Lymphocytes and

Herpes Simplex Virus 1/2

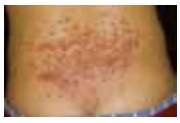
HSV - 1

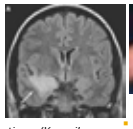
- Initial presentation:
  - Prodrome
  - **Gingivostomatitis**
- Recurrent lesions:
  - **Herpetiform vesicles on the vermilion border of lip**

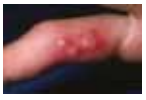
HSV 2

- Initial presentation:
  - Frequently asymptomatic
  - **Painful, erosive balanitis, vulvitis or vaginitis**
- Usually mild recurrence with resolution within 1 week

Other Clinical Presentations







- Eczema herpeticum (Kaposi's varicelliform eruption)
  - Infection in areas of dermatitis/skin barrier disruption
- Herpes Folliculitis
- Encephalitis
  - Temporal lobe
- Herpetic whitlow
- Ocular infections
  - branching dendritic corneal lesions
- Herpes Gladiatorum
- Chronic enlarging ulcers
- Neonatal HSV infection

Diagnosis / Treatment

DIAGNOSIS

- Tzanck smear
  - Multinucleated giant cells
- Direct Fluorescent antibody assay (DFA)
- Viral Culture
- Western Blot

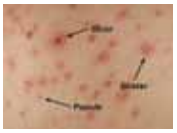
TREATMENT

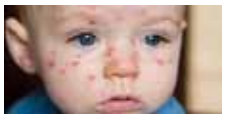
- Oral Antiviral medications
  - Orolabial Herpes and Genital Herpes (initiate within 24-48hrs of onset)
- **Foscarnet is used when acyclovir-resistant HSV is present**
- Chronic suppression in those with $\geq$ 6 outbreaks per year

Varicella-Zoster Virus (HHV-3)

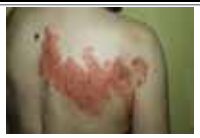
VARICELLA

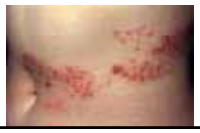
- Prodrome
- Clinically: pruritic, erythematous macules, papules and vesicles with a surrounding red halo (**"dew drop on a rose petal"**)
- **lesions in all stages of development**
- Patient is infectious from 1-2 days prior to presentation of skin lesions until all of the vesicles have crusted over





Varicella Zoster





- **Dormant in the dorsal root ganglion** and appears upon reactivation
- Prodrome of pruritus, tingling, tenderness, hyperesthesia and/or intense pain
- Development of painful **grouped vesicles on an erythematous base in a dermatomal distribution**
  - Can involve more than one dermatome and cross midline

Other Clinical Presentations

RAMSAY HUNT SYNDROME

- Reactivation involving the **geniculate ganglion of the facial nerve**
- Can cause ear pain, hearing loss, facial paralysis and loss of taste to anterior 2/3 of the tongue

HUTCHINSON SIGN

- Zoster affecting the nasal tip can lead to blindness due to direct effects on ophthalmic division of CN V1 via **nasociliary nerve**

Diagnosis

DIAGNOSIS

- Diagnosis is usually made clinically
- Tzanck smear and/or DFA
  - DFA used to differentiate between HSV and VZV
- Viral culture
- Serology
  - Requires fourfold increase in VZV titer to reveal positive test
- PCR
  - Use increasing, highly sensitive and rapid test

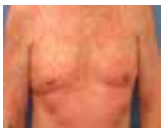
TREATMENT

- Symptomatic treatment
- Oral Antiviral medications within 24-72 hrs
- Vaccine recommended for all immunocompetent individuals >60

Human Herpes Virus 4 (EBV)

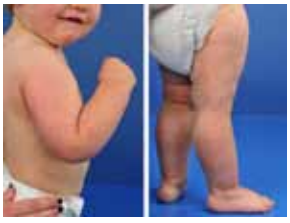
Infectious Mononucleosis:

- Prodrome
- Triad: fever, pharyngitis and lymphadenopathy
  - Nonspecific erythematous, morbilliform rash on trunk and proximal extremities with spread to face and forearms
  - Palatal petechiae
  - Hepatosplenomegaly
- Ampicillin-induced eruption
  - Hypersensitivity reaction
- Diagnosis: Monospot Test (specific), PCR, EBV titers
- Treatment: Supportive



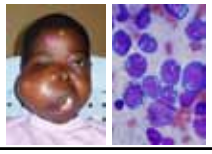
Gianotti-Crosti Syndrome

- "Infantile Papular Acrodermatitis"
- Self limited infection of young children
- EBV and HBV likely causes
- Clinically:
  - Abrupt onset of flesh-colored to pink-red papules on the cheeks, buttocks and extremities
- Treatment: supportive



EBV Lymphoproliferative Disorders

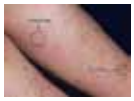
- Nasopharyngeal carcinoma
- Burkitt's lymphoma
  - EBV found as latent infection in 97% of endemic, 15-85% of sporadic and 30-40% of AIDS-linked Burkitt's lymphoma cases
  - Common African manifestation



Human Herpes Virus 5 (CMV)

MONONUCLEOSIS-LIKE SYNDROME

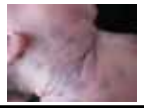
- Mononucleosis-like syndrome
  - Morbilliform eruption
  - Petechiae and purpura
  - Urticaria
  - Erythema nodosum
  - Ampicillin-induced eruption



CONGENITAL INFECTION

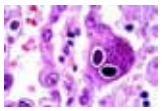
Congenital Infections:
"Blueberry muffin" lesions
(Extramedullary erythropoiesis)
Petechiae and purpura
Deafness, retardation

AIDS patients:
CMV retinitis → blindness



Human Herpes Virus 5 (CMV)

- Diagnosis:
- Serology, PCR, Cultures, CMV Antigenemia assay
- Biopsy of cutaneous lesions
  - **Intranuclear inclusions ("owl's eyes")**

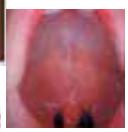


- Treatment:
- Uncomplicated CMV
  - Supportive
- Immunocompromised pts or complicated infections
  - Systemic therapy
    - Ganciclovir Intravenous
    - Valganciclovir Oral
    - Cidofovir
    - Foscarnet

Human Herpes Virus 6

ROSEOLA

- "Exanthem Subitum", "Sixth Disease"
- Clinically
  - Abrupt onset of high fever lasting 3-5 days followed by elliptical rose colored macules or papules on the trunk
  - **Nagayma spots** – red papules on the soft palate
  - **Berliners sign** – palpebral edema
- Complications
  - **Febrile seizures**
- Treatment: supportive



Human Herpes Virus 7

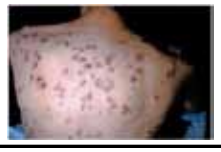
PITYRIASIS ROSEA

- Association with HHV-6 / 7
- Self limited papulosquamous eruption along Langer's lines of cleavage **(Christmas tree pattern).**
- Initial sign is a larger annular salmon colored plaque, **"Herald Patch"**

Human Herpes Virus – 8 (Kaposi Sarcoma-Associated Herpesvirus)

KAPOSI'S SARCOMA

- **Classic**
  - Red-purple plaques on lower extremities in older pts of Mediterranean descent.
- **AIDS-related**
  - Widely distributed: skin, oral and genital mucosa, GI tract
- **Immunosuppression-associated**
  - Exogenous immunosuppression
- **African endemic**
  - Aggressive form seen in young pts in Africa



Human Herpes Virus – 8 (Kaposi Sarcoma-Associated Herpesvirus)

HISTOLOGY

- Spindle cells forming slit-like vascular spaces
- "Promentory sign"
- Other associations:
  - Castleman's disease
  - Primary effusion lymphoma

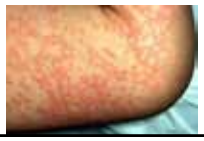
TREATMENT

- HAART IF AIDS-related
- Topical retinoids
- Surgery
- Radiation
- Systemic chemotherapy

Parvo Virus

Erythema Infectiousum

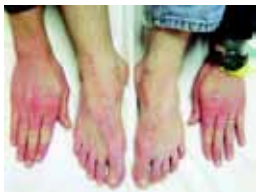
- "Slapped Cheek", "Fifth Disease"
- Self-limited course
- Clinically:
  - Bright red macular erythema over the cheeks and lacy reticulated eruption on the extremities following cessation of fever



Parvo Virus

PAPULAR PURPURIC GLOVES AND SOCKS SYNDROME

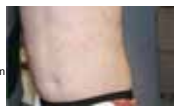
- Parvo B19
- Self-limited
- Clinically:
  - Erythema, edema, petechial and purpura involving the palms and soles
  - +/- associated burning and pruritus

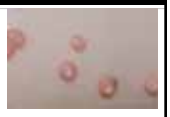


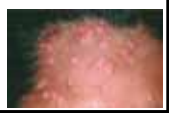
Molluscum Contagiousum

MOLLUSCIPOX VIRUS

- Self-limited condition
- Clinically:
  - Pink umbilicated papules
  - Larger lesions in AIDS pts
- Diagnosis:
  - Clinical, histology showing Henderson Patterson Bodies
- Treatment:
  - Cantharidin, Curretage, Cryotherapy, Zymaderm, Tretinoin, Imiquimod



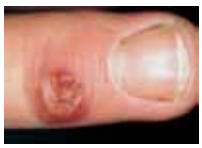




Milker's Nodule

PSUEDOCOWPOX / PARAVACCINA

- Parapox virus
- Self limited condition due to direct contact with infected cows or calves
- Clinically:
  - Slow growing solitary red-violaceous nodule on the finger
- Treatment:
  - supportive

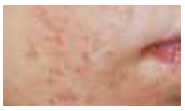


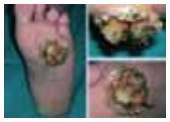
Human Papilloma Virus

- Non-enveloped dsDNA virus
- Infects basal keratinocytes in epithelium/mucosa
- Transmitted via direct skin contact
- Many subtypes and variable clinical presentation

Warts!

- Common – 1,2,4
- Plantar – 1
- Flat – 3, 10
- Butcher's – 7

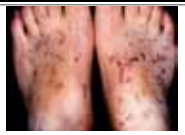


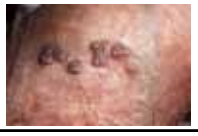


- Condylomma accuminata – 6, 11
- Verrucous carcinoma – 6,11

HPV subtypes

- Heck's disease – 13,32
- Epidermodysplasia verruciformis – 5, 8
- Bowenoid papulosis – 16,18
- Digital SCC – 16
- Cervical cancer – 16,18



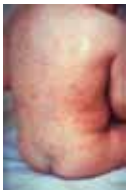


Measles

- Rubeola or "First disease"
- RNA virus, Paramyxovirus
- Clinically:
  - Prodrome
  - Koplik spots – buccal mucosa
  - Erythematous macules/papules on forehead, hairline, behind ears that spreads caudad
- Encephalitis (SSPE), otitis media, pneumonia, myocarditis

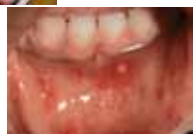
Rubella

- German measles or "Third disease"
- ssRNA virus, togavirus
- Clinically:
  - Mild prodrome with tender lymphadenopathy
  - Erythematous macules and papules on the face then spreads
- Soft palate petechiae = Forschheimer spots
- Arthritis/arthralgias, hepatitis, myocarditis, pneumonia



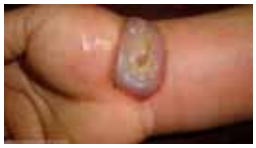
Hand-Foot-Mouth Disease

- RNA enteroviruses
  - Coxsackievirus A16
  - Enterovirus 71
- Clinically:
  - Fever, anorexia, abdominal pain
  - Elliptical grayish vesicles, pustules, erosions on hands, feet and buttocks
  - Vesicles, erosions on a red base in the mouth
- Myocarditis, pneumonia, meningoencephalitis



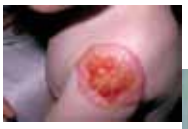
Orf

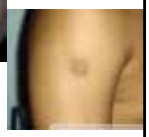
- Ecthyma contagiosum
- dsDNA virus, Parapox
- Transmitted via contact with goats/sheep
- Clinically:
  - Fever and lymphadenitis
  - Stages: maculopapular, targetoid, acute, regenerative, papillomatous, regressive



Vaccinia

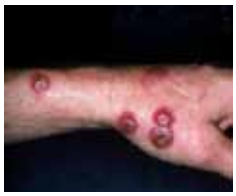
- dsDNA orthopox virus
- Local reaction to site of smallpox vaccination with live virus
- Clinically:
  - Erythema or pruritic papule
  - Heals with pitted scarring
- Eczema vaccinatum





Cowpox

- dsDNA orthopox virus
- Transmitted via an infected cow
- Clinically:
  - Site of contact with painful inflamed macule or papule that becomes vesicular then pustular with ulceration
  - Deep seated black eschar with erythema
  - Heals with scarring



References

- Jain, Sima. Dermatology. Springer, NY; 2012.
- Bologna, JL. et al. Dermatology 3rd Edition. Elsevier Saunders, Philadelphia; 2012.

INFECTIOUS DISEASES: BACTERIAL INFECTIONS

SAMPSON REGIONAL MEDICAL CENTER

Laura Sandoval, DO, PGY-3
Brianna McDaniel, DO, PGY-2
Angela Macri, DO, PGY-2

OBJECTIVES

- Describe bacterial skin infections commonly seen in the outpatient setting, including presentation, diagnosis, and treatment.
- Discuss antibiotic resistance and current recommendations.
- Discuss dermatologic surgical site infections.
- Describe infections associated with cosmetic procedures.

Common Bacterial Infections

MRSA

- MC of skin and soft-tissue infections in US since 1970's, prior was *Streptococcus pyogenes*
- 2 major subtypes of *S aureus:* Methicillin-sensitive *S aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA)
- MRSA-community associated (CA): Development in individual w/out h/o MRSA isolation or if + culture obtained in outpatient setting or w/in 48 hours of hospitalization
- Health care–associated (HA) MRSA: strain isolated in pt w/in 48 hours of hospitalization w/ risk factors of resistant infection (dialysis, previous colonization, surgery in past yr, a permanent medical device or catheter, or hospital, hospice, or nursing home admission)

Lloyd KM, Schammel L. Clinical Progression of CA-MRSA Skin and Soft Tissue Infections: A New Look at an Increasingly Prevalent Disease. Arch Dermatol. 2008;144(7):952-954.

MRSA

- Increased resistance to methicillin due to staphylococcal chromosome cassette mec (SCC mec), specifically **mecA** gene.
- Panton-Valentine leukocidin (PVL): in many CA- MRSA strains, associated with increased virulence(leukocyte destruction, necrosis).
- TSST-1: Staph superantigen involved in toxic shock syndrome.
- Exfoliative toxin (ET-A, ET-B): has protease activity, splitting desmoglein 1 at granular layer and can cause staphylococcal scalded skin syndrome and bullous impetigo

Moran GJ, Abrahamian FM, LoVecchio F, Talan DA. Acute Bacterial Skin Infections: Developments Since the 2005 Infectious Diseases Society of America (IDSA) Guidelines. J Emerg Med. 2013 Jun;44(6)e397-e412.

ABSCESS

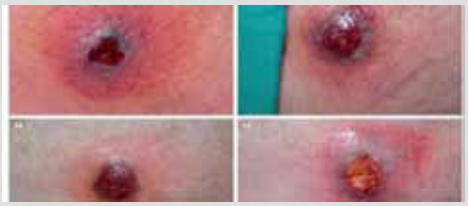
- MRSA can cause varied morphologies including abscesses, cellulitis, furuncles, carbuncles, folliculitis, impetigo, or paronychia to name a few.
  - Abscesses: collections of pus within the dermis and deeper skin tissues
  - Furuncle ("boil"): hair follicle infection in which purulent material extends through dermis into subcutaneous tissue → small abscess forms
  - Carbuncle: coalescence of several inflamed follicles into a single inflammatory mass with purulent drainage from multiple follicles
    - back of neck, face, axillae, and buttocks are common areas of involvement

Lloyd KM, Schammel L. Clinical Progression of CA-MRSA Skin and Soft Tissue Infections: A New Look at an Increasingly Prevalent Disease. Arch Dermatol. 2008;144(7):952-954.

MRSA

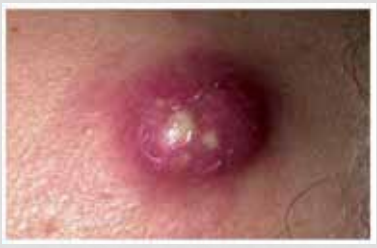
Medscape http://emedicine.medscape.com/article/228816-overview

MRSA



Lloyd KM, Schammel L. Clinical Progression of CA-MRSA Skin and Soft Tissue Infections: A New Look at an Increasingly Prevalent Disease. *Arch Dermatol.* 2008;144(7):952-954.

FURUNCLE



ABSCESS

- Skin and soft tissue caused by MRSA infections do not always produce pus and abscesses.
- MC presenting symptom: inflammation and necrosis. Pain and tenderness out of proportion to clinical presentation.
- Despite appropriate diagnosis and effective tx, response to tx can exceed 6 weeks.
- DDx of lesions with necrotic papules with marked inflammation:
  - brown recluse spider bites
  - cutaneous anthrax
  - cutaneous tularemia
  - cutaneous diphtheria
  - vibrio vulnificus infections

Lloyd KM, Schammel L. Clinical Progression of CA-MRSA Skin and Soft Tissue Infections: A New Look at an Increasingly Prevalent Disease. Arch Dermatol. 2008;144(7):952-954.

DDX FOR ABSCESS

- Other diagnoses to consider:
  - Folliculitis
  - Hidradenitis suppurativa
  - Sporotrichosis
  - Myiasis
  - Botryomycosis
  - Blastomycosis

Zabielinski M, McLeod M, Aber C, Izakovic J, Schachner L. Trends and antibiotic susceptibility patterns of methicillin-resistant and methicillin-sensitive Staphylococcus aureus in an outpatient dermatology facility. *JAMA Dermatol*. April 2013;149(4):427-432.
Lloyd KM, Schammel L. Clinical Progression of CA-MRSA Skin and Soft Tissue Infections: A New Look at an Increasingly Prevalent Disease. *Arch Dermatol.* 2008;144(7):952-954.

TREATMENT OF ABSCESSES

- Gram stain and culture are recommended, but treatment without these studies is reasonable in typical cases.
- Incision and drainage (I&D) is the recommended treatment for inflamed carbuncles, abscesses, and large furuncles.
- Patients with uncomplicated skin abscesses, I&D without administration of antibiotics sufficient.
  - Administration of antibiotics as an adjunct should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS).
- Antibiotic coverage for MRSA is recommended for patients with abscesses/carbuncles who have failed initial antibiotic treatment, have markedly impaired host defenses, or in patients with SIRS and hypotension.

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

TREATMENT OF ABSCESSES

- Recurrent abscesses:
  - I&D and culture early.
  - Treat with a 5 to 10 day course of an antibiotic effective against that pathogen.
  - Consider a 5-day decolonization regimen twice daily of intranasal Mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets and clothes for recurrent *S. aureus* infection.

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

SKIN SOFT TISSUE INFECTION TREATMENT

MSSA	
Nafcillin or oxacillin	1-2 g q4h IV
Cefazolin	1g q8h IV
Clindamycin	600 mg q8h IV or 300-450 mg qid PO
Dicloxacillin	500 mg qid PO
Cephalexin	500 mg qid PO
Doxycycline or Minocycline	100 mg bid PO
Trimethoprim-Sulfamethoxazole	1-2 DS tab bid PO

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

SKIN SOFT TISSUE INFECTION TREATMENT

MRSA	
Vancomycin	30 mg/kg/d in 2 divided doses IV
Linezolid	600 mg q12h IV or 600 mg bid PO
Clindamycin	600 mg q8h IV or 300-450 mg qid PO
Daptomycin	4 mg/kg every 24 h IV
Ceftaroline	600 mg bid IV
Doxycycline or Minocycline	100mg bid PO
Trimethoprim-Sulfamethoxazole	1-2 DS tab bid PO

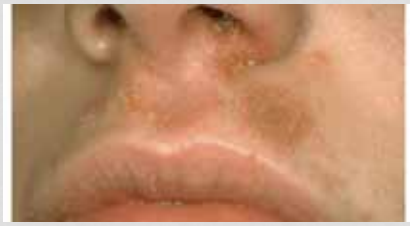
Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

IMPETIGO

- MC in children aged 2-5 years. MC infection in children worldwide.
- Group A strep (Streptococcus pyogenes) previously MCC, but now replaced by S. aureus.
- Nonbullous impetigo: accounts for 70% of cases→ erythematous papules and thin-walled vesicles on face and extremities . Can be painful. Usually resolve without tx in 2-3 weeks.
- Bullous impetigo: thin- roofed bullae and shallow erosions. S. aureus almost always causative pathogen(**phage II, type 71**). Develops in areas of trauma or intertriginous areas.

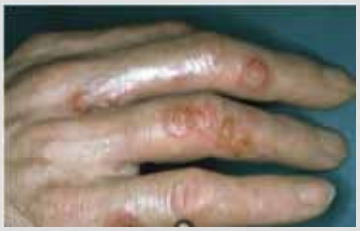
Bangert, S., Levy, M. and Hebert, A. A. Bacterial Resistance and Impetigo Treatment Trends: A Review. Pediatr Dermatol. 2012;29: 243–248.

NON-BULLOUS IMPETIGO



http://www.merckmanuals.com/professional/dermatologic-disorders/bacterial-skin-infections/impetigo-and-ecthyma

BULLOUS IMPETIGO



http://www.merckmanuals.com/professional/dermatologic-disorders/bacterial-skin-infections/impetigo-and-ecthyma

SECONDARY INFECTIONS

- Impetigo often complicates both acute and chronic skin diseases.
  - Atopic dermatitis
  - Psoriasis
  - Herpes Simplex Virus
  - Scabies
  - Poison Ivy
  - Pediculosis capitis
  - Insect bites

IMPETIGO TREATMENT

Oral	
Dicloxacillin	250 mg qid PO
Cephalexin	250 mg qid PO
Erythromycin	250 mg qid PO
Clindamycin	300-400 mg qid PO
Amoxicillin-clavulanate	875/125 mg bid PO
Topical	
Retapmulin ointment	Apply BID
Mupirocin 2% ointment	Apply BID

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

PARONYCHIA

- Caused by breakdown in barrier between nail plate and adjacent nail fold from minor trauma to nail bed →disrupts the fingertip's natural barrier to outside pathogens→ inoculation of perionychium.
- Paronychia often related to:
  - onychophagia (ie, nail biting)
  - finger sucking
  - picking at a hangnail
  - an ingrown nail
  - manicures
  - dishwashing,
  - puncture-type trauma w/ or w/out a retained foreign body
- Noninfectious etiologies such as chemical irritants, excessive moisture, systemic conditions, and medications also can cause paronychia.

Shafritz A, Coppage J. Acute and chronic paronychia of the hand. *J Am Acad Orthop Surg* .2014 March;22(3):165-174.

ETIOLOGY OF PARONYCHIA

- Acute form: < 6 weeks duration
  - *MCC S. Aureus.*
  - Other causative organisms include γ-hemolytic strep, Eikenella corrodens, group A b-hemolytic strep, and Klebsiella pneumoniae, Bacteroides, Fusobacteria species, Enterococcus faecalis, Proteus species, and Pseudomonas aeruginosa.
- Chronic: > 6 weeks duration.
  - Usually caused by a fungal infection.

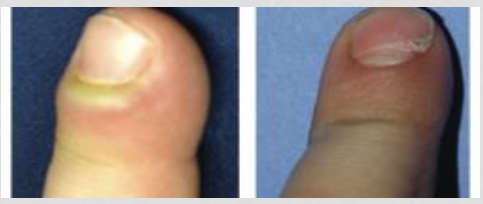
Shafritz A, Coppage J. Acute and chronic paronychia of the hand. *J Am Acad Orthop Surg* .2014 March;22(3):165-174.

PARONYCHIA PRESENTATION

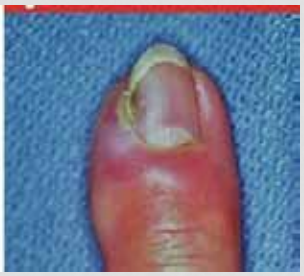
- Usually presents as localized pain, redness, inflammation, and edema of lateral nail fold typically limited to a single digit often 2-5 days after initial trauma.
- +/- Fluctuance of paronychium. Patients w/ delayed presentation may develop fluctuance extending around nail, involving eponychium as well as paronychium on both the radial and ulnar sides of the digit (ie, runaround infection).
- +/- Purulence may develop underneath the nail plate, causing the nail plate to pull away from sterile matrix.

Shafritz A, Coppage J. Acute and chronic paronychia of the hand. *J Am Acad Orthop Surg* .2014 March;22(3):165-174.
Durdu M, Ruocco V. Clinical and cytologic features of antibiotic-resistant acute paronychia. J Am Acad Derm. 2014 Jan; 70(1)120-126.

ACUTE PARONYCHIA



Shafritz A, Coppage J. Acute and chronic paronychia of the hand. *J Am Acad Orthop Surg*. 2014 Mar;22(3):165-174.



Shafritz A, Coppage J. Acute and chronic paronychia of the hand. *J Am Acad Orthop Surg*. 2014 Mar;22(3):165-174.

PARONYCHIA TREATMENT

- The most common organism causing acute paronychia is *S aureus*, followed by *S pyogenes, Pseudomonas pyocyanea*, and *Proteus vularis*.
- Can be treated with warm water soaks 3-4 x per day (with or without povidone or chlorhexidine) and oral antibiotics.
- If an abscess is present, I&D is recommended in conjunction with oral antibiotics.
- Cephalexin, clindamycin, or amoxicillin plus clavulanate have a wide spectrum of activity against most pathogens isolated from paronychia.
  - In areas where local methicillin-resistant *S aureus* penetration is relatively high, clindamycin remains a better option than amoxicillin plus clavulanate.
  - Oral trimethoprim-sulfamethoxazole can also be considered as a first-line agent.
- Removal of part of the nail plate may be required.

Osterman M, Draeger R, Stern P. Acute hand infections. J Hand Surg Am. 2014 Aug;39(8):1628-33.
Ritting AW, O'Malley MP, Rodner CM. Acute paronychia. J Hand Surg Am. 2012 May;37(5):1068-70.

CELLULITIS

- Infection of deep dermis and subcutaneous tissue presenting as ill-defined area with erythema, swelling, and tenderness. +/- fever, chills
- Caused by disruption in skin barrier in immunocompetent patients
- Predisposing factors: previous attack of cellulitis, older age, obesity, venous insufficiency, saphenous venectomy in CABG patients, edema, and a skin surface disrupted by trauma, ulceration, or inflammatory diseases of the skin, such as allergic contact dermatitis, atopic dermatitis, and venous eczema

Gunderson CG. Cellulitis: Definition, Etiology, and Clinical Features. Am J Med. 2011, 124(12):1113-1122.
Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: Part I. Lower limb cellulitis, J Am Acad Dermatol. 2012 Aug;67(2):163.e1-163.e12.

CELLULITIS

Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: Part I. Lower limb cellulitis, J Am Acad Dermatol. 2012 Aug;67(2):163.e1-163.e12.

ETIOLOGY OF CELLULITIS

- MCC: group A strep (GAS), often residing in interdigital toe spaces; less commonly S. Aureus.
  - Purulent cellulitis usually caused by MRSA
- Erysipelas: specific type of cellulitis involving more super- ficial dermal structures and distinguished clinically by raised borders and clear demarcation between involved and uninvolved skin.
  - Predominantly due to beta-hemolytic streptococci
- Infection with GAS causes antistreptolysin O (**ASO**), **anti-hyaluronidase**, and **anti-Dnase-B** antibody positivity
- S. pyogenes erythrogenic exotoxins: **SPE-A, SPE-B, SPE-C**

Gunderson CG. Cellulitis: Definition, Etiology, and Clinical Features. Am J Med. 2011, 124(12):1113-1122.
Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: Part I. Lower limb cellulitis, J Am Acad Dermatol. 2012 Aug;67(2):163.e1-163.e12.

CELLULITIS MIMICKERS

- Infectious
  - Necrotizing fasciitis
  - Erysipelas
  - Cutaneous abscess
  - Herpetic whitlow
  - Erythema migrans
- Dermatologic
  - Stasis dermatitis
  - Hypersensitivity reaction
  - Fixed drug reaction
- Inflammatory
  - Acute arthritis (gout)
  - Acute bursitis

Can be difficult to diagnose….
***74% of in-patient dermatology consults for cellulitis were pseudocellulitis*

Gunderson CG. Cellulitis: Definition, Etiology, and Clinical Features. Am J Med. 2011, 124(12):1113-1122.
Strazzula L, et al. Inpatient dermatology consultation aids diagnosis of cellulitis among hospitalized patients: A multi-institutional analysis. J Am Acad Dermatol. 2015 Jul;73(1):70-5.

CELLULITIS TREATMENT

- Cultures of blood, cutaneous aspirates, biopsies, and swabs are not routinely recommended.
  - Blood cultures however should be taken if systemic signs are present
    or
  - In patients with malignancy on chemotherapy, neutropenia, severe cell mediated immunodeficiency, immersion injuries, and animal bites.
- Typical cases of cellulitis should receive treatment against streptococci. Many clinicians also include coverage for MSSA.
- For coverage of streptococci and MRSA, use clindamycin or TMP-SMX w/ a B-lactam.

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

CELLULITIS TREATMENT

- When systemic signs of infection are present, inpatient treatment with intravenous antibiotics are indicated.
- For patients whose cellulitis is associated with penetrating trauma, MRSA infection elsewhere, IVDA, or SIRS, use vancomycin or another antimicrobial effective against both MRSA and streptococci.
- In severely compromised patients broad-spectrum antimicrobial coverage considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended for severe infections.

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

CELLULITIS TREATMENT

- Necrotizing infections require emergent debridement with IV antibiotics.
- The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved.
- Hospitalize if: there is a concern for deeper or necrotizing infection, cases of poor compliance, for those severely immunocompromised, or if outpatient treatment is failing.
- In lower extremity cellulitis, carefully examine the interdigital toe spaces because treating fissuring, scaling, or maceration may eradicate colonization with pathogens and reduce the incidence of recurrent infection.
- Prophylactic antibiotics, such as oral penicillin or erythromycin bid for 4-52 weeks, or IM benzathine penicillin every 2-4 weeks should be considered in those who have 3-4 episodes of cellulitis per year despite attempts to control predisposing factors.

Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue

ANTIBIOTIC RESISTANCE

- Antibiotics are among the most commonly prescribed drugs, however, up to 50% of the time antibiotics are not optimally prescribed, often done so when not needed, incorrect dosing or duration. (CDC)
- Staphylococcus epidermidis (S. epidermidis) is completely resistant to erythromycin and partially resistant to clindamycin and tetracycline after 12 weeks of treatment.
  - Evidence suggest the use of topical erythromycin and clindamycin – the most commonly used topical antibiotics in acne – has contributed to the gradual increase in resistance over the last 20 years. (Humphrey)

"Antibiotic/antimicrobial resistance, biggest threats." Centers for Disease Control and Prevention. Last updated Aug. 26,2015. Last accessed Sep. 1,2015. http://www.cdc.gov/drugresistance/biggest_threats.html.
Singh S. Antibacterial Treatment for Uncomplicated Skin Infections. N Engl J Med. 2015Jun18;372(25):2459-60.
Humphrey S. Antibiotic resistance in acne treatment. Therapy Lett. 2012 Oct;17(9):1-3.

ANTIBIOTIC RESISTANCE

- Dermatologist prescribed 9.5 million antibiotic prescriptions in 2009
  - Tetracyclines 69%
  - Cephalophorins 11%
  - TMP-SMX 7.5%
  - Aminopenicillins 5.1%
  - Macrolides 3.3%

Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. *Cutis* 2007;79:9-25.

ANTIBIOTIC RESISTANCE

- Tetracycline-resistant and erythromycin or clindamycin-resistant strains of *P acnes* were found in 20 and 50% of patients, respectively, in a European study.
- Resistance has also been found in other pathogens commonly associated with dermatology:
  - Macrolide-resistant *S. pyogenes* and *S. aureus*
  - Mupirocin-resistant *S. aureus*
  - Vancomycin-resistant *S. aureus*
  - Quinolone-resistant *S. aureus, P. aeruginosa,* and mycobacteria

Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. *Cutis* 2004;74:118-122.
Cooper AJ. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. *Med J Aust* 1998;169:259-261.
Ross JI, Snelling AM, Carnegie E et al. Antibiotic-resistant acne: lessons from Europe. *Br J Dermatol* 2003;148:467-478.

ANTIBIOTIC RESISTANCE

- Sub-antimicrobial doses doxycycline (20 mg BID) compared with antimicrobial doses (100 mg QD) in patients with moderate facial acne, both treatments significantly decreased inflammatory lesion counts
  - 20 mg dose led to an 84% and 90% reduction in the number of papules and pustules, respectively.
- Sub-antimicrobial dosing should be considered when possible to decrease the incidence of resistance and is being used in areas of medicine other than dermatology.

Toossi P, Farshchian M, Malekzad F, Mohtasham N, Kimyai-Asadi A. Subantimicrobial-dose doxycycline in the treatment of moderate facial acne. *J Drugs Dermatol* 2008;7:1149-1152.
Preshaw PM, Hefti AF, Jepsen S, Etienne D, Walker C, Bradshaw MH. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis. A review. *J Clin Periodontol* 2004;31:697-707.

DERMATOLOGIC SURGERY AND WOUND INFECTIONS

- Post-surgical wound infections are the most common adverse effect, but are not that common.
- In a large, multicenter, prospective study of Mohs procedures, there were 83 (0.4%) reported infections out of 20, 821 cases.
  - Similar low rates have been reported in smaller, multicenter prospective studies (0.07-0.9%).

Alam M, Ibrahim O, Nodzenski M et al. Adverse events associated with mohs micrographic surgery: multicenter prospective cohort study of 20,821 cases at 23 centers. *JAMA Dermatol* 2013;149:1378-1385.
Elliott TG, Thom GA, Litterick KA. Office based dermatological surgery and Mohs surgery: a prospective audit of surgical procedures and complications in a procedural dermatology practice. *Australas J Dermatol* 2012;53:264-271.
Merritt BG, Lee NY, Brodland DG, Zitelli JA, Cook J. The safety of Mohs surgery: a prospective multicenter cohort study. *J Am Acad Dermatol* 2012;67:1302-1309.

PREVENTING SURGICAL SITE INFECTIONS

Antibiotic prophylaxis or not?

- Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008 (JAAD) states antibiotics may be indicated for:
  - Procedures on the lower extremities or groin
  - Wedge excisions of the lip and ear
  - Skin flaps on the nose
  - Skin grafts
  - For patients with extensive inflammatory skin disease
  - For patients with high-risk cardiac conditions & a defined group of patients with prosthetic joints when the procedure involves breach of the oral mucosa
- Recent survey study sent to Mohs surgeons concluded dermatologic surgeons overuse perioperative antibiotics for prevention of surgical site infection, infective endocarditis, and prosthetic joint infection based on current recommendations.

Wright TI, Baddour LM, Berbari EF et al. Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008. *J Am Acad Dermatol* 2008;59:464-473
Bae-Harboe YS, Liang CA. Perioperative antibiotic use of dermatologic surgeons in 2012. *Dermatol Surg* 2013;39:1592-1601.

PREVENTING SURGICAL SITE INFECTIONS

Prepping of the skin

- A 2015 Cochrane review of current evidence found *some* evidence that preoperative skin preparation with 0.5% chlorhexidine in methylated spirits was associated with lower rates of surgical site infections following clean surgery than alcohol-based povidone iodine paint, however this data was from a poor single study.
- A similar review of literature found that while there are few well-controlled studies demonstrating superiority of a given regimen, alcohol-based iodophor and chlorhexidine products seem to exhibit greater efficacy than their aqueous counterparts.
- Both concluded ultimately it is up to the surgeon to choose and that future studies are needed.

Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2015;4:CD003949.
Echols K, Graves M, LeBlanc KG, Marzolf S, Yount A. Role of antiseptics in the prevention of surgical site infections. *Dermatol Surg* 2015;41:667-676.

PREVENTING SURGICAL WOUND INFECTIONS

How sterile do we need to be?

- In a prospective comparison study of 1,255 Mohs cases, infection risk was the same between high-cost (n = 5, 0.9%) and low-cost groups (n = 5, 0.7%).
  - High cost=
    - Sterile gloves for all stages & closure
    - Sterile half-drape for closure
    - Sterile knee length gown for closure
  - Low cost=
    - Sterile gloves for closure only
  - Concluded that It may be possible to further reduce costs without altering infection rate by using clean, nonsterile gloves during reconstruction as well.

Lilly E, Schmults CD. A comparison of high- and low-cost infection-control practices in dermatologic surgery. *Arch Dermatol* 2012;148:859-861.

PREVENTING SURGICAL WOUND INFECTIONS

Sterile gloves vs non-sterile gloves

- In 2,025 Mohs cases, there was no increase in prevalence of infection using sterile glove for both excision and reconstruction (0.5%) compared to the using non-sterile gloves (0.49%)
  - The cost of gloves was $5.66 for 1 sterile glove case and $1.63 for 1 non-sterile case
- Similar results were seen in previous smaller studies

Mehta D, Chambers N, Adams B, Gloster H. Comparison of the prevalence of surgical site infection with use of sterile versus nonsterile gloves for resection and reconstruction during Mohs surgery. *Dermatol Surg* 2014;40:234-239.
Xia Y, Cho S, Greenway HT, Zelac DE, Kelley B. Infection rates of wound repairs during Mohs micrographic surgery using sterile versus nonsterile gloves: a prospective randomized pilot study. *Dermatol Surg* 2011;37:651-656.
Rhinehart MB, Murphy MM, Farley MF, Albertini JG. Sterile versus nonsterile gloves during Mohs micrographic surgery: infection rate is not affected. *Dermatol Surg* 2006;32:170-176.

PREVENTING SURGICAL WOUND INFECTIONS

Topical antibiotics vs petrolatum/paraffin

- In a recent systematic review and meta-analysis, there was no statistically significant difference in incidence of postsurgical wound infections between the use of topical antibiotics and petrolatum/paraffin.
- There was also no significant difference between applying and not applying ointment to surgical wounds.
- Wounds at increased risk of developing surgical site infections
  - wounds in diabetics
  - wounds located in certain anatomic regions
  - wounds created by some surgical procedures

Saco M, Howe N, Nathoo R, Cherpelis B. Topical antibiotic prophylaxis for prevention of surgical wound infections from dermatologic procedures: a systematic review and meta-analysis. *J Dermatolog Treat* 2015;26:151-158.

COSMETIC PROCEDURES AND INFECTIONS

Dermal Fillers

- According to a recent JAAD CME article, infections associated with cosmetic procedures are rare
  - 0.2% infections with soft tissue filler injections
    - 4 cases of cellulitis with calcium hydroxylapatite filler out of 2,089 soft filler injections
- Rare infections can occur:
  - 3 cases of mycobacterium chelonae from one plastic surgery clinic
    - Source was tap water from clinic→ pts used nonsterile ice pre-procedure

Lolis M, Dunbar SW, Goldberg DJ, Hansen TJ, MacFarlane DF. Patient safety in procedural dermatology: Part II. Safety related to cosmetic procedures. *J Am Acad Dermatol* 2015;73:15-24.
Daines SM, Williams EF. Complications associated with injectable soft-tissue fillers: a 5-year retrospective review. *JAMA Facial Plast Surg* 2013;15:226-231.
Rodriguez JM, Xie YL, Winthrop KL et al. Mycobacterium chelonae facial infections following injection of dermal filler. *Aesthet Surg J* 2013;33:265-269

COSMETIC PROCEDURES AND INFECTIONS

Lasers

- Reported bacterial infection rates post-CO2 procedures range from 2.2%-8.2%, with some evidence that antibiotic prophylaxis may decrease infection rates.

- Rare infections have been reported:
  - M. chelonae skin infection has been associated with ablative laser procedures such as CO2 and fractional CO2 laser resurfacing.
  - M. chelonae skin infection developed 1 week after a hair removal session with variable-pulsed alexandrite laser performed on both legs at a beauty center.

Uslan DZ, et al. Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. *Arch Dermatol* 2006;142:1287-1292.
Culton DA, et al. Nontuberculous mycobacterial infection after fractionated CO(2) laser resurfacing. *Emerg Infect Dis* 2013;19:365-370.
Palm MD, et al. Mycobacterium chelonae infection after fractionated carbon dioxide facial resurfacing (presenting as an atypical acneiform eruption): case report and literature review. *Dermatol Surg* 2010;36:1473-1481.
Shamsaldeen O, et al. The adverse events of deep fractional CO(2): a retrospective study of 490 treatments in 374 patients. *Lasers Surg Med* 2011;43:453-456.
Manuskiatti W, et al. Prophylactic antibiotics in patients undergoing laser resurfacing of the skin. *J Am Acad Dermatol* 1999;40:77-84

REFERENCES

- Zabielinski M, McLeod M, Aber C, Izakovic J, Schachner L. Trends and antibiotic susceptibility patterns of methicillin-resistant and methicillin-sensitive Staphylococcus aureus in an outpatient dermatology facility. *JAMA Dermatol*. April 2013;149(4):427-432. D.M.
- Elston. Community-acquired methicillin-resistant Staphylococcus aureus. J Am Acad Dermatol, 56 (2007), pp. 1–16.
- Kirkland EB, Adams BB. Methicillin-resistant Staphylococcus aureus and athletes. J Am Acad Dermatol. 2008 Sep;59(3):494-502.
- Lloyd KM, Schammel L. Clinical Progression of CA-MRSA Skin and Soft Tissue Infections: A New Look at an Increasingly Prevalent Disease. *Arch Dermatol*. 2008;144(7):952-954.
- Bangert S, Levy M, Hebert A A. Bacterial Resistance and Impetigo Treatment Trends: A Review. Pediatr Dermatol. 2012;29: 243–248.
- Moran GJ, Abrahamian FM, LoVecchio F, Talan DA. Acute Bacterial Skin Infections: Developments Since the 2005 Infectious Diseases Society of America (IDSA) Guidelines. J Emerg Med. 2013 Jun;44(6):e397-e412.
- Shafritz A, Coppage J. Acute and chronic paronychia of the hand. *J Am Acad Orthop Surg*. 2014 Mar;22(3):165-174.
- Durdu M, Ruocco V. Clinical and cytologic features of antibiotic-resistant acute paronychia. J Am Acad Derm. 2014 Jan; 70(1)120-126.
- Gunderson CG. Cellulitis: Definition, Etiology, and Clinical Features. Am J Med. 2011, 124(12):1113-1122.

REFERENCES

- Stevens, D. "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". Infectious Diseases Society of America. Accessed 9/1/2015. http://www.idsociety.org/Organ_System/#Skin%20&%20Soft%20Tissue
- Hirschmann JV, Raugi GJ, Lower limb cellulitis and its mimics: Part I. Lower limb cellulitis, J Am Acad Dermatol. 2012 Aug;67(2):163.e1-163.e12.
- Osterman M, Draeger R, Stern P. Acute hand infections. J Hand Surg Am. 2014 Aug;39(8):1628-33.
- Ritting AW, O'Malley MP, Rodner CM. Acute paronychia. J Hand Surg Am. 2012 May;37(5):1068-70.
- Wright TI, Baddour LM, Berbari EF et al. Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008. *J Am Acad Dermatol* 2008;59:464-473.
- Bae-Harboe YS, Liang CA. Perioperative antibiotic use of dermatologic surgeons in 2012. *Dermatol Surg* 2013;39:1592-1601.
- Saco M, Howe N, Nathoo R, Cherpelis B. Topical antibiotic prophylaxis for prevention of surgical wound infections from dermatologic procedures: a systematic review and meta-analysis. *J Dermatolog Treat* 2015;26:151-158.

REFERENCES

- Martin JE, Speyer LA, Schmults CD. Heightened infection-control practices are associated with significantly lower infection rates in office-based Mohs surgery. *Dermatol Surg* 2010;36:1529-1536.
- Lilly E, Schmults CD. A comparison of high- and low-cost infection-control practices in dermatologic surgery. *Arch Dermatol* 2012;148:859-861.
- Mehta D, Chambers N, Adams B, Gloster H. Comparison of the prevalence of surgical site infection with use of sterile versus nonsterile gloves for resection and reconstruction during Mohs surgery. *Dermatol Surg* 2014;40:234-239.
- Xia Y, Cho S, Greenway HT, Zelac DE, Kelley B. Infection rates of wound repairs during Mohs micrographic surgery using sterile versus nonsterile gloves: a prospective randomized pilot study. *Dermatol Surg* 2011;37:651-656.
- Rhinehart MB, Murphy MM, Farley MF, Albertini JG. Sterile versus nonsterile gloves during Mohs micrographic surgery: infection rate is not affected. *Dermatol Surg* 2006;32:170-176.
- Elliott TG, Thom GA, Litterick KA. Office based dermatological surgery and Mohs surgery: a prospective audit of surgical procedures and complications in a procedural dermatology practice. *Australas J Dermatol* 2012;53:264-271.
- Merritt BG, Lee NY, Brodland DG, Zitelli JA, Cook J. The safety of Mohs surgery: a prospective multicenter cohort study. *J Am Acad Dermatol* 2012;67:1302-1309.
- Lolis M, Dunbar SW, Goldberg DJ, Hansen TJ, MacFarlane DF. Patient safety in procedural dermatology: Part II. Safety related to cosmetic procedures. *J Am Acad Dermatol* 2015;73:15-24.

REFERENCES

- Daines SM, Williams EF. Complications associated with injectable soft-tissue fillers: a 5-year retrospective review. *JAMA Facial Plast Surg* 2013;15:226-231.
- Rodriguez JM, Xie YL, Winthrop KL et al. Mycobacterium chelonae facial infections following injection of dermal filler. *Aesthet Surg J* 2013;33:265-269.
- De B, V, Ballestero M, Mendieta M, Gardeazabal J. Mycobacterium chelonae infection after laser hair removal. *J Am Acad Dermatol* 2013;69:e255-e257.
- Uslan DZ, Kowalski TJ, Wengenack NL, Virk A, Wilson JW. Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. *Arch Dermatol* 2006;142:1287-1292.
- Culton DA, Lachiewicz AM, Miller BA et al. Nontuberculous mycobacterial infection after fractionated CO(2) laser resurfacing. *Emerg Infect Dis* 2013;19:365-370.
- Palm MD, Butterwick KJ, Goldman MP. Mycobacterium chelonae infection after fractionated carbon dioxide facial resurfacing (presenting as an atypical acneiform eruption): case report and literature review. *Dermatol Surg* 2010;36:1473-1481.
- Shamsaldeen O, Peterson JD, Goldman MP. The adverse events of deep fractional CO(2): a retrospective study of 490 treatments in 374 patients. *Lasers Surg Med* 2011;43:453-456.
- Manuskiatti W, Fitzpatrick RE, Goldman MP, Krejci-Papa N. Prophylactic antibiotics in patients undergoing laser resurfacing of the skin. *J Am Acad Dermatol* 1999;40:77-84.
- Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2015;4:CD003949.

REFERENCES

- Echols K, Graves M, LeBlanc KG, Marzolf S, Yount A. Role of antiseptics in the prevention of surgical site infections. *Dermatol Surg* 2015;41:667-676.
- Strazzula L, Cotliar J, Fox LP et al. Inpatient dermatology consultation aids diagnosis of cellulitis among hospitalized patients: A multi-institutional analysis. *J Am Acad Dermatol* 2015;73:70-75.
- Alam M, Ibrahim O, Nodzenski M et al. Adverse events associated with mohs micrographic surgery: multicenter prospective cohort study of 20,821 cases at 23 centers. *JAMA Dermatol* 2013;149:1378-1385.
- Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. *Cutis* 2007;79:9-25.
- Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. *Cutis* 2004;74:118-122.
- Cooper AJ. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. *Med J Aust* 1998;169:259-261.
- Ross JI, Snelling AM, Carnegie E et al. Antibiotic-resistant acne: lessons from Europe. *Br J Dermatol* 2003;148:467-478.
- Alam M, Ibrahim O, Nodzenski M et al. Adverse events associated with mohs micrographic surgery: multicenter prospective cohort study of 20,821 cases at 23 centers. *JAMA Dermatol* 2013;149:1378-1385.

REFERENCES

- Elliott TG, Thom GA, Litterick KA. Office based dermatological surgery and Mohs surgery: a prospective audit of surgical procedures and complications in a procedural dermatology practice. *Australas J Dermatol* 2012;53:264-271.
- Merritt BG, Lee NY, Brodland DG, Zitelli JA, Cook J. The safety of Mohs surgery: a prospective multicenter cohort study. *J Am Acad Dermatol* 2012;67:1302-1309.
- Medscape http://emedicine.medscape.com/article/228816-overview
- http://www.merckmanuals.com/professional/dermatologic-disorders/bacterial-skin-infections/impetigo-and-ecthyma

Thank You!

Fungal Infections

Eugene Sanik, D.O.
3rd Year Dermatology Resident

Disclosures

- No financial relationships to disclose

Learning Objectives

- Understand the causes of fungal infections
- Illustrate and recognize their clinical presentations
- Review latest evidence-based treatment guidelines

Introduction to Mycology

- Fungi first appeared 1.5 billion years ago
- Among earliest organisms domesticated by humans
- Serious problem only since 20th century
- 1.5 million fungal species known
- Less than 100 are pathogenic to humans
- Except for dermatophytes, not contagious

Classification of Fungal Diseases

- Superficial
  - Do not have ability to invade skin, hair, or nails
- Cutaneous
  - Dermatophytes
- Deep
  - Localized subcutaneous (implantation or dermal spread)
  - Dimorphic systemic (hematogenous spread)
  - Opportunistic (immunocompromised patients)

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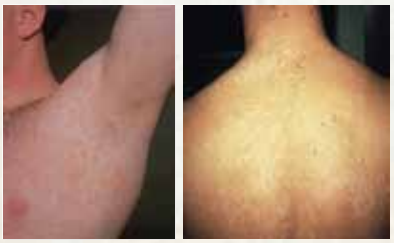
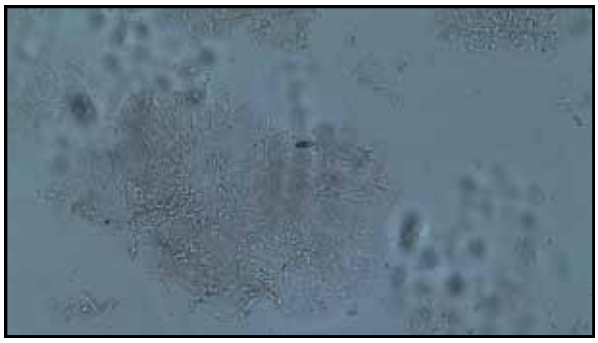
Superficial Fungal Infections

- Pityriasis versicolor
- Tinea nigra
- Black piedra
- White piedra

Pityriasis Versicolor

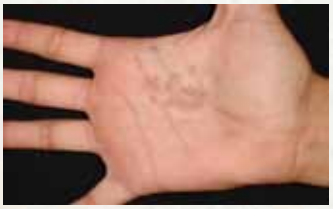




Treatment of Pityriasis Versicolor

- Topical ketoconazole very effective against *Malassezia*
- Oral fluconazole and itraconazole as effective with lower recurrence
- Oral ketoconazole not recommended (FDA warning)
- Oral terbinafine not effective

Tinea Nigra



Hortaea werneckii (melanin-producing yeast)

Black Piedra and White Piedra

Piedra Hortae

Trichosporon beigelii

Differential Diagnosis of Piedras

Trichomycosis axillaris
Corynebacterium

Head Lice
Pediculus humanus capitis

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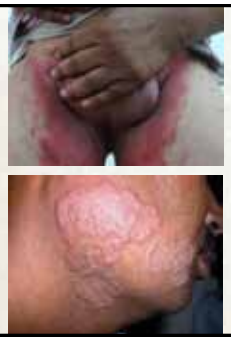
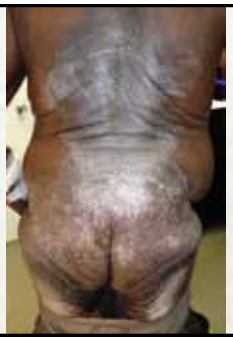
Cutaneous Mycoses

- Dermatophytoses of skin, hair, and nails
- Candidiasis of skin, mucous membranes, and nails
- Do not invade subcutaneous tissue

Dermatophytosis

- *Microsporum*, *Trichophyton*, and *Epidermophyton*
- Most common causes:
  - Tinea capitis – *T. tonsurans*
  - Tinea faciei – *T. rubrum*
  - Tinea corporis – *T. rubrum*
  - Tinea pedis – *T. rubrum*
  - Bullous tinea pedis – *T. mentagrophytes*
  - White superficial onychomycosis – *T. mentagrophytes*
  - Distal & proximal subungual onychomycosis – *T. rubrum*





Clinical and mycological effect of clotrimazole/betamethasone dipropionate cream versus ketoconazole cream in patients with tinea cruris

RJ Pariser & DM Pariser

- betamethasone did not compromise the antifungal effects of clotrimazole
- clinical endpoints consistently favored the combination drug, which relieved symptoms more rapidly

Evidence-based topical treatments for tinea cruris and tinea corporis: a summary of a Cochrane systematic review

- Once daily application is as effective as twice daily, with better compliance
- Azoles, benzylamines, and allylamines show no difference in clinical effectiveness
- Azole-corticosteroid combination achieved higher clinical cure rates than azole monotherapy
- Duration inadequately addressed

Oral treatments for fungal infections of the skin of the foot

- When given for 2 weeks, Terbinafine has statistically significantly better cure rates than Itrazonazole, Fluconazole, Ketoconazole, and Griseofulvin.
- Itraconazole for 4 weeks as effective as 2 weeks of Terbinafine

Tinea Treatment: Summary

TOPICAL

- Any topical antifungal, once daily for 2-4 weeks
  - optional: add moderate potency topical steroid

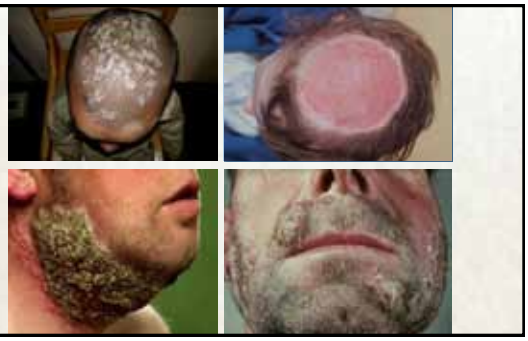
ORAL

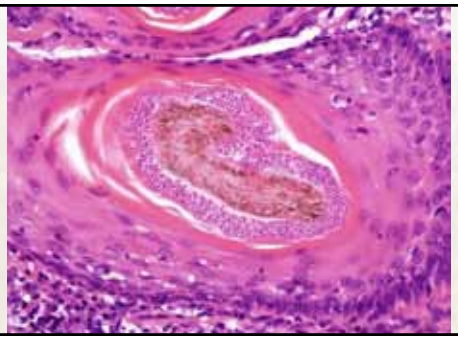
- Terbinafine 250mg once daily for 2 weeks

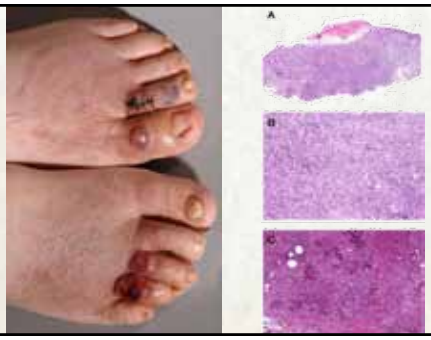
Fungal folliculitis

- Tinea capitis
- Tinea barbae
- Majocchi's granuloma

- Require treatment with oral antifungals







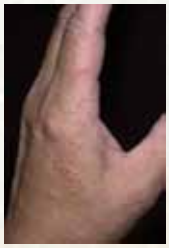
Trichophyton mentagrophytes-associated Majocchi's granuloma treated with cryotherapy

- Fungi thought to have evolved to survive harsh winters and resist temperatures < 50°C, but authors conjecture:
  - Fungi may be secondarily destroyed as tissue necrosis occurs
  - Rapid cooling forms intracellular ice crystals and disrupts the cell membrane
  - rewarming damages the cell membrane again and stimulates the immune system

Experimental study on cryotherapy for fungal corneal ulcer

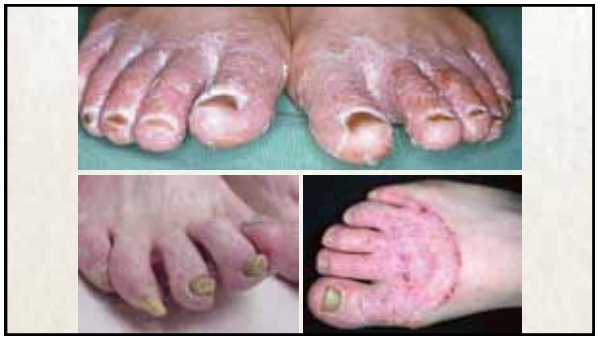
Dermatophytid ("id") reaction

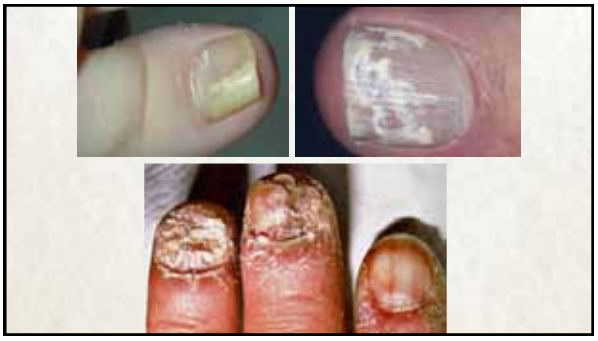
- Hypersensitivity reaction to dermatophyte antigens
- Classic presentation is vesicular eruption on the sides of fingers with inflammatory tinea pedis
- Examine the feet in all cases of suspected hand eczema!
- Eruptions can also be urticarial and panniculitic

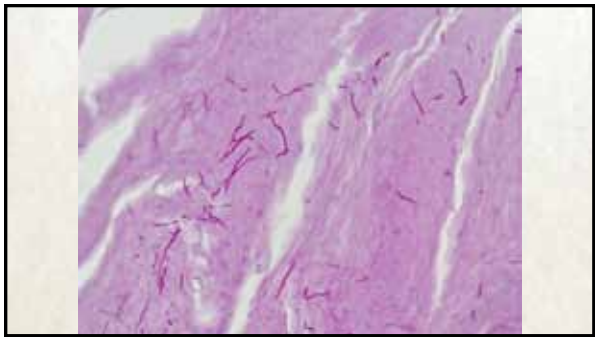


Onychomycosis (Tinea Unguium)

- *T. rubrum* (most common), yeast, nondermatophyte molds
- Superficial white onychomycosis
- Distal lateral subungual onychomycosis
- Proximal subungual onychomycosis





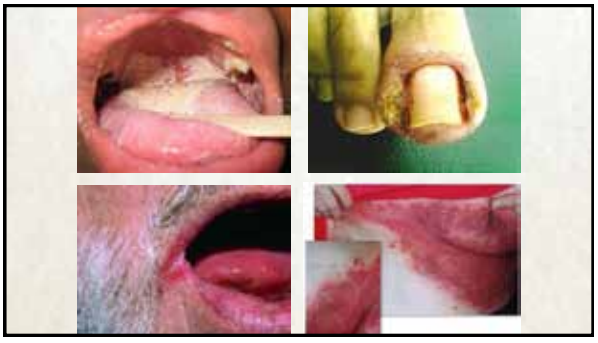


Onychomycosis Treatment

	Mycologic Cure Rate (negative KOH and culture)
Topical Ciclopirox (Penlac)	29%
Topical Tavaborole (Kerydin)	35%
Topical Efinaconazole (Jublia)	55%
Oral Fluconazole (Diflucan)	48%
Oral Itraconazole (Sporanox)	54%
Oral Terbinafine (Lamisil)	77%

Candidiasis

- *C. albicans* inhabits skin, GU, and GI tract
- Opportunistic pathogen
- Frequently infects intertriginous areas
- Predisposing factors include hygiene, diabetes, antibiotic use, and immunosuppression
- Clinical spectrum can range from short-lived superficial to overwhelming systemic infections



Candidiasis Treatment

TOPICAL

- Any topical antifungal for cutaneous candidiasis
- Rinse-and-spit with fluoconazole solution is superior to nystatin and amphotericin B for thrush

ORAL

- Fluconazole 50-100mg/day (95%+ success rate)

Classification of Fungal Diseases

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- Cutaneous
  - Dermatophytes
- Deep
  - Localized subcutaneous (implantation or dermal spread)
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Deep Fungal Infections

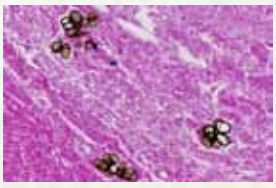
Subcutaneous	Systemic	Opportunistic
Sporotrichosis Phaeohyphomycosis Chromomycosis Mycetoma (Madura foot) Lobomycosis Rhinosporidiosis Zygomycosis	Blastomycosis Histoplasmosis Coccidioidomycosis Paracoccidioidomycosis	Cryptococcosis Aspergillosis Fusariosis Mucormycosis Penicilliosis

Sporotrichosis

- DDX: Atypical mycobacterium, Nocardia, Leishmania, Tularemia

Chromomycosis

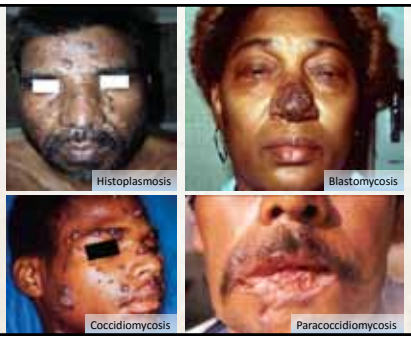
- *Fonsecaea pedrosoi* (most common cause)



Madura Foot (Mycetoma)

Lobomycosis

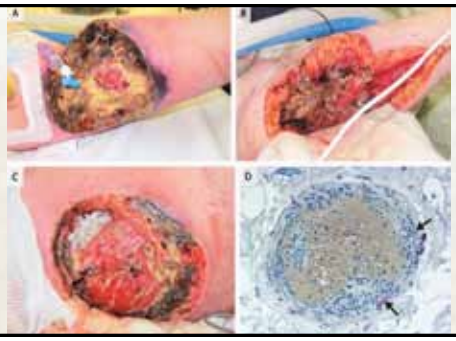
- *Lacazia loboi*
- "keloidal blastomycosis"
- Dolphins



Opportunistic Systemic

- Disseminate in immunocompromised patients
  - Organ transplant, post-chemotherapy, HIV
- *Candida* species most common

Mucormycosis



References

1. Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology. 3rd edition. Saunders Elsevier, Pa; 2012.
2. James WD, Berger TG, Elston DM. Andrews' Diseases of the Skin e-Clinical Dermatology. 11th edition. Saunders Elsevier, Pa; 2011.
3. Ally R, Schlamm D, Ezekiel M, Cortes C, Zagulianger K, Dupont B. Itraconazole Candidiasis Study Group. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis. 2003;36:1487–96.
4. Tal Goredier J, Bonnell C, Zimmerman M. A comparison of fluconazole and amphotericin B oral suspension in older patients with oropharyngeal candidiasis. Multicenter Study Group. Age Ageing. 2000;29:117–23.
5. López-Martínez R. Candidosis, a new challenge. Clin Dermatol. 2010;28:178–84.
6. Gallagher N, Gibbert R, Bilsland N et al. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: a double-blind randomised controlled trial. J Dermatol. 2010;37:699–702.
7. Kaaman T, Tennvesden J. Dermatophytid – a misdiagnosed entity? Acta Derm Acta Derm Venereol. 1985;65:450–4.
8. Rebbeh Fenton R et al. N Engl J Med. 2011;367:2216–2225.
9. Garcia-Cuesta C, Sarrion-Pinto MD, Bagán JV. Current treatment of oral candidiasis: A literature review. J Clin Exp Dent. 2014 Dec 1;6(5):e576–82.
10. Van Zuuren EJ, Fedorowicz Z, El-Gohary M. Evidence-based topical treatments for tinea cruris and tinea corporis: a summary of a Cochrane systematic review. Br J Dermatol. 2014 Mar;170(3):616–41.
11. El-Gohary M, van Zuuren EJ, Fedorowicz Z et al. Topical antifungal treatments for tinea cruris and corporis. Cochrane Database Syst Rev. 2014;3:CD009963.
12. Shenkel MH. A double-blind study comparing the superiority of a combination antifungal (clotrimazole/betamethasone dipropionate) product. Cutis. 1992;50:259–61.
13. Reiko J, Degelmann PE, Chuki MP et al. Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed treatment comparisons meta-analysis involving 14 treatments. . JAMA Dermatol. 2015;149:561–9.
14. Reiko J, Chuki MP, Tarnchou AC et al. Efficacy of topical antifungal drugs in different dermatomycoses: a systematic review with meta-analysis. Rev Socio Med Bras 2012; 18:308–18.
15. Smith EG, Fleischer AB Jr, Feldman SR. Nondermatologists are more likely than dermatologists to prescribe antifungal/corticosteroid products as oral polyvalent mix for cutaneous fungal infections, 1992–1994. J Am Acad Dermatol. 1998;39:63–7.
16. Reiko J, Sanchez G, Gonçalves PR et al. Efficacy and safety of topical antifungals in the treatment of dermatomycosis: a systematic review. Br J Dermatol 2012; 166:927–33.
17. Pontasch KL, Tomczewski K, Kerkstra J, Peczkowski T, Dykes S, Dorcus A, Wilgenbus A, Tertsch P, Zmudzinski D. Trichophyton interdigitale pyogranuloma treated with cryotherapy. Folia Histochem Cytobiol. 2012;Oct 6;50(3):466–9.
18. Romano C, Ruboga P, Dichiara S, Fimiani M. A case of fastidious kinesophilia with dermatophytid reaction caused by Trichophyton violaceum. Mycoses. 2006 May;49(3):249–50.
19. Elgart GW. Subcutaneous (deep) fungal infections. Semin Cutan Med Surg. 2014 Sep;33(3):143–53.
20. Fernandez-Flores A, Saeb-Lima M, Arenas-Guzman R. Morphological findings of deep cutaneous fungal infections. Am J Dermatopathol. 2014 Jul;36(7):521–53.
21. Baxi SN. Therapeutic update: Onychomycosis. J Drugs Dermatol. 2014 Oct;13(10):1173–5.
22. Gupta AK, Ryder JE, Konnikova, Cooper EA. Superficial fungal infections: an update on pityriasis versicolor, onychomycosis, tinea capitis, and onychomycosis. Clin Dermatol. 2020 Sep–Oct;25(5):417–25.
23. Tirall G, Gray SF, Jabbehe FA, Duncan MD, Fox S, Verling NC, Ian NE, Jabbehe JM, Holland E, Blaine R, Sadow P, Rochtch E, Chrabieh N, Team MD. Invasive fungal disease after cross-endorhin: a comparison between mucormycosis and Aspergillus. Br J Ophthalmol. 2015 Jun 25.
24. Paramythiotou E, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014 Jan 17;19(1):1085–139.
25. Teixeira CA, Medeiros PB, Leuchner F, Almeida F. Rhinocerebral mucormycosis: literature review: apropos of a rare entity. BMJ Case Rep. 2013 Feb 5;2013.

Neonatal Dermatology

Palisades Medical Center
North Bergen, NJ
AOCD 2015

David Posnick D.O. PGY4
Sunny Chun D.O. PGY4
Lauren Keller D.O. PGY3
Tanasha Simela D.O. PGY3
Tyler Vukmer D.O. PGY3
Brittany Grady D.O. PGY2

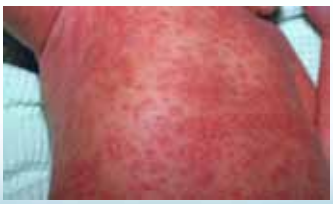
Neonatal Skin

- Skin of infant differs from adult skin
  - Thinner (40-60%)
  - Less hair
  - Weaker attachment between epidermis & dermis
  - BSA/Weight ratio: 5 x adult
  - ↑TEWL 2° immature stratum corneum (esp. premature)
    - Morbidity 2° dehydration, electrolyte imbalance, thermal instability
    - Percutaneous toxicity from topically applied substances

Skin Care of the Newborn

1. Does not have protective skin flora at birth
2. At least 1 or 2 open surgical wounds
   - Umbilicus
   - Circumcision site
3. Exposed to fomites & other personnel that potentially harbor a variety of infectious agents

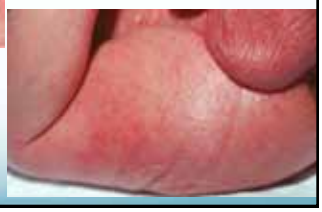
Erythema Toxicum Neonatorum (ETN)



Erythema Toxicum Neonatorum

- Occurs in 50% or more of healthy normal newborns
- 1st-3rd day of life
- Resolves spontaneously ~2 weeks
- Classic eruption:
  - Erythematous blotchy macules, papules or pustules
  - Mainly on trunk, face and proximal limbs

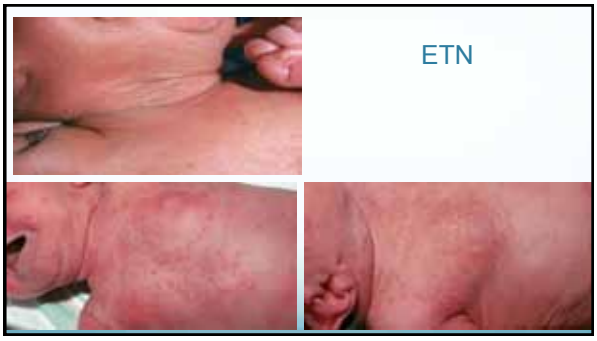
ETN



ETN

- Appears 1st on **FACE** → trunk & extremities or anywhere on the body **EXCEPT** palms/soles
- **Histologically**:
  - Subcorneal pustule filled with eosinophils and occasional neutrophils
- 15% peripheral **eosinophilia**

ETN



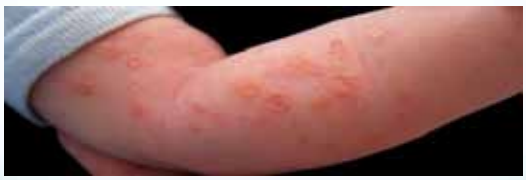
Etiology of ETN

- **Etiology**: Unknown
  - GVH against maternal lymphocytes
  - Immune response to microbial colonization through hair follicles
- **Dx**: Clinical appearance alone
  - Wright/Giemsa stain→sheets of eos w/ few scattered neuts.
  - Skin Bx is rarely needed
- **Tx**: Parental reassurance

Transient Neonatal Pustular Melanosis (TNPM)

- Lesions are present from birth
- Location: chin, forehead, nape of neck, back, buttocks, shins, and **palms and soles**.
- ~5% of black infants, M=F
- Term infants are more likely than pre-term infants
- Dx: Clinical examination
- Tzanck smear (ie. Wright-Giemsa stain) →predominance of **neutrophils** and occasional eosinophils
- No treatment is necessary

Clinical Examination



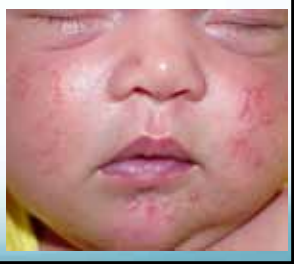
At delivery, vesicopustules w/o erythema rupture leaving a collarette of scale and later hyperpigmented brown macules persisting for months

Acne Neonatorum

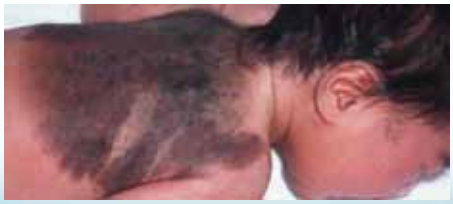
- "Neonatal Cephalic Pustulosis"
- Occurs in 20% of newborns
- Etiology: An inflammatory response to *Malassezia*
- Appears at 2 weeks of age and resolves within the first 3 months of life.
- Treatment: topical imidazoles (e.g. ketoconazole 2% cream)
- Parental reassurance alone is usually adequate

Clinical Examination

- Small papulopustules (typically not comedones)
- Cheeks and nasal bridge



Congenital Nevus



Congenital Nevus

- Melanocytic nevi present at birth (rarely after birth or within 2 years)
- Locations: Buttocks, thighs, and trunk. Also on face, extremities and sometimes palms, soles, and scalp.
- Changes in thickness, color, and hair content occur through childhood and adolescence.

Congenital Nevus: Classification

- Small: <1.5 cm in diameter
- Medium: 1.5–19.9 cm
- Large: ≥20 cm in diameter
  - Significant greater risk of developing melanoma

Congenital Nevus

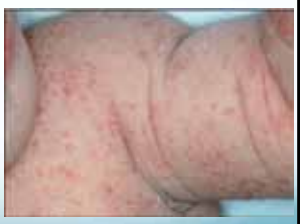
- **Special considerations:**
  - May be an associated **neurocutaneous melanocytosis** when large CMN involves axial skin
- **Management of CMN:**
  - Observation
    - Small- to medium (<20 cm)
    - Photographs
  - Surgical
    - Giant CMN (>20 cm) to reduce risk of malignant change.
  - Consultation w/ Neurologist
    - Head or spine involvement

Neonatal Candidiasis

- MCC ***Candida albicans*** *(*term and preterm)
- Usually acquired **during delivery or post natally**
- Appears in first week of life
- If premature or very low birth weight→ cultures of blood, urine, and CSF
- First line therapy→ topical anti yeast medications (e.g. Imidazole creams
- Treatment with parenteral antifungals should be considered if there are signs of systemic disease

Neonatal Candidiasis

- Primarily diaper area and oral mucosa
- Red papules, plaques, w/ sharp demarcation and scale
- Classically w/ surrounding "satellite" pustules
- Erosions may be present



Congenital Candidiasis

- More widespread eruption
- Evident at birth or 6th day of life
- Acquire **in utero**
- Risk factors: foreign body in cervix, premature infants, maternal vaginal candidiasis
- Skin lesions: face, trunk, extremities (**diaper area and oral mucosa spared**)
- Erythematous papular eruption appears first and is followed by pustules and **desquamation**

Congenital Candidiasis

- Numerous pink papules with small superficial pustules
- Desquamation
- **Plantar involvement**

Congenital Candidiasis

- Treatment
  - **Premature or Weight < 1500g**→parenteral antifungal agents after cultures from the blood, urine and CSF
  - **More advanced gestational age** with no evidence of systemic infection→ topical imidazole therapy
  - **Respiratory distress**, elevated **WBC** w/ a left shift, or signs of **systemic dz**→systemic antifungal therapy

Seborrheic Dermatitis

- ~1 week after birth and may persist several months.
- Initially, scaling and hyperkeratosis adhere to the vertex and anterior fontanelle of the scalp
- Inflammation & exudate may develop→a scaly, crusted lesions on scalp→"**CRADLE CAP**"
- Can become **ERYTHRODERMIC**.

Neonatal Seborrheic Dermatitis "Cradle Cap"

Early | Late | Disseminated






Neonatal Seborrheic Dermatitis Pathogenesis[1]

- Often occurs in areas w/ active sebaceous glands.
- In neonates, sebum is produced a few weeks after birth
- Suspected role of immune mechanisms against *M. furfur*

Neonatal Seborrheic Dermatitis Treatment

- Mild shampoos are recommended to remove scale/crust.
- Ketoconazole cream 2% is indicated in more extensive or persistent cases[3].
- Short courses of low-potency topical corticosteroids may be used.

Neonatal Scabies General Overview

- Infestation w/ mite *Sarcoptes scabiei* var. *hominis*.
- Secondary infection with *Streptococcus pyogenes* or *Staphylococcus aureus* may develop.
- Transmission usually occurs from direct close contact with an infested person.

Neonatal Scabies Pathogenesis

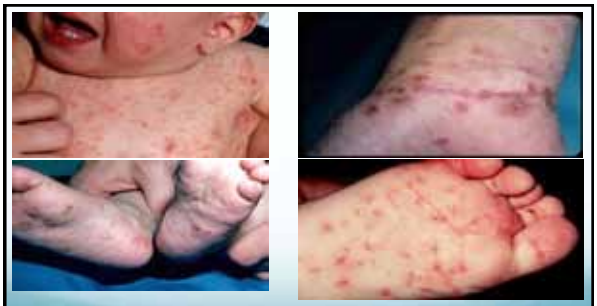
- Incubation period can range from days to months.
  - First time exposure can take 2-3 weeks before the host's immune system becomes sensitized
  - Subsequent infestation is usually symptomatic within 24-48 hours.
  - Asymptomatic scabies-infested individuals are common.

Neonatal Scabies Clinical Features

- Pruritus is severe, worse at night.
- All skin surfaces are susceptible, including the scalp and face.
- Small erythematous papules, often w/ vesicles, nodules, eczematous dermatitis and secondary bacterial infection.

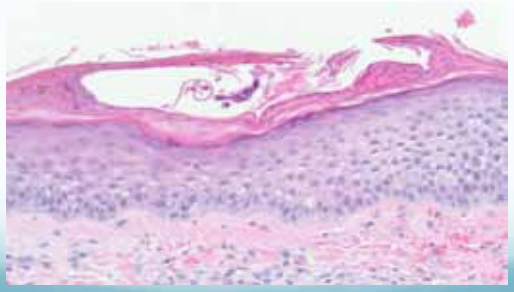
Neonatal Scabies

- Acral vesiculopustules can represent a clue to Dx of scabies in infants.
- Dx confirmation: Light microscopy of mineral oil preparations of skin scrapings



Infantile Scabies Pathology

- Patchy to diffuse infiltrate of:
  - eosinophils, lymphocytes and histiocytes is seen in dermis.
- Mites may be seen
- Chitin “pigtail” structures
- Scybala
- Eggs



Scybala

Eggs

Neonatal Scabies Tx

- Two topical treatments (1 week apart) with a prescription antiscabietic medication applied overnight to the entire body surface, from head to toe, in infants and the elderly.
- Permethrin Cream (5%) - FDA approved for infants >/= 2 months of age.
  - **Good efficacy, but some signs of tolerance developining**
- Sulfur ointment (5-10%) - considered safe for infants
- Crotamiton lotion/cream (10%) - considered safe for infants.
  - **Very poor efficacy, does have antipruritic properties.**

Neonatal Lupus (NLE)

James WD, Berger TG, Elston DM eds. Andrews Diseases of the Skin Clinical Dermatology. Eleventh Edition. Saunders; 2011.

- Annular erythematous macules and plaques with a predilection for the **periorbital region and scalp.**

Bolognia JL, Jorizzo JL, Schaeffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

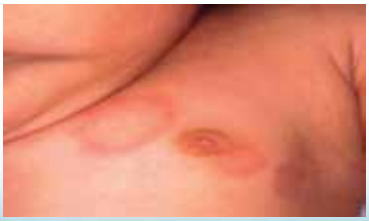
NLE

- No lesions at birth, but develops during the **first few weeks** of life.
- Most commonly occurs in girl infants whose mothers have **anti-Ro/SSA** autoantibodies.
- Linkage to **HLA-DR3** in the mother.
- Almost 100% of babies are anti-Ro/SSA +.

NLE

- Resolves spontaneously by **6 months of age** without scarring
  - Dyspigmentation may persist for many months
  - Residual telangiectasias.
- Lesions are histologically identical to those of SCLE in adults.
- Risk that 2nd child will have NLE is **25%**
- **Photosensitivity** is very common in NLE, but sun exposure is not required for lesions to form

- Annular Erythematous lesions of NLE

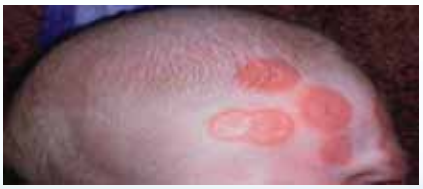


James WD, Berger TG, Elston DM eds. Andrews Diseases of the Skin Clinical Dermatology. Eleventh Edition. Saunders; 2011.

NLE

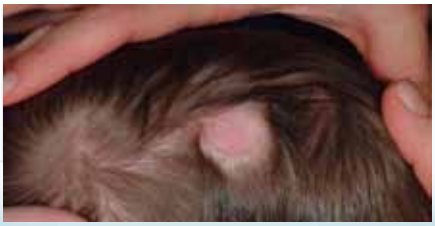
- Extracutaneous findings include:
  - **Congenital heart block** (Almost always present at birth)
  - **Hepatobiliary** disease
  - **Thrombocytopenia**.
- Cardiac NLE has a mortality rate ~20%
  - 2/3 children require pacemakers.
- Evaluation of NLE includes:
  - Physical Exam
  - EKG
  - CBC
  - LFTs

Indurated coalescing lesions of NLE



James WD, Berger TG, Elston DM eds. Andrews Diseases of the Skin Clinical Dermatology. Eleventh Edition. Saunders; 2011.

Aplasia Cutis Congenita (ACC)



Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

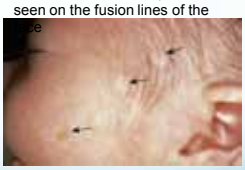
- Localized or widespread areas of skin that are absent or scarred at birth.
- **Scalp** is the MC site for ACC at or near vertex .
- ACC may be an isolated defect, or with other anomalies and disorders.
- Appearance ranges from an erosion, deep ulceration, scar, or membrane covered ovoid defect
- Etiologies: genetics, vascular compromise, trauma, teratogens and intrauterine infections.

Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

ACC

- **Membranous aplasia cutis**
  - Most common form
  - Presents as a "punched-out" oval defect covered by a thin, translucent, glistening epithelial membrane surrounded by a "**Hair collar sign**."
    - May represent a **neural tube defect.**

Membranous ACC may also be seen on the fusion lines of the face



Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

Membranous ACC with a large defect of the underlying skull

Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

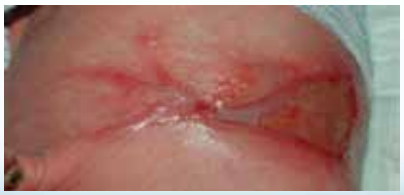
ACC

- **Stellate ACC**
  - 2nd major type of ACC consists of
  - Stellate or angulated lesions, which are thought to result from vascular abnormalities and/or intrauterine ischemic events.

Stellate ACC on the midline scalp of a neonate

Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

Stellate ACC on the lateral trunk of a neonate



Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd Edition. Saunders; 2012.

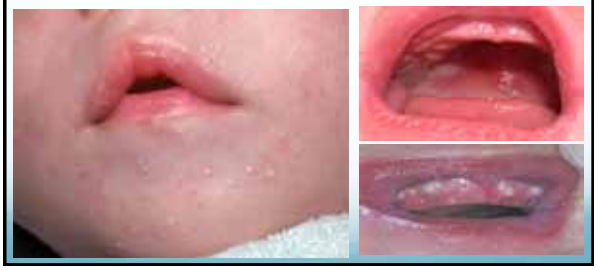
ACC

- **Imaging studies**
  - underlying bone defects
  - vascular anomalies
  - brain malformations.
- **Elevated α-fetoprotein** in mid-trimester,
- Elevated **acetylcholinesterase** in the amniotic fluid
  - neither sensitive nor specific for this condition.

ACC

- Small lesions heal within the first few months of life
  - Leave an atrophic or, less often, hypertrophic ("lumpy") scar.
  - Underlying skull defects tend to resolve spontaneously
- Complications
  - **Sagittal sinus hemorrhage/thrombosis** and **meningitis**
  - Complications increase if the period of healing is prolonged.
- Management
  - Daily cleansing & application of a topical ABX
  - Early surgical repair: large stellate scalp lesions, dural defect, exposure of the sagittal sinus.

MILIA

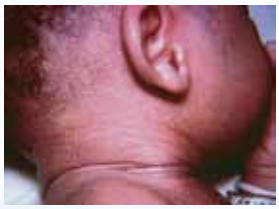


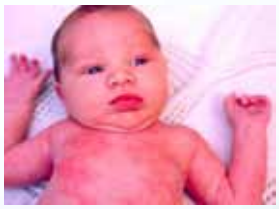
MILIA

- **Onset**: Birth, 15% of newborns.
- MC seen on face.
- 1-2 mm pearly white subepidermal papules.
- Milia in newborns can be seen on:
  - Hard palate (Bohn's nodules) or
  - Gum margins (Epstein's pearls).
- Spontaneous resolution in 1st month
  - NO Tx necessary.
- Widespread distribution may be a/w DEB, Bazex, ROMBO, or hereditary trichodysplasia.

MILIARIA

- 2 main types:
  - Miliaria Crystallina (MC)
    - Birth to 1st wk
  - Miliaria Rubra (MR).
    - After 1st wk.
- MC- Clear, small "dew drop" vesicles.
- MR- Erythematous papules and pustules MCseen in intertriginous areas.
- Caused by obstruction of eccrine sweat ducts in the stratum corneum (MC) or malpighian layer (MR) of epidermis.
- Resolves w/ cooling and removal of occlusion.





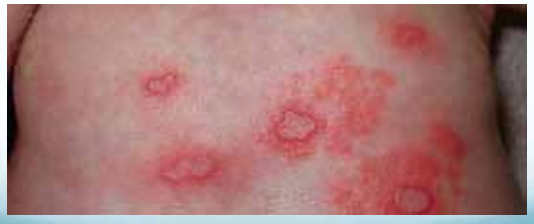
MILIARIA CRYSTALLINA MILIARIA RUBRA

Neonatal Herpes Simplex Virus Infection

- Occurs in 1:10,000 newborns in US
- Exposure to HSV during vaginal delivery
- Transmission is greatest (30-50%) for women who acquire a primary genital HSV infection during pregnancy

Bolognia, JL, Jorizzo JL, Schaffer JV. (2012). 3rd edition. Dermatology. St. Louis: Mosby

Neonatal HSV: Grouped papulovesicles on erythematous base; scalloped borders in areas of lesion coalescence



Bolognia, JL, Jorizzo JL, Schaffer JV. (2012). 3rd edition. Dermatology. St. Louis: Mosby

Neonatal HSV

Visualdx.com

Neonatal HSV

Visualdx.com

Neonatal Herpes Simplex Virus

- Risk of transmission to newborn is **LOW** (<1-3%) in women w/**recurrent** genital herpes
- Neonatal infxn can be 2/2 to **HSV-2** or **HSV-1**
  - **HSV-1** infection accounts for **30-50%** of cases

Bolognia, JL, Jorizzo JL, Schaffer JV. (2012). 3rd edition. Dermatology. St. Louis: Mosby

Risk Factors for Mother-to-Child Transmission of HSV

- Vaginal delivery
- Prolonged duration of rupture of membranes
- Maternal infection with HSV-1 or HSV-2
- Use of fetal scalp electrode (disrupts the infant's cutaneous barrier)

James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Infection. Infect Dis Clin North Am. 2015 Jul 4 epub ahead of print

Use of Fetal Scalp Monitor Associated with HSV Infection

Andrews Diseases of the Skin, 11th edition,Figure 19.8

Neonatal HSV Infection

- Onset: birth to 2 weeks of age
  - Usually ~5 days of age
- Lesions:
  - Localized, favoring the scalp and trunk, or
  - Disseminated cutaneous lesions
- Involvement of oral mucosa, eye, CNS, and internal organs may occur

Bolognia, JL, Jorizzo JL, Schaffer JV. (2012). 3rd edition. Dermatology. St. Louis: Mosby

Neonatal HSV Infection

- Encephalitis may present with
  - lethargy, irritability, poor feeding, temperature instability, seizures, bulging fontanelle
- MORTALITY for CNS dz or Disseminated dz
  - >50% without Tx
  - ~15% w/ Tx
- Many survivors have neurologic defects

Bolognia, JL, Jorizzo JL, Schaffer JV. (2012). 3rd edition. Dermatology. St. Louis: Mosby

Best Tests for Diagnosis

- **Tzanck smear**
- **Direct fluorescent** antibody test
- **Viral Cx**
- **PCR** from CSF
- Serologic studies are NOT recommended for diagnostic purposes
- **Prompt recognition and timely initiation of antiviral therapy is critical**

James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Infection. Infect Dis Clin North Am. 2015 Jul 4 epub ahead of print

Treatment of Neonatal HSV

Recommended Treatment

- **Disseminated & CNS dz:**
  - Acyclovir 20 mg/kg body weight IV q8 hours (60 mg/kg/day) x 21 days
- **Dz limited to the skin and mucous membranes**
  - Acyclovir 20 mg/kg IV q8 hours x 14 days
- **Toxicity of acyclovir** is limited to transient neutropenia during therapy (monitor neutrophil counts)

James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Infection. Infect Dis Clin North Am. 2015 Jul 4 epub ahead of print

Treatment of Neonatal HSV

- **Ophthalmologic evaluation**
- Prophylactic topical ophthalmic preparation

Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology. 4th edition

Treatment of Neonatal HSV

- After completion of full course of parenteral Tx, administering a **suppressive course** of oral acyclovir has been shown to be beneficial
  - **Suppressive regimen is 300 mg/m2/dose, TID x 6 mo**
- **Monitor neutrophil count**
  - 2nd and 4th week of suppressive treatment,
  - Then monthly
- Hold acyclovir if neutrophil count drops to:
  - <500 cells/microliter

James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Infection. Infect Dis Clin North Am. 2015 Jul 4 epub ahead of print

Treatment of Neonatal HSV

- **Supportive care**
  - management of possible seizure,
  - management of respiratory distress
  - metabolic derangements
- **Contact precautions**

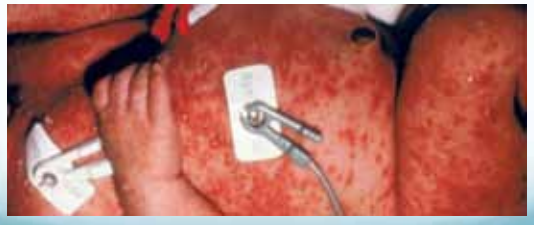
Visualdx.com – Neonatal Herpes Treatment

Neonatal Varicella

- Respiratory secretions or direct contact
- Children < 1 year have more severe illness
- Transmission to neonate can occur
  - In utero (sx before 10 days of life)
  - After birth by direct contact (sx after 10 days)

Sauerbrei A, Wutzler P. Neonatal Varicella. Journal of Perinatology 2001: 21 (545-549

Neonatal Varicella



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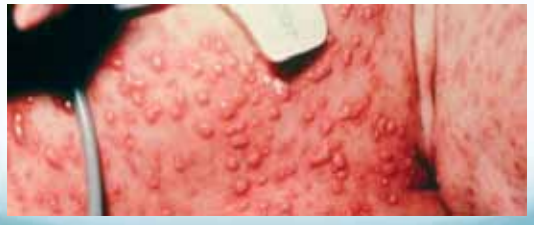
Neonatal Varicella



Visualdx.com

Neonatal Varicella

Visualdx.com

Clinical Features and Diagnosis

- RAPIDLY progressive vesiculopustular eruption
- Crops of lesions develop over 3-4 days & are crusted over by 6-7 days
- **Pathognomonic** features:
  - **simultaneous lesions in DIFFERING stages of evolution**
- Mucous membranes may be affected

Timing of Transmission

- **Generalized neonatal varicella** leading to **DEATH** is more likely if **mother develops the disease between 4 days before and 2 days after delivery**

Sauerbrei A, Wutzler P. Neonatal Varicella. Journal of Perinatology 2001: 21 (545-549

Timing of Disease Onset

- FATAL outcome more likely if neonatal disease occurs between 5-10 days of life
- Neonatal varicella within first 4 days of life is comparatively mild

Sauerbrei A, Wutzler P. Neonatal Varicella. Journal of Perinatology 2001: 21 (545-549

Diagnosis

- Most sensitive, specific method is:
  - **PCR** for viral DNA
  - **Immunofluorescent staining**

Sauerbrei A, Wutzler P. Neonatal Varicella. Journal of Perinatology 2001: 21 (545-549)

Treatment & Prophylaxis

- Acyclovir 10-15 mg/kg q 8 hours x 5-7 days
- Tx ALL symptomatic neonates **within 48 hours** of rash onset

Sauerbrei A, Wutzler P. Neonatal Varicella. Journal of Perinatology 2001: 21 (545-549

Prophylaxis

- **Mother has signs of varicella 5-7 days before delivery or 2-3 days after delivery**
- Hospitalized premature infants <1000 g birth weight or under 28 weeks of age **when exposed to varicella**, regardless of maternal history
- Hospitalized premature infants born 28 weeks or later to mothers with a negative or unreliable history of varicella, **when exposed to varicella**

Sauerbrei A, Wutzler P. Neonatal Varicella. Journal of Perinatology 2001: 21 (545-549

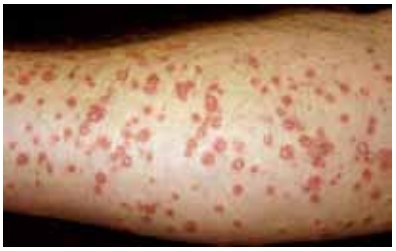
References

1. Bolognia JL, Jorizzo JL, Schaffer JV eds. Dermatology. 3rd ed. Saunders; 2012
2. Freedberg, Irwin M., ed. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. pp.1373-1374, 2010-2011. New York: McGraw-Hill, 2003.
3. Hoppe, Jorg and the Antifungal Group. Treatment of oropharyngeal candidiasis in immunocompetent infants: a randomized multicenter study of miconazole gel vs.nystatin suspension. The Pediatric Infectious Disease Journal. March 1997.
4. Katsambas AD, Katoulis AC, Stavropoulos P. Acne neonatorum: a study of 22 cases. *Int J Dermatol*. 1999;38(2):128–130.
5. Mengesha YM, Bennett ML. Pustular skin disorders: diagnosis and treatment. *Am J Clin Dermatol*. 2002. 3(6):389-400
6. Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence. 4th ed. Saunders; 2011.
7. Patterson WM, Lefkowitz A, Schwartz RA, Lambert WC, Rao BK. Melanoma in children. *Cutis*. 2000 May. 65(5):269-72, 275
8. Ravanfar P, Wallace J, Nicole C. Diaper Dermatitis: a review and update. Current Opinion in Pediatrics. Volume 24(4), August 2012. p 472–479
9. James WD, Berger TG, Elston DM eds. Andrews Diseases of the Skin Clinical Dermatology. Eleventh Edition. Saunders; 2011.

Pediatric Papulosquamous and Eczematous Disorders

St. John's Episcopal Hospital
Program Director- Dr. Suzanne Sirota-Rozenberg
Dr. Brett Dolgin, DO
Dr. Asma Ahmed, DO
Dr. Anna Slobodskya, DO
Dr. Stephanie Lasky, DO
Dr. Louis Siegel, DO
Dr. Evelyn Gordon, DO
Dr. Vanita Chand, DO

Pediatric Psoriasis



Epidemiology

- Psoriasis can first appear at any age, from infancy to the eighth decade of life
- The prevalence of psoriasis in children ages 0 to 18 years old is 1% with an incidence of 40.8 per 100,000 ppl
- ~ 75% have onset before 40 years of age

What causes psoriasis?

- Multifactorial
- Genetics
  - HLA associations (Cw6, B13, B17, B57, B27, DR7)
- Abnormal T cell activation
  - Th1, Th17 with increased cytokines IL 1, 2, 12, 17, 23, IFN-gamma, TNF-alpha
- External triggers:
  - Injury (Koebner phenomenon)
  - medications (lithium, IFNs, β-blockers, antimalarials, rapid taper of systemic corticosteroids)
  - infections (particularly streptococcal tonsillitis).

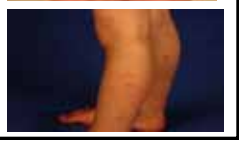
Pediatric Psoriasis

Types:

- Acute Guttate Psoriasis – Small erythematous plaques occurring after infection (MOST common in children)
  - **40% of patients with guttate psoriasis will progress to develop plaque type psoriasis**
- Chronic plaque Psoriasis – erythematous plaques with scaling
- Flexural Psoriasis – Erythematous areas between skin folds
- Scalp Psoriasis – Thick scale found on scalp
- Nail Psoriasis – Nail dystrophy
- Erythrodermic Psoriasis– Severe erythema covering all or most of the body
- Pustular Psoriasis – Acutely arising pustules
- Photosensitive Psoriasis – Seen in areas of sun exposure

Guttate Psoriasis



Psoriasis Treatment

- 1st line- Topical corticosteroids
- Topical calcipotriene (Vit D analogue)
- Phototherapy
- Retinoids like Acitretin can be used in children starting at 6 months of age
- Methotrexate is used as "rescue therapy" in children; important to not exceed 0.7 mg per kg per week
- Important to supplement MTX with Folate to minimize GI toxicity and possibility of bone marrow suppression
- Biologics

Psoriasis Treatment

Biologic Agents: Etanercept

- Soluble tumor necrosis factor receptor fusion protein
- Works by binding and inhibiting TNF, reducing inflammation and altering immune response
- Has the most evidence, including a placebo randomized trial and multiple case reports

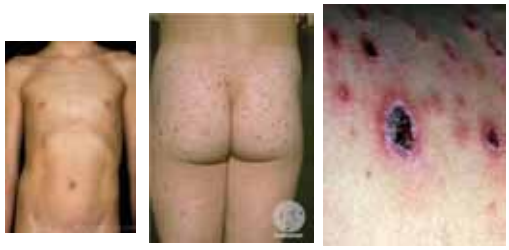
Psoriasis Treatment

Etanercept:

- Phase 3 randomized study showed statistically significant reductions in disease severity as early as week 2 of weekly treatment with Etanercept at 0.8 mg/kg in children and adolescents with moderate to severe psoriasis

Etanercept treatment for children and adolescents with plaque psoriasis, Paller et al., NEJM , January 2008

Pityriasis Lichenoides



Pityriasis Lichenoides

- Unknown etiology
- Most often affects adolescents and young adults
- Males > females
- Acute: PLEVA
- Chronic: PLC

Pityriasis Lichenoides et varioliformis acuta (PLEVA)

- Abrupt eruption of erythematous papules and vesicles with crusted or necrotic centers
- Lesions are painful and itchy
- Usually distributed over trunk, buttocks, and extremities, but sometimes may be widespread, covering any part of the body
- Involutes within weeks to months

PLEVA

Typical hemorrhagic crusted papules of pityriasis lichenoides et varioliformis acuta

PLEVA

Pityriasis Lichenoides Chronica (PLC)

- Reddish brown papules with adherent scale
- Heals with PIH
- More chronic course lasting months to years with exacerbations and remission

PLC

Scaling papules of pityriasis lichenoides chronica

PLC

Note papules in different stages of evolution and the scale with frosted-glass appearance in the lower right-hand corner

PLEVA/PLC -Treatment: First line

- Symptomatic
- Local wound care for larger ulcerations
- Topical steroids
- Topical immunomodulators, tacrolimus, pimecrolimus
- Oral erythromycin (children) and doxycycline (adults)

PLEVA/PLC- Treatment

Second-line therapies include:
- Phototherapy – UVB or PUVA

Third-line therapies include:
- Systemic steroids
- Methotrexate orally or by IM injection
- Acitretin
- Dapsone
- Cyclosporine

Pityriasis Rubra Pilaris (PRP)

Pityriasis Rubra Pilaris (PRP) Background

- Chronic papulosquamous disorder of unknown etiology characterized by reddish orange scaly plaques, PPK and keratotic follicular papules.
- Etiology unknown. Nearly always acquired. Occasional familial cases described with AD inheritance recently linked to CARD gene.
- May be caused by immune response to antigen
- Cases described after strep infections

Pityriasis Rubra Pilaris (PRP) Presentation

- Orange-red or salmon-colored scaly plaques with sharp borders, may expand to cover entire body
- Areas of uninvolved skin referred to as islands of sparing

Pityriasis Rubra Pilaris (PRP) Presentation

- Follicular hyperkeratosis commonly seen on dorsal aspects of proximal fingers, elbows and wrists.

Pityriasis Rubra Pilaris (PRP) Presentation

- PPK with orange hue

Pityriasis Rubra Pilaris (PRP) Presentation

- Nail changes include subungual hyperkeratosis and nail plate thickening
- May rapidly evolve into erythroderma

Pityriasis Rubra Pilaris (PRP)- Adult Forms

- Type I (Classic Adult): More than 50% of cases, sudden onset of symptoms with duration 2-5 years
- Type II (Atypical Adult): about 5% of cases, slow onset with alopecia, localized lesions and more chronic course
- Type VI (HIV-associated PRP): Presents with acneiform lesions and elongated follicular plugs. Resistant to standard Tx, but may respond to antiretroviral therapy.

Pityriasis Rubra Pilaris (PRP)- Juvenile Forms

- **Type III (Classic Juvenile):** Resembles classic adult form, with early onset (first 2 years of life); most resolve within 3 yrs; 10% of cases
- **Type IV (Circumscribed Juvenile Form):** Most common in children (25% of cases), lesions on extensor surface and present in prepubertal years; about 50% may persist into adulthood
- **Type V (Atypical Juvenile Form**): Similar to Type III + scleroderma-like changes on hands and feet. This form accounts for about 5% of all cases and most familial cases. More chronic course.

Pityriasis Rubra Pilaris (PRP) DDx

- CTCL
- Erythroderma
- Erythrokeratoderma Variabilis
- Psoriasis
- Seborrheic dermatitis

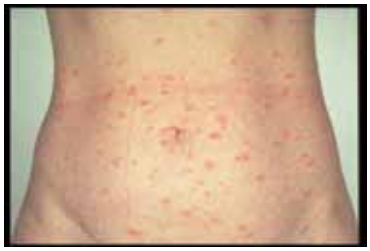
Pityriasis Rubra Pilaris (PRP) Workup

- Diagnosis based on correlation between clinical findings and histological findings
- No lab tests indicated

Pityriasis Rubra Pilaris (PRP)-Tx

- No set protocols, evidence for specific therapies sparse
- Topical steroids
- Tazarotene reported to improve Type IV
- Emollients, especially for hands
- NB-UVB
- Isotretinoin
- Cyclosporine, Azathioprine, Methotrexate
- TNF-alpha inhibitors
- Ustekinemab

Pityriasis Rosea



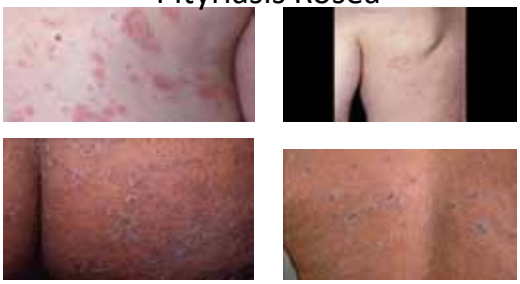
Pityriasis Rosea

- Self limited papulosquamous eruption seen primarily in healthy adolescents and young adults
- First the rash begins with a solitary oval 2-5 cm scaly pink patch with a slightly raised advancing margin, classically on the trunk, which enlarges over several days
- Hours to days later similar smaller scaly patches appear on the trunk, but may also present on the proximal extremities and neck
- Usually a "Christmas tree" pattern is described on the back due to the long axis of the lesions following Langer's lines of cleavage
- Patients may complain of upper respiratory symptoms prior to the outbreak
- Assoc. with HHV-7 and to a lesser extent HHV-6 infection (Drago et. al 2009)

Pityriasis Rosea

- May or may not be pruritic
- Typically resolves spontaneously in approximately 6 weeks
- Usually does not recur
- Treatment: Antipruritic lotions, low to medium strength topical steroids and antihistamines for symptomatic relief from itch
- More severe cases: UVB therapy
- No evidence that Azithromycin is effective (Pandhi et. al 2015)
- No evidences that antivirals are effective (Chuh et. al 2005)

Pityriasis Rosea



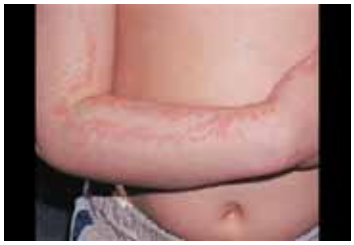
Pityriasis Rosea Variants

- Papular PR - young kids and darker skinned patients
- Inverse pattern - flexural accentuation
- Vesicular
- Pustular
- Urticarial

Pityriasis Rosea Differential Diagnosis

- **Drug eruption**
- **Secondary syphilis**
- **Pityriasis lichenoides**
- **Nummular dermatitis**
- **Guttate psoriasis**
- Tinea corporis
- Tinea versicolor
- Parapsoriasis
- Erythema multiforme
- Urticaria
- Erythema dyschromicum perstans (ashy dermatosis)

Lichen Striatus



Lichen Striatus

- Uncommon self-limited skin disorder of younger children of unknown etiology
- Has been reported in children as young as 3 months
- Presents with linear bands of slightly scaly, pinpoint, and lichenoid papules that follow the lines of Blaschko
- The onset it usually fairly rapid and may reach maximal involvement within a few days to weeks

Lichen Striatus

- Asymptomatic, rarely pruritic
- Lesions are usually on an extremity but can occur anywhere
- Often subtle and resolve leaving hypopigmentation or hyperpigmentation
- Treatment: Disease is self-limited, so aggressive treatment is not indicated
- Topical steroids for pruritus
- Typically resolves spontaneously within 1-2 years
- In adults, studies show good results with tacrolimus

Lichen Striatus

Lichen Striatus
Differential Diagnosis

- Linear epidermal nevus
- Inflammatory epidermal nevus
- Linear Darier's disease
- Linear porokeratosis
- Incontinentia pigmenti
- Linear lichen planus

Atopic Dermatitis

Atopic Dermatitis

- Common inflammatory skin condition that typically begins during infancy, but occasionally in adulthood
- Occurs in 10-15% children
- Characterized by intense pruritus and a chronic or chronically relapsing course
- Th2 cytokine profile during the acute phase but transitions into a Th1 cytokine profile during the chronic phase

Bolognia, 3rd Edition

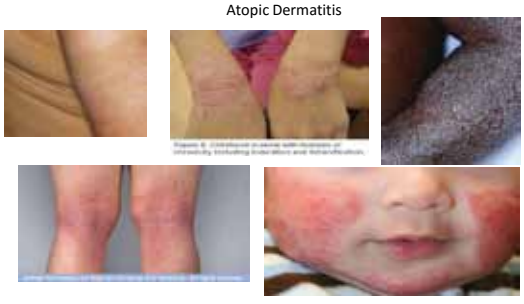
Filaggrin (FLG gene)
*fil*ament-*agg*regating prote*in*

- FLG is expressed in the granular layer of the stratum corneum. Encodes a protein that aggregates keratin filaments during terminal differentiation of the epidermis
- Encoded within the epidermal differentiation complex on chromosome 1q21 (Brown, 2008)
- Mutation responsible for Ichthyosis Vulgaris and in up 20-60% AD, depending on study (Elias, 2011)
- Various other genes that lead to increased susceptibility of AD, include KLK7, SPINK5, and CSTA..many others; FLG remains the most prominent (Cork, 2009)
- Presence correlated with AD that's early onset, relatively severe, persists into adulthood

Atopic Dermatitis Clinical Features

- Infants: usually 2nd-3rd mo of life involving cheeks (often sparing central face), scalp, neck and extensor aspects of the extremities and trunk
- Children: shifts to more chronic inflammation with lichenification and a predilection for flexural sites; classic - antecubital and popliteal fossae, neck, wrists, ankles
- Adults: Also flexural. May present with hand derm, face (eyelid)

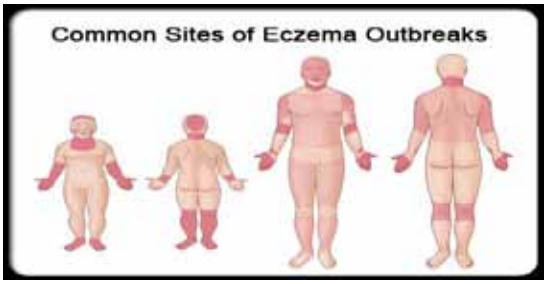
Atopic Dermatitis



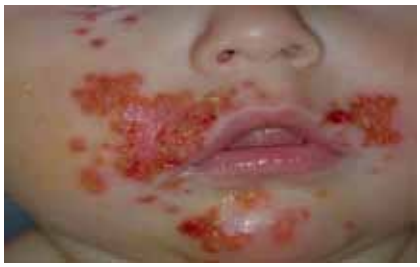
Pityriasis Alba

- Frequently affects children and adolescents with AD
- Characterized by multiple ill defined hypopigmented patches with fine scaling
- Typically face, but can occur on shoulders, arms
- Most obvious in individuals with darkly pigmented skin and or following sun exposure
- Thought to result from a low grade eczematous dermatitis that disrupts the transfer of melanosomes from melanocytes to keratinocytes

Pityriasis Alba



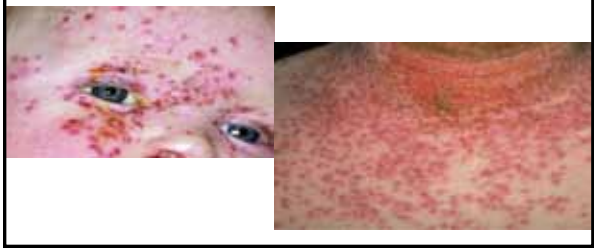
Complications: Impetigo



Complications: Impetigo

- Bacterial and viral infections represents the most common complication of AD.
- Considering that Staph Aureus colonizes the skin of majority of AD patients, its not surprising that impetigo occurs quite frequently.
- Bacterial infections may also exacerbate AD by stimulating the inflammatory cascade; such as through Staph exotoxins that act as superantigens.

Complications: Eczema Herpeticum



Complications: Eczema Herpeticum

- Rapid dissemination of HSV over the eczematous skin of AD patients
- Present with vesicles, monomorphic punched out erosions with hemorrhagic crusting. Frequently widespread and may occur at any site, with a predilection for head, neck, and trunk.
- Often associated with fever, malaise, and LAD, and complications may include 2ndary bacterial infection.

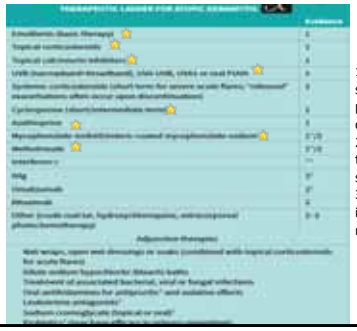
Complications: Molluscum Contagiosum

Ocular complications:

- Keratoconjunctivitis – ocular itching, burning, tearing, discharge, blepharitis, eyelid dermatitis
- Subcapsular cataracts (anterior more specific to AD, posterior more common)
- Keratoconus
- Retinal detachment

AD Treatment

- The main idea…
  - a proactive approach to management is recommended, including avoidance of trigger factors, daily use of emollients, and anti-inflammatory therapy to control subclinical inflammation as well as overt flares



Bologna, 3rd Edition

1= evidence based support from prospective controlled trial
2 =retrospective trial or large case series
3=small series or individual case reports

Recommendations for nonpharmacologic interventions for the treatment of atopic dermatitis
(AAD Guidelines for AD care 2014)

- **Moisturizers** - **strong evidence** that their use can **reduce disease severity** and the need for pharmacologic intervention
- **Bathing** is suggested - there is **no standard for the frequency** or duration of bathing
- **Moisturizers should be applied soon after bathing** to improve skin hydration
- **Limited use** of nonsoap **cleansers** (that are neutral to low pH, hypoallergenic, and fragrance free)
- Addition of oils, emollients, and most other additives to bath water and the use of acidic spring water cannot be recommended at this time, because of insufficient evidence.
- Use of **wet-wrap therapy with or without a topical corticosteroid** can be **recommended for patients with moderate to severe AD**

Recommendations for the use of topical antimicrobials and antiseptics for the treatment of atopic dermatitis
(AAD Guidelines for AD care 2014)

- Except for bleach baths and intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with AD, and is not routinely recommended.
- In patients with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity.

References-Psoriasis

- Collin, B., Vani, A. & Ogboli, M. (2009). Methotrexate treatment in 13 children with severe plaque psoriasis. Clinical and Experimental Dermatology. 2009;34(3):295–8.
- Cordoro KM. Systemic and light therapies for the management of childhood psoriasis: part II. Skin Therapy Lett. 2008;13(4):1-3.
- Cordoro KM. Topical therapy for the management of childhood psoriasis: part I. Skin Therapy Lett. 2008;13(3):1-3.
- Marji, JS., Marcus, R. & Moennich, J. (2010). Use of biologic agents in pediatric psoriasis. Journal of Drugs in Dermatology. 2010;9(8):975–86.
- Paller et al., Etanercept treatment in children and adolescents with plaque psoriasis, NEJM 2008; 358:241-251, January 2008.
- Strowd LC, Yentzer BA, Fleischer AB Jr, Feldman SR. Increasing use of more potent treatments for psoriasis. J Am Acad Dermatol. 2009;60(3):478-481.
- Tollefson MM, Crowson CS, McEvoy MT, Maradit Kremers H. Incidence of psoriasis in children: a population-based study. J Am Acad Dermatol. 2010;62(6):979-987.
- Vogel et al. Trends in pediatric psoriasis outpatient healthcare delivery in the United States. Arch Dermatol. 2012;148(1):66-71.

References-PLEVA/PLC

- Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. J Am Acad Dermatol 2006;55:557-72.
- Fernandes NF, Rozdeba PJ, Schwartz RA, et al. Pityriasis lichenoides et varioliformis acuta: a disease spectrum. Int J Dermatol 2010; 49:257.
- Fernández-Guarino M, Harto A, Reguero-Callejas ME, et al. Pityriasis lichenoides chronica: good response to photodynamic therapy. Br J Dermatol 2008; 158:198.
- Lazaridou E, Fotiadou C, Tsorova C, et al. Resistant pityriasis lichenoides et varioliformis acuta in a 3-year-old boy: successful treatment with methotrexate. *Int J Dermatol.* 2010 Feb. 49(2):215-7.
- Shah, Deepam J et al. "Steroid Unresponsive Case of Ulcerative Mucha-Habermann Disease (Febrile Ulcernecrotic Mucha-Habermann Disease) Treated with Methotrexate." *Indian Journal of Dermatology* 59.6 (2014): 631.*PMC*. Web. 29 Aug. 2015.
- Macias VC, Marques-Pinto G, Cardoso J. "Phototherapy for pityriasis lichenoides: our experience." Cutan Ocul Toxicol. 2013 Jun;32(2):124-7. PMID: 22974328 Web 29 Aug 2016.

References-PRP

- Remedios IM, Jensen JD, Beckum K, McKay K, Kissel R. Paraneoplastic pityriasis rubra pilaris as the presenting manifestation of metastatic squamous cell carcinoma. J Drugs Dermatol. 2014 May. 13(5):610-2.
- Fuchs-Telem D, Sarig O, van Steensel MA, et al. Familial Pityriasis Rubra Pilaris Is Caused by Mutations in CARD14. Am J Hum Genet. 2012 Jul 13. 91(1):163-70.
- Cox V, Lesesky EB, Garcia BD, O'Grady TC. Treatment of juvenile pityriasis rubra pilaris with etanercept. J Am Acad Dermatol. 2008 Nov. 59(5 Suppl):S113-4.
- PD Shenefelt, DM Elston. Pityriasis Rubra Pilaris. 2014 Sept 12th
- Karimian-Teherani D, Parissa M, Tanew A. Response of juvenile circumscribed pityriasis rubra pilaris to topical tazarotene treatment. Pediatr Dermatol. 2008 Jan-Feb. 25(1):125-6.

References- PR/Lichen Striatus

- Chuh A, Zawar V, Lee A. Atypical presentations of pityriasis rosea: case presentations. J Eur Acad Dermatol Venereol. 2005;19:120-126.
- Chuh AA, Dofitas BL, Comisel GG, et al. Interventions for pityriasis rosea. Cochrane Database Syst Rev. 2007;(2):CD005068.
- Drago F, Vecchio F, Rebora A. Use of high-dose acyclovir in pityriasis rosea. J Am Acad Dermatol. 2006;54:82-85.
- Pandhi D, Singal A, Verma P, Sharma R. The efficacy of azithromycin in pityriasis rosea: a randomized, double-blind, placebo-controlled trial. Indian J Dermatol Venereol Leprol 2014; 80:36.
- Patrizi A, Neri I, Fiorentini C, et al. Lichen striatus: clinical and laboratory features of 115 children. Pediatric
- Dermatol. 2004;21:197–204.
- Yildirim M, Aridogan BC, Baysal V, et al. The role of human herpes virus 6 and 7 in the pathogenesis of pityriasis rosea. Int J Clin Pract. 2004;58:119-121.

References-Atopic Dermatitis

- Bolognia, J, Jorizzo JL, Schaffer. Dermatology, 3rd ed, Elsevier, Philadelphia 2012. Vol 1, p.203-217.
- Brown, SJ. Irvine AD. Atopic eczema and the filaggrin story. Semin Cutan Med Surg. 2008 Jun;27(2):128-37
- Cork MJ, Danby SG, Vasilopoulos Y, et al. Epidermal barrier dysfunction in atopic dermatitis. J Invest Dermatol. 2009 Aug;129(8):1892–908.
- Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014 Feb. 70(2):338-51.
- Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014 Jul. 71(1):116-32.
- Elias PM, Wakefield JS. Therapeutic implications of a barrier-based pathogenesis of atopic dermatitis. Clin Rev Allergy Immunol. 2011 Dec; 41(3):282–95.
- Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006 Apr;38(4):441–6.
- Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014 Aug. 71(2):327-49.
- Sidbury R, Tom WL, Bergman JN, Cooper KD, Silverman RA, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014 Sep 25.

PEDIATRIC PIGMENTED LESIONS

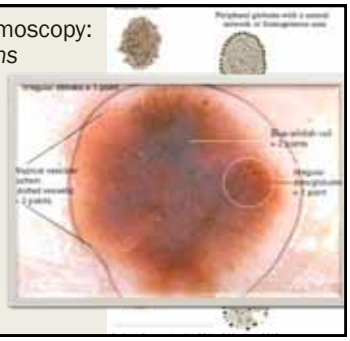
ST. BARNABAS HOSPITAL DERMATOLOGY RESIDENCY
MARISA WOLFF, DO, OGME IV
LACEY BETH ELWYN, DO, OGME III
CHRISTOPHER MANCUSO, DO, OGME II
CINDY HOFFMAN, DO, FACOD

Approach to pediatric pigmented lesions

- Clinical features
- Dermatoscopic features
- Evidence based management
- Congenital melanocytic nevi
- Acquired nevi in childhood and adolescence
- Spitz nevi
- Pediatric melanoma

Approach to Dermoscopy: *Pigmented lesions*

- **Global features**
  - *Symmetrical or Asymmetrical*
  - *Color uniformity or multi-colored*
- **Pigmented Patterns**
  - ***Reticular***
  - ***Globular***
  - ***Homogenous***
  - ***Starburst***
- **Local concerning features**
  - *Atypical network*
  - *Streaks*
  - *Atypical dots or globules*
  - *Irregular blood vessels*
  - *Regression*
  - *Blue-white veil*



CONGENITAL MELANOCYTIC NEVI

Current definition, clinical and dermatoscopic features, melanoma risk, and neurocutaneous melanocytosis

Photo: Clinics in Dermatology (2015) 33, 368 -386

Congenital melanocytic nevi (CMN)

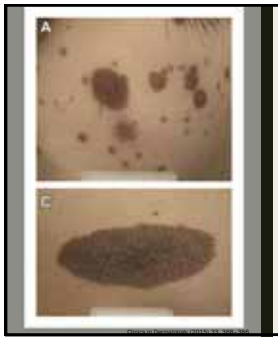
- Present at birth
- 2-3% of neonates
  - *Small and medium size – common*
  - *Large and Giant – 1/20,000-50,000 live births*

CMN Classification

- Size (projected adult size)
  - *Small (<1.5 cm)*
  - *Medium (1.5 – 20 cm)*
  - *Large (>20 cm)*
  - *Giant (>40 cm)*

CMN enlarge in proportion to child's growth
Final diameter is predicted by estimate
- **size increase from infancy to adulthood by a factor of: 1.7 on head 2.2 on legs and 2.8 in other sites**

- Clinical characteristics
  - *Location*
  - *Number of satellite nevi*
  - *Color heterogeneity*
  - *Surface rugosity*
  - *Dermal and subcutaneous nodularity*
  - *Hypertrichosis*



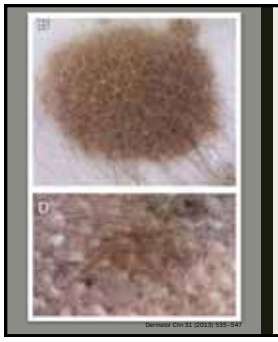
Dynamic evolution

- **Morphologic change common**
- Flat, evenly pigmented patch → thin plaque → polychromatic with mammillated, rugose, verrucous or ceribriform surface
- Superimposed papules and nodules may undergo rapid growth, ulceration, black or red color, and/or regression
- **While changes warrant biopsy they do not necessarily herald malignancy in this subset of pigmented lesions**

"Comparative study of Proliferative Nodules and Lethal Melanomas in Congenital Nevi from Children" *Yelamos et al* Am J Surg Pathol. 2015 Mar;39(3):405-15.

- **Benign proliferative nodules** may arise within large CMN during infancy
  - *Histologic features may mimic melanoma or less often an undifferentiated spindle cell neoplasm*
- Melanomas more likely seen in ulcerated nodules
- Comparative genomic hybridization
  - *Proliferating nodules: whole copy aberrations +/- partial aberrations*
  - *Melanoma: partial chromosomal gain or loss*

Clinics in Dermatology (2015) 33, 368–386



Dermatol Clin 31 (2013) 535–547

Dermoscopy

- **Globular or "cobble stoned" pattern predominates**
  - *Lower extremities may have reticular pattern*
- Additional associated features:
  - *Perifollicular hypopigmentation*
  - *Milia-like cysts*
  - *Hypertrichosis*

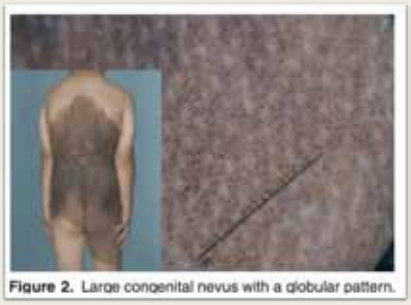


Figure 2. Large congenital nevus with a globular pattern.

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Melanoma risk

Small and medium CMN

- Less than 1% risk
- After puberty
- Arise superficially with evidence seen at DEJ
  - *Periphery of nevus MC site*
  - ***Monitor with dermoscopy***

Large and Giant CMN

- 2-5% risk
- Highest risk <5 yrs of age
- Arise from deep dermis or subcutis
  - ***Less dermatoscopic utility***
- Sites: Trunk > Head and neck
- Satellite lesions --- low to no risk

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Photo: Clinics in Dermatology (2015) 33, 368–386

Screening: MRI of brain and spine for large CMN in first 6-8 mo of life, especially if overly spine, repeat at puberty

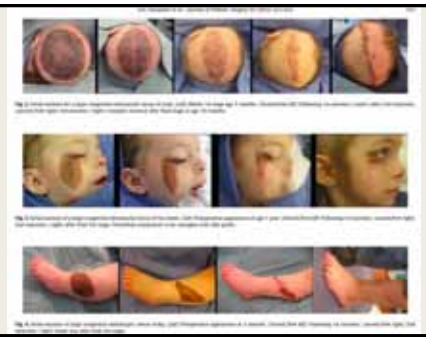
Follow up: serial neuro exam, head circumference, and developmental assessments

Neurocutaneous melanosis (NCM)

- Proliferation of melanocytes in CNS in addition to skin
  - *Pia matter of meninges*
- **Satellite/Numerous CMN (any size) is strongest risk factor for NCM**
- No increased risk for MM
- Symptomatic → worse prognosis
  - *Lethargy, seizures, hydrocephalus, irritability, photophobia, HA, N/V*
  - *melanocytic cells obstructing flow of CSF*

Management in high risk CMN

- **Prophylactic early and complete surgical removal is ideal**
  - *Difficult, sometimes impossible (size, deep extension to fat, fascia, muscle)*
  - *Staged excision (down to fascia) with flap reconstruction and tissue expansion*
- Common recurrence of pigment at and around scar
- **Excision of nevus does not eliminate risk of malignancy**
  - *Melanoma developing under skin graft has been reported*
  - *Primary MM may arise in CNS or other extracutaneous sites*
- Curettage, dermabrasion, ablative laser (CO2, erbium:YAG), or pigment specific laser may also have cosmetic benefit[1]
  - **Ablative laser: first 1-2 months of life a/w favorable risk/benefit ratio d/t active nevomelanocytes concentrated in upper dermis** (decreased scarring)



ACQUIRED NEVI IN CHILDHOOD AND ADOLESCENCE

Clinical and dermatoscopic features, Dynamic evolution over time
Evidence based management

Acquired nevi in childhood and adolescence

- Melanocytic nevi are an almost ubiquitous finding
- Nevus counts by the end of the 1st decade of life[1]
  - Caucasian children: ***15-30 nevi***
  - African, Asian, or Native American: ***5-10*** *nevi*
- Number of nevi peaks in 3rd decade[1]

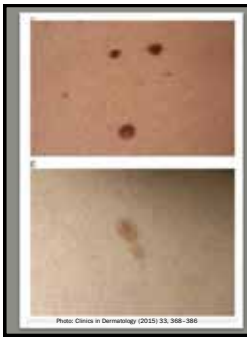


Photo: Clinics in Dermatology (2015) 33, 368–386

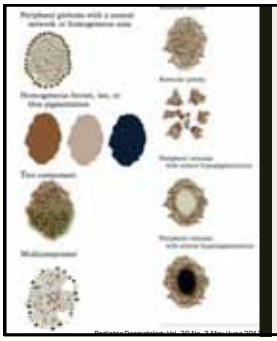
Acquired nevi in childhood and adolescence

- ***Solid brown***
- ***Solid pink***
- ***Fried egg-like***
- ***Tan centrally with brown rim***
- ***Eccentric focus of hyperpigmentation "Bolognia sign"***

Arch Dermatol. 2006;142(4):479-483.

Bolognia sign

- Described in 1994
- **Nevus with eccentric peripheral hyperpigmentation**
  - *may have gray-black focus of hyperpigmentation in absence of other melanoma dermatoscopic features*
- Common in children, benign



Dermoscopy

- Fitzpatrick I, II
  - *Globular pattern predominates*
  - *Head, neck, upper trunk*
- Fitzpatrick III, IV
  - *Smaller nevi with reticular pattern*
- Acquired in adulthood:
  - *Reticular pattern*

Nevus development

Environmental Factors

- **Intense and intermittent sun exposure**
  - *influence on number and location of nevi in childhood as well as later risk of melanoma*
- Higher peak nevus # at earlier age seen in children living in tropical climate[1]
  - *peak of ~50 nevi at age 15 vs temperate location ~25 at age 25*

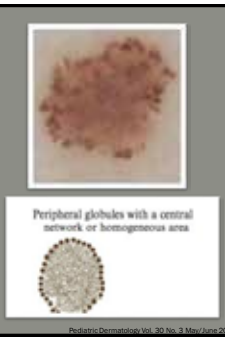
Genetic factors

- **Genetic predisposition**
  - *Several genes linked to nevus development (#, pattern)*
  - *IRF4, TERT, CDKN1B, MTAP, and PARP1*
- **Pigmentary phenotype**
  - *Light skin – higher nevus counts*
  - *Dark skin – predisposition to nevi on palms and soles (unrelated to sun exposure)*

Photo: Clinics in Dermatology (2015) 33, 368–386

Two pathways in evolution

1. **Formation of soft, skin-colored papules (Intradermal nevi)**
   - Linked to nevi with **globular pattern**
   - Favor head/neck and dorsal trunk
2. **Gradual fading away via atrophy or fibrosis (regression)**
   - Linked to nevi with **reticular pattern**
   - Favor extremities



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Dermoscopy

- Enlargement is often characterized by a **peripheral rim of brown globules**
- Up to 50% of nevi in children enlarge over 1 year period, and this is not a/w histologic atypia
  - *Changing nevi are nearly 2x as likely to have histologic evidence of atypia in adults (63%) than in children and adolescence (35%)*

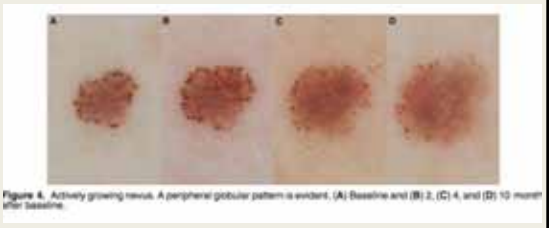

Figure 4. Actively growing nevus. A peripheral globular pattern is evident. (A) Baseline and (B) 2, (C) 4, and (D) 10 month after baseline.

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Management

- **Change in nevus should not be used as sole criterion for excision in pediatric patient**
- **Nevus phenotype manifests during first decade of life**
  - ***Signature mole to find the "ugly duckling"***
- **Atypical nevi tend to appear around puberty and continue to develop during adulthood**
  - *Majority with benign behavior*
- Biopsy: avoid sampling unless lesion is large or in cosmetically sensitive area
- >50 acquired nevi and presence of clinically atypical nevi → risk for melanoma
  - *FBSE beginning at puberty*
- **Lifetime risk of any particular nevi turning into melanoma 1/10,000[1]**
  - ***More than 50% of melanomas arise de novo***

PEDIATRIC SPITZ NEVI

Clinical features, Power of dermoscopy, When to be concerned, Evidence based Management

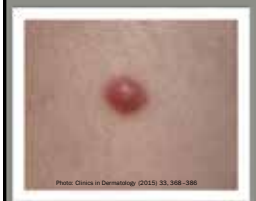
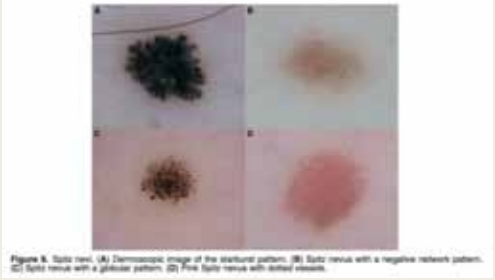


Photo: Clinics in Dermatology (2015) 33, 368–386

Solitary pediatric papule Ddx:
- Spitz Nevi
- JXG
- Mastocytoma

Spitz Nevi

- Benign melanocytic neoplasm
  - *Spindled and epitheloid cells*
- <20 years of age
- Solitary pink, red, or brown papule
  - *Face or lower extremity*
- Rapid growth
- Smooth or verrucous surface
  - *Ddx: wart, pyogenic granuloma, DF, JXG, mastocytoma*
- Clinical and histopathologic overlap with melanoma



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Pigmented Spitz *Reed nevi*

- Starburst pattern
- Central dark, homogenous pigment surrounded by peripheral streaks (radial streaming with pseudopods)
- Multiple studies examining dermatoscopic progression:
  - *Reticular or homogenous pattern → regress over months/years*

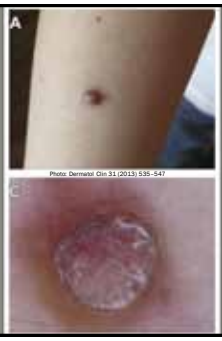
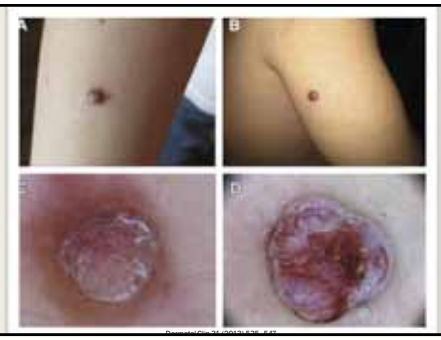


Photo: Dermatol Clin 31 (2013) 535–547

Non-pigmented Spitz Nevi

- Dotted vessels and negative (white) network



Dynamic evolution of Spitz Nevi

Natural evolution of Spitz Nevi. *Argenziano et al,* Dermatology 2011;222:256-260

- *Large study of non-pigmented and pigmented Spitz nevi in children and young adults (mean age 10 yrs) found that* ***80%*** *(51/64)* ***underwent involution over a mean of 25 months***

Management

Atypical features:
Amelanotic papulonodular
Large size >8-10mm
Excessive growth
Asymmetry
Ulceration at any age

- Controversial due to histopathologic overlap with melanoma
- Several groups endorse **longitudinal follow-up** with classic clinical and dermatoscopic features **in children less than 12** years[1]
  - *Monitor q 3-6 months until stabilize*
- **Postpubertal** new spitz nevi, or those with atypical features → biopsy[1]

Management of Atypical spitzoid neoplasms

- **Borderline histologic features indistinguishable from melanoma**
- **Uncertain malignant potential**
- **Excisional biopsy with normal margin preferred over shave biopsy for diagnostic accuracy and tx[2]**
  - ***Careful follow up recommended***
- **Positive SLNB is NOT a/w prognostic significance in any age group or for melanomas in children**
- Systematic review of 303 SLNB with atypical spitzoid neoplasms
  - *119/303 (39%) were positive, only one died at mean follow-up of 5 years*
- No evidence that further lymph node dissections or adjuvant systemic therapy are efficacious for pts with positive SLNB and atypical spitzoid neoplasm
  - *Risk long term complications and lymphedema*

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Additional diagnostic tools: Spitz nevus vs Melanoma

- Spitz nevi, atypical spitzoid neoplasms and spitzoid melanoma exist on a spectrum
- Comparative Genomic Hybridization
  - *Detects chromosome copy number and changes within genome*
- Fluorescent in situ hybridization
  - *Detects chromosome copy number and changes in loci*
- Both promising to distinguish between – Spitz, atypical spitz and melanoma
  - *Limited accessibility, high cost, ?inconsistent results*

S100-A6 histologic stain for distinguishing atypical spitz vs melanoma

PEDIATRIC MELANOMA

clinical features, modified ABCDEs, dermoscopy tips, management

Pediatric Melanoma

- **Melanoma extremely rare in childhood**
  - *~4% arise in patients less than 20 years of age*[2]
  - *< 0.5% of melanomas occur in patients younger than 10 years of age*[1,2]
- **Appear amelanotic and nodular** – presenting like a rapidly growing "bump" may mimic pyogenic granuloma, keloid or wart rather than a changing nevus[1]
- Main risk factor in pediatrics: **large congenital nevus**
  - *Other: atypical spitzoid neoplasms, immune suppression, genetic syndromes (ie. XP)*
- **Atypical nevi arise after puberty** → regular follow-up esp in children with Fhx of melanoma, fair skin, and hx of sunburns

Codoro et Al. JAAD June 2013

Modified ABCDEs for pediatric melanoma

Cordoro et al. JAAD 2003

- **Amelanotic**
- **Bleeding, bump**
- **Color uniformity**
- **De novo (any diameter)**
- **Evolution**

Pediatric vs Adult melanoma

Retrospective study of 33 cases of childhood melanoma from a single institution. Ferrari et all. Pediatrics 2005; 115:649-54

- Higher breslow thickness at presentation
- Higher incidence of lymph node involvement
- Overall better prognosis
- Family history melanoma – important risk factor in all ages
- Genetic influence in younger children (0-9 cohort)
- Environmental exposure (sunburn >3) and greater # nevi in older children

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Dermoscopy

- Atypical pigment network
- Streaks
- Negative pigment network
- Crystalline structures
- Atypical dots and globules
- Off center blotch
- Blue-white areas over raised areas
- White-scar like (regression) structures
- Atypical vascular (Milky red, dotted or twisted vessels)
- Peripheral brown structureless areas

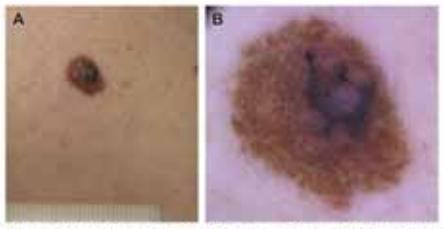

Fig. 10. (A) Melanoma in situ arising within a congenital nevus in a 17-year-old girl. The patient had a fair skin phototype and multiple nevi. (B) Dermoscopy shows a diffuse cobblestone pattern with a focal area of blue-white structures (the latter corresponding to in situ melanoma).

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Pediatric melanoma

- Treatment mainstay: EARLY DETECTION
- Suspicious lesion – Excisional biopsy with narrow margin
  - *Spitz nevi after puberty or changing spitz nevi (large, ulcerated, rapid growth, nodular)*
  - *Solitary amelanotic or bleeding bump*
- Histopathology from reliable dermatopathologist
- If confirmed → excision with wide margins
- Regular dermoscopic follow up
- Skin exams starting in puberty (high risk)
- ?Role of SLNB
- ?Role of adjuvant therapies

Take home points:

- Dermoscopy is a powerful diagnostic tool for pediatric pigmented lesions
- All large and giant congenital melanocytic nevi should be monitored appropriately for risk of melanoma and neurocutaneous melanosis
- All nevi have the capacity for subtle change over time, such as growth in proportion to the patient, appearing lighter or darker in color, regressing, or slowly becoming thicker in depth, over the course of years.
- Identify the patient's "signature nevus" pattern, and use "ugly duckling sign" for lesions needing close evaluation and consideration for biopsy
- "Classic Spitz nevus" appears in childhood, with typical history and clinical features, can be managed conservatively by clinical monitoring
- Atypical spitz nevi (at any age) and classic spitz nevi developing during or after puberty should be excisionally biopsied
- Pediatric-specific ABCDE melanoma criteria: amelanosis, bleeding bump, color uniformity, denovo development (diameter variability), evolution

References

1. Schaffer J. Update on melnaocytic nevi in children. Clinics in Dermatology. 2015 (33); 368-386
2. Moscarella et al. Problematic Lesions in Children. Deratol Clin. 2013 (31). 535-547
3. Haliasos et al. Dermoscopy for the Pediatric Dermatologist Part III: Dermoscopy of Melanocytic Lesions Pediatric Dermatology. 2013; 30 (3):281-293
4. Price et al. Practical Application of the New classification scheme for congenital melanocytic nevi. 2014; 32 (1): 23-27
5. Hassanein et al. Management of challenging congenital melanocytic nevi: outcomes study of serial excision. Journal of Ped Surgery. 2015; 50: 613-618
6. Reed et al. Controversies in the evaluation and management of atypical melanocytic proliferations in children, adolescents and young adults. 2013; 11 (6):679-686
7. Bronsnick et al. Outcomes of biopsies and excisions of dysplastic acral nevi: A study of 187 lesions. Am society for Derm Surgery. 2014; 40:455-459
8. Neri et al. Spitz nevi: defining features and management in children. Giornale Italiano Di Dermatolgica E. Venereologia. 2014; 149 (6):675-82
9. Cordoro et al. Pediatric Melanoma: Results of a large cohort study and proposal for modified ABCD detection criteria for children. 2013; 68 (6): 913-925
10. Han et al. Unique Clinical Characteristics of Melanoma Diagnosed in Children. 2014; 19: 3888-3895
11. Blum et al. Dermoscopy of Pigmented Lesions of the Mucosa and the Mucocutaneous Junction Results of a Multicenter Study by the International Dermoscopy Society (IDS). Arch Dermatol. 2011;147(10):1181-1187
12. Lewis et al; *Trends in pediatric melanoma mortality in the United States, 1998- 2004.* Dermatologic Surg 2007; 34; 152-9

Thank you!

Pediatric Bullous Disease

Lehigh Valley Health Network/PCOM
Kelly L. Reed, D.O., PGY-4

Overview

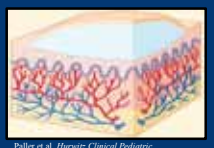
- Briefly review the various categories of pediatric bullous dermatoses
- Discuss some of the most common, board relevant and life threatening pediatric bullous diseases
  - Clinical features
  - Pathogenesis
  - Histopathology and immunofluorescence findings
- Updates on new studies and treatment options

Pediatric Bullous Disease

- Infectious
  - Staphylococcal scalded skin syndrome
    - Bullous impetigo
  - Bullous tinea, eczema herpeticum
  - Blistering distal dactylitis
  - Bullous scabies
  - Varicella virus, herpes simplex virus
- Infectious or medication induced
  - Stevens Johnson Syndrome & Toxic epidermal necrolysis
- Hereditary
  - Epidermolysis Bullosa (EB)
    - Subtypes (simplex, junctional, dystrophic)
  - Kindler syndrome
  - Bullous CIE- Epidermolytic Hyperkeratosis
  - Incontinentia Pigmenti
- Autoimmune
  - Linear IgA bullous dermatosis of childhood
  - Dermatitis herpetiformis
  - Bullous systemic lupus erythematosus
  - Epidermolysis bullosa acquisita
  - Bullous pemphigoid (BP)
  - Pemphigus (foliaceous, vulgaris, drug induced PNP, IgA)
  - Herpes gestionis
- Miscellaneous
  - Contact dermatitis
  - Phytodermatitis
  - Phytophotodermatitis
  - Bullous Erythema Multiforme
  - Bullous Fixed drug
  - Bullous Mastocytosis
  - Porphyrias

Pediatric Bullous Disease

- Blisters- Fluid filled lesions on skin or mucous membranes
  - Vesicles <1cm (Hurwitz)
  - Bullae ≥1cm
- Nikolsky sign
  - Spread of blister with lateral pressure
- Asboe-Hansen sign
  - Spread of blister with perpendicular pressure



Paller et al. *Hurwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

Infectious Bullous Disease

- Staphylococcal Scalded Skin Syndrome (SSSS)
  - Bullous impetigo
- Bullous tinea, eczema herpeticum
- Blistering distal dactylitis
- Bullous scabies
- Varicella virus, herpes simplex virus

Staphylococcal Scalded Skin Syndrome (SSSS)

Clinical Presentation

- Neonates and young children
  - Irritability, fever, malaise, poor feeding
  - Due to infection of conjunctivae, nares, perioral region or perineum
  - Generalized erythema then fragile sterile blisters of flexures
    - Positive Nikolsky sign
  - Perioral radial fissuring is common
    - No mucous membrane involvement

SSSS

http://pediatrics.ucsf.edu/blog/unknowns-part-2#.VcZGCbqd1.zl

Paller et al. *Hurwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

SSSS

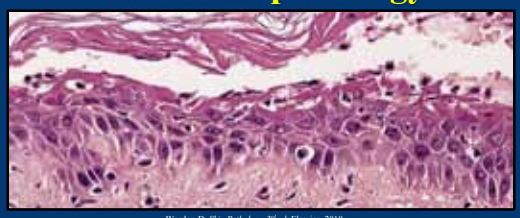
Pathogenesis

- Toxin mediated disease produced by *S. aureus* type 71 of phage group II
  - Exfoliative toxins ETA and ETB
  - Targets desmoglein 1 in superficial epidermis (stratum granulosum)
    - Bullous impetigo localized form
  - Poor renal clearance and low titers of antibodies

Diagnosis

- Bacterial culture from pustule or site of colonization (nares, nasopharynx, perineum)
  - Blisters are typically sterile

SSSS Histopathology



Weedon D. *Skin Pathology* 3rd ed. Elsevier, 2010.

SSSS Treatment

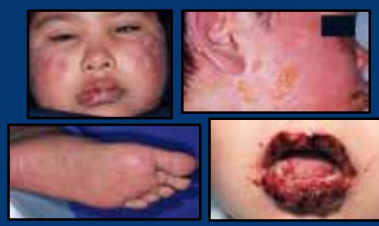
- Eradicate toxin producing bacteria
  - Anti-staphylococcal antibiotics
    - SSSS requires systemic therapy
      - Penicillinase resistant penicillin, 1st or 2nd generation cephalosporins, clindamycin, vancomycin
    - Bullous impetigo may be treated topically or systemically
- Studies suggested fresh frozen plasma or IVIG to neutralize exfoliative toxin

Stevens Johnson Syndrome (SJS) & Toxic Epidermal Necrolysis (TEN)

Clinical presentation

- Life threatening
  - Older children and adults
- Prodromal period 1-14 days
  - High fever, malaise, poor feeding, arthralgias, cough
  - Mucosal symptoms may precede skin findings by 1-2 days
- Painful erythematous or purpuric macules, develop dusky color and bullae become confluent
- Full thickness epidermal detachment
  - Positive Nikolsky and Asboe-Hansen signs
- Visceral involvement and lab abnormalities

SJS/TEN

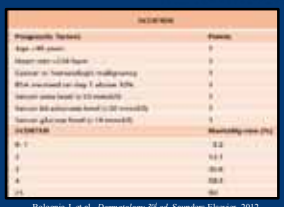


Paller et al. *Hurwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

SJS/TEN

Bolognia J, et al. *Dermatology 3rd ed.* Saunders Elsevier. 2012.

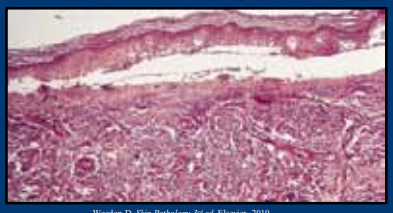
SCORTEN



Bolognia J, et al. *Dermatology 3rd ed.* Saunders Elsevier. 2012.

- Lower chance of mortality
- 70% experience morbidity with long term sequelae
- SCORTEN better predicts morbidity in pediatric patients
  - Days on mechanical ventilation
  - Infectious complications

SJS/TEN histopathology



Weedon D. *Skin Pathology 3rd ed.* Elsevier, 2010.

SJS/TEN

- Pathogenesis
  - SJS-*Mycoplasma pneumoniae* infection and medications
  - TEN- medications (antibiotics & anticonvulsants in children)
  - Fas-Fas ligand mediated keratinocyte apoptosis
- Treatment
  - Discontinue medications, treat underlying infection, supportive care, wound care and prevention of infection
    - IVIG
    - Systemic corticosteroids
    - Anti-TNF alpha
    - Cyclophosphamide
    - Cyclosporine
- Retrospective study by Ahluwalia et al demonstrated corticosteroids as monotherapy or with IVIG result in shorter length of stay and fewer febrile days in mycoplasma-associated SJS

Hereditary Bullous Diseases

- Epidermolysis Bullosa
  - Simplex
  - Junctional
  - Dystrophic
- Kindler syndrome
- Congenital Ichthyosiform Erythroderma
  - Bullous and non-bullous
- Incontinentia Pigmenti

Epidermolysis Bullosa (EB)

Group of >30 inherited blistering disorders

- Blisters and scarring from minor trauma due to skin fragility from inherited structural defects
- EB Simplex
  Split: Epidermal Basal Layer
- Junctional EB
  Split: Basement Membrane (Lamina Lucida)
- Dystrophic EB
  Split: Dermal (Sublamina Densa)
- Kindler syndrome

Bolognia J. et al. *Dermatology essentials 1st ed.* Saunders Elsevier. 2014. Print.

Epidermolysis Bullosa

A: EBS-localized (Weber–Cockayne)

B: Dominant DEB (Cockayne–Touraine)

C: Recessive DEB-severe generalized

D: Recessive DEB-severe generalized

E: EBS Dowling-Meara

F: EBS Dowling-Meara

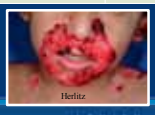
http://www.skin-disease-care.com/815bullous_diseases.php

EB Simplex

Subtype	Inheritance	Defective Protein	Clinical
EBS-Dowling-Meara (herpetiformis)	AD	K5/K14	Onset at birth, mucosal membrane involvement, nail dystrophy, scarring, early death
EBS-localized (Weber-Cockayne)	AD	K5/K14	Onset childhood, palmoplantar bullae/erosions, heals without scarring
EBS-other generalized (Koebner)	AD	K5/K14	Generalized bullae at birth, PPL, nail dystrophy, heals without scarring
EBS Muscular Dystrophy	AR	Plectin	Widespread bullae at birth, muscular dystrophy, scarring, early death
EBS Mottled Pigmentation			Resembles localized and generalized EBS, reticulated hyperpigmentations over trunk

Junctional EB

Subtype	Inheritance	Defective Protein	Clinical
Herlitz	AR	Laminin 332 (5)	Nonhealing exuberant granulation tissue, enamel defects, mucosal involvement, early death
Non-Herlitz	AR	Laminin 332 (5) or BPAG2 (Type XVII collagen)	Heals with atrophic scars, widespread bullae at birth, scarring alopecia
JEB with Pyloric Atresia	AR	Alpha 6 beta 4 integrin	Severe congenital blistering, pyloric atresia, hydronephrosis, mucosal erosions, aplasia cutis congenita, malformed ears



Herlitz

Non-Herlitz

JEB with pyloric atresia

Paller et al. *Hurwitz Clinical Pediatric Dermatology: a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

Dystrophic EB

Subtype	Inheritance	Defective Protein	Clinical
Recessive DEB-severe generalized (Hallopeau-Siemens)	AR	Type VII collagen	Severe widespread bulla at birth, heals with atrophic scarring, "mitten deformity", mucosal scarring, esophageal involvement, high risk of SCCs
Recessive DEB, other	AR	Type VII collagen	Less severe than the HS variant, skin changes localized to acral/bone prominences
Dominant DEB (Cockayne-Touraine)	AD	Type VII collagen	Bullae mainly over extremities, heals with scarring, nail dystrophy
Pasini Variant (DDEB-P)	AD	Type VII collagen	Similar to Cockayne subtype + white perifollicular papules

Epidermolysis bullosa acquisita (EBA) – autoimmune T-cell mediated and neutrophilic blistering disease Type VII collagen with linear IgG +/- C3 in sublamina densa (U-serrated pattern)

- Subtypes: inflammatory, non-inflammatory & cicatricial pemphigoid

Kindler Syndrome

Name	Inheritance	Defective Protein	Clinical
Kindler Syndrome	AR	Kindlin-1 (mediates anchoring between anchoring fibrils and ECM) due to mutation in KIND1 (FERMT1)	Acral blistering during infancy +/- digital webbing, PPK, photosensitivity, progressive poikiloderma "cigarette paper"atrophy, gingivitis, colitis, stenoses, ectropion

Paller et al. *Hurwitz Clinical Pediatric Dermatology: a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

Ashton G, Mohsin I, Smith A, et al. Recurrent mutation in Kindler's, a novel keratinocyte focal contact protein, in the autosomal recessive skin fragility and photosensitivity disorder, Kindler syndrome. *J Invest Dermatol*. 2004;122:78-83.

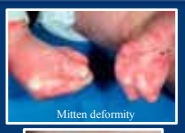
EB

Diagnosis

- Genetic analysis
- Transmission electron microscopy
- Immunofluorescence antigen mapping (IFM)

Treatment

- Avoidance of mechanical trauma
- Preventing infections
- Non-adherent dressings
  - Prevent "mitten deformity" (pseudosyndactyly) in DEB
  - Petrolatum-impregnated gauze, soft silicone dressings
- Biopsy non-healing ulcers to exclude SCC
- Multidisciplinary approach



Mitten deformity

Paller et al. *Hurwitz Clinical Pediatric Dermatology: a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

New Therapies Dystrophic EB

- Gene therapy
  - Viral vector used to insert functional collagen into skin
- Cell-based therapy
  - Intradermal injections of allogenic fibroblasts used to generate new collagen
- Protein therapy
  - Recombinant collagen produced in vitro is injected into blistering skin
- Bone marrow derived stem cell transplantation
  - Donor cells localize to skin and Type VII collagen deposition at DEJ

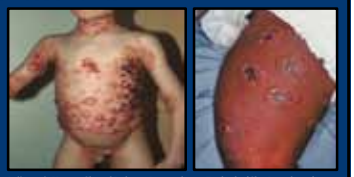
Autoimmune Bullous Diseases

- Linear IgA bullous dermatosis
- Dermatitis herpetiformis
- Bullous systemic lupus erythematosus
- Epidermolysis Bullosa Acquisita
- Bullous pemphigoid
- Pemphigus (foliaceous, vulgaris, PNP, drug-induced)

Linear IgA Bullous Dermatosis (LABD)

Chronic bullous disease of childhood

- Clinical Presentation
  - Tense, clear or hemorrhagic bullae
    - lower trunk, thighs & groin
  - Annular or rosette-like lesions with sausage-shaped blisters
  - Annular erythema with blisters
    - "Crown of jewels"



Paller et al. *Hurwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

LABD Pathogenesis

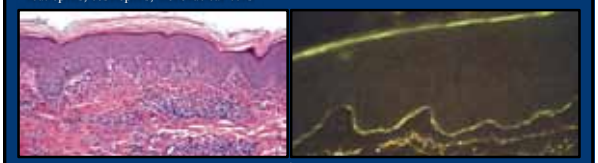
- Immune-mediated subepidermal blistering disease in both adults and children
  - Idiopathic, autoimmune disorders, malignancy
  - Medications- vancomycin, amoxicillin-clavulanate, TMP-SMX
- Linear IgA deposits in two distinct patterns:
  - Classic
    - IgA antibodies to 97-kDa and/or 120 kD fragment of BP180
    - Split in the lamina lucida
  - Recently described

Type VII Collagen Is the Major Autoantigen for Sublamina Densa–Type Linear IgA Bullous Dermatosis

LABD Histopathology and DIF

H&E: Subepidermal bullae with edema of adjacent dermal papillae and dermal infiltrate of neutrophils, eosinophils, mononuclear cells

DIF: linear IgA along DEJ
IIF: Epidermal side of salt split skin



Weedon D. *Skin Pathology. 3rd ed.* Elsevier, 2010. Print.

LABD Treatment

- Spontaneous remission often occurs within months-years
  - typically by puberty
- Dapsone
  - Clinical improvement 48-72 hours
- Oral corticosteroids
- Antibiotics: dicloxacillin, erythromycin, tetracycline (age >9), trimethoprim/sulfamethoxazole
- Refractory: mycophenolate mofetil, azathioprine, IVIG

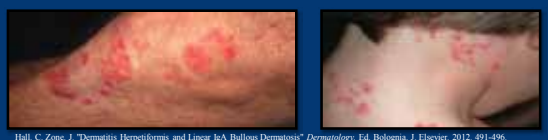
Dermatitis Herpetiformis (DH)

- DH is the specific cutaneous manifestation of celiac disease
  - Sensitivity to gluten found in wheat, barley, and rye
    - Gliaden soluble fraction
    - >90% of patients with DH have evidence of gluten sensitive enteropathy
    - 20% have intestinal symptoms of celiac disease
- Genetic association with HLA-DQ2 and DQ8

Dermatitis Herpetiformis (DH)

- Symmetric grouped vesicles or herpetiform polymorphic lesions
  - Extensor surfaces
  - Knees, elbows, sacral region, shoulders, buttocks, neck, face & scalp
- Intensely pruritic
  - Associated diseases
    - Hashimoto's thyroiditis
    - Insulin dependent diabetes
    - Enteropathy associated T-cell lymphoma
- IgA autoantibodies to tissue transglutaminase (endomysial)
  - Form complexes in the papillary dermis with epidermal transglutaminase-3

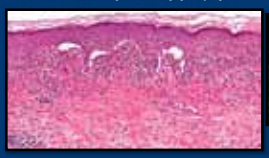
DH Clinical Features



Hall, C, Zone, J. "Dermatitis Herpetiformis and Linear IgA Bullous Dermatosis" *Dermatology*. Ed. Bolognia, J. Elsevier. 2012. 491-496.

DH Histopathology and DIF

H&E: subepidermal vesicles and blisters with accumulation of neutrophils at the papillary tips



Hall, C, Zone, J. "Dermatitis Herpetiformis and Linear IgA Bullous Dermatosis" *Dermatology*. Ed. Bolognia, J. Elsevier. 2012. 491-496.

DIF: Granular or fibrillar IgA at the tips of the dermal papillae, along BMZ

Bolotin D, Petronic-Rosic V. *Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis*. J Am Acad Dermatol. 2011 Jun;64(6):1027-33.

DH Treatment

- Gluten free diet
- Dapsone
  - sulfasalazine, sulfapyridine, sulfamethoxypyridazine
- Superpotent topical corticosteroids
- Systemic corticosteroids or antihistamines for pruritis

- Case reports:
  - topical dapsone, cyclosporin A, azathioprine, colchicine, heparin, tetracyclines, nicotinamide, mycophenolate mofetil, and rituximab

DH Potential New Therapies

- Prevention
  - Late introduction of gluten to infants with first degree relatives with celiac disease
- Enzyme therapy
  - Supplemental bacterial-derived peptidases may promote digestion of gluten proteins
    - ALV003, is currently in clinical trials and has shown promising safety and efficacy data.
  - Pretreatment of foods with peptidases to decrease gluten content

DH Potential New Therapies

- Immunomodulatory strategies
  - Selective inhibition of TTG in the small intestine to counter the immunotoxic response to dietary gluten
- Correction of the intestinal barrier defect
  - An investigational agent, larazotide acetate, a zonulin inhibitor, decreases intestinal permeability abnormalities and exposure to dietary gluten

Bullous Systemic Lupus Erythematosus (BSLE)

Clinical presentation
- Recurrent blistering disease
- Pruritic vesicles and tense bullae in patients with SLE
- Sun exposed sites
- 30% have mucosal lesions
- Young African American women & adolescents

Pathogenesis:
- Circulating antibodies to **type VII collagen** (same as EBA)
  - HLA-DR2 positive

Bullous SLE

Paller et al. *Hurwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence*, 2011.

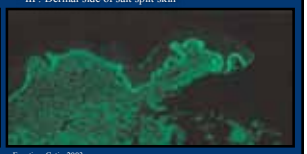
Camacho I. Bullous systemic lupus erythematosus. *Medscape emedicine*. http://emedicine.medscape.com/article/1065402-overview

Bullous SLE Histopathology

H&E: Subepidermal blister with neutrophil predominant inflammation

DIF : "full house" continuous granular pattern at BMZ of IgG, IgM, IgA, C1q and/or C3
- U-serrated pattern

IIF: Dermal side of salt split skin



Harris-Stith et al. Bullous Eruption. Cutis. 2003.

BSLE Treatment Update

- Review article by Duan et al in the Journal of Immunology Research 2015 on the treatment of BSLE:
  - Dapsone resulted in dramatic response
    - Methotrexate
    - Prednisolone
    - Colchicine
    - Azathioprine
    - Cyclophosphamide
    - Mycophenolate mofetil
    - Rituximab
- Prognosis:
  - Determined largely by visceral manifestations of SLE
  - Good response to dapsone correlates with better prognosis

Summary

- Many diseases present with blisters and bullae in the pediatric population
- Diagnosis is made based on thorough clinical history, physical exam, biopsy, immunofluorescence findings and/or serology
- Studies to further delineate pathogenesis and treatment options to improve patient outcomes

References

1. Antiga E, Caproni M. The diagnosis and treatment of dermatitis herpetiformis. Clin *Cosmet Investig Dermatol*. 2015;8:257-265.
2. Ashton G, Mclean I, South A, et at. Recurrent mutations in Kindlin-1, a novel keratinocyte focal contact protein, in the autosomal recessive skin fragility and photosensitivity disorder, Kindler syndrome. *J Invest Dermatol*. 2004;122:78-83.
3. Barzegar M, Asani-Kani Z, Mozafari N, et al. Using immunofluorescence (antigen) mapping in the diagnosis and classification of epidermolysis bullosa: a first report from Iran. *Int J Dermatol*. 2015:IJD12804.Epub.
4. Beck A, Quirke K, Gamelli R, et al. Pediatric toxic epidermal necrolysis: Using SCORETEN and predictive models to predict morbidity when a focus on mortality is not enoubg. *J of Burn Care & Research*. 2015;36(1):167-177.
5. Berk DR, Jazayeri L, Marinkovich MP, et al. Diagnosing epidermolysis bullosa type and subtype in infancy using immunofluorescence microscopy: the Stanford experience. *Pediatric Dermatol*.2013;30(2):226-233.
6. Bolognia JL, Jorizzo JL, Scaffer JV, et al. *Dermatology. 3rd ed*. Saunders 2012
7. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis. *J Am Acad Dermatol*. 2011;64(6):1027-33.
8. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part I. Epidemiology, pathogenesis, and clinical presentation. *J Am Acad Dermatol*. 2011;64(6):1017-24.
9. Chen S, Mattei P, Fischer M, et al. "Linear IgA Bullous Dermatosis" from interesting case series. Dept of Dermatology and Dermatopathology and Department of Plastic and Reconstructive Surgery, Johns Hopkins School of Medicine, Baltimore, MD.

References

10. Chmel N, Danescu S, Gruler A. A Deep-intronic FERMT1 mutation causes Kindler Syndrome: An explanation for genetically unsolved cases. *J of Invest Dermatol*. 2015; online.
11. Duan L, Chen L, Zhong S, et al. Treatment of bullous systemic lupus erythematosus. *J of Immunol Res*. 2015; 6 pages. http:dx.doi.or/10.1155/2015/167064.Web.
12. Handler MZ, Schwartz RA. Staphylococcal scalded skin syndrome: diagnosis and management in children and adults. *J of the European Acad of Dermatol and Venereology. 2014;28:1418-1423.*
13. Fasano A. Novel therapeutic/integrative approaches for celiac disease and dermatitis herpetiformis. *Clin Dev Immunol*. 2012:2012:959-61.
14. Heras M, Navedo DL. Linear IgA Bullous Dermatosis of Childhood: Good Response to Antibiotic Treatment. *Clin Exp Dermatol*. 2013;39(3): (395-97).Web,
15. Intong LR, Murrell DF. Inherited epidermolysis bullosa: New diagnostic criteria and classification. *Clin Dermtol* 2012;30: 70-77.
16. Kanwar AJ, Sandu K, Handa S. Chronic bullous dermatosis of childhood in north India. *Pediatr Dermatol*, 2004; 21:(610-612).
17. Lugwig R. Clinical presentation, pathogenesis, diagnosis and treatment of epidermolysis bullosa acquisita. *ISRN Dermatology*.2013;Article ID 812029. 25 pages.
18. Lyngs K, Bygum A. Linear IgA Bullous Dermatosis: A Retrospective Study of 23 Patients in Denmark. *Acta Dermato-Venereologica*, 2015;95(466-71). Web.

References

19. Müruauer EM, Gache Y, Gratz IK, et al. Functional correction of type VII collagen expression in dystrophic epidermolysis bullosa. *J Invest Dermatol* 2011;131:74-82.
20. Moleiro S, Santos V. Atypical Response to Treatment in Linear IgA Bullous Dermatosis of Childhood: Revision of Literature. *Dermatology Online Journal* 5(h:scr. 2011;17(6):Web. 16 Aug. 2015.
21. Paek S, Steinberg S, Katz S. Remission in dermatitis herpetiformis: a cohort study. *Arch Dermatol*. 2011;147:301-301.
22. Paller AS, Mancini AJ. Bullous Disorders of Childhood. *Hurwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence*. London: Elsevier Health Sciences. 2011. Print.
23. Patsatsi A. Chronic Bullous Disease or Linear IgA Dermatosis of Childhood –Revisited. *J Genet Syndr Gene Ther*. 2013;4(6). Web. 16 Aug. 2015.
24. Quirke K, Beck A, Gamelli R, et al. A 15-year review of pediatric toxic epidermal necrolysis. *J of Burn Care & Research*. 2015;36(1):130-136.
25. Tsuchisaka A, Koji O, Norito I, et al. Type VII Collagen Is the Major Autoantigen for Sublamina Densa–Type Linear IgA Bullous Dermatosis. *J Investig Dermatol Journal of Investigative Dermatology*. 2014;135(2): 626-29.Web.
26. Uitto J. Epidermolysis bullosa: Prospects for cell-based therapies. *J Invest Dermatol* 2008; 128:2140-2142.
27. Vargas TJS, Fialho M, Santos LT, et al. Linear IgA dermatosis associated with ulcerative colitis: complete and sustained remission after total colectomy. *Anais Brasileiros de Dermatologia*. 2013; 88(4): 600-603. Retrieved August 16, 2015, from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0365-05962013000400600&lng=en&tlng=en. 10.1590/abd1806-4841.20131949.
28. Weedon D. *Weedon's Skin Pathology. 3rd ed*. Elsevier. 2010. Print

Thank you!

- AOCD
- Stephen Purcell, D.O.
- Tanya Ermolovich, D.O.
- Co-residents
- LVHN
- ADA

GOLTZ SYNDROME

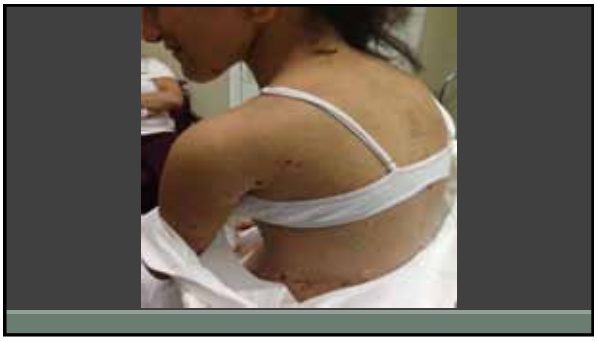
NSU-COM / LARKIN COMMUNITY HOSPITAL

PRESENTERS: ANN REED, DO, HYUNHEE PARK, DO, JULIE FREDERICKSON, DO.

PROGRAM DIRECTOR: STANLEY SKOPIT, DO, MSE, FAOCD

Case presentation

- 17 year old female with established diagnosis of Goltz syndrome presented to our office Jan. 2011 with c/o "Dry skin and itchy scalp"
- PE: Syndromic facies w/ aniridia, microphthalmia, short stature, sparse hair, hypodontia, syndactyly, blaschko linear hyper and hypopigmentation, perioral papillomas, scaly scalp and xerotic skin
- Dx: Xerosis Cutis , Seborrhea and alopecia in patient with Goltz
- Tx: Ketoconazole 2% shampoo MWF alt with T/Sal
  Lidex solution BID x 2 weeks to scalp
  Cerave/Cetaphil to body
  Biotin 2500 mcg daily
- Bx's: 3/8/11 Shave biopsy (R labial commissure) - Verruca with candidiasis
  3/22/11 Shave biopsy (L labial commissure) - Impetiginized Verruca with candidiasis
  Ketoconazole 2% cream BID given for topical treatment

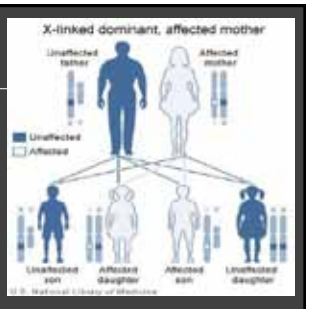


Goltz Syndrome Overview

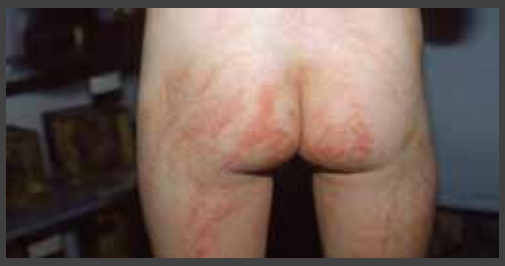
- Focal Dermal Hypoplasia or Goltz-Gorlin syndrome
- Rare genodermatosis
- Multiple abnormalities of mesodermal and ectodermal tissues
- First described by Dr. Goltz in 1962
- Approximately 300 reported cases worldwide

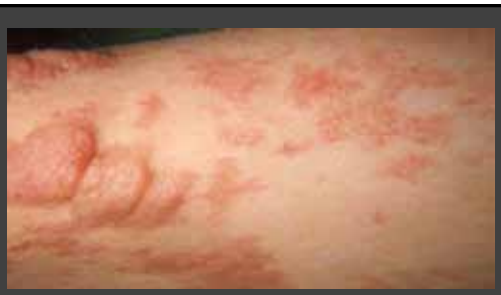
Inheritance

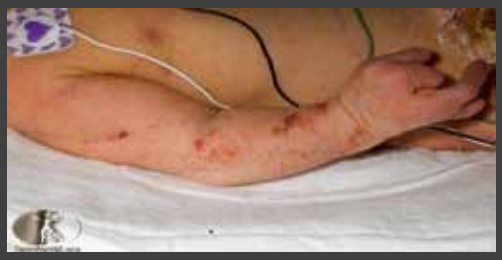
- X-linked dominant
  - 90% female
  - Lethal in males with non-mosaic hemizygous mutations
  - 10% affected individuals: males with genomic or functional mosaicism
- 95% of cases are sporadic
- Gene locus Xp11.23
- Mutation in *PORCN* gene
  → lack of Wnt signaling
- Variability in clinical severity (lyonization)

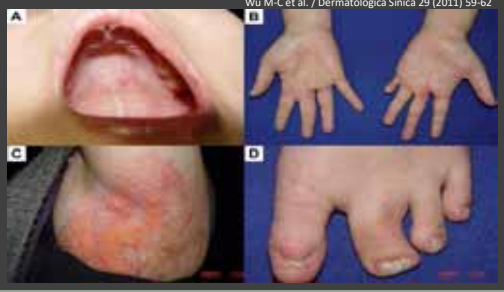


Goltz Syndrome
Cutaneous Findings







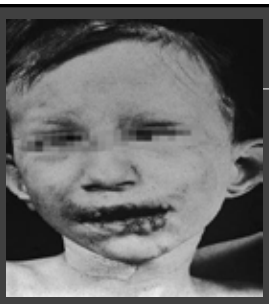


Wang L et al. Focal dermal hypoplasia updates. *Oral Diseases. 2014; 20:17–24*

Goltz Syndrome Extracutaneous Findings

Non Cutaneous features include:

- Facial abnormalities
- Skeletal features
- CNS features
- Ear, Dental and Ocular abnormalities
- Cardiopulmonary
- GI
- GU

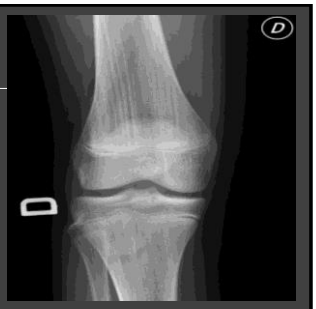


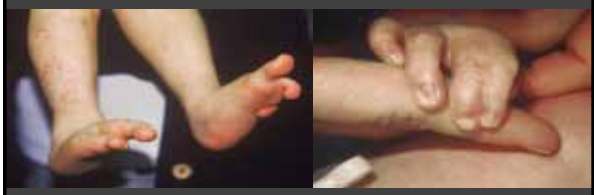
- Asymmetry of the face
- Low-set protruding ears
- Narrow nasal bridge and broad nasal tip with unilateral notch of the nasal alae
- Pointed chin

Colobomas, anophthalmia, microphthalmia, strabismus, nystagmus, and ectopia lentis

Prognathism, agenesis or dysplasia of the teeth, delayed tooth formation/eruption, microdontia, irregular spacing and malocclusion, enamel defects, notching of the incisors or extra incisors.

Osteopathia Striata





- Gastrointestinal features:
  - Malrotation of the intestine
  - Papillomatous lesions of the esophagus leading to obstruction
  - Gastric polyps
  - Gastric reflux with laxity of the hiatus
  - Diaphragmatic hernia
  - Omphalocele
  - Hernias, rectal prolapse, and perianal papillomas
- Genitourinary features:
  - Abnormalities of the kidneys or ureters (eg, bifid ureter, renal pelvis)
  - Horseshoe kidney
  - Hypoplastic or absent kidney

FOCAL Mnemonic

Female gender

Osteopathia striata

Coloboma

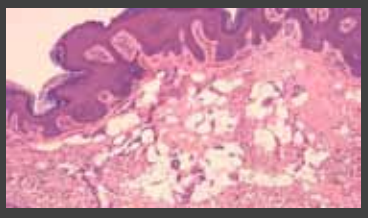
Absent ectodermis-, mesodermis-, and neurodermis-derived elements

Lobster claw deformity

Work-up

- Chest x-ray:
  - Costovertebral defects
  - Diaphragmatic hernia
- Eye examination: Colobomas
- Abdominal MRI: Diaphragmatic hernia
- Renal ultrasound: Structural anomalies of the kidneys and urinary collecting system
- Hearing evaluation
- Medical genetics consultation

Pathology



- Reduction in dermal collagen
- Telangiectasia
- Adipocytes of varying sizes in upper dermis

Labs

- No associated lab abnormalities reported with this syndrome in > 350 journal articles searched on PubMed
- Follow routine surveillance guidelines established for the general population

Monitoring

- Dermatologist – for painful and pruritic erosive lesions
- Otolaryngologist – papillomas of the larynx
- Dental – Every 6 months for enamel hypoplasia leading to dental caries
- Physical/occupational therapy and Orthopedic surgeon – hand and foot malformations, etc.
- Ophthalmologist – eye abnormalities

Management

- Supportive
- Subspecialist referral
- Pulsed dye laser (telangiectasias)
- Cryotherapy (giant papillomas)
- Prevention of secondary complications
- Genetic counseling

Prenatal Diagnosis

- Prenatal ultrasonographic findings variable:
  - Nonspecific fetal growth delay to specific organ and/or developmental anomalies
  - Contingent on the degree to which an individual is affected
- Prenatal molecular genetic testing is possible for pregnancies at increased risk if the disease-causing mutation in the family has been identified:
  - Amniocentesis (15-18 weeks)
  - Chorionic villus sampling (10-12 weeks)

Support Resources

- National Foundation for Ectodermal Dysplasias www.nfed.org
- Ectodermal Dysplasia Society www.ectodermaldysplasia.org

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References

1. Alster TS, Wilson F. Focal dermal hypoplasia (Goltz's syndrome). Treatment of cutaneous lesions with the 585-nm flashlamp-pumped pulsed dye laser. *Arch Dermatol.* 1995 Feb. 131(2):143-4
2. Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology. 3rd ed. 2012. Elsevier Saunders. 2012: 951.
3. Calonje E. McKee's Pathology of the Skin, With Clinical Correlations. Saunders; 2012.
4. Castelo-Soccio L. **Focal Dermal Hypoplasia Syndrome Clinical Presentation.** Updated: Dec 16, 2014. Accessed on 08/25/15. http://emedicine.medscape.com/article/1110936-overview#a6.
5. James WD, Berger TG, Elston DM. Andrews' Diseases of the Skin Clinical Dermatology. 11th ed. Philadelphia: Elsevier. 2011: 565-566.
6. Liu J, Hsu PT, VanderWielen BA, Teng JM. Treatment of recalcitrant excessive granulation tissue with photodynamic therapy in an eight-year-old patient with focal dermal hypoplasia syndrome. Pediatr Dermatol. 2012 May-Jun;29(3):324-6.
7. Murakami C, De oliveira lira ortega A, Guimarães AS, Gonçalves-bittar D, Bönecker M, Ciamponi AL. Focal dermal hypoplasia: a case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(2):e11-8.

References

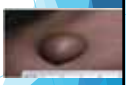
8. Patterson JW, Ph.D. GA. Weedon's Skin Pathology. Churchill Livingstone; 2015.
9. Perioral and Genital Lesions. Copyright 2003-2006 by AOCD Grand Rounds. Submitted on: Mar 14, 2010, Accessed on 08/25/15
10. Purvis, D. Alkindi, S. **Focal Dermal Hypoplasia (Goltz Syndrome).** DermNet NZ. Accessed on 08/25/15 http://www.dermnetnz.org/systemic/goltz.html
11. Sakar S, Patra C, Das, A, Roy S. Goltz Syndrome: A newborn ectrodactyly and skin lesions. Indian J Dermatol 2015;60:215
12. Sutton VR, Van den Veyver IB. Focal Dermal Hypoplasia. 2008 May 15 [Updated 2013 Apr 11]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov.ezproxylocal.library.nova.edu/books/NBK1543/
11. Wang L et al. Focal dermal hypoplasia updates. *Oral Diseases. 2014; 20:17–24.*
12. Wu, Meng-Chi et al. **Focal dermal hypoplasia: report of a Taiwanese case.** Dermatologica Sinica, Volume 29, Issue 2, 59-62

Pediatric Dermatology: Tumors of Fat, Muscle and Bone

Broward Health Medical Center

10/18/15

Benign Tumors of Fat: Lipoma



Introduction:

- The most common benign tumors of fat are lipomas. Lipomas are composed of mature lipocytes. They are among the most common neoplasms and represent the most common mesenchymal neoplasms

Clinical Evaluation:

- Asymptomatic, soft, subcutaneous nodule arising from any site

Associations:

- Bannayan-Riley-Ruvacalba, Gardner's syndrome, Proteus syndrome, MEN1, Familial multiple lipomatosis, Dercum's dz, Madelung's dz, CLOVE syndrome

Lipoma

Pathology:

- Proliferation of normal-appearing adipose in subcutaneous fat, (+) adipophyllin, (+) oil-red-O (must be frozen sections)

Differential Diagnosis:

- Epidermoid cyst
- Dermoid cyst
- Angiolipoma
- Metastatic malignancy
- Abscess
- Leiomyoma

Treatment

- Excision

Angiolipoma

Epidemiology:

- Young adults in their late teens or early twenties. About 5% of cases are familial

Clinical Evaluation:

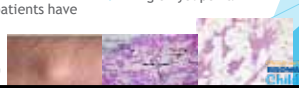
- Soft subcutaneous nodules, usually less than 2cm in diameter, may be painful. Tumors are found on the forearms (2/3 of pts), less commonly the trunk and upper arms. An estimated two-thirds of patients have multiple tumors

Pathology:

- Mature adipose tissue is admixed with a variable number of small vessels occ w/ thrombi
- No malignant transformation noted

Differential Diagnosis:

- Angiomyolipoma



Spindle cell/pleomorphic lipoma

Introduction:

- Represent a group of histologically distinct tumors composed of mature fat cells, a population of spindle cells, and strands of dense collagen. Pleomorphic lipomas also contain an admixture of bizarre, often multinucleated cells ("floret-like cells")

Epidemiology:

- Majority found in middle-aged to older men

Clinical Evaluation:

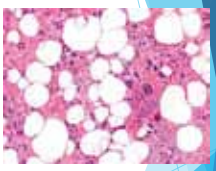
- Usually a solitary, slow growing, mobile and painless subcutaneous nodule without epidermal change on posterior neck

Treatment:

- Surgical excision is curative for this benign tumor. It is rare for spindle cell lipomas to recur after complete excision

Spindle cell/pleomorphic lipoma

Pathology:



- Spindle cell: (+)CD34 requires the presence of three components (1) mature fat cells; (2) small, uniform spindle cells; and (3) strands of dense, eosinophilic ("ropey") collagen
- Pleomorphic: hyperchromatic adipocytes, bizarre floret giant cells, overlapping nuclei, pseudomalignant appearance, resembles liposarcoma but rare lipoblasts and no necrosis
- Spindle cells in both spindle cell and pleomorphic lipomas are CD34-positive and rarely S100-positive

Hibernoma

Introduction:

- Young adults in their late teens or early twenties. About 5% of cases are familial

Epidemiology:

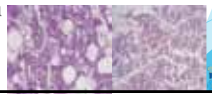
- Indistinguishable from lipoma, interscapular area, thighs, shoulder, neck, chest, arms and abdominal cavity/retroperitoneum

Pathogenesis:

- Overall unknown, clonal chromosomal abnormalities consist of structural rearrangements of 11q13 and 11q21

Pathology:

- Characteristic tan to deep red-brown color; pronounced lobulation; vascular interlobular septa surround individual lobules
- Characteristic brown fat cells with a small central nucleus and multivacuolated to granular eosinophilic cytoplasm, "Mulberry cells" admixed w/ mature fat cells and pale multivacuolated cells



BROWARD HEALTH

Hibernoma

Differential Diagnosis:

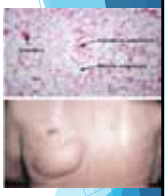
- Lipoma, Liposarcoma, Neurofibroma, Angiolipoma, Lymphoma, Rhabdomyoma, Rhabdomyosarcoma

Diagnostic Evaluation:

- Core needle biopsy is contraindicated if suspecting hibernoma due to hypervascularity and risk of hemorrhage.
- Ultrasound, CT, MRI can be used to help in diagnosis

Therapy:

- Complete surgical excision
- May be difficult to excise as they often are in close proximity to neurovascular structures



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Nevus lipomatosus superficialis

Clinical Features:

- Rare, clustered papules or nodules of buttocks, hips and thighs with onset at birth or within first two decades of life

Pathology:

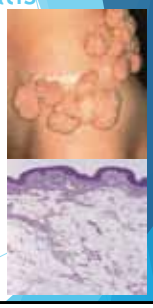
- Adipose in superficial dermis, increased dermal blood vessels

DDX for "adipose in superficial dermis" :

- Proteus syndrome
- Michelin tire baby
- Lipedematous alopecia
- Connective tissue nevus (Clinical)

Treatment

- Excision



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Lipoblastoma/lipoblastomatosis

Introduction:

- Benign neoplasm of immature fat cells that typically occurs on extremities
- Circumscribed form = lipoblastoma, diffuse = lipoblastomatosis

Epidimeology:

- Young children, M>F

Pathology:

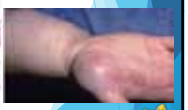
- Cannot be distinguished from myxoid liposarcoma; poorly circumscribed or encapsulated subcutaneous tumor of immature fat cells w/ lipoblasts (lipid vacuoles displace the nuclei), mucinous stroma

Differential Diagnosis:

- Liposarcoma - Lack of cellular atypia and rare mitoses help to distinguish it histologically from liposarcoma

Treatment:

- May recur after excision but do not metastasize



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Malignant Tumors of Fat: Liposarcoma/Atypical Lipomatous Tumor

Introduction:

- Uncommon soft tissue sarcoma, five histopathologic subtypes
- Range in behavior from locally aggressive tumors to highly malignant depending on the subtype

Key Points:

- Comprise < 5% of all soft tissue sarcomas in children
- Rarely arise in children younger than 10 years of age
- Arise de novo and not in pre-existing lipomas

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Liposarcoma/Atypical Lipomatous Tumor

Clinical Presentation:

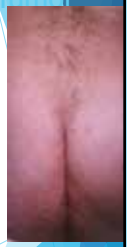
- Affects dermis > subcutis
- Dome-shaped or polypoid
- LE > UE, retroperitoneum
- 1-20 cm in size

Differential Diagnosis:

- Lipoblastoma, lipoblastomatosis, spindle cell/pleomorphic lipoma

Histopathology:

- Presence of lipoblasts
- Five subtypes:
  - Well-differentiated
  - Myxoid
  - Round cell
  - Pleomorphic
  - Dedifferentiated



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Liposarcoma/Atypical Lipomatous Tumor

Treatment/Prognosis:

- Wide excision performed with the use of proper imaging techniques to rule out growth into underlying muscle and fascial planes
- Post operative radiotherapy and chemotherapy have been used
- Prognosis depends on histologic subtype
- High-grade pleomorphic tumors can metastasize to lungs

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Malignant Tumors of Muscle: Rhabdomyosarcoma

Introduction:

- Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. Various forms include: embryonal, botryoid, alveolar, and undifferentiated type. Localized disease has over 80% 5-year survival, however metastatic rates are less than 30%

Clinical Evaluation:

- RMS usually presents with an expanding mass. Pain and swelling are the most common symptoms and are location dependent

Radiologic Evaluation:

- Studies include: MRI, CT, PET scan, Ultrasonography, Echocardiography and bone scans

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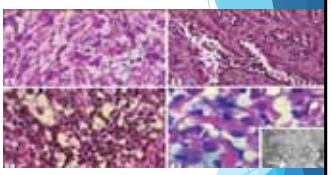
Rhabdomyosarcoma

Pathology:

- Small round blue cells with positive staining for desmin, vimentin, myoglobin, actin and transcription factor myoD



Treatment:

- Chemotherapy, radiation therapy and surgical removal.

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Leiomyosarcoma

Epidemiology:

- Extremely rare in children, < 1% of primary sarcomas in children less than 20
- EBV-associated leiomyosarcomas (EBV-LMS) in HIV patients
- Gastrointestinal or other visceral locations most common

Staining:

- **(+) Actin,** (+) Desmin, (-) cytokeratin, (-) s100, (-) CD68

Treatment/Prognosis:

- Treatment of dermal tumors is simple excision; subcutaneous is wide excision with careful examination of all surgical margins
- Usually low-grade morphology with better prognosis than adult
- Subcutaneous tumors metastasize in 25-40% of patients

Clinical features	Most Common location	DDX
Firm skin-colored to red-brown dermal or subcutanous nodules, may have overlying ulceration ± pain	Trunk (back, abdomen and chest wall), lower limb, neck	Infantile myofibromatosis, rhabdomyosarcoma, synovial sarcoma

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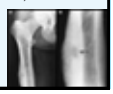
Benign Bone Tumors: Bone-forming tumors

Osteoid Osteoma		
Clinical features	**Most common locations**	**Plain radiographic features**
• 10 to 20 years • M > F • Nocturnal pain promptly relieved by NSAIDs; limp, scoliosis	• Cortex of the metaphysis or diaphysis (less common) of the proximal femur • proximal tibia • distal femur • spine • proximal humerus • phalanges	• Small round intracortical lucency (nidus) with sclerotic margin • special imaging studies (bone scan, CT, or MRI) often needed for spine



Bone-forming tumors

Osteoblastoma		
Clinical features	**Most common locations**	**Plain radiographic features**
• Any age (usually 10 to 20 years) • M > F • Chronic pain; less responsive to NSAIDs than osteoid osteoma; spine lesions may cause neurologic symptoms	• Posterior elements of the spine or sacrum; less commonly occurs in the metaphysis of the proximal femur or tibia	Variable(oftenrequires CT or MRI for diagnosis)

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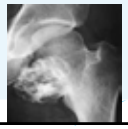
Cartilage-forming tumors

Osteochondroma & hereditary multiple osteochondromas

Clinical features	Most common locations	Plain radiographic features
• 10 to 20 yrs • M > F • Pain, functional problems, deformity, pathologic fracture, palpable near the ends of long bones • Risk of malignant transformation to chondrosarcoma in adults (in HME)	• Metaphysis of the distal femur, proximal tibia, and proximal humerus	• Bony spur arising from the surface of the cortex; the cortex of the spur is continuous with the cortex of underlying bone



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Cartilage-forming tumors

Enchondromatosis (Ollier syndrome, including Maffucci syndrome*)

Clinical features	Most common locations	Plain radiographic features
• <10 years • Intracranial enchondromas may cause headache and cranial nerve deficit • Risk of malignant transformation to chondrosarcoma and increased risk of nonsarcomatous neoplasms	• Metaphysis, diaphysis of any bone	• Oval, well-circumscribed central (medullary), lucent lesions with or without matrix calcifications or expansion of the cortex

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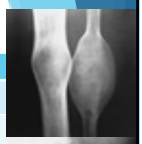
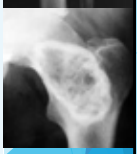
Fibrous Lesions

Fibrous Dysplasia

Clinical Features	Most Common Locations	Plain Radiographic Features
• Portions of bone replaced by fibrous connective tissue • Originates in medullary cavity • Single or multiple • Teens or 20s • Most asymptomatic	• Any bone, MC: • Proximal femur • Tibia • Ribs • Skull	• Lytic lesion in the metaphysis or diaphysis with a "ground glass" appearance • Expansion of the bone and possible bowing





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Miscellaneous Bone Tumors

Langerhans cell histiocytosis

Clinical Features	Most Common Locations	Plain Radiographic Features
• Any age (most common 5 to 10 years) • M > F • Painful swelling of affected site, pathologic fracture, proptosis, thirst, refractory otitis media	• Skull, ribs, pelvis, long bones, mandible, vertebrae	• Well-defined lytic lesion with or without sclerotic margins; variable periosteal reaction; flattening of vertebral body; "floating" teeth (with mandibular involvement)

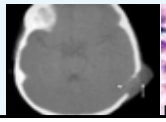

Image from Pathologyoutlines

Miscellaneous Bone Tumors

Giant cell tumor

Clinical Features	Most Common Locations	Plain Radiographic Features
Young adults (peak incidence in 20s to 30s) F > M Pain, swelling, limitation of joint movement, pathologic fracture	• Epiphysis of the distal femur, proximal tibia, distal radius, sacrum	• Expansile, eccentric, lytic lesion in epiphysis and adjacent metaphysis, may extend to subchondral plate; absence of matrix calcification and periosteal reaction

Image orthoinfo.aaos.org

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Malignant Tumors of Bone

Introduction:

- Most common malignant tumors of bone in pediatric population 1st- Osteosarcoma, 2nd- Ewing's sarcoma

Clinical Evaluation:

- Osteosarcoma MC presents with pain (pathologic fracture uncommon)
- Ewing's sarcoma MC presents with pain of hips, back with localized swelling

Radiographic Findings:

- Osteosarcoma: Sunburst pattern, Codman's triangle
- Ewing's sarcoma: Onion-skin periosteal reaction, lytic lesion of pelvis

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Osteosarcoma

Etiology:

- May arise as a de novo lesion or develop secondarily to a known premalignant lesion such as Paget disease, osteogenesis imperfecta, bone lesion, chronic osteomyelitis, fibrous dysplasia, giant cell tumor, osteoblastoma or radiation therapy
- Some familial cases: esp in familial bilateral retinoblastoma
- Increased risk with inherited diseases- **Rothmund-Thompson, Li-Fraumeni syndrome, Bloom syndrome**

Epidemiology:

- Most common non-hematologic primary malignant tumors of bone in both children and adults
- Bimodal age distribution 10-25 yo, and >60 yo
- Metaphysis of long bones, MC distal femur (75%)

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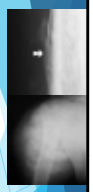
Osteosarcoma

Radiographic findings:

- Large infiltrating metaphyseal lesion arising in medullary bone with a mixed **lytic and sclerotic** appearance. Can be purely osteolytic (about 30% of patients), purely osteoblastic (about 45% of patients), or both.
- **Codman's triangle**: Elevation of the periosteum
- **Sunburst pattern**: Extension of tumor through the periosteum may result in sunburst appearance (~60% of patients)



Associated dermatologic disorders:

- **Rothmund-Thompson syndrome** *(AR, RECQL4, photosensitive genodermatosis, poikiloderma, hypoplastic thumbs)*
- **Li-Fraumeni syndrome** *(AD, P53 mutation, multiple malignancies)*
- **Bloom syndrome** *(AR, RECQL2, RECQL3, photosensitive, decreased IgM)*
- **Neutrophilic eccrine hidradenitis**

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Ewing's Sarcoma

Etiology:

- Translocation mutation t(11;22) fuses one of many observed combinations of exons from *EWS* and *FLI1* forming fusion message, MC: *EWS* exon 7 fused to *FLI1* exon 6 (type 1 translocation) found in 50-64% of ewing sarcomas

Epidemiology:

- 2nd MC primary malignant bone tumor in adolescents and young adults, annual incidence of 1 in 1 million, 50% of Ewing sarcomas in pts aged 10-20, peaking in later teenage years, higher incidence in Caucasians (9x higher)

Clinical presentation:

- Patients usually present with pain, palpable mass, back pain may indicate a paraspinal, retroperitoneal, or deep pelvic tumor. Most commonly found in axial skeleton, particularly in the pelvis
- Systemic sx: fever, weight loss can occur and may indicate metastatic dz

Radiographic findings:

- Peri-osteal "onion-skinning" reaction, lytic or sclerotic primary bone lesions

Associated dermatologic disorders:

- **Can have petichiae or purpura secondary to tumor induced thrombocytopenia**

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Which of the following statements is false regarding infantile myofibromatosis ?

A) Visceral involvement carries a high mortality rate within months d/t compromise of vital organ function

B) With ONLY soft tissue and bony involvement there is a very good prognosis

C) Lesions are only rarely present at birth

D) Although this entity is rare, it is the most common of the juvenile fibromatoses

E) Tumors tend to regress

Answer : 50% of lesions are present at birth and more present with in the first 2 years of life

Bolognia J, Jorizzo J, Schaffer, J. 2012. fibrous proliferations of the skin and tendons. In *Dermatology* (pg 1970). Elsevier Saunders publication.

BROWARD HEALTH MEDICAL CENTER

This syndrome illustrated by the photo on the right has characteristic venous malformations of the distal extremities. For which of the following neoplasms are these patients at risk of developing?

- A. lung CA
- B. adrenal CA
- C. chondrosarcomas
- D. enchondromas
- E. C & D
- F. A & C
- G. All of the above

Answer: E. Benign enchondromas which can compromise bone strength and lead to chondrosarcomas.

Bolognia J, Jorizzo J, Schaffer, J. 2012. Vascular malformations. In *Dermatology* (pg 1972) Elsevier Saunders publication

What is the defect responsible for Mafucci's syndrome?

- A. ALK1
- B. PTH/PTHrP
- C. TIE2
- D. LMX1B

Answer: B

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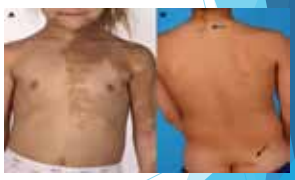
Osteosarcomas are associated with all of the following syndromes except

- A) Rothmund-Thompson syndrome
- B) Li-Fraumeni syndrome
- C) Bloom syndrome
- D) Blue rubber bleb syndrome

BROWARD HEALTH MEDICAL CENTER

Polyostotic Fibrous Dysplasia

- What is a another name for **polyostotic fibrous dysplasia** and what is its genetic mutation?
  - **McCune-Albright syndrome**
  - **GNAS 1 mutation**
- Large **café-au-lait macules**
  - geographic borders
- **Precocious puberty**
- Pathologic fractures
- **Endocrine abnormalities**
  - Hyperparathyroidism
  - Hyperthyroidism
  - Acromegaly



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References

1. Radiological case: Ewing's sarcoma. Medscape Website. http://www.medscape.com/viewarticle/575091. Published 2008. Accessed August 23, 2105.
2. Ewing's sarcoma. Medscape website. http://emedicine.medscape.com/article/990378-overview. Updated June 18, 2014. Accessed August 23, 2015.
3. Pediatric osteosarcoma. Medscape website. http://emedicine.medscape.com/article/988516-overview. Updated September 24, 2013. Accessed August 23, 2015.
4. Imaging in classical osteosarcoma. Medscape website. http://emedicine.medscape.com/article/393927-overview. Updated July 11, 2013. Accessed August 23, 2015.
5. de Saint Aubain Somerhausen N1, Fletcher CD. Leiomyosarcoma of soft tissue in children: clinicopathologic analysis of 20 cases. Am J Surg Pathol. 1999 Jul;23(7):755-63.
6. Kraft S1, Fletcher CD. Atypical intradermal smooth muscle neoplasms: clinicopathologic analysis of 84 cases and a reappraisal of cutaneous "leiomyosarcoma". Am J Surg Pathol. 2011 Apr;35(4):599-607.
7. McClain KL1, Leach CT, Jenson HB, Joshi VV, Pollock BH, Parmley RT, DiCarlo FJ, Chadwick EG, Murphy SB. Association of Epstein-Barr virus with leiomyosarcomas in children with AIDS. N Engl J Med. 1995 Jan 5;332(1):12-8.
8. Kaddu S, Kohler, S (2012). Muscle, Adipose and Cartilage Neoplasms in Bolognia JL, Jorizzo JL, Schaffer JV (Editors), *Dermatology* (pp 1989-91). Elsevier.
9. Gozman, A. (2013, July 9). Pediatric Liposarcoma. *eMedicine*. Retrieved 8/30/2015 from Krause, RS. (2010, Mar 15). Anaphylaxis. eMedicine. Retrieved 2/28/2011 from http://emedicine.medscape.com/article/987446-overview
10. Images courtesy of Ronald P. Rapini, MD and Richard Kempson, MD.

BROWARD HEALTH

Pediatric Vascular Disorders

Presenter: Christina Steinmetz-Rodriguez DO, Dermatology Resident
West Palm Hospital/PBCGME
October 18, 2015

Contributors: Shana Rissmiller DO, Christina Steinmetz-Rodriguez DO, Leslie Mills DO

Introduction: History & Classification

- 1982-- Proposed classification for vascular birthmarks based on clinical appearance, biologic behavior and histopathologic features
  1. Hemangiomas
  2. Vascular malformations
- 1996-- International Society for the Study of Vascular Anomalies (ISSVA)
  - Classification was modified to reflect the awareness that other vascular tumors (ex: tufted angiomas, pyogenic granuloma) could arise in infancy
  1. Vascular Tumors
  2. Vascular Malformations

Introduction: Vascular Tumor & Vascular Malformation

- Vascular tumor
  - Primarily due to excess angiogenesis
- Vascular malformation
  - Result from errors in vascular development and remodeling
  - Classified according to distorted vessel type
  - Can cause significant morbidity as a result of hemorrhage, mass effect, induction of connective tissue hypertrophy, and limb asymmetry and pain

1996 ISSVA Classification: Vascular Tumors vs. Malformations

Vascular Tumors	Vascular Malformations
Infantile Hemangioma	Capillary Malformation: (Slow flow): ex: Port-Wine stains, Telangiectasias
Congenital Hemangioma, Rapidly Involuting Congenital Hemangioma (RICH), or Noninvoluting Congenital Hemangioma (NICH)	Venous Malformation: (Slow flow): ex: Cavernous hemangioma, Phlebectasia
Congenital hemangiopericytoma	Lymphatic malformation (slow flow): Macrocytic or Microcystic
Spindle cell Hemangioma	Glomuvenous malformation
Pyogenic Granuloma	Arteriovenous malformation (fast flow)
Kaposiform Hemangioendothelioma	Combined malformation (slow or fast flow): ex: angiokeratoma, cutis marmorata telangiectatic congenita
Tufted Angioma	

Infantile Hemangiomas

Introduction:

- Various other names have been used in the literature including:
  - *Nevus maternus*
  - *Angioma simplex*
  - *Angioma cavernosum*
  - *Angiodysplasia*
  - ***Strawberry nevus***
  - ***Capillary hemangioma***

Introduction:

- Hemangioma is the most common soft tissue tumor of infancy
- Neoplasm of benign endothelial cells
- Typical growth pattern characterized by early proliferation→ gradual, spontaneous involution

Epidemiology

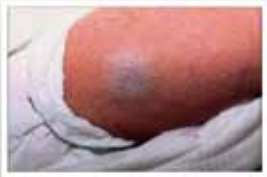
- 4-5% of infants
- Female : Male ratio of 2–5 : 1
- More frequent in premature infants
- Threefold increased incidence in infants born following chorionic villus sampling

Pathogenesis

- Not fully elucidated
- Theories include:
  - Mutations involving vascular endothelial growth factor **(VEGF)** signaling
  - Placental hypothesis (shared immunohistochemical phenotype)
    - Glucose transporter protein-1 **(GLUT-1)** expression
    - Other placenta-associated vascular antigens, including **merosin, FcγRII and Lewis Y antigen**, are present in hemangioma specimens and placental chorionic villi
  - Association with hypoxia
    - Upregulates expression of GLUT-1 and VEGF

Presentation

- Become evident during the first few weeks of life
- Precursor lesions
  1. Telangiectasias surrounded by a vasoconstricted halo
  2. Pink macules or patches
  3. Blue bruise-like patches

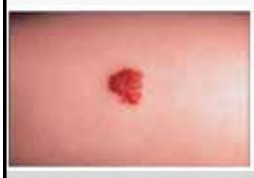


Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Infantile Hemangiomas." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1691-1709. Print.

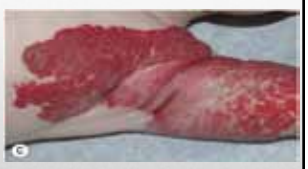
Presentation: Common Types

- Superficial hemangiomas
  - Most common type
- Larger plaque-type or segmental pattern
  - Less common and more worrisome
  - More likely to be associated with regional extracutaneous anomalies, including PHACE(S) and LUMBAR syndromes
- Deep hemangiomas
  - Warm, ill-defined, light blue–purple masses with minimal or no overlying skin changes
  - A thrill may be felt or a bruit auscultated

Presentation: Superficial and Segmental



Superficial Hemangioma



Segmental Hemangioma

Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Infantile Hemangiomas." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1691-1709. Print.

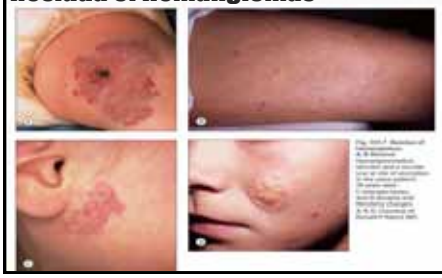
Presentation: Deep Hemangiomas

Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Infantile Hemangiomas." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1691-1709. Print.

Natural History

1. **Early proliferation**
   - Rapid increase in size
   - 80% reach their final size by the end of 3 months
2. **Late proliferation**
   - Continued growth at a slower rate
3. **Plateau**
   - Existence as a distinct phase debated
4. **Involution**
   - May begin during first year of life
   - Earliest signs: color change from bright red to gray–purple and flattening of the surface
     - 30% of lesions involute fully by 3 years of age
     - 50% by 5 years
     - 70% by 7 years
     - 90% by 9 years
   - Some involute completely, while others leave atrophic, fibrofatty or telangiectatic residua

Residua of Hemangiomas



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Complications

- Include:
  - **Ulceration**
    - Most common complication
    - Those on the lip and in the anogenital region or other skin folds (e.g. the neck) have the greatest tendency to ulcerate
  - **Disfigurement**
    - Vulnerable locations: Periocular, Nasal Tip, Lip, Ear, Breast, Anogenital
  - **Functional impairment**
    - Periocular: Most commonly cause astigmatism
      - Should be evaluated by an ophthalmologist
  - **Systemic Involvement**

Systemic Involvement- Large facial hemangiomas

- ***PHACES*** *syndrome*:
  - ***P***osterior fossa and other structural brain malformations
  - ***H***emangioma
  - ***A***rterial anomalies of cervical and cerebral vessels
  - ***C***ardiac defects (especially ***c***oarctation of the aorta)
  - ***E***ye anomalies
  - ***S***ternal defects and ***s***upraumbilical raphe

Systemic Involvement- "beard" hemangiomas

- Lower facial or beard hemangiomas associated with airway involvement
  - Typically subglottic
  - Noisy breathing or subglottic stridor
- Onset of symptoms ranges from a few weeks to several months of age
- Refer to ENT

Systemic Involvement- Large hemangiomas on the lower body

- ***LUMBAR*** *syndrome*:
  - ***L***ower body/lumbosacral hemangioma and ***l***ipomas or other cutaneous anomalies
  - ***U***rogenital anomalies and ***u***lceration
  - ***M***yelopathy (spinal dysraphism)
  - ***B***ony deformities
  - ***A***norectal and ***a***rterial anomalies
  - ***R***enal anomalies

Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Infantile Hemangiomas." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1691-1709. Print.

Multiple Hemangiomas

- Evaluation for visceral involvement is recommended when ≥5
- Most infants with both internal and skin involvement have many small, superficial cutaneous hemangiomas
- Liver is the most common site of visceral hemangiomas
  - Screening test: Ultrasound
  - Complications:
    - High-output CHF due to AV or arterioportal shunts
    - Abdominal compartment syndrome related to massive hepatomegaly
    - Hypothyroidism

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Hypothyroidism

- ↑ levels of type 3 iodothyronine deiodinase have been identified in tissue from proliferating hemangiomas→ hypothyroidism
  - enzyme that deactivates thyroid hormone
- Screening for hypothyroidism in the immediate neonatal period is **inadequate**

Differential Diagnosis

- **Capillary Malformation**
- Kaposiform hemangioendothelioma
- **Pyogenic granulomas**
- Tufted angioma
- Infantile hemangiopericytoma
- Spindle cell hemangioma
- Eccrine angiomatous hamartoma
- Congenital fibrosarcoma
- Infantile myofibromatosis
- Lipoblastoma
- Nasal glioma
- Neuroblastoma
- Primitive neuroectodermal tumor
- Lymphoblastic lymphoma
- Dermatofibrosarcoma protuberans
- Rhabdomyosarcoma

Treatment: Infantile Hemangiomas

- Goals of management:
  1. Preventing or reversing life-or function threatening complications
  2. Treating ulcerations
  3. Preventing permanent disfigurement
  4. Minimizing psychosocial distress to patients and their families
  5. Avoiding overly aggressive potentially scarring procedures

Treatment

- Small hemangiomas with an excellent prognosis for spontaneous resolution with a good cosmetic outcome
  - No intervention required
- Ulceration
  - Local wound care +/- treatment of infection +/- additional therapies

Treatment: Local Therapies

- Local therapies
  - Intralesional corticosteroids
    - Localized lesions such as **small lip hemangiomas**
    - Do not exceed 3-5 mg/kg per treatment session
    - Dosages vary from 5-40 mg/ml of triamcinolone acetonide
  - Topical corticosteroids
    - Class 1 topical steroid
    - Further studies needed, but likely thinner lesions will respond better
  - Topical β-Blockers
    - Timolol 0.5% gel or solution
    - Anecdotal reports of improvement

Treatment: Systemic Therapies

- Systemic Corticosteroids (Prednisone or prednisolone)
  - Treatment of life-or function threatening hemangiomas, disfiguring, or persistently ulcerated lesions
  - Suppresses VEGF production
  - Adverse reactions include:
    - Immunosuppression
      - Pneumocystis jiroveci (carinii) pneumonia has been described
      - **live-virus vaccines should be avoided** while an infant is receiving corticosteroids and until they have been discontinued for at least 1 month
  - Prednisone 2-3 mg/kg/day most commonly used
    - Maintain dosage until cessation of growth or shrinkage occurs
    - Then taper gradually

Treatment: Systemic Therapy

- β-Blockers (Propranolol)
  - 2-3 mg/kg/day divided BID or TID
    - Usually 2 mg/kg/day
  - 6 months average of treatment
  - ADR
    - Hypotension, bradycardia, hypoglycemia (can lead to seizures), bronchospasm, sleep disturbances
    - May increase the risk of stroke in children with PHACE syndrome
      - Drops BP and may attenuate flow through absent, occluded, narrowed or stenotic vessels
      - Do MRI/MRA of head, neck and cardiac vessesls

Treatment: Systemic Therapy

- β-Blockers
  - Pretreatment
    - Consider EKG
    - Inpatient hospitalization for initiation of treatment if infants ≤ 8 weeks or comorbid conditions
    - Outpatient initiation if >8 weeks with adequate social support and no significant comorbid conditions
  - CV monitoring
    - Check BP and HR 1 & 2 hours after first dose and after significant dose increase
  - Blood glucose
    - Routine screening not indicated
    - Administer during daytime hours with a feeding shortly after administration

Treatment: Laser Therapy

- PDL (585-600 nm)
  - Greater efficacy for superficial lesions
- Nd: YAG
  - May have greater efficacy for deeper lesions
  - Higher risk of scarring

Vascular Malformations

Vascular Malformations

- Localized defects in embryonic vascular morphogenesis
- Persistent and tend to worsen over time if not treated
- Majority sporadic
- 1. Slow-flow malformations
  - Capillaries, veins, lymphatics
  - Most apparent at birth or become evident within 1st few months or yrs of life
- 2. Fast-flow malformations
  - AV shunting
  - Some present at birth but majority become evident in childhood or adulthood

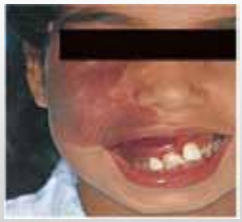
Vascular Malformations

- **Capillary malformations (CMs)**
- Venous malformations (VMs)
- Lymphatic malformations (LMs)
- Arteriovenous malformations (AVMs)
- Complex-Combined malformations (CCMs)

Capillary Malformations

- Slow-flow
- Most common vascular malformation
- Major types
  - 1. Nevus flammeus "stork bites"
  - 2. Port-wine stain
    - Often develop deeper red hue, especially those in V1-V2 areas
    - Pinkish-red (birth) to purplish-red (adulthood)
    - Skin may thicken and become nodular
  - 3. Telangiectasias
    - Punctate, stellate, or linear red lesions
    - Localized, segmental, or generalized

Port-Wine Stain (PWS)



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Syndromic Capillary Malformations

- **Sturge-Weber syndrome**
- **Klippel-Trenaunay syndrome**
- Proteus syndrome
- CLOVES syndrome
- CLAPO syndrome
- Macrocephaly-capillary malformation

Sturge-Weber Syndrome (SWS)

- Sporadic
- Facial PWS (typically V1) + ipsilateral ocular and leptomeningeal/brain anomalies
- Ocular involvement:
  - Glaucoma (especially PWS in both V1 and V2)
- Neurologic involvement:
  - Cerebral hemiatrophy and gyriform calcifications later in childhood (**tram track**)
  - MRI with gadolinium
- Complications
  - Seizures (partial motor)
  - Contralateral hemiparesis or hemiplagia
  - Developmental delays (attention deficits)

Sturge-Weber Syndrome (SWS)

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Klippel-Trenaunay Syndrome (KTS)

- Limb CVM or CLVM with progressive overgrowth of affected extremity
- Sharply demarcated geographic appearance along lateral aspect of thigh, knee, and leg
- Associations:
  - Chronic coagulopathy
  - Hand/foot malformations
  - GI or GU tract bleeding if involved
  - Lymphedema
- Doppler U/S for vascular anomalies
- MRI for extent of soft tissue and bone involvement
- Colonoscopy or capsule endoscopy for GI bleeding

Klippel-Trenaunay Syndrome

Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1711-1728. Print.

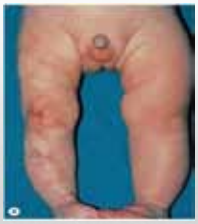
Capillary Malformations: Telangiectasias Associations

- **Cutis marmorata telangiectatic congenita**
- **Hereditary hemorrhagic telangiectasia**
- Ataxia-telangiectasia
- Angiokeratomas
- Cerebral capillary malformation and hyperkeratotic cutaneous capillary-venous malformation

Cutis Marmorata Telangiectatica Congenita (CMTC)

- Dark red-purple, broad reticulated lesions intermingled with telangiectasias
- Persists upon warming
- Often lightens after 1st year
- Up to 50% have associated:
  - Hypoplasia (girth > length) of affected limb
  - Glaucoma (facial CMTC)
  - Neurologic defects (> generalized CMTC)

Cutis Marmorata Telangiectatica Congenita (CMTC)



Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1711-1728. Print.

Hereditary Hemorrhagic Telangiectasia (HHT)

- *Osler-Weber-Rendu disease*
- Autosomal dominant
- Mutations in endothelial transforming growth factor-β (TGF-β) receptors
  1. HHT1 – *endoglin (ENG)* gene
     - Higher risk of pulmonary/cerebral AVMs
  2. HHT2 – *activin receptor-like kinase 1 (ACVRL1)* gene
     - Higher risk liver AVMs
- Presents with epistaxis in childhood
- Telangiectasias of skin and oral mucosa after puberty

Hereditary Hemorrhagic Telangiectasia (HHT)

http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=338

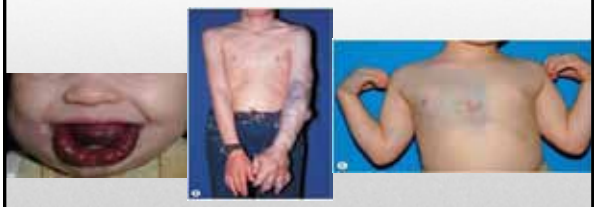
Vascular Malformations

- Capillary malformations (CMs)
- **Venous malformations (VMs)**
- Lymphatic malformations (LMs)
- Arteriovenous malformations (AVMs)
- Complex-Combined malformations (CCMs)

Venous Malformations (VMs)

- *"cavernous hemangioma"* – misnomer
- Recognized by their blue hue, softness, compressibility, and tendency to fill with dependency
- Syndromic Associations
  - **Maffucci syndrome**
  - **Blue rubber bleb nevus syndrome**
  - Glomuvenous malformation
  - Familial cutaneous and mucosal venous malformation

Venous Malformations (VMs)



Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology.*

Blue Rubber Bleb Nevus Syndrome (BRBNS)

- Sporadic disease
- Widely distributed dark blue papules and nodules with skin-colored compressible protuberances "rubber blebs"
- GI VMs
  - Melena, iron deficiency anemia
  - Check hemoccult
- Less commonly, CNS, lungs, and heart lesions

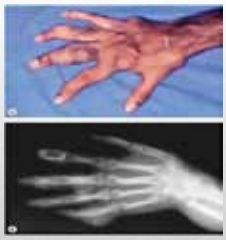
Blue Rubber Bleb Nevus Syndrome (BRBNS)

Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology*. 3rd ed. Vol. 2. St. Louis: Mo.: Mosby/Elsevier, 2008. 1711-1728. Print.

Maffucci Syndrome

- Sporadic disorder
- Blue to skin-colored nodules (VMs) + enchondromas
- Most commonly on extremities, leading to orthopedic and cosmetic defects

Maffucci Syndrome: Venous Malformations and Enchondromas



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Vascular Malformations

- Capillary malformations (CMs)
- Venous malformations (VMs)
- Lymphatic malformations (LMs)
- **Arteriovenous malformations (AVMs)**
- Complex-Combined malformations (CCMs)

Arteriovenous Malformations (AVMs)

- Fast-flow vascular malformations with direct communications (AV shunts) between arteries/veins
- Least common but most dangerous vascular anomaly!
- Visible at birth (40%)
- Most common location is cephalic (~70%)
- Puberty (75%), pregnancy (25%), and trauma worsen AVMs
- Ultrasound and MRI to diagnosis and determine extent of lesion
- Syndromic Associations:
  - **Cobb syndrome**
  - Parkes Weber syndrome
  - PTEN hamartoma tumor syndrome
  - Stewart–Bluefarb syndrome

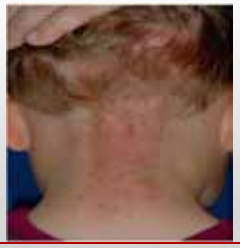
Arteriovenous Malformations (AVMs)

Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology*.

Cobb syndrome

- Sporadic
- Cutaneous, vertebral, and intraspinal AVMs
- Spinal AVMs
  - 20% have congenital red or red-brown vascular stains mimic PWS (stage 1 AVM) or throbbing masses with dilated veins (stage 2 AVM)
  - Neurologic deficits usually present in young adulthood due to mass effect on spinal cord and subarachnoid hemorrhage
    - Back pain, radiculopathy, rectal or bladder dysfunction, paraparesis, paraplegia
  - Diagnose by MRI and angiography

Cobb Syndrome



Bolognia, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology.*

Treatment: Vascular Malformations

- Unlike hemangiomas, medical treatment is **not as effective** in vascular malformations
  - In general surgical resections, embolization, sclerotherapy, may provide benefit for selected lesions
  - Many vascular malformations remain unresectable or too extensive for destructive modalities
- Low-molecular weight heparin or ASA if coagulopathy present

Treatment: Vascular Malformations

- Capillary malformations (Port-wine stains & telangiectasias)
  - **PDL is treatment of choice**
  - Treat early in life to avoid lesional thickening
- Venous malformations (VM)
  - Goals of therapy is to prevent distortion of facial features, limit bony deformation, preserve function and minimize painful swelling
  - Must obtain coagulation profile FIRST to rule out underlying coagulopathy
  - **Can treat with surgery, sclerotherapy or a combination of both**
  - Elastic compression garments

Treatment: Vascular Malformations

- Arteriovenous malformations (AVMs)
  - Partial treatment results in recurrences that may be more difficult treat
    - If not disfiguring or impairing function **follow closely** and avoid premature partial treatment
  - Extreme pain, ulceration, bleeding and extensive enlargement are indications for treatment
    - pre-operative embolization + surgical resection to prevent excessive bleeding

Conclusions

- Majority of vascular anomalies of infancy and childhood can be classified as hemangioma or vascular malformation
  - Hemangiomas proliferate rapidly in infancy only to involute in early childhood
  - Vascular malformations are vessel abnormalities due to errors of vascular morphogenesis
    - They derive from embryonal capillary, venous, arterial, or lymphatic channels, or combinations thereof
    - They persist and often require a thorough work-up

Summary

Vascular Birthmark	Clinical	Epidemiology	Immunohistochemistry
Infantile Hemangioma	▪ Absent at birth ▪ Rapid proliferation for several months ▪ Spontaneous involution over years	▪ More common in girls premature/low birth weight infants ▪ Infants whose mothers underwent CVS sampling	GLUT-1+, Lewis Y antigen +, Merosin +, FcγRII+
Vascular Malformation	▪ Evident at birth ▪ Slow expansion ▪ Grow proportionately with child ▪ Persists into childhood	▪ No gender or gestation predilection	GLUT-1-, Lewis Y antigen -, Merosin-, FcγRII-

Thank you!

References

1. Al Dhaybi R, Powell J, McCuaig C, Kokta V. Differentiation of vascular tumors from vascular malformations by expression of Wilms tumor 1 gene: evaluation of 126 cases. J Am Acad Dermatol. 2010 Dec;63(6):1052-7.
2. Bologna, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Infantile Hemangiomas." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1691-1709. Print.
3. Bologna, Jean, Joseph L. Jorizzo, and Jospeh L. Jorizzo. "Vascular Malformations." *Dermatology*. 3rd ed. Vol. 2. [St. Louis, Mo.]: Mosby/Elsevier, 2009. 1711-1728. Print.
4. Drolet BA, Frommelt PC, Chamlin SL Haggstrom A, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013 Jan;131(1):128-40.
5. Fishman SJ, Mulliken JB. Hemangiomas and vascular malformations of infancy and childhood. Pediatr Clin North Am. 1993 Dec;40(6):1177-200.
6. Garzon MC, Enjolras O, Frieden IJ. Vascular tumors and vascular malformations: Evidence for an association. J Am Acad Dermatol. 2000 Feb;42(2 Pt 1):275-9.
7. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982:412-420.
8. Van Zele D, Heymans O, Gilon Y, Flandroy P, Fissette J. Management of hemangiomas and vascular malformations. Rev Med Liege. 2001 Jun;56(6):420-6.
9. Suh K, Frieden IJ. Infantile Hemangiomas With Minimal or Arrested Growth: A Retrospective Case Series. *Arch Dermatol*. 2010;146(9):971-976.
10. Dermatology Atlas: http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=338

Pediatric Epidermal and Appendageal Tumors: An Update

NSUCOM/Largo Medical Center Dermatology Residency Program
Program director, Richard Miller, D.O., FAOCD
Presented by Brandon Shutty, D.O., PGY-4

NOVA SOUTHEASTERN UNIVERSITY
LARGO MEDICAL CENTER
GRADUATE MEDICAL EDUCATION
Medical Education in the Sun Coast Tradition

Objectives

- Review ***epidermal nevi*** and their associations
- Examine the implications after the diagnosis of a ***nevus sebaceous***
- Discuss various etiologies and appropriate management for ***melanonychia striata*** in the pediatric population

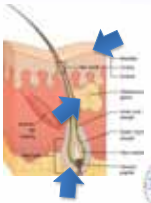
Pre-test question

- Which percentage of pediatric melanonychia striata in the dermatologic literature has been reported to result in invasive melanoma?
  - A. 0%
  - B. 1%
  - C. 6%
  - D. 14%

Epidermal Nevi

What is an epidermal nevus (EN)?

- Hamartoma characterized by ***hyperplasia*** of epidermal structures
- Usually present at ***birth***
- Classified according to their predominant component:
  - Nevus verrucosus (***keratinocytes***)
  - Nevus sebaceous (***sebocytes***)
  - Nevus comedonicus (***hair follicles***)
  - Nevus syringocystadenosus papilliferus (***apocrine glands***)[1]



Etiology of epidermal nevi (EN)

- Activating fibroblast growth factor receptor 3 (***FGFR3***) mutations have been demonstrated in some non-epidermolytic EN[2]
- Acanthosis nigricans, EN, and seborrheic keratoses ***share*** many histopathological features
  - *FGFR3* mutations have also been implicated in these tumors
  - Acanthosis nigricans and EN have been reported in the same tumor[3]
- Some patients with EN develop ***urothelial carcinoma*** at an unusually early age, in which a role of *FGFR3* has again been associated[4]
- ***PIK3CA*** mutations are also implicated

Clinical manifestations of epidermal nevi

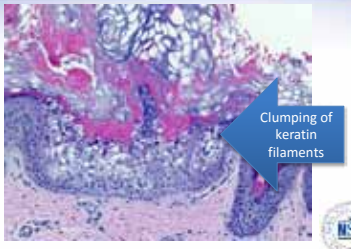
- Favored site: ***extremities***
- Distributed in a "***Blaschkoid***" pattern of alternating stripes of involved and uninvolved skin
  - Mosaicism
- Result of ***migration of skin cells*** during embryogenesis

Nevus unius lateris

- Describes ***extensive unilateral*** epidermal nevus
  - May involve an entire half of the body
- "***Systematized epidermal nevus***" describes extensive bilateral lesions with predominant truncal involvement[5]

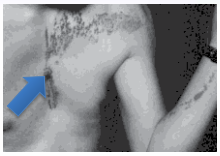
Epidermolytic hyperkeratosis

- Upon histologic evaluation of extensive epidermal nevi, look for ***epidermolytic hyperkeratosis***
- This may imply a ***mosaic*** disorder of ***keratin*** genes
- When extensive, may ***transmit*** these mutations to offspring[6]
  - Epidermolytic ichthyosis



Malignancy in EN

- ***Squamous cell carcinoma***, ***adnexal carcinoma***, and as well as ***basal cell carcinoma*** have been reported to develop within epidermal nevi
- The youngest recorded patient in which a squamous cell carcinoma developed was ***17 years of age***[7]
- While ***linear lesions*** are more likely to be associated with ***neurologic*** abnormalities, ***round lesions*** are more ***tumorprone*** later in life[8]



Inflammatory linear verrucous epidermal nevus (ILVEN)

ILVEN

- First characterized by Altman in ***1971***
- Presents in a Blaschkoid distribution like other keratinocytic EN, but clinically is similar to psoriasis with ***more erythema*** and ***intense pruritus***
- Far ***less common*** than non-inflammatory EN
- Usually present in ***infancy***[9-10]

Is ILVEN related to psoriasis?

- Literature somewhat ***controversial***
- Clinically, intractable ***pruritus*** can be a characteristic of ILVEN when compared to psoriasis
- Histologically, ILVEN appears ***similar*** with regular psoriasiform hyperplasia
- Pathophysiologically, ***T-cell*** mediated dysregulation has been implicated in ILVEN
- Some reports suggest ILVEN may resemble linear psoriasis and improvement with classic topical ***anti-psoriatic treatments*** and ***etanercept*** has been shown[10-14]

ILVEN systemic implications

- Associated systemic abnormalities are ***rarely*** reported
  - ***No*** associated neurologic defects as could potentially be seen in other epidermal nevi
- Rarely ***ipsilateral skeletal abnormalities*** have been reported

Epidermal Nevus Syndrome

Epidermal nevus syndrome (ENS)

- Group of neurocutaneous disorders
- Characterized by ***epidermal nevi*** associated with ***systemic defects***[15]

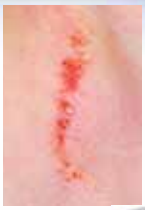
Neurologic

Musculoskeletal

Ocular

Classification of ENS

- Originally, Happle *et al* classified ENS into these clinical subtypes:
  - ***Nevus comedonicus syndrome***
  - ***Pigmented hairy epidermal nevus syndrome***
  - ***CHILD syndrome***
  - ***Proteus syndrome***
  - ***Schimmelpenning syndrome***[16-17]

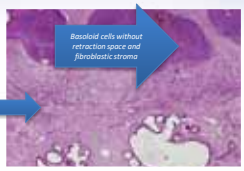


Nevus Sebaceous

Nevus sebaceous

- A congenital ***organoid nevus*** with epithelial and adnexal components
- Typically on the ***head and neck*** as a yellow hairless patch
  - Enlarges at puberty
- Associated with ***secondary neoplasms***, most of which are ***benign***

Secondary neoplasms in nevus sebaceous

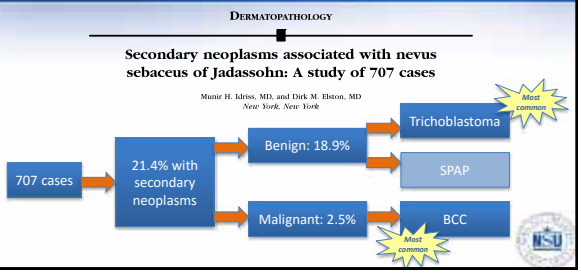


TRICHOBLASTOMA

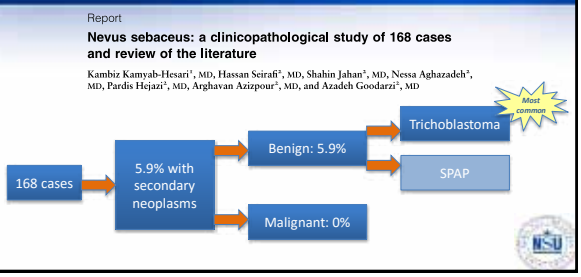
Secondary neoplasms in nevus sebaceous

- As many as 40 different types of ***secondary neoplasms*** have been reported in nevus sebaceous
- While ***basal cell carcinoma*** appears to be the most common ***malignant*** neoplasm associated, the most common ***benign*** neoplasm remains ***controversial***

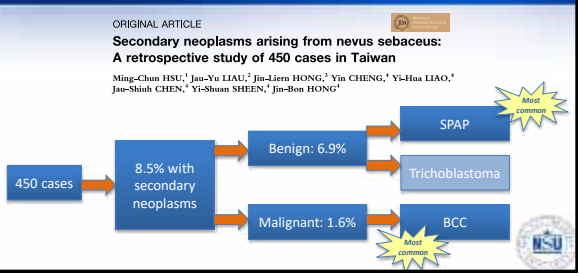
February 2014, Journal of the American Academy of Dermatology[18]



September 2015, International Journal of Dermatology[19]



September 2015, Journal of Dermatology[20]



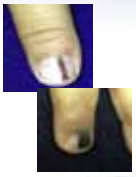
Management of nevus sebaceous

- Prophylactic excision is ***controversial***
  - In ***children***, may elect to observe clinically due to general anesthesia risks
  - As most secondary tumors arise ***after puberty***, this may be an appropriate age to first consider elective excision
- Since ***BCC*** is the most common malignant neoplasm, new nodules presenting in a nevus sebaceous ***should be biopsied*** at any age

Melanonychia striata

Melanonychia striata

- Melanocytic proliferations of the ***nail matrix or bed***
  - Can be congenital or acquired
- Very rare in Caucasians
  - 2.5% of black infants
  - 23% of Asian infants[21]
- ***Hutchinson's sign*** is suggestive, but not pathognomonic of melanoma
  - May be noted in benign nevi of the nails in children



Differential diagnosis for melanonychia striata

- ***Multiple*** pigment bands of the nails
  - Addison's or Cushing's disease
  - Peutz-Jeghers syndrome
  - Pernicious anemia
  - Laugier-Hunziker syndrome (*only* reported in adults)
  - Adults with AIDS
  - HIV-positive patients on zidovudine (AZT)
- ***Single*** pigmented band of the nail
  - Congenital or acquired melanocytic nevus
  - Lentigo
  - Bacterial pigment from Gram-negative organisms
  - Mycotic pigment (*Aspergillus*, *Exophiala*, *Alternaria*)
  - Subungual hematoma
  - Atypical melanocytic hyperplasia
  - Melanoma

Nail unit pediatric melanoma

- While 6% of adult melanomas present as melanonychia striata, only a ***few cases*** have been reported in childhood
- All childhood cases reported to date have been ***melanoma in situ***
- These cases may not have the same biological activity as melanoma in situ in an adult[21]

Worrisome features of melanonychia striata in the child

- Pigment bands broader than 3 mm
- Changing pigmentation or shape
- Associated nail dystrophy
- Hutchinson's sign
- Non-homogenous color bands
- Blurred lateral borders
- Irregular lines that are not parallel on dermoscopy
- Rapid evolution

Management of pediatric melanonychia striata[21]

ORIGINAL ARTICLES

A clinical, histopathologic, and outcome study of melanonychia striata in childhood

Chelsea Cooper, BA,[a] Nicoleta C. Arva, MD,[c] Christina Lee, BA,[a] Oriol Yélamos, MD,[c] Roxana Obregon, BA,[a] Lauren M. Sholl, MS,[c] Annette Wagner, MD,[c] Lisa Shen, MD,[c] Joan Guitart, MD,[c,b] and Pedram Gerami, MD[c,b]
Chicago, Illinois

JAAD May 2015

- Majority of cases of melanonychia striata in those under 18 years of age can be ***managed conservatively*** with clinical follow-up alone
- Biopsy reserved for those cases with ***concerning features*** (e.g.: Hutchinson's sign)
- Aggressive surgery, with excision of nail matrix, reserved for cases in which ***melanoma cannot be excluded*** after expert review of clinical and histologic findings

Take home points

- Activating fibroblast growth factor receptor 3 (***FGFR3***) mutations have been demonstrated in some epidermal nevi as well as acanthosis nigricans and seborrheic keratoses
- Children with extensive epidermal nevi should be monitored for ***neurologic*** and ***muscloskeletal*** defects
- Secondary neoplasms may develop around puberty in nevus sebaceous, with ***basal cell carcinoma*** being the most common malignant neoplasm
- In current literature, ***no*** cases of ***melanonychia striata*** have been reported to result in invasive melanoma in pediatric patients

Post-test question

- Which percentage of pediatric melanonychia striata in the dermatologic literature has been reported to result in invasive melanoma?
  - A. 0%
  - B. 1%
  - C. 6%
  - D. 14%

References

1. Rogers M, McCrossin I, Commens C. Epidermal nevi and the epidermal nevus syndrome. J Am Acad Dermatol 1989; 20: 476–488
2. Hafner C, van Oers JMM, Vogt T, et al . Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi . J Clin Invest . 2006;116:2201–2206.
3. Erovy-Evans S, Sahin S, Mancini AJ, Paller AS, Guitart J. . The acanthosis nigricans form of epidermal nevus. J Am Acad Dermatol. 2006;55(4):690-6.
4. Hafner C, Hartmann A, Vogt T. FGFR3 mutations in epidermal nevi and seborrheic keratoses: lessons from urothelium and skin. J Invest Dermatol. 2007;127(7):1572-3.
5. Mishra V, Saha A, Bandyopadhyay D, Das A. Bilateral systematized epidermolytic verrucous epidermal nevus: a rare entity. Indian J Dermatol. 2015;60(4):397-9.
6. Paller AS, Syder AJ, Chan YM, Yu QC, Hutton E, Tadini G, Fuchs E. Genetic and clinical mosaicism in a type of epidermal nevus. N Engl J Med. 1994;331:1408–1415.
7. Cramer SF, Mandel MA, Hauler R, et al. Squamous cell carcinoma arising in a linear epidermal nevus. Arch Dermatol 1981; 117: 222–224. 17 year old.
8. Ceylan C, Ozdemir F, Ozturk G, Akalin T. A case of basal cell carcinoma arising in epidermal nevus. Int J Dermatol. 2002;41(12):926-7.
9. Altman J, Mehregan AH. Inflammatory linear verrucous epidermal nevus. Arch. Dermatol. 1971; 104: 385–9.
10. Lee SH, Rogers M: Inflammatory linear verrucous epidermal naevi: a review of 23 cases. Australas J Dermatol 2001;42:252–256.
11. Happle, Rudolf. "Linear psoriasis and ILVEN: Is lumping or splitting appropriate?." Dermatology 212.2 (2006): 101-102.
12. Lee SH, Rogers M: Inflammatory linear verrucous epidermal naevi: a review of 23 cases. Australas J Dermatol 2001;42:252–256.
13. Renner, Regina, Andreas Colsman, and Michael Stücherling. "ILVEN: Is it psoriasis? Debate based on successful treatment with etanercept." Acta dermato-venereologica 88.6 (2008): 631-632.
14. Mitova LG, Dourmishev AL, Schwartz RA. Inflammatory linear verrucous epidermal nevus. cutis 2001; 68: 327–330
15. Vujevich JI, Mancini AJ. The epidermal nevus syndromes: multisystem disorders. J Am Acad Dermatol 2004:50:957–961
16. Happle R. How many epidermal nevus syndromes exist? J Am Acad Dermatol 1991;25:550-6.
17. Happle R. Epidermal nevus syndromes. Semin Dermatol 1995; 14:111-21.
18. Idriss MH, Elston DM. Secondary neoplasms associated with nevus sebaceus of Jadassohn: a study of 707 cases. J Am Acad Dermatol 2014; 70: 332–337.
19. Kamyab-Hesari K, Seirafi H, Jahan S, Aghazadeh N, Hejazi P, Azizpour A, Goodarzi A. Nevus sebaceous: a clinicopathological study of 168 cases and review of literature. Int J Dermatol. 2015 Sep 17 (Epub ahead of print)
20. Hsu MC, Liau JY, Hong JL, Cheng Y, Liao Yh, Chen JS, Sheen YS, Hong JB. Secondary neoplasms arising from nevus sebaceous: a retrospective study of 450 cases in Taiwan. J Dermatol. 2015 Sep 12 (Epub ahead of print)
21. Cooper C, Arva N, Lee C, Yelamos O, Obregon R, Sholl L, Wagner A, Shen L, Guitart J, Gerami P. A clinical, histopathologic, and outcome study of melanonychia striata in childhood. J Am Acad Dermatol. 2015, 773-779.
22. Schachner L, Hanson R. Pediatric Dermatology 4th Ed. 2011. Mosby Elsevier.
23. Bolognia J, Jorizzo J, Schaffer J. Dermatology 3rd Ed. 2012. Elsevier Saunders.

Thank you!

NOVA SOUTHEASTERN UNIVERSITY
LARGO MEDICAL CENTER
GRADUATE MEDICAL EDUCATION
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A Man with Asymptomatic Brown Spots on His Lower Extremities

Adam Allan, DO | Wei Su, MD | David Altman, MD

St. Joseph Mercy Ann Arbor, Ypsilanti, MI

SAINT JOSEPH MERCY HEALTH SYSTEM

History

An 86-year-old man presented with a six-year history of an asymptomatic eruption over the bilateral shins extending up both thighs. It began as a 15 cm patch on the right inner thigh that spread rapidly over one year to involve the majority of his lower extremities.

Examination

Physical examination revealed scattered 1-2 mm brown macules coalescing into patches, extending from bilateral ankles to thighs. There was no scale or induration with palpation and no associated lower extremity swelling.

Laboratory

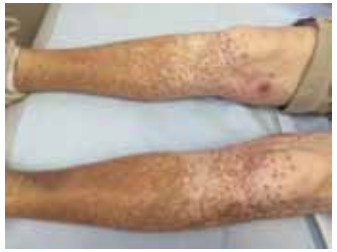
All laboratory values were within normal limits, including CBC, CMP, UA and lipid profile.

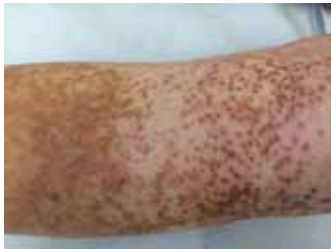
Histopathology

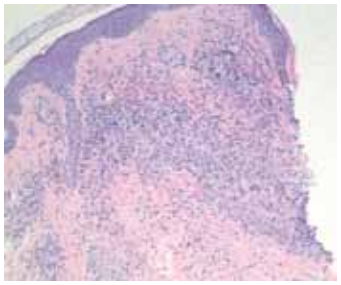
Punch biopsy revealed a superficial to mid dermal perivascular lymphocyte-predominant infiltrate with associated siderophages and a focal granulomatous infiltrate comprised of histiocytes. PAS, AFB and Fite stains were negative for microorganisms. No eosinophils or leukocytoclasis was seen.

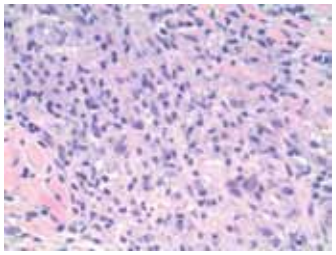
Course and Therapy

The patient showed no improvement with topical steroids.









Discussion

Granulomatous pigmented purpuric dermatosis is a rare histological variant of PPD which most commonly affects individuals from Far East Asia and presents on the distal lower extremities. Several other variants of PPD are recognized and include Schamberg's disease, purpura annularis telangiectaticum (of Majocchi), pigmented purpuric lichenoid dermatitis of Gougerot and Blum, eczematoid-like purpura of Doucas and Kapetanakis, itching purpura of Lowenthal, lichen purpuricus, lichen aureus, transitory pigmented purpuric dermatosis and linear pigmented purpuric dermatosis.

Granulomatous PPD has a total of 18 cases documented in the literature, 13 Asian and five Caucasian. It has a mean age of onset of 51 years and a female predilection. Currently the etiology is unknown; however, 10 of the reported cases have been associated with hyperlipidemia. This has led to the speculation that the two may be related. There are single case reports of associations with other systemic derangements such as hepatitis C, Sjögren syndrome, hypertension, seizure disorder, ulcerative colitis, diabetes mellitus, and chronic obstructive pulmonary disease.

Clinically, granulomatous PPD presents with asymptomatic petechiae and bronze discoloration. The clinical presentation can vary from a solitary lesion, a localized eruption typically on the lower extremities, or rarely in a widespread eruption. This variant is characterized histopathologically by ill-defined, non-necrotizing granulomas admixed with a lymphocytic infiltrate. Erythrocyte extravasation and hemosiderin in the absence of vasculitis is often seen.

Granulomatous PPD, particularly when arising in the context of idiopathic inflammatory bowel disease, may be confused with cutaneous Crohn disease. PPD as a group has a propensity to simulate mycosis fungoides (MF), but there have been no reported cases of granulomatous PPD progressing into MF. However, this possibility should always be considered and clinical follow-up is advised in cases of diagnostic uncertainty. The granulomatous variant of PPD may be under-recognized, particularly when the granulomatous component is subtle. This variant is an important entity for pathologists to be aware of and consider in dermal granulomatous infiltrates showing signs of vascular injury.

Treatment with oral and topical steroids has been unsuccessful. Due to the suspected hyperlipidemia association, acquiring a lipid profile is warranted. There is no increased risk of mortality and the prognosis is excellent.

Conclusion

Granulomatous pigmented purpuric dermatosis is a rare histological variant of PPD which should be considered in patients presenting with asymptomatic petechiae and bronze discoloration of the lower extremities, especially individuals from Far East Asia. An association with hyperlipidemia is suspected and a lipid profile is suggested. Pathologists should consider this variant in granulomatous infiltrates show sings of vascular injury. Effective treatment is currently unknown, but prognosis is excellent.

References

1. Kaplan J, Burgin S, Sepehr A. Granulomatous pigmented purpura: report of a case and review of the literature. J Cutan Pathol. 2011;38:984-989.
2. Kerns MJ, Mallott BD, Shamma HN. Granulomatous Pigmented Purpura: An Unusual Histological Variant. Am J Dermatopathol. 2009;31:77-80.
3. MacKenzie AI, Biswas A. Granulomatous Pigmented Purpuric Dermatosis: Report of a Case With Atypical Clinical Presentation Including Dermatoscopic Findings. Am J Dermatopathol. 2014;0:1-4.
4. MacQuarrie EK, Pasternak S, Torok M, et al. Persistent pigmented purpuric dermatitis: granulomatous variant. J Cutan Pathol. 2011;38:979-983.
5. Wang J, Wu Y, Hsiao P, et al. Granulomatous pigmented purpuric dermatoses: report of three cases and review of the literature. Dermatologica Sinica. 2010;28:77-81.

DEPARTMENT OF INTERNAL MEDICINE · ST. JOSEPH MERCY ANN ARBOR

Ingenol Mebutate Gel 0.015% for the topical treatment of Nodular Basal Cell Carcinoma

Dylan Alston, DO[1]
[1]South Texas Osteopathic Dermatology Residency
University of North Texas Health Science Center

Introduction

The incidence of non-melanoma skin cancer (NMSC) continues to rise and is currently the most common malignancy seen in medicine. There is currently a need for treatment of existing cancer by non-surgical and tissue-sparing modalities and medications. This study explores the use of IM for the treatment of nBCC in a non-surgical candidate.

Ingenol mebutate (IM) has FDA approval for the treatment of actinic keratosis. IM is extracted from the sap of the plant Euphorbia peplus via an extensive extraction and crystallization process. IM appears to induce local lesional cell death and promote an inflammatory response characterized by an infiltration of neutrophils and other immunocompetent cells.

History

A 66-year-old Caucasian male with severe cardiac disease requiring coronary stent placement in 2009, HTN, hyperlipidemia and a recent diagnosis of paroxysmal atrial fibrillation presented to the clinic with his third case of nBCC in 10 years. This patient has been previously treated with surgical excision of a 1.5cm nBCC on the right outer canthus in 2009 and a 2.2 cm nBCC of the left eyebrow in 2001. At this time, the patient was taking warfarin, aspirin and required transfusion of 2 units of PRBCs for hemorrhage following routine colonoscopy and polypectomy.

Methods

The patient was treated with three applications of IM 0.015% over three consecutive days for nBCC involving the right temple. IM was applied to the nBCC covering a 2x2 inch area.

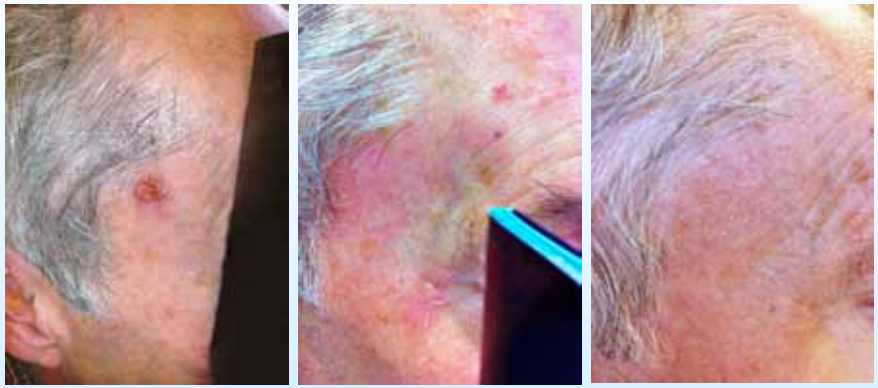
Physical Exam

Physical examination revealed a 2.5 cm raised, erythematous, pearly nodule with rolled, ragged edges, an ulcerated center and telangiectasias located along the hairline of the right temple. Numerous actinic keratoses were noted over the vertex of the scalp, face and arms but were not treated with IM at this time. The patient was treated with three applications of IM 0.015% over three consecutive days for nBCC involving the right temple.

Results

At day 37, the site previously occupied by this 2.5cm nBCC could not be distinguished from the surrounding skin. Local skin reactions following initial application included an intense burning sensation, marked erythema progressing to a flaking scale with desquamation. Overall, the patient's satisfaction was high, citing convenience, simplicity of treatment, avoidance of surgery and excellent cosmetic results as his reasons.

Day 0 | Day 10 | Day 37



Conclusion

Ingenol Mebutate 0.015% gel may be considered for the treatment of nBCC in patients where surgery is a relative or absolute contraindication. We found this therapy to be safe, effective, well tolerated and cosmetically appealing. This case report raises the need for a large, randomized, controlled study to investigate the effectiveness of IM for the treatment of nodular BCC with histological confirmation.

A Man with a Lump on the Left Lower Leg

Benjamin Bashline DO[1] | James Ramirez MD[1] | Murray Cotter MD, PhD[2]

St. Joseph Mercy Ann Arbor, Ypsilanti, MI[1] | Dermatology Associates of Northern Michigan, Petoskey[2]

Introduction

A 69-year-old man with a 20-year history of chronic lymphocytic leukemia (CLL) and a six-year history of mantle cell lymphoma (MCL) presented with a solitary lesion on his left leg. The patient had received multiple courses of chlorambucil for treatment of CLL and rituximab as well as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for treatment of MCL. Both conditions were in remission at the time of presentation.

Examination

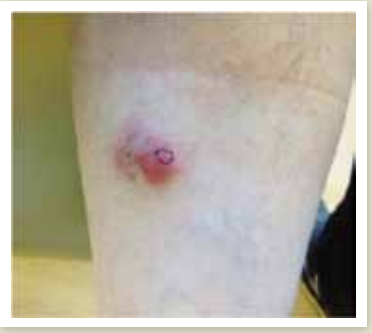
Physical examination revealed a 4x4 cm red to violaceous dermal nodule on the left anterior lower leg.

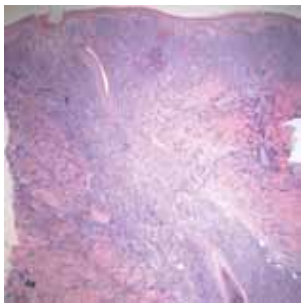
Histopathology

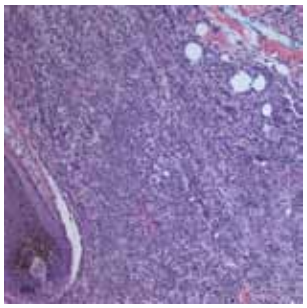
Biopsy of the lesion demonstrated a sheet-like proliferation of highly atypical lymphoid cells in the dermis and subcutaneous fat. The tumoral cells were blastoid in appearance and possessed high nuclear to cytoplasmic ratios, vesicular chromatin, and large, irregular and prominent nucleoli. Multiple apoptotic bodies and mitoses were evident. Immunohistochemical staining for CD20, BCL-2, BCL-6, MUM-1, and cyclin D1 were positive in lesional cells. Sox-11, TDT, and CD10 were negative. Break-apart FISH for cyclin D1 was positive for the cyclin D1 rearrangement (11q13).

Course and Therapy

The patient was referred to oncology for systemic treatment. No surgical exicison was performed.







Blastoid Mantle Cell Lymphoma

Discussion

Mantle cell lymphoma (MCL) is a rare, aggressive variant of non-Hodgkin's lymphoma (NHL). MCL is named based on its involvement of lymphocytes from the mantle zone of lymph nodes. MCL typically occurs in middle-aged males and represents 2-10% of all non-Hodgkin's lymphomas. The disease is often identified at later stages, with involvement of multiple lymph nodes and/or the spleen. Patients commonly present with constitutional symptoms including fever, chills, weight loss, night sweats, as well as generalized lymphadenopathy, splenomegaly and hepatomegaly.

Skin involvement in MCL is rare, found in only 2-6% of patients. Cutaneous disease typically occurs as a progression of the common lymphoid form, but rarely may be the primary manifestation of MCL. Clinically, lesions appear as solitary or multiple non-descript erythematous papules and nodules.

MCL presents with a blastoid histological morphology in 10-20% of cases, a feature which is more commonly associated with cutaneous manifestations. Histopathologic examination reveals a dense dermal proliferation of atypical lymphoid cells displaying lymphoblastic morphology, which stain positively for CD20, BCL-2, BCL-6, MUM-1, and cyclin D1. MCL is associated with the chromosome translocation t(11:14)(q13;q32). This translocation results in overexpression of cyclin D1, a protein involved in cell cycle regulation, specifically the progression of cells from G1 phase to S phase. Immunohistochemical stains are positive for cyclin D1 in 98% of patients.

The differential diagnosis of MCL is broad, and includes other cutaneous forms of NHL, such as diffuse large B-cell lymphoma (DLBCL). Clinically, DLBCL presents as a rapidly enlarging mass, most commonly in an area with a high density of lymph nodes, such as the axilla or groin. Histologically DLBCL can be indistinguishable from blastoid MCL. Both lymphomas can be MUM-1 and cyclin D1 positive, however the translocation t(11;14)(q13;q32)/CCND1-IGH is only seen in MCL. Recent use of sex-determining region Y-box11 (SOX-11), a transcription factor involved in tumorigenesis, has also been very useful in distinguishing cyclin D1 positive DLBCL from MCL, as it is typically only positive in MCL.

MCL is associated with a poor prognosis, as it is generally unresponsive to traditional chemotherapy, with a median survival rate of four to five years. Treatment differs with presentation, age of the patient and staging at the time of diagnosis. Treatment for elderly patients or those with multiple comorbidities involves rituximab and CHOP. Younger patients are typically treated more aggressively with hyperCVAD (cyclophospharnide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine). Autologous or allogeneic stem cell transplantation is also recommended for younger and lower risk patients. Newer agents such as lenalidomide have shown good efficacy for recurrent cases and may be used in combination with rituximab.

References

1. Casinoro AM, Bettelli S, Maccio L, et al. Primary cutaneous mantle cell lymphoma of the leg with blastoid morphology and aberrant immunophenotype: A diagnostic challenge. Am J Dermatopathol. 2014;36(2):16-18.
2. Ek S, Dictor M, Jerkeman M, et al. Nuclear expression of the non-B-cell lineage Sox11 transcription factor identifies mantle cell lymphoma. Blood. 2008;111(2):800-805.
3. Phelps A, Gorgan M, Blaba Z, et al. CD10-positive blastoid mantle cell lymphoma with secondary cutaneous involvement. J Cutan Pathol. 2013;40:765-767.
4. Vose JM. Mantle cell lymphoma: 2013 update on diagnosis, risk-stratification, and clinical management. Am J Hematol. 2013; 88(12):1082-1088.

Mysterious Vasculitis-Like Rash In A Young Female

Jon Bielfield DO, Lisa Swanson MD, Jules Vandersarl MD, Reagan Anderson DO
Colorado Dermatology Institute, Rocky Vista University

INTRODUCTION

- Vasculitis disorders can present with a variety of cutaneous findings. Livedo reticularis rashes can be physiologic or associated with vessel wall pathology. This can be seen in diseases such as polyarteritis nodosa, autoimmune connective tissue diseases, hypercoaguable states, and cryoglobulinemia. A newly described lymphocytic thrombophilic arteritis phenomenon has been associated with livedo reticularis. It was observed mainly over the lower extremities in a case series of young females.

- We report the case of a 12 year old female with a chronic livedo-reticularis rash located on her lower extremities. Her clinical, laboratory, and histological findings are not conclusive for a specific diagnoses. However, her presentation meets some criteria for lymphocytic thrombophilic arteritis and cutaneous polyarteritis nodosa.

CASE REPORT

- A 12 year old female presented with a one year history of livedo reticularis-like changes on her bilateral lower extremities (Figure 1). The rash initially looked like bruises and was pruritic intermittently. Hydroxyzine gave her some relief from the itching. The initial lesions were noted several months after she started menstruation. No correlation was noted between her menstrual cycles and the cutaneous signs. She denied any pain. The rash was not temperature or elevation dependent. She once noticed aggravation of the rash with hiking on inclined hills/mountains. She complained of occasional joint pains in her shoulders and knees which responded to massages and have resolved. She would get vague abdominal pain that would last a day. This has also resolved. There is a history of low grade fevers that have stopped as well. Her primary complaint, outside of the cutaneous findings, was generalized fatigue. This has improved when we met with the patient on her most recent visit in June, 2015. Overall, the patient's rash was slightly faded at this visit. She was on a trial of naprosyn without any noticeable changes.

- Laboratory analysis included a complete blood count with differential, comprehensive metabolic panel, coagulation studies, thyroid function studies, iron studies, EBV profile, ASO titers, ESR, CRP, ANA, RF, p-ANCA, c-ANCA, and cryoglobulins. All studies were negative/unremarkable.

- Punch biopsies were performed on three separate clinic visits. The most recent biopsy was taken from a palpable area of the livedo reticularis on the shin. All three biopsies had non-specific findings. They showed a superficial and mid-dermal perivascular dermatitis without evidence of vasculitis or panniculitis (Figure 2).

- The patient was referred to pediatric hematology and rheumatology for further evaluation. There was no evidence of a hematological disorder. Furthermore, rheumatology concluded there was no definitive support for a systemic autoimmune diagnosis.

FIGURE 1. LIVEDO RETICULARIS RASH WITH BRUISE-LIKE LESIONS ON THE LOWER EXTREMITIES (A) INITIAL PRESENTATION (B) JUNE, 2015

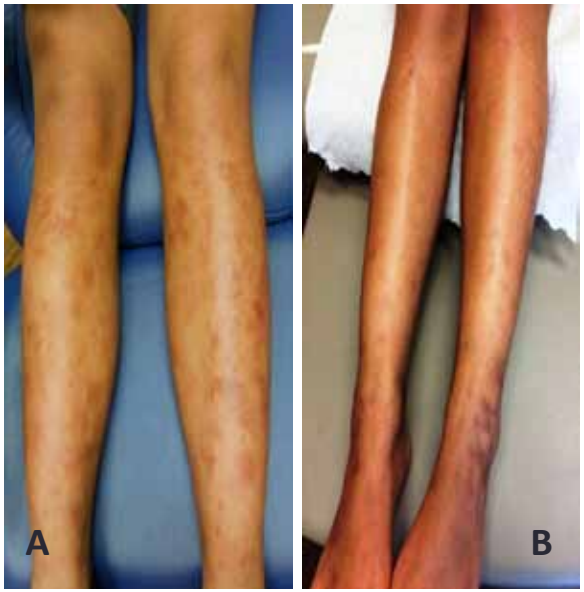
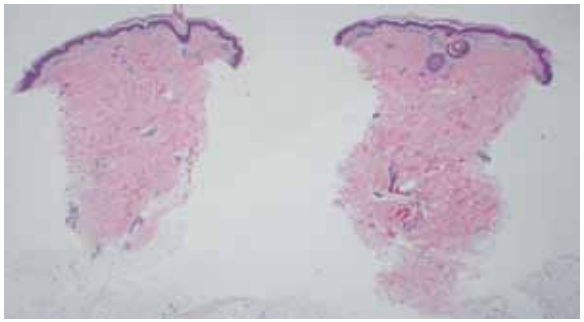


FIGURE 2. HISTOLOGICAL ANALYSIS SHOWED A MILD SUPERFICIAL AND MID-DERMAL PERIVASCULAR DERMATITIS



DISCUSSION

- The current working diagnosis for this case is lymphocytic thrombophilic arteritis (LTA) versus cutaneous polyarteritis nodosa (CPA).

- LTA presents with slowly progressive patchy hyperpigmentation, and livedo reticularis primarily located on the lower extremities. The cases described in the literature appear to predominantly affect younger women. Four out of five patients had antiphospholipid antibodies. Three out of five patients had elevated erythrocyte sedimentation rates. Histologically, LTA presents with lymphocytes and histiocytes infiltrating the muscular walls of small arterioles, located at the dermosubcutaneous junction. Furthermore, a characteristic fibrin ring is present with nuclear dust in the lumen. The condition may respond to prednisone.

- It is currently unknown if there is any significant role for antiphospholipid antibodies in the pathogenesis of LTA. Several factors mitigate a prominent role for this finding. These include: low serum levels in the patients studied, no systemic involvement in the patients presented, no histological evidence of macrovascular thrombosis, and the presence of a dense lymphocytic infiltrate.

- CPA can present with livedo reticularis, palpable purpura, painful nodules, ulceration, and severe digital ischemia. Histologically, a neutrophilic infiltration with fibrinoid necrosis of medium and small-sized arteries is characteristic.

- Our patient seems to clinically and demographically match better with the diagnosis of LTA. However, she lacks the characteristic deeper vessel involvement and intraluminal fibrin ring development histologically. She lacks the nodular and ulcerative lesions more classic for CPA. However, she experienced some temporary bouts of joint pains, abdominal pain, and fatigue which could fit more within the diagnosis of CPA or a mild systemic form of polyarteritis nodosa. Her overall histological interpretation is non-specific. Currently, she is asymptomatic, and has elected to abstain from any pharmacological intervention.

REFERENCES

1. Lee JS-S, Kossard S, McGrath MA. Lymphocytic thrombophilic arteritis: a newly described medium-sized vessel arteritis of the skin. *Arch Dermatol*. 2008;144(9):1175-1182.

2. Leboit PE. The enigma of lymphocytic vasculitis. *Arch Dermatol*. 2008;144(9):1215-1216.

3. Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatol*. 1997;136(5):706-713.

4. Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology. Third edition. Elsevier Saunders;2012:405-407.

Generalized Linear Porokeratosis: A Case Report and Discussion

Stephanie Blackburn, DO,[1] Zaina Rashid, DO,[2] Joan Moad, MD,[3] Michelle Duff, DO,[4] Jason Barr, DO,[5]

[1]PGY-2, Affiliated Dermatology, Scottsdale, AZ, USA; [2]Assistant Professor, Midwestern University, Glendale, AZ, USA; [3]Laboratory Director Dermatopathologist, Dayton, OH, USA; [4]PGY-3, Affiliated Dermatology, Scottsdale, AZ, USA; [5]Program Director, Affiliated Dermatology, Scottsdale, AZ, USA

Background

Linear porokeratosis is a clinical variant of porokeratosis that usually arises in infancy or childhood.[1] It consists of one or more plaques that are similar in appearance to classic porokeratosis, but the plaques follow the lines of *Blaschko* and are most common on the extremities.[2] Of all the different subtypes of porokeratosis, linear porokeratosis has the greatest chance of malignant transformation, with squamous cell carcinoma and basal cell carcinoma being the most common.[3]

Methods

- Review of the literature on Linear porokeratosis was conducted
- Diagnosis of Linear porokeratosis based on:
  - Biopsy
  - Morphology
  - Clinical course of disease
  - Distribution of lesions

Case Presentation

We present a case of a 57-year-old man with a 45 year history of reddish-brown skin lesions showing central atrophy with surrounding scale, hyperpigmentation, and erythema on the right posterior back, right arm, right lateral leg and buttock (Fig 1). There was significant actinic damage on his legs (Fig 2) that resolved with treatment (Fig 3).

Treatment Options & Considerations

- Generally disappointing
- Risk of malignancy
- Size & morphology of lesions
- Age of patient
- Cosmetic outcome
- Topical imiquimod
- Topical fluorouracil
- Topical steroids
- Topical retinoids & keratolytics
- Surgical options

Fig 1

Fig 2

Fig 3

Differential diagnosis

- Linear Darier's
- Linear lichen planus
- Linear psoriasis
- Incontinenitia pigmenti

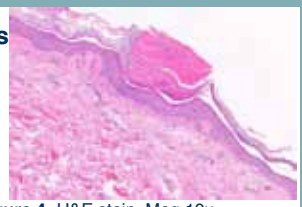


Figure 4: H&E stain, Mag 10x

Histology

Two biopsies taken of the lower extremity showed definitive cornoid lamellae with thin and flattened epidermis. Subtle interface change with few necrotic keratinocytes was also noted. There was mild superficial perivascular lymphocytic inflammation with melanophages. Focal parakeratosis with few superficial epidermal dyskeratotic keratinocytes was noted (Figure 4).

Table 1: Comparison of porokeratosis subtypes[4]

Selected Characteristics of Porokeratosis Variants

Variant	Location	Characteristics	Inheritance	Sequelae
Classic porokeratosis of Mibelli	Extremities, anywhere	Prominent cornoid lamellae, typically few lesions (<20 cm)	Autosomal dominant	Increase in number and size, malignant degeneration reported
Disseminated superficial actinic porokeratosis	Anywhere (disseminated variant); sun-exposed areas (actinic variant)	Indistinct cornoid lamellae development; uniform lesions (≤1.0 cm)	Autosomal dominant	Rapid dissemination, malignant degeneration reported
Porokeratosis palmaris et plantaris disseminata	Palms, soles, disseminates across body	Cornoid lamellae, prominent keratotic ridge, disseminated, uniform lesions (≤1.0 cm)	Autosomal dominant	Malignant degeneration reported, bone and nail dystrophy
Linear porokeratosis	Distal extremities with unilateral linear distribution	Prominent cornoid lamellae characteristics, large plaques can develop	Mosaicism	Malignant degeneration reported, bone and nail dystrophy
Punctate porokeratosis	In association with other porokeratosis variants, palms and soles	Discrete, punctate, hyperkeratotic, keratotic lesions; thin peripheral ridge; uniform lesions; cornoid lamellae	Autosomal dominant	None reported

Discussion

Linear porokeratosis rarely affects adults and has two clinical variants.[5] The most common variant is unilateral and confined to one extremity, while the rarer version affects multiple extremities and the trunk in a unique zosteriform pattern.[5]

Malignant transformation can occur in all porokeratosis. Linear porokeratosis has the greatest risk of developing into Bowen's disease, SCC, and basal cell carcinoma.[6] Risk factors include excessive sun exposure, radiation therapy, internal malignancies, and a family history of porokeratosis.[2] It has been hypothesized that linear porokeratosis has increased malignant potential due to allelic loss and overexpression of the tumor suppressor gene p53.[7]

Conclusion

Monitoring for suspicious lesions is key for patients with porokeratosis.

References

Sotiriou P, von Felbert V, Mogabgab M. Porokeratosis: present concepts. Journal of the European Academy of Dermatology and Venereology. 2012; 26: 404-412.

Maubec E, Duvillard P, Margulis A, Bachellier R, Dupuis G, Avril MF. Common skin cancers in porokeratosis. British Journal of Dermatology. 2005; 152: 1360-1366.

Chow KY. Linear Porokeratosis. Hong Kong Dermatology and Venereology Bulletin. 2000; 8: 21-23.

Wang Y, Ma L, Zhang J, Zheng M, Gao X. Linear porokeratosis: a clinicopathological and verrucous porokeratosis in an elderly woman: Update on the genetics and clinical expression of porokeratosis. J Am Acad Dermatol. 2010; 63:886.

Imakado S, Ortuka F, Ishibashi Y, et al. Abnormal DNA ploidy in cells of the epidermis a case of porokeratosis. Arch Dermatol.1988; 124: 331-2

Magee, JW, McLaimont, TH, Lalkoi PS. Over-expression of p53 tumor suppressor protein in porokeratosis. Arch Dermatol.1988; 124: 331-2

Pallotelli GM, Torchia D. Porokeratosis of Mibelli and Superficial disseminated porokeratosis. J Cutan Pathol. 2008; 35 253-5

Stankiewicz P, Lupski JR. Gene, Genomic, and Chromosomal Disorders. IN: Goldman L, Schafer AI, eds. Cecil Medicine. 24th ed. Philadelphia, PA: Saunders Elsevier; 2011: chap 46.

Schwartz RA, Fenske NA. Disseminated superficial "actinic" porokeratosis. J Am Acad Dermatol. 1984;11:724.

Gilead L, Gabestean D, Horogovski A, et al. Immunosuppression-induced porokeratosis of Mibelli: Complete regression of lesions upon cessation of immunosuppressive therapy. J Eur Acad Dermatol Venereol. 1995; 5:178.

Tsunokawa D, Sakhpasheva T. Disseminated superficial porokeratosis: complete remission subsequent to discontinuation of immunosuppression. J Am Acad Dermatol. 1993; 28: 651.

in two unrelated children from parents with localized linear form, and prenatal diagnosis. J Invest Dermatol. 2006;126(12):2715-7. [PMID: 16998484]

Case Report: Germline BAP1 Mutation

George Brant DO, Reagan Anderson DO
Colorado Dermatology Institute, Colorado Springs, CO

Introduction

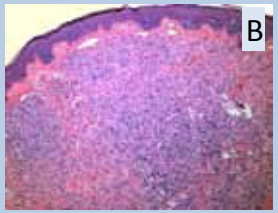
BRCA1-Associated Protein-1 (BAP-1) plays an important role in the regulation a number of cellular processes involved in tumor suppression. Inheritance of a germline mutation in the gene encoding BAP1 results in a syndrome characterized by distinct melanocytic tumors and a predisposition to several malignancies.

Case Report

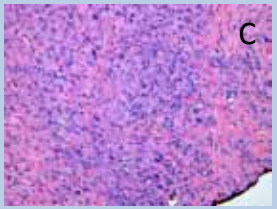
- A 37 yo male with a history of significant actinic damage, basal cell carcinoma and squamous cell carcinoma presented for a full body skin exam. He had no specific complaints.
- Family history was remarkable for his father having died of mesothelioma.
- A 6mm red-brown papule under the left chin (Figure A), present for an unknown duration, was discovered on exam. Clinical impression was an irritated intradermal nevus vs an atypical nevus and a shave biopsy of the lesion was performed.
- Histopathologic diagnosis proved challenging as the specimen demonstrated features of both an atypical Spitz nevus and melanoma (Figures B and C).
  - Special stains were performed (Figures C,D,E and F)
  - Additional tests, including genomic studies were performed (Table 1)
  - After review by multiple dermatopathologists specializing in melanocytic tumors a diagnosis of a "chiefly dermal melanocytic proliferation with desmoplastic and Spitzoid features, consistent with a melanoma of at least 1.3mm depth," was agreed upon.
- The lesion was excised with 1cm margins.
- A sentinel lymph node biopsy was performed and 2 of 3 nodes in the right neck were positive for melanoma.
  - A PET/CT following the SLNB revealed bilateral upper cervical lymphadenopathy
  - Completion dissection was only performed on the right neck given the morbidity associated with bilateral neck dissection.
  - No additional positive nodes were found.
- A 6 month follow-up scan revealed a mass on the left kidney, which was removed via robotic partial nephrectomy and found to be a clear cell renal cell carcinoma.
- Two years following the initial melanoma diagnosis a suspicious red-brown papule on the left upper back was discovered and biopsied.
- Microscopic examination revealed a biphasic atypical melanocytic proliferation, with both large epithelioid and small, bland appearing melanocytes. (Figure G)
  - The dermatopathologist, familiar with the patient's case, felt this lesion might represent a "BAPoma," one term for the characteristic lesion of the germline BAP1 mutation syndrome
  - Immunohistochemical staining demonstrated loss of BAP1 expression of the large epithelioid melanocytes (Figure G)
- The patient was diagnosed with a germline BAP1 mutation and is now followed closely at our clinic and at university based melanoma and oncology clinics.

Clinical and Histologic Findings

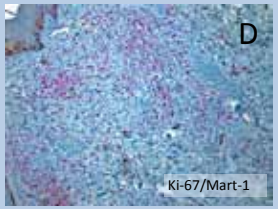
A. 6mm red-brown papule, under left chin.



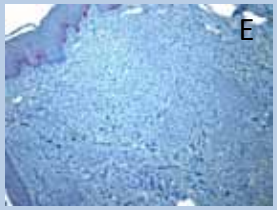
B. Dermal proliferation of atypical melanocytes.



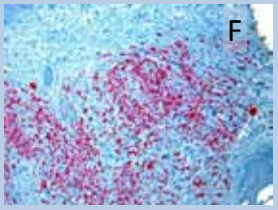
C. Enlarged melanocytes with abundant eosinophilic cytoplasm and nuclear pleomorphism.



D. Ki-67 – low proliferative index for dermal melanocytes. Mart-1 – positively stains the dermal melanocytes.



E. HMB-45 – no staining of dermal melanocytes.



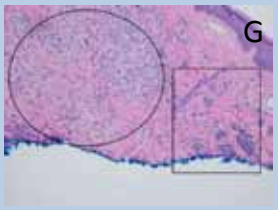
F. P16 – strong staining within enlarged dermal melanocytes.

Additional Tests

BRAF Testing
BRAF V600E mutation – positive

Fluorescence In-Situ Hybridization
CCND1 abnormality (chromosome 11)

Comparative Genomic Hybridization
Chromosomal abnormalities: 3,9,10



G. Large epithelioid melanocytes adjacent to a population of minute, bland appearing melanocytes.

Discussion

- BRCA-associated protein 1 (BAP1) is a member of the ubiquitin carboxy-terminal hydrolase (UCH) system, which is involved in several important cellular functions.[1]
- Somatic mutations of BAP1 have been discovered in a number of malignancies, including uveal melanoma (UM), cutaneous melanoma (CM), renal cell carcinoma (RCC), mesothelioma (MM), breast cancer, small cell and non-small cell lung cancers, cholangiocarcinoma and perhaps many more that have yet to be elucidated.[2,3]
  - Uveal melanoma, in particular, is associated with a high rate of BAP1 mutation, with as many as 47% harboring mutations.[4]
- Mutations in the BAP1 gene may be inherited in an autosomal dominant fashion, predisposing individuals to several malignancies, including UM, CM, mesothelioma, RCC, and basal cell carcinoma.[5]
- Germline BAP-1 mutations appear to be associated with a distinct melanocytic tumor.[6]
  - Clinical appearance of these lesions are consistently described as flesh-toned to reddish-brown, well circumscribed, dome-shaped or pedunculated papules.
  - Characteristic morphologic features include dermal aggregates of large, epithelioid melanocytes with abundant cytoplasm and nuclear pleomorphism.
  - These appear in the first two decades of life and then increase in number, with some individuals having more than 50. Despite this, there are far fewer cases of cutaneous melanoma relative to the number of these tumors, thus they are thought to rarely evolve into melanoma.[6]

Conclusion

- Dermatologists and dermatopathologists play an important role in the identification of patients with a number of inherited cancer syndromes, many of which initially present with cutaneous manifestations.
- Increased awareness of this syndrome will facilitate earlier recognition of affected patients, allowing for more appropriate management, such as increased surveillance for associated malignancies and genetic counseling.

References
1. Jensen DE, Proctor M, Marquis ST, et al. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. Oncogene. 1998;16(9):1097–112.
2. Bott M, Brevet M, Taylor BS, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma. Nat Genet. 2011;43:668–72.
3. Churi CR, Shroff R, Wang Y, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. Plos One. 2014 Dec 23;9(12):e115383 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4275227/. Accessed April 2, 2015.
4. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science. 2010;330:1410–3.
5. de la Fouchardiere A, Cabaret O, Savin L, et al. Germline BAP1 mutations predispose also to multiple basal cell carcinomas. Clin Genet. 2014. doi: 10.1111/cge.12472. http://onlinelibrary.wiley.com/doi/10.1111/cge.12472/full. Accessed May 2, 2015.
6. Wiesner T, Obenauf AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. 2011;43(10):1018-1021

Diffuse Dermal Angiomatosis of the Breast

Gina M. Caputo, DO, Roxanne Rajaii, DO, Gary Gross, MD and Daniel S. Hurd, DO, FAOCD

LewisGale Hospital Montgomery / Edward Via College of Osteopathic Medicine

Case Report

A 60-year-old Caucasian female presented with a 3-month history of exquisitely tender, ulcerating, and bleeding breasts, with a tremendous amount of exuded material bilaterally. This eruption started approximately 6 weeks after cardiac surgery. During the procedure, the patient received heparin, but was not placed on coumadin. She denied exacerbating or alleviating factors. Past medical history is significant for cardiovascular disease, transient ischemic attack, hypertension, and hypercholesterolemia. The patient was a smoker when she was evaluated for this eruption. Her medications upon evaluation included atorvastatin, clopidogrel, lisinopril, metoprolol, and topical lidocaine. Family history was noncontributory. All labs were found to be within normal limits.

Physical exam revealed livedo reticularis on the breasts, bilaterally. The left breast was much more affected than the right, with associated healed punctuate ulcerations and changes of healed infarcts. The rest of her cutaneous exam was negative (Figures 2,3).

Histologic sections of a punch biopsy from the left breast revealed a diffuse capillary proliferation within the dermis and extending into the subcutis in a patchy distribution. There was no evidence of vasculitits or a thrombotic vasculopathy to suggest either coumadin or heparin necrosis. There was also no evidence of endothelial atypia or malignancy. This pattern was consistent with diffuse dermal angiomatosis, a form of reactive angioendotheliomatosis (Figure 1). Treatment included pain control and isotretinoin at a dose of 40mg PO twice daily for a duration of 4 months, to which the patient had a positive result.

Discussion

First described in 1994 by Krell et al., diffuse dermal angiomatosis (DDA) is a rare skin condition primarily affecting females and characterized by erythematous, violaceous, indurated plaques which are often ulcerated and tender and commonly localized to the lower extremities.[1,2,3] Although the pathogenesis is unknown, it is often noted in patients with severe peripheral vascular disease among other co-morbidities.[2-5] A few authors have reported a correlation between DDA and trauma, namely from surgery.[1] While DDA is rare, with 14 total cases reported, involvement of the breast is even less frequently diagnosed.[1,2] To date, only 5 cases of DDA of the breast (DDAB) have been described.[1] Although often affecting large pendulous breasts bilaterally, these patients presented in an otherwise atypical fashion without relevant medical history or vaso-occlusive disorder.[2] Histologically, however, they demonstrated diffuse dermal vascular and endothelial cell proliferation between collagen bundles and uniform positivity with immunoperoxidase stains CD31 and CD34, vascular markers characteristic of DDA.[1,4,5] HHV-8 is also often used to aid in diagnoses and is uniformly negative in DDA.[1]

The exact process underlying the development of DDA has yet to be determined but is thought to be a result of tissue ischemia.[1] The current hypotheses regarding the pathogenesis of the disease are as follows: "1) atherosclerotic plaques may embolize to distal small vessels and create endothelial hyperplasia; (2) vascular steal syndromes can give rise to ischemic necrosis with subsequent ulceration; or (3) ischemia leads to increased vascular endothelial growth factor and subsequent endothelial proliferation."[6] Given this understanding, it is believed that reversing ischemia and achieving revascularization can be beneficial in improving the clinical signs of disease.[6] Despite a clear mechanism of disease development, several associations have been made between DDA and other co-morbid conditions. Many authors have reported associations between DDA and peripheral vascular atherosclerosis, arteriovenous fistulas, anti-cardiolipin antibodies, hypercoagulable states, and breast ulceration.[2,6,7] The most common and widely accepted association, however, has been vascular occlusive disease.[6] Smoking and DDA have also been found to be strongly associated, with patient's often having a significant clinical history of long-term tobacco-use. Hypertension has also been reported to be associated with DDA.[1,4]

Figures

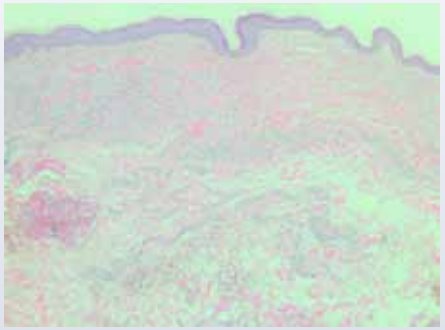


Figure 1

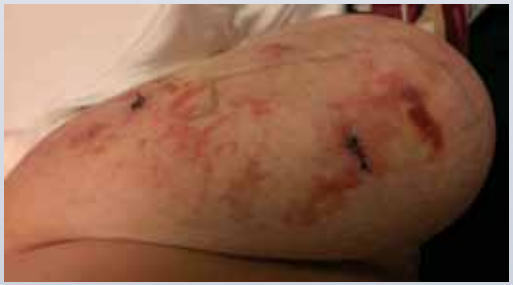


Figure 2

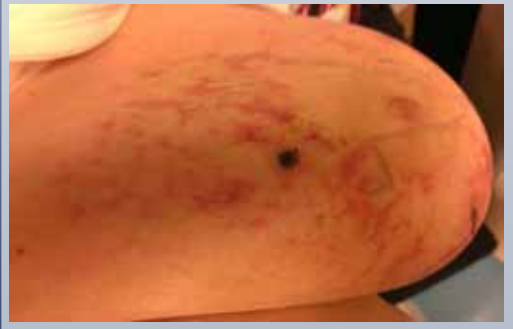


Figure 3

As noted above, the management of DDA and DDAB is centered on improving the underlying ischemia and achieving revascularization. Many modalities have been implemented in the treatment of DDA and DDAB, including the use of oral corticosteroids, isotretinoin, reduction mammoplasty, and stent placement in extreme cases of vaso-oclussive disease.[1,8] Morimoto et al., as well as other authors, have described successful revascularization procedures facilitating the healing of DDA ulcers.[9] In this case report, we describe not only a classic presentation of DDAB, but also successful treatment with isotretinoin at a dose of 40mg PO twice daily for a duration of 4 months. Isotretinoin is a retinoid compound most often used to treat severe acne. Its antiangiogenic properties, however, have proved to also be beneficial in the treatment of DDAB.[10] A similar finding was reported by Mclaughlin et al., in which they reported a similar response to isotretinoin therapy. This study found that treatment with a dose of 1 mg/kg of isotretinoin (Accutane) over 2 months resulted in complete resolution of the ulceration in this patient with DDAB.[5] Although the exact mechanism of action of isotretinoin in the treatment of DDAB is unknown, it has been postulated that it may involve the inhibition of angiogenesis and/or protease production, stimulation of fibrinolysis, and possibly enhancement of keratinocyte migration.[5,10]

Although the use of isotretinoin in the treatment of DDAB has proven to be promising, the drug is not without risk. It must be highly regulated due to its effect as a teratogen. Other possible side effects include dry skin, chapped lips, epistaxis, cheilitis, severe depression, and suicidal ideation. Therefore, although found to be effective in this patient population, all the risks and benefits of isotretinoin therapy must be thoroughly considered on a case-by-case basis.[10]

References

1. Tollefson MM, McEvoy MT, Torgerson RR, Bridges AG. Diffuse dermal angiomatosis of the breast: Clinicopathologic study of 5 patients. *J Am Acad Dermatol*. 2014;71(6):1212-1217.
2. Yang H, Ahmed I, Mathew V, Schroeter AL. Diffuse dermal angiomatosis of the breast. *Arch Dermatol*. 2006;142(3):343-347.
3. Krell JM, Sanchez RL, Solomon AR. Diffuse dermal angiomatosis: a variant of reactive cutaneous angioendotheliomatosis. *J Cutan Pathol*. 1994;21(4):363-370.
4. Sanz-Motilva V, Martorell-Calatayud A, Rongioletti F, Escutia-Muñoz B, López-Gómez S, Rodríguez-Peralto JL, Vanaclocha F. Diffuse dermal angiomatosis of the breast: clinical and histopathological features. *Int J Dermatol*. 2014;53(4):445-449.
5. McLaughlin ER, Morris R, Weiss SW, Arbiser JL. Diffuse dermal angiomatosis of the breast: response to isotretinoin. *J Am Acad Dermatol*. 2001;45(3):462-465.
6. Bauer J, Maroon M, Rodenhaver T. Diffuse dermal angiomatosis: Characterization of a rare and evolving proliferative vascular endothelial process. *J Am Acad Dermatol*. 2007;56(2):AB81.
7. Sommer S, Merchant WJ, Wilson CL. Diffuse dermal angiomatosis due to an iatrogenic arteriovenous fistula. *Acta Derm Venereol*. 2004;84(3):251-252.
8. Villa MT, White LE, Petronic-Rosic V, Song DH. The treatment of diffuse dermal angiomatosis of the breast with reduction mammaplasty. *Arch Dermatol*. 2008;144(5):693-694.
9. Morimoto K, Iioka H, Asada H, Kichikawa K, Taniguchi S, Kuwahara M. Diffuse dermal angiomatosis. *Eur J Vasc Endovasc Surg*. 2011;42(3):381-383.
10. Adams BJ, Goldberg S, Massey HD, Takabe K. A cause of unbearably painful breast, diffuse dermal angiomatosis. *Gland Surg*. 2012;1(2).

Hailey-Hailey Disease Masquerading as Intertriginous Candidiasis for 10 Years

Jennifer M. Conde, DO (PGY-3)[1], Miguel Villacorta, DO (PGY-1)[2], Brittany P. Smirnov, DO (PGY-3)[1], Carlos H. Nousari, MD[3]

1) Dermatology Resident, Department of Dermatology, Broward Health Medical Center 2) Traditional Rotating Intern, Broward Health Medical Center 3) Program Director, Department of Dermatology, Broward Health Medical Center, Fort Lauderdale, FL 33316

BACKGROUND

Hailey-Hailey disease (HHD), also known as benign familial pemphigus, is a rare genodermatosis first described by the Hailey brothers in 1939.[1] The disease is inherited in an autosomal dominant fashion with complete penetrance but variable phenotypic expression. It can also present as a de novo mutation.[2] Affecting males and females equally, HHD typically presents in the second or third decade of life, with an overall estimated incidence of 1/50,000.[3,4] The disease is caused by a mutation of the ATP2C1 gene, which encodes the ATP-powered calcium pump protein, hSPCA1, that sequesters calcium into the Golgi apparatus.[5] The impaired calcium pump protein leads to lower calcium levels inside the Golgi apparatus, causing impaired production of calcium binding transmembrane glycoproteins and subsequent loss of cellular adhesion in the stratum spinosum. Histologically, the acantholysis classically seen is often described as having a "dilapidated brick wall appearance" with the retention of basilar layer adherence to the dermis.[3] Other histologic features include intraepidermal vesicles, perinuclear eosinophilia, mild dyskeratosis, moderate dermal lymphocytic infiltrate, and variable hyperkeratosis.[6] Direct immunofluorescence testing is negative.[7]

Hailey-Hailey disease presents as flaccid vesicles or bullae in intertriginous locations such as the axilla, groin, gluteal cleft, and inframammary folds. These fragile vesicles are easily ruptured and often absent on physical examination. The remaining erosive erythematous plaques commonly present with crusting, maceration and fissures. Patients can experience increases in morbidity as affected areas can become painful, pruritic, and malodorous. The disease course fluctuates between episodic remission and exacerbation aggravated by friction, heat, sweat, tight clothing, increased weight, and infection.[3] Additionally, bacterial or fungal infection can be superimposed on the affected areas convoluting diagnosis and complicating management of the disease. Longitudinal leukonychia has been described in approximately 70% of individuals

CASE PRESENTATION

A 63-year old Haitian female with a past medical history of hypertension and diabetes presented with complaints of a painful, irritated rash on her posterior neck, bilateral axilla, inframammary, intergluteal and inguinal folds present for approximately 10 years. Initial treatment included betamethasone cream to affected areas, as well as oral and topical antibiotics, antifungals, and topical corticosteroids for the treatment of intertrigo and candidiasis. The patient reported waxing and waning of the eruption, occasionally resolving entirely, but eventually recurring. She originally denied a family history of skin disorders or cancers. Physical examination revealed violaceous to brown hyperpigmented plaques with erosions and maceration located on her posterior neck, bilateral axillae, inframammary folds and groin, with scant surrounding satellite macules. Following years of ineffective treatment for intertriginous candidiasis, the patient presented to our clinic, and upon further questioning, reported similar eruptions in three of her sisters, as well as her mother.

Suspecting possible Hailey-Hailey disease, a 4-mm punch biopsy was performed in the left axilla. Histopathologic examination revealed a large focus of acantholytic dyskeratotic cells in a "dilapidated brick wall" pattern, with perinuclear eosinophilia. PAS stain was negative for dermatophytes, and fungal and bacterial cultures performed at time of biopsy were positive for only light growth of Pseudomonas aeruginosa. The patient was treated with appropriate anti-pseudomonal antibiotics. A complete blood count, comprehensive metabolic panel, and lipid panel were ordered in preparation for possible soriatane treatment. She was prescribed oral diflucan and topical pimecrolimus in the interim.

CLINICAL IMAGES

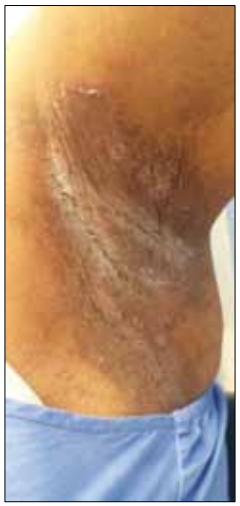


Figure 1. (left) Left axilla demonstrating thickened hyperpigmented eroded plaque with linear fissuring and maceration present.

Figure 2. (top right) Posterior neck demonstrating hyperpigmented nummular thickened plaques.

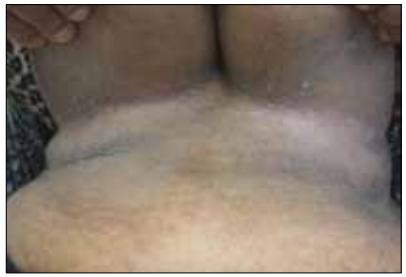
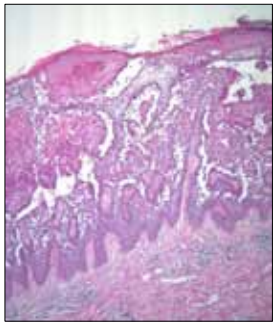
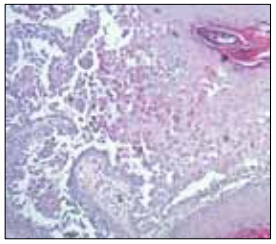


Figure 3. (mid right) Inframammary folds demonstrating erythema, thickening, and scaling of skin folds.

PATHOLOGY





CLINICAL DIFFERENTIATION

Hailey-Hailey Disease	Intertriginous erosive erythematous plaques Crusting, maceration, and fissures	2nd or 3rd decade of life + waxing and waning symptoms Longitudinal leukonychia
Intertriginous Candida	Satellite lesions with peripheral papules and pustules Well demarcated, erythematous, patches	+ KOH Prep
Inverse Psoriasis	Erythematous, sharply demarcated plaques Smooth, moist, macerated, +/- fissures	Absent scales +Nail involvement
Tinea Cruris	Well demarcated erythematous plaques Central clearing and elevated scaling borders	+/- Pustules or vesicles
Erythrasma	Reddish-brown macules coalescing into patches Well defined borders	C. minutissimum - coral red fluorescence (Wood's) Pseudomonas - green fluorescence (Wood's)
Seborrheic Dermatitis	Sharply marginated erythematous eruption + Erosions and fissures	+/- Yellow greasy scales

TREATMENT & MANAGEMENT

Individualized Combination Therapy	**Evidence Level**
Topical Steroids	
Clobetasol (Acute Flare)	IIA, III
Tacrolimus (Maintenance)	IIA, III
Antimicrobials	
First Line: *Topical*	
Clindamycin, Gentamicin, Mupirocin, Ketoconazole	IIA, III
Second Line: *Systemic*	IIA, III
Doxycycline	III
Dapsone, Erythromycin, Penicillin	
Refractory to Treatment	IIA, III
Excision	IIA, III
Botulinum Toxin A	III
Dermabrasion, NBUVB, Laser Therapy	
General measures	V
Avoidance of hot and humid weather	V
Bleach or chlorhexidine baths	V
Weight loss	V
Lightweight and loose clothing	V
Barrier and drying agents	

Figure 4 & 5. (mid & bottom left) Hematoxylin & eosin (H&E) staining of lesional skin at 10x & 40x magnification demonstrating diffuse acantholytic dyskeratosis in a "dilapidated brick-wall" pattern. A PAS stain was negative for dermatophytes.

Table 1. (top right) Treatment and management of HHD

Table 2. (bottom right) Clinical differentiation of intertriginous dermatitides.

DISCUSSION

The clinical differential diagnosis of Hailey-Hailey disease includes candidiasis, inverse psoriasis, intertrigo, tinea cruris, contact dermatitis, seborrheic dermatitis, hidradenitis suppurativa, and erythrasma. Histologic differential diagnosis includes other intraepidermal acantholytic processes such as pemphigus vulgaris, darier's disease, and grover's disease. History and physical examination along with a biopsy help to support the diagnosis. Our case highlights the importance of a proper full history and early biopsy which could have led to an earlier diagnosis.

A fungal infection, such as intertriginous candidiasis, can be separated clinically by the presence of satellite lesions with peripheral papules and pustules.[8] A potassium hydroxide stain will help to confirm the diagnosis but care should be taken as a superimposed fungal infection can often mask underlying Hailey-Hailey disease and lead to a misdiagnosis, as in this case.

Inverse psoriasis presents in intertriginous areas similarly to HHD. It presents as erythematous, sharply demarcated, smooth, non-scaly, moist plaques with or without maceration and fissures.[9] Typically patients have a family history of psoriasis and psoriasiform lesions with evidence of typical psoriatic nail involvement, including onycholysis and nail pitting.[10]

Intertrigo clinically appears very similar to HHD as erythematous plaques with maceration and inflammation of the skin folds. These lesions are prone to bacterial or fungal infections such as candida. A Wood's light can help to distinguish a pseudomonal infection from cutaneous erythrasma caused by C. minutissimum. Pseudomonas fluoresces green under Wood's light while C. minutissimum fluoresces as coral red patches with well-defined borders.[11]

Tinea corporis is distinguished from HHD by the appearance of a raised and annular active border of pustules or vesicles with either central scale in early lesions or central clearing in advanced lesions.[12] Tinea cruris may appear similarly as well-demarcated erythematous plaques with central clearing and elevated scaling borders that may be active with pustules or vesicles, and may be confirmed by KOH examination.[13]

HHD has no known cure and treatment therapies are aimed at reducing exacerbations and increasing periods of remission. Many treatment modalities have been attempted with most modalities demonstrating Level III evidence in the literature. Some patients are refractory to treatment, thus individual therapy tailored to each patient is necessary.

General measures should be considered for each patient such as avoidance of hot and humid weather, use of bleach or chlorhexidine baths, weight loss, and use of lightweight loose clothing such as cotton. The use of absorbent pads, barrier and drying agents such as zinc oxide, petrolatum, aluminum sulfate, and talcum powder may be used to keep skin dry and clean.[14,15]

First line treatment should consist of a combination of topical antimicrobials and topical steroids.[3,16,17] Based on Level IIa and III evidence, clobetasol should be used for acute flares and topical tacrolimus for maintenance.[18] The topical antimicrobials that have shown some degree of success include clindamycin, gentamicin, mupirocin, and ketoconazole.[3,16]

Systemic therapy may be necessary if a patient fails the topical antimicrobial and topical steroid combination therapy. Doxycycline has been shown as the most appropriate first line oral antibiotic with Level IIa and III evidence.[18] Second line oral therapy includes erythromycin, penicillin, and dapsone with limited Level III studies.

If a patient is refractory to therapy, additional therapies including surgical excision, botulinum toxin type A, dermabrasion, NBUVB, and laser therapy have had limited success. Of these treatment modalities, excision and botulinum toxin A have the highest level of evidence (Level IIa and III) with some degree of success. Other treatment modalities have limited Level III evidence.

HHD may be difficult to diagnose from other intertriginous diseases. Diagnosis is more difficult if a superimposed bacterial and fungal infection is

REFERENCES

1. Hailey H, Hailey H. Familial benign chronic pemphigus. Arch Dermatol Syph. 1939;39:679-85.
2. Poblete-gutiérrez P, Wiederholt T, König A, et al. Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest. 2004;114(10):1467-74.
3. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. Br J Dermatol. 1992;126(3):275-82.
4. Missiaen L, Dode L, Vanoevelen J, Raeymaekers L, Wuytack F. Calcium in the Golgi apparatus. Cell Calcium. 2007;41(5):405-16.
5. Hu Z, Bonifas JM, Beech J, et al. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. Nat Genet. 2000;24(1):61-5.
6. Bolognia J, Jorizzo JL, Schaffer JV. Dermatology: Sect. 12. Infections, infestations and bites. Bacterial diseases. Saunders; 2012.
7. Abdullah L, Abbas O. Darriscaces. Can you identify this condition? Benign familial chronic pemphigus. Can Fam Physician. 2011;57(10):1157-8.
8. Wolff K, Johnson R, eds. Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. 6th ed. New York: McGraw-Hill; 2009.
9. Van de kerkhof PC, Murphy GM, Austad J, Ljungberg A, Camisasca F, Dunold LB. Psoriasis of the face and fissures. J Dermatolog Treat. 2007;18(6):351-60.
10. Wang G, Li C, Gao T, Liu Y. Clinical analysis of 48 cases of inverse psoriasis: a hospital-based study. Eur J Dermatol. 2005;15(3):176-8.
11. Jarmiger CK, Schwartz RA, Szepietowski JC, Reich A. Intertrigo and common secondary skin infections. Am Fam Physician. 2005;72(5):833-8.
12. Habif TP, ed. Skin Disease, Diagnosis and Treatment. 3rd ed. Philadelphia: Elsevier Saunders; 2011.
13. Ambrose MG, Burns M. Common tinea infections in children. Am Fam Physician. 2008;77:1415-20.
14. Black JM, Gray M, Bliss DZ, et al. MASD part 2: incontinence-associated dermatitis and intertriginous dermatitis: a consensus. J Wound Ostomy Continence Nurs. 2011;38(4):359-70.
15. Gutfeld J, Woodley DT. Intertrigo: a practical approach. Compr Ther. 1994;20(7):402-5.
16. Gallenbeck RL, Kowalczuk AM, Bianchi O, Bonino MV, Garcia garcia A. Chronic benign familial pemphigus. Int J Dermatol. 1998;27(7):495-500.
17. Ikeda S, Suga Y, Ogawa H. Successful management of Hailey-Hailey disease with potent topical steroid ointment. J Dermatol Sci. 1993;5(3):205-11.
18. Charavaidul A, Payetta M. Hailey-Hailey disease and review of management. J Drugs Dermatol. 2014;13(10):1254-7.

Cutaneous Botryomycosis Secondary to Trauma

A Case Presentation and Review of Literature

Jennifer David DO, MBA Department of Dermatology

GRADUATE MEDICAL EDUCATION at Larkin Community Hospital

ABSTRACT

CASE DESCRIPTION: A 52-year-old Caucasian male with a past medical history of hypertension presented to our clinic complaining of growths on bilateral forearms that developed two months prior. The lesion on his right forearm began as small pink papules that grew over the course of a few weeks, ulcerated and developed a crusted scab. His main concern was regarding the growing lesion on the right arm. He admitted to occasional mild pruritus but denied any associated pain, tenderness or burning sensation of involved skin. Of note, he worked as a HVAC (heating, ventilation and air conditioning) repairman with a history of repeated trauma to his forearms due to reaching through confined spaces of larger industrial units.
On physical exam patient presented with 4cm pink exophytic vegetative plaque with central ulceration, crusting and background of excoriations and pink atrophic scars on left forearm. (Figure 1) On the right forearm were scattered excoriations, pink/tan papules and a 1 cm crusted ulceration (Figure 2)
Tissue cultures were obtained and showed to be negative for acid-fast mycobacteria and fungal/yeast elements however did grow heavy amounts of *Staphylococcus aureus*.
Deep shave skin biopsy displayed pseudoepitheliomatous hyperplasia with sinus tract formation, focal supprative inflammation and focal granuloma formation with gram-positive cocci within the pseudoepitheliomatous hyperplasia in henatoxylin-eosin staining. (Figure 3) PAS staining was negative.
On higher power radiating deposits of amorphous, eosinophilic, hyaline material around colonies of cocci bacteria were noted, characterizing the Splendore-Hoeppli phenomenon. (Figure 4)
A diagnosis of localized cutaneous botryomycosis was established and the patient was treated with oral cephalexin 500mg and topical mupirocin ointment twice daily for two weeks. His follow up physical exam two weeks after treatment revealed a significant improvement in all skin lesions. (Figure 5)

DISCUSSION: Botryomycosis is a rare, chronic, supprative, granulomatous infectious disease that affects the skin and occasionally the viscera. *Staphylococcus aureus* (40%) is the most common causative organism however it can also be caused by *Pseudonomas aeruginosa* (20%), coagulase-negative staphylococci, *Streptococcus* spp, *Escherichia coli*, and *Proteus* spp. (1-3) There are few cases reported in literature and it occurs in areas of the skin that are exposed and subject to repeated trauma . The pathogenesis of the disease has not been well established. It is thought to be related to low virulence of agents, large local bacterial inoculum, change in specific cellular immunity (decreased number of T lymphocytes, like in agammaglobulinemia, aplastic anemia, agranulocytosis and AIDS), or in humoral immune response (reduced IgA or increased IgE levels) (2).

CONCLUSION: Cutaneous botryomycosis is a relatively rare infectious disease process . Most patients will present with localized disease on the extremities that may be preceded by trauma (2,3). Cutaneous botryomycosis is the most common form of botryomycosis and usually occurs following cutaneous inoculation of bacteria due to trauma, surgery, or in conjunction with the presence of a foreign body. Lesions characteristically develop slowly and may evolve and enlarge for several months and, rarely, even years.

INTRODUCTION

- Botryomycosis is a rare, chronic, supprative, granulomatous infectious disease that affects the skin and occasionally the viscera.
- *Staphylococcus aureus* (40%) is the most common causative organism however it can also be caused by *Pseudonomas aeruginosa* (20%), coagulase-negative staphylococci, *Streptococcus* spp, *Escherichia coli*, and *Proteus* spp. (1-3).
- Skin lesions can be single or multiple and present as cysts, accesses, fistulas, nodules, ulcers or plaques. (3)

CASE DESCRIPTION

- A healthy 52-year-old Caucasian male with a past medical history of hypertension presented to our clinic complaining of growths on bilateral forearms that developed two months prior.
- The lesions began as small pink papules that grew over the course of a few weeks, ulcerated and developed a crusted scab.
- He admitted to occasional mild pruritus but denied any associated pain, tenderness or burning sensation of involved skin.
- Of note, he worked as a HVAC (heating, ventilation and air conditioning) repairman with a history of repeated trauma to his forearms due to reaching through confined spaces of larger industrial units.

PHYSICAL EXAM

- Left forearm: 4cm pink exophytic vegetative plaque with central ulceration, crusting and background of excoriations and pink atrophic scars on left forearm. (Figure 1)
- Right forearm : scattered excoriations, pink/tan papules and a 1 cm crusted ulceration (Figure 2)

CLINICAL PRESENTATION

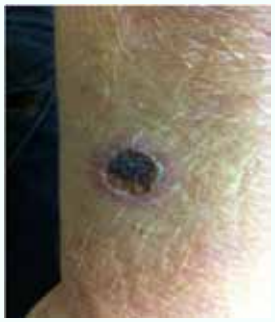


Figure 1: Right forearm exhibiting a1cm crusted ulceration with surrounding erythema

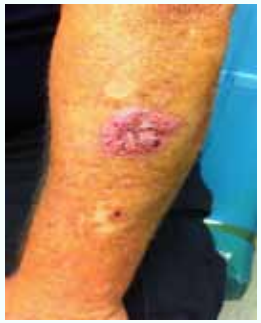


Figure 2: Left forearm exhibiting a 1 cm crusted ulceration with sur**Figure 1:** Right forearm exhibiting a1cm crusted ulceration with surrounding erythema
rounding erythema

PATHOLOGY

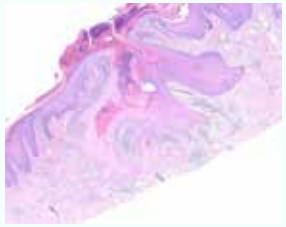


Figure 3: Deep shave biopsy (HE 10X) demonstrating pseudoepitheliomatous hyperplasia with sinus tract formation, focal supprative inflammation and focal granuloma formation with gram ositive cocci within the pseudoepitheliomatous hypersplasia.

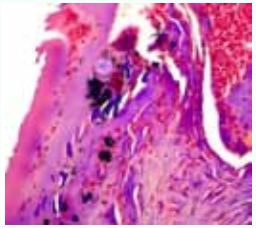


Figure 4: On higher power (HE, 40X) radiating deposits of amorphous, eosinophilic, hyaline material around colonies of cocci bacteria were noted, characterizing the Splendore-Hoeppli phenomenon

MANAGEMENT / OUTCOME

- Tissue cultures were obtained and showed to be negative for acid-fast mycobacteria and fungal/yeast elements however did grow heavy amounts of *Staphylococcus aureus*.
- Deep shave biopsy of lesion on left forearm
- Patient was treated with oral cephalexin 500mg and topical mupirocin ointment twice daily for two weeks.

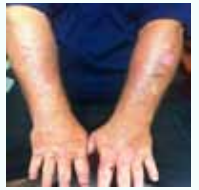


Figure 5: Patient's lesions clearing, two weeks after treatment with oral cephalexin and topical mupirocin

DICUSSION

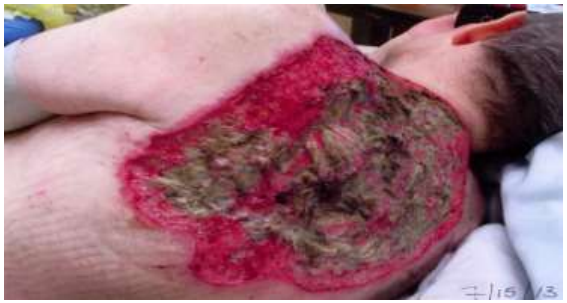
The term botryomycosis is derived from the Greek word botrys (meaning "bunch of grapes") and mycosis (a misnomer, due to the presumed fungal etiology in early descriptions) (1). Other terms used to describe botryomycosis include bacterial pseudomycosis, staphylococcal actinophytosis, granular bacteriosis, and actinobacillosis. The most frequent etiological agent is *Staphylococcus aureus* (40%), followed by *Pseudomonas sp* (20%). Other microorganisms reported include *Escherichia coli, Proteus vulgaris, Bacillus spp, Actinobacillus lignieresii* (1,2).
The pathogenesis of the disease has not been well established. It is thought to be related to low virulence of agents, large local bacterial inoculum, change in specific cellular immunity (decreased number of T lymphocytes, like in agammaglobulinemia, aplastic anemia, agranulocytosis and AIDS), or in humoral immune response (reduced IgA or increased IgE levels) (2).
Most patients will present with localized disease on the extremities that may be preceded by trauma (2,3). Cutaneous botryomycosis is the most common form of botryomycosis and usually occurs following cutaneous inoculation of bacteria due to trauma, surgery, or in conjunction with the presence of a foreign body. Lesions characteristically develop slowly and may evolve and enlarge for several months and, rarely, even years.
The histopathologic appearance of botryomycosis is characterized by a central focus of necrosis surrounded by a chronic inflammatory reaction containing histiocytes, epithelioid cells, multinucleated giant cells, and fibrosis (4). Unlike the sulfur granules seen in actinomycosis (which contain filamentous branching organisms), the granules seen in botryomycosis contain bacteria surrounded by an eosinophilic matrix containing club-like projections. This histologic appearance is commonly referred to as the Splendore-Hoeppli phenomenon, although it may not always be present (4).
Diagnosing botryomycosis includes clinical suspicion and microbiologic studies. In general, patients should receive antibiotic therapy until signs and symptoms of infection have resolved. Antibiotics for cutaneous disease include: oral trimethoprim-sulfamethoxazole (10-12 mg/kg /d), oral clindamycin (30-40mg/kg/d), cephalexin (500mg QID), minocycline (100mg BID), doxycycline (100mg BID) or erythromycin (500 mg QID). (5,6)

BIBLIOGRAPHY

1. . D.A. Mehregan, W.P. Su, J.P. Anhalt Cutaneous botryomycosis J Am Acad Dermatol, 24 (1991), pp. 393–396
2. Bonifaz A, Carrasco E. Botryomycosis. Int J Dermatol. 1996;35:381-8
3. Mechow N, Göppner D, Quist S, et al. Cutaneous botryomycosis diagnosed long after an arm injury. *Journal Of The American Academy Of Dermatology*. October 2014;71(4):e155-6.
4. Schlossberg D, Pandey M, Reddy R. The Splendore-Hoeppli phenomenon in hepatic botryomycosis. J Clin Pathol 1998; 51:399
5. Askari, K., Seyed Saadat, S., Seyed Saadat, S., Yousefi, N., Ghorbani, G., & Zargari, O. (2014). Cutaneous botryomycosis caused by Staphylococcus aureus in a patient with diabetes. *International Journal Of Dermatology*, *53*(4), 413-415
6. Fernandes NC, Maceira JP, Knackfuss IG, Fernandes N. Botriomicose cutânea. An Bras Dermatol. 2002;77:65-70

A Rare Case of Super Giant Basal Cell Carcinoma and Review of Vismodegib

Bryce Desmond, DO; Lauren Boudreaux, DO; John Young, MD



Abstract

Giant basal cell carcinoma is defined as a lesion larger than 5 cm and comprises only 0.5% of BCCs. Lesions larger than 20 cm in diameter are termed "super giant basal cell carcinoma" and are exceedingly rare with only nine previous cases reported. We present a case of a 70 year old male with a 25 x 20 cm lesion on his upper back present for 35 years secondary to poor medical follow up.

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer in the world, with 750,000 cases reported annually in the U.S. alone[1,2]. Due to the relatively obvious nature of expanding, bleeding lesions, the cancers are usually discovered and treated while fairly small. It is rare to see a BCC grow beyond 5 cm in diameter; when this does occur, the term "giant basal cell carcinoma" applies. Furthermore, if the lesion grows beyond 20 cm in diameter, the lesion is then termed "super giant basal cell carcinoma"[3]. Due to the fact that only nine reports of basal cell skin cancer of this proportion exist in literature, there is no consensus on treatment and each is considered on a case-by-case basis. While surgery and radiation have generally been considered the mainstays of therapy, recent development and use of vismodegib has allowed a less invasive alternative to consider. This case report illustrates a case of a super giant basal cell carcinoma that developed in a modern western society secondary to neglect and poor follow up.

Case Presentation

The patient is a 70-year-old educated, accomplished, artist and sculptor. He not only holds a bachelor's and master's degree from prestigious North American universities but was also employed as a university professor for many years. He presented to the hospital complaining of intractable diarrhea, malaise, and lethargy. Upon physical exam, a large bath towel was discovered to be taped to the back with masking tape. Removal of the towel revealed a necrotic, purulent, malodorous, bleeding lesion with erythematous, sharply demarcated, and rolled borders measuring 20 x 25 cm. Muscle tissue, as well as friable flesh, was also evident. The patient admitted to having had this wound for roughly 35 years. He reported that the lesion initially started out as a "spider bite" on his left upper shoulder in 1978. This lesion slowly expanded over the course of five years until he sought medical attention in 1983.

At that time, his primary care doctor diagnosed the lesion as a basal cell carcinoma and attempted to remove the lesion via standard excision. The patient claims that the excision site never fully healed and he never followed up for additional care. Over the next decade, the lesion continued to expand and would exhibit frequent bleeding, purulence, and slow but steady growth. The wound was becoming so large and necrotic, that with the help of his wife, he began adhering gauze, washcloths, and other linens to the wound each morning before work to prevent staining his dress shirts with blood, tissue, and exudate. The patient reported that he did not seek medical attention for the wound during this time due to a "busy schedule" of sculpting and teaching.

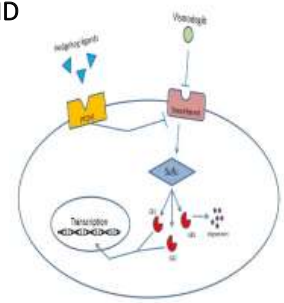
In 1995, the patient moved to a new region of the United States, which prompted him to seek out the opinion of new doctors in the area regarding the troublesome and expanding lesion, which was now roughly 10 cm in diameter. The patient sought a more "holistic approach" since he believed traditional western medicine had failed him in the past. This led him to seek the opinion of a local chiropractor who, along with spinal manipulation, began treating the lesion with a "blue light". Eventually, after months of poor results, the chiropractor recommended the patient be evaluated by a physician. The patient agreed to do so and was seen by a dermatologist who biopsied the lesion and, again, diagnosed the patient with basal cell carcinoma. Interestingly, the patient decided not pursue any further treatment after this diagnosis because he claims he was treated so poorly by the biopsying physician and his staff that he wished to "never return".

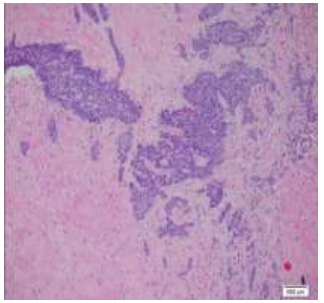
Over the next 20 years the lesion continued to grow and the only treatment he received was consistent blue light therapy directly over the lesion and spinal manipulation from his chiropractor. According to the patient and his wife, these methods seemed to be working to reduce the lesion. It wasn't until July of 2013 when the patient fell ill with headache, diarrhea, and lethargy that the super giant basal cell was, again, discovered on his back. At this time, the wound edges were biopsied and infiltrative basal cell skin cancer with skeletal muscle invasion was proven. A CT scan was ordered and oncology was consulted. CT scan revealed a mass in the liver consistent with probable metastasis. The patient refused liver biopsy, therefore metastasis was assumed but never proven. Due to the patient being a poor surgical candidate and lesion being too large for complete excision, oncology recommended the patient be treated with vismodegib. Unfortunately, the patient passed away from "complications of cancer" before the drug was received.

Discussion

While typically an indolent, slow growing cancer, basal cell carcinoma can become aggressive and locally invasive if left untreated. Giant basal cell carcinoma only accounts for 0.5% of BCCs[4] and super giant basal cell carcinoma is exceedingly rarely reported. Literature review revealed only nine previously reported cases [4, 5]. These lesions are most commonly found on the trunk and other areas usually covered by clothing. Typically, these lesions are allowed to expand due to ongoing neglect by the patient[6]. Archotaki, et al. published a review of 51 cases of giant BCCs (>5 cm) with the risk of metastases estimated around 6%. Patients with negative lymph nodes had a measured 17.07% mortality risk versus those with metastasis at 37.5%[7].

Previously, treatment options for these patients were limited to surgical excision, radiation therapy, and chemotherapy. Vismodegib, a hedgehog pathway inhibitor, was approved by the FDA in 2012 and has proven to be a viable treatment option for locally advanced and metastatic BCCs2. Dosing is 150 mg orally daily. Response rates were measured at 30% and 43% for metastatic and locally advanced BCC, respectively. Median duration of treatment was 7.6 months[8]. While response rates remain low, one must consider that this treatment option offers a chance of tumor reduction or clearance for those who might otherwise have no options for treatment.





Adverse events occurred in more than 30% of patients taking vismodegib including: muscle spasms, alopecia, taste disturbance, weight loss, and fatigue. Serious adverse events were reported in 25% of patients with seven deaths noted in the phase I trials[8]. Of the patients treated with continuous vismodegib, 21% developed at least one tumor regrowth, which is defined as "secondary resistance". It is postulated that resistance develops due to mutations in the smoothened protein targeted by vismodegib, resulting in decreasing binding of the drug[9]. It is still uncertain whether resistance will hinder the long term efficacy of vismodegib, but the drug remains a relatively effective and well tolerated treatment for metastatic and locally invasive BCC[10].

Conclusion

Giant BCCs greater than 20 cm in diameter are exceedingly rare; we report the tenth case in literature. Treatment is often difficult; metastatic rates and mortality dramatically increases with these large lesions. A relatively new therapy, vismodegib has proven to be an option for some patients in which treatment may not have previously been available or beneficial for metastatic and locally aggressive BCC.

References

1. Mae, G., Leffell, D., Ziegler, A., Gross, E., Brash, D., & Bale, A. (1995). Relationship Between Sunlight Exposure and a Key Genetic Alteration in Basal Cell Carcinoma. Journal of the National Cancer Institute, 88(6), 349-354.
2. Amin S, Motamedi K, Ochsner M, et al. Mechanisms and Efficacy of Vismodegib in the Treatment of Basal Cell Carcinoma. Discovery Medicine 2013.
3. Arnaiz J, Gallardo E, Piedra T. Giant basal cell carcinoma on the lower leg: MRI findings. J Plast Reconst Aesthet Surg 2007; 60: 1167-1168.
4. De Bree E, Laliotis A, Manios A, et al. Super giant basal cell carcinoma of the abdominal wall: still possible in the 21st century. Int J Dermatol 2010; 49: 806-809.
5. Pierer G, Pulzi P, Deluca J, et al. Extraordinary giant basal cell carcinoma with full-thickness infiltration of the abdominal wall: single-staged resection and simultaneous reconstruction. J Cutan Med Surg 2014; 18(2): 127-131.
6. Kikuchi M, Yano K, Kubo K, et al. Giant basal cell carcinoma affecting the lower abdominal, genital and bilateral inguinal regions. Br J Plast Surg 2002; 55: 445–448.
7. Archontaki M, Stavrianos S, Korkolis D, et al. Giant Basal Cell Carcinoma: Clinicopathological Analysis of 51 Cases and Review of the Literature. Anticancer Research 2009; 29: 2655-2664.
8. Sekulic A, Migden M, Oro A, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. The New England Journal of Medicine 2012; 366, 2171-2179.
9. Chang A, Oro A. Initial Assessment of Tumor Regrowth After Vismodegib in Advanced Basal Cell Carcinoma. Arch Dermatol 2012; 148: 1324-1325.
10. Kelm J, Magliaro T, Anderson M, et al. Vismodegib Provides a Novel Treatment for Advanced Basal Cell Carcinoma. J Cancer Therapy 2012; 5: 217-221.

Recurrent Varicella in an Immunocompetent Adult: A Case and Review

Joseph Dyer DO, Melinda Greenfield DO, & Richard Miller DO
Albany Dermatology Clinic, Albany, GA & Largo Medical Center, Largo, FL

CASE REPORT

- A 52-year-old African-American female presented after 5 days of pruritic, generalized vesicles, papules, and crusts which did not congregate within a single dermatome.
  - Reported a similar rash 4 years earlier.
  - Denied fever, chills, diaphoresis, or fatigue.
  - Worked in food services, but no known sick contacts.
- Past medical history was remarkable for oral herpes simplex virus (HSV) and 2 prior cases of varicella (see table below).
  - The first case was pediatrician-diagnosed at age 5.
  - Our clinic previously diagnosed the second bout of varicella, at age 48, confirming it clinically and with supportive histopathology.
  - No exceptional sinopulmonary or gastrointestinal infections.
- Routine blood work demonstrated a normal leukocyte count.
- Serology confirmed varicella-zoster virus (VZV) infection.
  - VZV IgM (+), VZV IgG (+)
  - HSV IgM (-), HSV IgG (+)
- The patient completed a course of acyclovir, and the rash subsided after 2 weeks without sequelae.
- Subsequent immunologic studies including CD4+ T lymphocyte count and immunoglobulin subtype analysis, as well as human immunodeficiency virus screen, were unremarkable.

VARICELLA IN OUR PATIENT

		Type of Evidence for Varicella Infection			
Case of Varicella	Age	History only	Clinical Presentation	Pathology	Serology
1	5	X			
2	48		X	X	
3	52		X		X

DISCUSSION

- As denoted by its hyphenate name, varicella-zoster virus is classified by its ability to inflict 2 infections.
  - Primary infection results in varicella, the generalized exanthem predominantly seen in childhood.
  - Secondary expression typically results in herpes zoster, the unilateral eruption with lesions confined to a dermatome.
- Recurrent varicella in those with intact immunity is purportedly rare, as indicated by a paucity of published case reports.
  - A search of PubMed returned **only 41 cases** in English language literature (see table below).

RECURRENT VARICELLA REVIEW

Immunocompetent[a] Patients with Recurrent Varicella Reported in the Literature

Reference	Year of Publication	No. of Patients	Demographic Information	Episodes of Varicella Documented	Evidence for Former Infection	Special Notes on Subject(s)
Weller	1983	1	Child	2	History	Author's son
Gershon et al	1984	3	2 Adults, 1 child	2	History, serology	-
Gurevich et al	1990	3	Adults	2	Serology	Hospital employees
Junker et al	1991	14	Children	2 - 5	History, serology[b]	-
Takayama et al	1992	2	Elderly	2	History, serology	-
Junker et al	1994	9[c]	Children	2 – 3	History	-
Martin et al	1994	4	Women	2	Serology	Pregnant
Terada et al	1996	3[d]	Children	2	History	-
Ku et al	2005	1	Woman	2	History, serology	Nurse
Johnson et al	2011	1	Woman	2	History, serology	Physician

[a]Patients without conditions associated with impaired immunity (eg, human immunodeficiency virus/AIDS, diabetes mellitus) or conditions requiring treatment with systemic immunosuppressive therapy.
[b]Four subjects were seropositive for varicella-zoster virus prior to repeat varicella episodes.
[c]Study described 23 total subjects, but 14 were previously described by Junker et al (1991).
[d]Study described one additional subject whose history included acute lymphocytic leukemia.

FURTHER DISCUSSION

- Surveillance studies have challenged this apparent rarity.
- From **6.9% to 21%** of Americans report a history of repeat varicella infection.[1,2]
  - A reported history of varicella is a reliable indicator of immunity, correlating to serologic evidence of immunity in 97% to 100% of cases.[3,4]
- Immunity against VZV is imprecisely understood.
  - Varicella is more likely to disseminate in lymphopenic patients,[5] while its course is uninfluenced in patients with hypogammaglobulinemia.[6]
  - Ethnicity may impact immunoglobulin persistence, as Fitzpatrick type V and VI skin tones may experience reduced viral shedding and less antigenic boosting from secondary varicella cases in a household.[7]
- At least 3 to 5 major genotypes of VZV have been recognized, and these vary geographically.[8]
  - After infection with 1 strain, it is unclear the level of immunoprotection afforded against the others

CONCLUSION

- Most physicians presume varicella can occur only once.
- Our report reminds the thoughtful diagnostician to consider reinfection with VZV, despite positive history or titers.

REFERENCES

1. Hall S, et al. Second varicella infections: are they more common than previously thought? *Pediatrics.* 2002;109(6):1068-1073.
2. Marin M, et al. Varicella among adults: data from an active surveillance project, 1995-2005. *J Infect Dis.* 2008;197(Suppl 2):594-100.
3. Perella DM, Fiks A, Spain CV. Validity of reported varicella history as a marker for varicella-zoster virus immunity [abstract 692]. In: Programs and abstracts of the 2005 Pediatric Academic Societies Annual Meeting (Washington, DC). The Woodlands, TX: Pediatric Academic Societies, 2005.
4. Ferson JM, Bell SM, Robertson PW. Determination and importance of varicella immune status of nursing staff in a children's hospital. *J Hosp Infect.* 1990;15:347-351.
5. Arvin AM, et al. Selective impairment of lymphocyte reactivity to varicella-zoster virus antigen among untreated patients with lymphoma. *J Infect Dis.* 1978;137:531-540.
6. Arvin AM. Varicella-zoster virus. *Clin Microbiol Rev.* 1996;9:361-381.
7. Ayres KL, Talukder Y, Breuer J. Humoral immunity following chickenpox is influenced by geography and ethnicity. *Journal of Infection.* 2010;61:244-251.
8. Loparev VN, et al. Identification of five major and two minor genotypes of varicella-zoster virus strains: a practical two-amplicon approach used to genotype clinical isolates in Australia and New Zealand. *J Virol.* 2007(Dec);81(23):12758-12765.

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College of Osteopathic Medicine

Livedo reticularis: A helpful clue in the diagnosis of intravascular large B-cell lymphoma

Samuel Ecker DO[1]; Andrew Jensen DO[2]; László Kárai MD, PhD[3];
Carlos Ricotti MD, FAAD[3]; Francisco Kerdel MD, FAAD[4]; Stanley Skopit DO, MSE FAOCD[5]

[1]Dermatology Resident, Larkin Community Hospital, Miami, FL; [2]Intern, Larkin Community Hospital, Miami, FL; [3]DermDx Dermatopathology Services, Miami Lakes, FL; [4]Florida Academic Dermatology Center, Coral Gables, FL; [5]Program Director, Larkin Community Hospital, Miami, FL

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of malignant, extranodal lymphoma characterized by the selective growth of neoplastic B-cells in the microvasculature. The disease is extremely aggressive and often rapidly fatal when diagnosis and treatment are delayed.[1] This condition is often diagnosed postmortem given its rapid and aggressive clinical course.[1-3] This disease can affect any organ system and can present with any myriad of nonspecific symptoms making the diagnosis difficult. Cutaneous findings are often an early manifestation therefore dermatologists need to be aware of its existence.[4] Additional findings that may aid diagnosis include fever, cognitive impairment, stroke-like symptoms and elevated serum lactate dehydrogenase levels.[5] Early diagnosis and treatment have been shown to improve survival outcome, however the decision to initiate chemotherapy can be difficult and requires definitive diagnosis.

CASE PRESENTATION

Presentation: 76 year-old female with livedo reticularis and painful subcutaneous nodules on her breasts, flanks, abdomen, buttocks, inguinal folds and upper thighs x 3 months. She reported generalized fatigue and muscle weakness in her lower extremities one month prior to the rash. She was previously seen by a rheumatologist and a dermatologist who performed an incisional biopsy of her left thigh. She was referred to our care after she failed treatment with prednisone and plaquenil. Review of symptoms was significant for an unintentional twelve pound weight loss in the last month.

Medical history: MMIS, CHF, AFib, HLD

Medications: Prednisone, Plaquenil, Carvedilol, Ramipril, Spironolactone, Coumadin, Digoxin, Flonase, Crestor

Clinical Examination: Livedo reticularis and painful subcutaneous nodules on the lateral aspects of the back, breast, abdomen, buttocks, inguinal folds and upper thighs (Figure 1).

Labs: CBC, CMP WNL, PT/INR therapeutic, ANA (+), anti-dsDNA (+), atypical pANCA (+), ESR 100, CRP 12.30, Hepatitis panel negative

Imaging: PET-CT and bone marrow biopsy were negative

Pathology: Intravascular atypical, hyperchromatic lymphocytes were seen within the lumen of scattered vessels and small capillaries of the fat leading to distention of the capillary network and fibrin deposition (Figure 2). The atypical intravascular cells stained strongly positive with CD20 and Mum-1 (Figures 3, 4). Molecular studies for B-cell gene rearrangement showed the presence of a clonal process. The previous biopsy was also reanalyzed and found to contain the same atypical intravascular cells. B-cell gene rearrangement results confirmed the presence of the same neoplastic clone in all biopsy specimens.

Figure 1. Lateral back initial presentation

Figure 5. Lateral back immediately following two treatments with R-CHOP

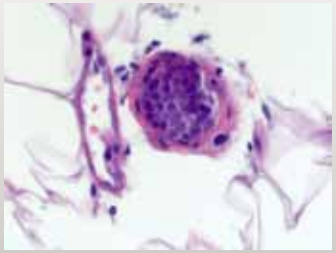

Figure 2. Cutaneous biopsy H&E (60x) demonstrating atypical intravascular lymphocytes

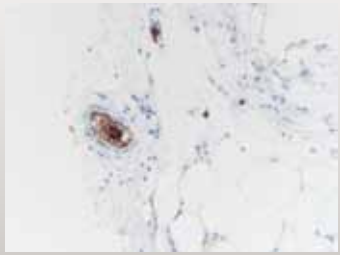

Figure 3. Cutaneous biopsy CD20 (10x) immunostain demonstrating atypical intravascular lymphocytes

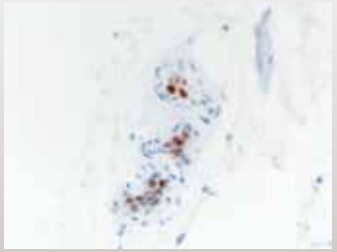

Figure 4. Cutaneous biopsy Mum-! (40x) demonstrating atypical intravascular lymphocytes

DIAGNOSIS AND TREATMENT

Diagnosis: Intravascular large B-cell lymphoma
- Confirmed in multiple biopsies spanning two months

Treatment: Patient was referred to an oncologist for combination chemotherapy with Rituximab, cyclophosphamide, etoposide, vincristine, prednisone (R-CHOP).

FOLLOW UP

Initially, the patient responded well to chemotherapy; she reported complete resolution of pain and nearly 100% clearance of her skin lesions a few days after her first treatment with R-CHOP. Soon after her second treatment, she developed several complications including severe bone pain, muscle weakness, pancytopenia, and was hospitalized for an acute exacerbation of CHF. The oncologist postponed further treatment and her symptoms slowly returned. Several weeks later, she was hospitalized a second time with sepsis and died four months after the date of her diagnosis.

DISCUSSION

Intravascular large B-cell lymphoma is a rare aggressive disease that carries a grim prognosis and death frequently occurs within two years.[6] Diagnosis may rely on subtle histopathologic findings that require serial biopsies. Levido reticularis warrants an increased level of suspicion as this clinical picture is often the result of occluded vascular channels.

Combination chemotherapy with R-CHOP is the treatment of choice and early intervention has been shown to offer the greatest chance of survival.[5] A 2008 retrospective analysis of 106 IVLBCL patients treated with chemotherapy alone versus chemotherapy plus rituximab found the 2-year survival rate was 46% in patients treated with chemotherapy alone, whereas the 3-year survival rate was 60% in patients who received combination chemotherapy with rituximab.[7] Unfortunately, our patient was unable to tolerate treatment and her death illustrates the clinically frustrating nature of this malevolent disease.

REFERENCES

1. Orwat DE, Batalis NI. Intravascular Large B-cell Lymphoma. Arch Pathol Lab Med 2012; 136:333-338.
2. Zuckerman D, Seliem R, Hochberg E. Intravascular lymphoma: the oncologist's ''great imitator.'' Oncologist 2006; 11(5):496–502.
3. Ferreri AJ, Campo E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant.' Br J Haematol 2004; 127:173-183.
4. Perniciarc C, Winkelmann RK, Daoud MS, et al. Malignant angioendotheliomatosis is an angiotropic intravascular lymphoma. Am J Dermatopathol 1995; 17(3):242-248.
5. Shimada K, Kinoshita T, Naoe T, et al. Presentation and management of intravascular large B-cell lymphoma. Lancet Oncol 2009; 10:895-902.
6. Saab J, Nassif S, Boulos F. Asian-type intravascular large B-cell lymphoma of the spleen and bone marrow with Hodgkin-like morphology and immunophenotype. Br J Haematol 2013; 163:294.
7. Shimada K, Matsue K, Yamamoto K, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. J Clin Oncol 2008; 26:3189–3195.

Imiquimod Induced Hypopigmentation Following Treatment of Periungual Verruca Vulgaris

Natalie Edgar DO, Largo Medical Center, Largo, FL; Stacey Seastrom DO, Largo Medical Center, Largo, FL;
Daniel J. Hogan MD, Nova Southeastern University College of Osteopathic Medicine, Largo, FL

CASE REPORT

A 51-year-old Caucasian male with past medical history significant for vitamin D deficiency, vitamin B12 deficiency, tinea pedis, and basal cell carcinoma presented to the clinic with periungual verruca. The patient was prescribed imiquimod 5% cream to be applied 3 times weekly for 3 months. At his 5-month follow-up examination, the patient complained of new-onset, vitiligo-like patches of hypopigmentation involving his hands and feet. The patient reported that the hypopigmentation began abruptly, 3 months after initiating treatment with imiquimod. On exam, he had several hypopigmented patches with well-defined irregular borders on bilateral dorsal hands and feet (Figures 1 and 2). The patient denied any personal or family history of vitiligo, thyroid, or autoimmune disease. Thyroid function and autoimmune panels were unremarkable. The patient denied applying imiquimod to areas other than the periungual verruca. The patient declined a biopsy of the lesions. He was prescribed tacrolimus to be applied twice daily to hypopigmented areas. At follow-up, the hypopigmented patches were spread. Despite hypopigmentation, the periungual verruca persist.

DISCUSSION

Imiquimod is a topical, immune-modifying medication with antiviral and antitumoral properties commonly used to treat skin conditions. The most common adverse effect of imiquimod is application site reaction/inflammation. Pigmentary changes, though less common, have also been reported. From 1997 to 2003, there were 51 reported cases of vitiligo, hypopigmentation, or depigmentation associated with imiquimod.[4] The imiquimod package insert indicates that all adverse effects are more frequent and severe with daily application as compared to three times weekly application.[5] Several cases of imiquimod-induced hypopigmentation have been reported in the literature.

To date, hypopigmentation has been reported in imiquimod treatment of condyloma accuminata, superficial and nodular basal cell carcinoma, and extramammary Paget's disease.[6-8] Reported duration of therapy to onset of hypopigmentation ranged from 7-28 weeks in the literature.[9] Interestingly, no cases of hypopigmentation have been reported with imiquimod use for the treatment of actinic keratoses. It has been proposed that this may be due to the FDA-recommended twice weekly imiquimod dosing regimen for the treatment of actinic keratosis, which may be below the minimum threshold for hypopigmentation.[9] Our patient, applied 5% imiquimod to periungual verruca vulgaris 3 times weekly for 3 months which may have met the dosing threshold for depigmentation.

Imiquimod-induced hypopigmentation has primarily been limited to the site of drug application. However, one case in the literature reported "spreading" of hypopigmentation to an area adjacent to the application site.[10] This finding supports the notion that cytokines induced by imiquimod have localized paracrine activity.[11] Our patient had unique findings of hypopigmentation present at the application site, adjacent to application site, and at distant sites. Although it is possible that our patient unintentionally spread imiquimod to these distant sites, it is less likely that this would have been sufficient enough over time to cause hypopigmentation. Though systemic absorption of topical medications varies depending upon multiple factors, the systemic absorption of imiquimod is reported as minimal.[5]

FIGURES

The distant vitiligo-like hypopigmentation in our patient was possibly a systemic side effect of imiquimod therapy.

Several mechanisms have been proposed for this depigmentation including upregulation of proinflammatory and proapoptotic cytokines.[13] Imiquimod-induced melanocyte apoptosis specifically involves elevated caspase 3, decreased Bcl-2, altered mitogen activated protein kinase expression, and ubiquitin-mediated proteolysis.[14,15] Additionally, increased levels of IL-6 appear to increase melanocyte binding molecules (ICAM) and increase melanocyte-leukocyte interactions. Another proposed theory targets TLR-7 receptors on melanocytes which are acted upon directly by imiquimod.[11,15] In contrast, vitiligo following trauma (Koebner phenomenon) is not uncommon and the immune effects induced by imiquimod may mimic those simply seen with trauma.[16] Unfortunately, the depigmentation associated with imiquimod is generally permanent. Only one case in the literature has shown repigmentation upon cessation of imiquimod use.[12] Our patient's hypopigmentation remains unchanged despite treatment with tacrolimus ointment.

CONCLUSION

Additional research is needed to further investigate the association of imiquimod and vitiligo-like hypopigmentation. Additionally, it is imperative that clinicians are aware of the potential for hypopigmentation with imiquimod therapy and carefully consider the risk when prescribing this medication.

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A Rare Variant of Schnitzler Syndrome: A Case Study

Lacey Beth Elwyn, DO*, Shawn Michael Walls, DO**, Zachary Jason Fischer***, Cindy Hoffman, DO****, Damian DiCostanzo, MD*****

*Dermatology resident, OGME-IIII Saint Barnabas Hospital Department of Dermatology, Bronx, NY
**Internal medicine resident, OGME-II, University Hospitals Regional Hospitals Richmond Medical Center Department of Medicine, Richmond Heights, OH
***Undergraduate, BS, Quinnipiac University, Department of Health Science, Hamden, CT
****Dermatology Residency Program Director, Saint Barnabas Hospital Department of Dermatology, Bronx, NY
*****Dermatopathologist, Dermpath Diagnostics, Port Chester, NY

Abstract

Schnitzler Syndrome is a rare auto-inflammatory disease characterized by a chronic urticarial neutrophilic dermatosis and an IgM monoclonal gammopathy. We report a rare case of the syndrome consisting of a chronic urticarial lymphocytic dermatosis, an IgG and IgA kappa light chain biclonal gammopathy, and multiple systemic symptoms including fatigue, arthralgias, and bone pain. For a decade, this patient suffered from musculoskeletal pain and a persistent cutaneous eruption refractory to multiple pharmacologic interventions. This condition carried with it a history of multiple different biopsy confirmed diagnoses but ultimately was diagnosed as a rare Schnitzler Syndrome variant. Subsequently, this patient is achieving resolution of symptoms on the IL-1 receptor antagonist, Kineret. We report this unusual case of probable Schnitzler Syndrome in hopes to bring attention to the disease, both clinically and dermatopathologically, revisit its proposed pathophysiology, and consider the possibility of rare variations of this often overlooked syndrome.

Introduction

Schnitzler syndrome is a chronic auto-inflammatory disease with no reported spontaneous remissions and a potential to progress into a lymphoproliferative malignancy. Diagnosis requires chronic neutrophilic urticarial dermatosis (Figure 1), IgM monoclonal gammopathy, and at least 2 systemic inflammatory symptoms (Table 1.1). Rare variants of Schnitzler syndrome, such as IgG monoclonal and IgA biclonal proteins are reported in the literature[21]. The most common histopathological feature of Schnitzler syndrome is neutrophilic urticaria with intact vasculature and mild papillary dermal edema (Figure 2). The histopathological differential diagnosis includes neutrophilic urticarial dermatoses[18] (Table 2). The patho-mechanism of Schnitzler syndrome is reported to involve the activation of inflammasome, IL-1. IL-1 receptor inhibition is the best-known treatment for Schnitzler syndrome[17].

Figure 1: Clinical manifestation of a patient with Schnitzler syndrome. Reprinted from Lipsker Orphanet Journal of Rare Diseases 2010 5:38. Copyright 2010. Lipsker. Reprinted with permission.

Figure 2: Most common histopathology seen in Schnitzler syndrome shows a neutrophilic infiltrate of the dermis with mild papillary dermal edema, and no vasculitis. Reprinted from Lipsker Orphanet Journal of Rare Diseases 2010 5:38. Copyright 2010 Lipsker. Reprinted with permission.

Case Report

A 51 year old Caucasian woman presented with an asymptomatic, chronic red eruption, originally on her abdomen with extension centrifugally to proximal extremities that has remained stable for greater than 12 years. Past medical history includes osteoarthritis, anxiety, microcytic anemia, monoclonal gammopathy of undetermined significance and positive lupus anticoagulant. Review of systems positive for fatigue, arthralgia, and bone pain. Medications included Effexor 150mg with no known drug allergies. Examination of her trunk revealed diffuse urticarial plaques (Figure 3a) and extremities revealed pale rose macules with few raised papules and plaques (Figure 3b). Tenderness to palpation was appreciated over the tibia and iliac bones. Axillary lymphadenopathy was also present. Laboratory studies: positive ANA 1:160, homogenous pattern, and negative reflex screen; normal complement C3, C4, and CH50;elevated p-ANCA 1:40; normal ESR; positive for lupus anticoagulant, low positive for cardiolipin antibody; slightly elevated IgG and IgM titers; normal beta-2 microglobulin; elevated PTT; microcytic anemia; stable IgG and IgA kappa monoclonal proteins on serum immunofixation with borderline high kappa/lambda ratio; free kappa monoclonal light chains in urine immunofixation; Quantitative IgG, IgM, and IgA levels within normal limits. Skeletal survey negative for osteolytic lesions. This patient was given the diagnosis of an atypical variant of Schnitzler syndrome and was started on an IL-1 receptor antagonist at a dose of 1.2mg/kg/ day. After 1 month of treatment, patient reported significant improvement in her pain and dermatologic eruption (Figure 8). Complications of treatment included injection site reaction, which reportedly occur in 80% of patients with average resolution over 1-2 months. Her injection reactions were controlled with topical clocortolone cream and oral antihistamines.

Dermatopathology

Multiple punch biopsies revealed sparse superficial perivascular lymphocytic infiltrate with mild papillary dermal edema, suggestive of urticaria. (Figures 4, 5, 6). The most recent biopsy was taken from the left abdomen indicating an urticarial dermatitis with rare neutrophils and telangiectasia (Figure 7). The findings are subtle and non-specific but could represent a stage in evolution of a neutrophil rich dermatosis, such as Schnitzler syndrome.

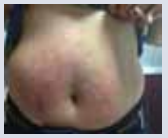

Figure 3a: Clinical presentation of central abdomen and left flank revealing diffuse urticarial plaques.

Figure 3b: Clinical presentation of upper and lower extremity revealing pale rose macules and few slightly raised papules.

Figure 4 : Telangectasias and sparse perivascular lymphocytic infiltrate with rare neutrophils and a normal epidermis

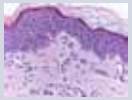

Figure 5: Sparse superficial perivascular dermatitis with telangiectasias. No evidence of vasculitis or thrombi.

Figure 6: Superficial and deep perivascular lymphocytic dermatitis.

Figure 7: Urticarial dermatitis with rare neutrophils and telangiectasias.

Discussion

Schnitzler syndrome is a rare, under diagnosed disorder characterized by chronic urticarial dermatosis, monoclonal gammopathy, and systemic inflammation. A retrospective study at the Mayo Clinic highlighted that this disease is highly under-diagnosed by identifying 46 undiagnosed cases by cross-referencing from their dysproteinemia data base with medical records from all patients with chronic urticaria at the institution[22]. Nineteen percent of reported patient's with Schnitzler syndrome developed lymphoproliferative disorders[9] which highlights the importance of recognizing the diagnosis and subsequent follow-up in these patients. Liliane Schnitzler was the first to recognize and report the particular combination of chronic urticaria and a monoclonal gammopathy in 1972.[21]Schnitzler syndrome is a diagnosis of exclusion based on established diagnostic criteria originally presented by Lipsker et al in 2001 and later accepted by Koning et al in 2007 (Table 1.1). Our patient suffered from chronic urticarial dermopathy, biclonal gammopathy, and systemic symptoms including lymphadenopathy, anemia, arthralgia, and bone pain. By definition, this patient was diagnosed with Schnitzler syndrome and is believed to have an atypical biclonal variant of the classic presentation. Although IgM monoclonal gammopathy is the biological hallmark of the disease, variants have been reported in <10% of cases[4,5,6,21]. A literature search completed by de Koning revealed IgM kappa subtype in 85% of patients[21]. Variant cases of IgG subtype constituted 7% of the reported cases and a biclonal gammopathy was present in 7 cases[21]. We present the first case of a biclonal gammopathy including IgG kappa monoclonal protein in addition to an IgA kappa monoclonal protein. IL-1 plays the major role in the pathophysiology of Schnitzler syndrome. The dermatologic manifestation is a mast cell independent urticarial dermatosis. A local inflammatory response, via IL-1, is thought to induce the skin lesions. It is postulated that mutations of genes in the IL-1 pathway may be responsible for disease[21]. Currently, the majority of data supports that the monoclonal gammopathy is caused by the systemic inflammation[21]. Chronic urticaria and monoclonal gammopathy are both considered to be common in the general population, however, Bida et al observed that the prevalence of MGUS and chronic urticaria occurring together in the same patient is actually quite low[19] which may suggest a single etiology being more likely than multiple etiologies in a single patient. Although Schnitzler syndrome is traditionally considered a neutrophilic urticarial dermatosis (Table 2), a small percentage of specimens do demonstrate a superficial perivascular mononuclear infiltrate suggestive of chronic urticaria and lymphocytic inflammation, as was evident in earlier biopsies in this patient. This highlights the notion of neutrophil-rich dermatosis being a stage of evolution in Schnitzler syndrome.

Figure 8: Clinical presentation of patient after 1 month of Anakinra. Evidence of injection site reactions are seen.

Conclusion

We report an atypical case of Schnitzler syndrome consisting of a chronic urticarial neutrophilic dermatosis, an IgG and IgA kappa light chain biclonal gammopathy, and multiple systemic inflammatory symptoms. In recent years, treatment with IL-1 receptor antagonist leads to complete remission of the dermatologic manifestations and musculoskeletal pain in patients with Schnitzler syndrome[10]. The malignant potential and available success in treatment, prompted reporting of this unusual case in hopes to expand the differential diagnosis to consider Schnitzler syndrome in any patient whom presents with a chronic urticarial dermatosis and monoclonal gammopathy. This patient is finally achieving resolution of symptoms and overall improvement in quality of life on an IL-1 receptor antagonist.

References

1. Asero R, Tedeschi A, Coppola R, et al. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticarial. J Allergy Clin Immunol. 2007;119:705-10.
2. Angles-Cano El et al. Antiphospholipid antibodies and the coagulation cascade. Rheum Dis Clin North Am. 2001 Aug;27(3):573-86.
3. Famularo et al. Severe thrombophilia with antiphospholipid syndrome and hyperhomocysteinemia in a patient with Schnitzler's syndrome. Clin Exp Rheumatol. 2003 May-Jun;21(3):366-8.
4. Patel, S. et al. Chronic urticaria with monoclonal IgG gammopathy: a clinical variant of Schnitzler syndrome? Ann Allergy Asthma Immunol. 109 (2012) 147-149.
5. Carlesimo M. Et al. Chronic vasculitis urticaria associated to a monoclonal gammopathy of IgM and IgA type, a Schnitzler Syndrome Eur J Dermatol. 2000 Nov-Dec;20(6):838-9.
6. Carlesimo M, et al. Chronic urticaria and IgG paraproteinaemia: unusual spectrum of Schnitzler Syndrome. Clin Ter. 2011;162(3):85-87.
7. Doegkas HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including physical urticarias. Br J Dermatol. 1975;93:135-43.
8. Bizzaro, N. et al. False-positive results for IgA anti-phospholipid antibodies in patients with IgA monoclonal gammapthy. Clinical Chemisstry 45, No. 11, 1999.
9. Kyle RA et al. Long term follow-up of IgM monoclonal gammopathy of undetermined significance. Blood 2003, 102(10):3759-64.
10. Gilson M, et al. Treatment of Schnitzler syndrome with anakinra. Clin Exp Rheumatol 2007, 25-931.
11. Tohyama M, et al. A marked increase in serum soluble Fas ligand in drug-induced hypersensitivity syndrome. Br J Dermatol 2008; 159:981-4.
12. Guicciardi ME, et al. Apoptosis: a mechanism of acute and chronic liver injury. Gut 2005; 54:1024-22.
13. Wang, F. et al. Activation of the blood coagulation cascade is involved in patients with chronic urticaria. J Allergy Clin Immunol (2)34. 972-73.
14. H.D. de Koning et al. Schnitzler Syndrome: beyond the case reports: Review and Follow up of 94 patients with an emphasis on prognosis and treatment. 137-148.
15. Dinarello CA. Blocking IL-1 in systemic inflammation. J Exp Med 2005; 201:1355-9.
16. Nakamura I, et al. Regulation of osteoclast differentiation and function by interleukin-1. Vitam Horm 2006; 74:357-70.
17. Lipsker. Orphanet Journal of Rare Diseases. 2010. 5:38.
18. Kaeffer C, et al. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. Medicine (Baltimore). 2009 Jan;88(1):23-31.
19. Bida JP, Kyle RA, Therneau TM, Melton II LJ, Plevak MF, Larson DR, et al. Disease associations with monoclonal gammopathy of undetermined significance; a population based study of 17,398 patients. Mayo Clin Proc. 2009;84(8):685-93.
20. Niels W.C.J. van de Donk, et al. The clinical relevance and management of monoclonal gammopathy of undertemined significance and related disorders: recommendations from the European Myeloma Network. Haematologica. 2014 March; 99(6): 984-996.

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Amar Agadi, MD
Clinique Dermatologique, Faculté de Médecine, Université de Strasbourg and Hôpitaux Universitaires
Daniel Lipsker, MD

Correspondence

Lacey Elwyn, DO
St. Barnabas Hospital
Bronx, NY
Lacey.elwyn@gmail.com

Indolent course of Cutaneous Gamma-Delta T-Cell Lymphoma:

A Case Report and Literature Review

Dawnielle Endly DO, Largo Medical Center, Largo, FL; Richard Weenig MD, Dermatopathology Associates, Fridley, MN; Margot Peters MD, David Viswanatha MD, and Nneka Comfere MD, Mayo Clinic, Rochester, MN

INTRODUCTION

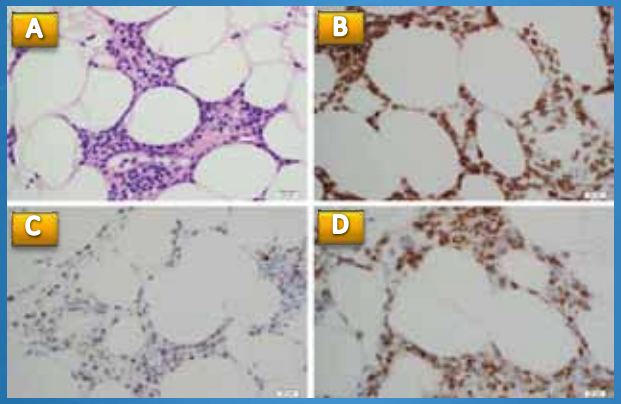
- Cutaneous gamma-delta T-cell lymphoma (CGD-TCL) is a rare primary cutaneous lymphoma.
- Poor prognosis with a 5-year survival rate of 11%.
- Lupus erythematosus panniculitis (LEP) shares clinical and histopathologic features with CGD-TCL.
    - Violaceous nodules +/- ulceration, interface changes, adipocyte rimming, fat hyalinization or necrosis, and lymphocyte atypia

CASE REPORT

- 57-year-old female presented with 3 year history of intermittent, painful, ulcerating nodules on her legs.
- **ROS**: Unremarkable.
- **Past Medical History**:
    - Chronic leg ulcers of unknown etiology dating back to 1997
    - Parapsoriasis diagnosed in 1980 unsuccessfully treated with phototherapy
    - Essential thrombocytopenia
- **Physical Exam**:
    - Multiple 3-cm red, warm subcutaneous nodules on left leg
    - Ill-defined red, atrophic patches on lower abdomen and buttocks
- **6 Month follow up:**
    - Worsening of leg ulcerations and new onset night sweats
    - Dramatic healing of ulcers and resolution of nodules within several weeks of initiating systemic steroids

FIGURES

A) Initial presentation with scattered red nodules.
B) 6 Month follow up with large ulcerated nodules.
C) Rapid improvement after 3 months of systemic steroids.



Immunohistochemical profile of atypical lymphoid cells demonstrating adipocyte rimming, Punch biopsy (x40).
A) Hematoxylin & Eosin, B) CD3+
C) TIA-1+, D) TCR gamma-delta+

DISCUSSION

- Not all cases of CGD-TCL will uniformly experience an aggressive clinical course.
- A literature review revealed 7 other similar cases, all of which were female, average age of 43 years, with subcutaneous involvement of atypical lymphocytes that stained with TIA-1 and/or gamma-delta.
- Indolent cases can be very difficult to distinguish from LEP, but a predominantly gamma-delta T-cell infiltrate is concerning for lymphoma
    - LEP has 5% or less of the infiltrate as gamma-delta T cells

CONCLUSION

- Localized disease, slow progression, and absence of persistent fevers or weight loss should alert provider to an indolent course.
- Widespread involvement, rapid progression, and poor performance status should herald aggressive disease.
- Recognition of CGD-TCL with an indolent course would enable avoidance of unnecessary multi-agent chemotherapy or stem cells.
- Indolent cases still require close clinical monitoring for progression and development of hemophagocytic lymphohistiocytosis.

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C22

Lymphoepithelioma-like Carcinoma of the Skin: A Case Of One Individual Presenting with Two Primary Cutaneous Neoplasms

Jacqueline C. Fisher, DO, Rachel M. White, BA, and Daniel S. Hurd, DO, FAOCD

LewisGale Hospital Montgomery / Edward Via College of Osteopathic Medicine

Case Report

An 83-year-old Caucasian female was referred to our dermatology clinic for surgical excision of a previously biopsied lesion on her left neck reported initially as a nodular basal cell carcinoma with focal morpheaform features. The patient also complained of an asymptomatic, slowly-enlarging lesion to her left parietal scalp believed to be present for at least three months. Clinical examination revealed a solitary 2.0 x 2.2cm tan to pink indurated ulcerative plaque (Figure 1). There were no naso-oropharyngeal abnormalities or regional lymphadenopathy. A shave biopsy was performed to the left parietal scalp to exclude both basal cell carcinoma and squamous cell carcinoma. The patient's past medical history was non-contributory and she denied any constitutional symptoms at the time of clinical presentation.

The histopathological findings for both the left neck and left parietal scalp neoplasms showed a dermal proliferation of atypical epithelioid cells forming well-defined nests invested by a dense lymphocytic infiltrate (Figure 2). The atypical epithelioid cells were basophilic and featured enlarged nuclei with prominent nucleoli. A central ulceration was present under microscopic examination of the cutaneous biopsy on the patient's left parietal scalp. The overlying epidermis appeared uninvolved in both samples. Each specimen stained positive for cytokeratin (CK) 5/6 and epithelial membrane antigen (EMA) suggesting tumors of epithelial origin. Staining for CK7 and CK20 yielded negative results excluding Paget's disease and Merkel cell carcinoma (MCC), respectively, from the differential diagnosis. Due to the concern for an underlying metastatic undifferentiated nasopharyngeal carcinoma or lymphoepithelioma-like carcinoma (LELC) of another internal organ, an in situ hybridization for Ebstein-Barr virus-encoded RNA (ISH/EBER) was performed for detection of an active or latent EBV infection (Figure 3). The patient's histologic slides were compared to a control ISH/EBER immunohistochemical stain (Figure 4). The negative ISH/EBER stain for both lesions strongly favors two primary LELSC in our patient and does not favor a metastatic disease related to an EBV-driven undifferentiated nasopharyngeal carcinoma or internal LELC. Our patient was referred to an oncologist for medical evaluation to exclude cutaneous metastasis of an undifferentiated nasopharyngeal carcinoma or lymphoepithelioma-like carcinoma of other internal organs. Given the patient's advanced age and frail status, the patient refused oncologic examination as she planned to decline systemic treatment if an underlying internal malignancy was discovered. She plans to undergo surgical excision of both cutaneous neoplasms and remains free from systemic symptoms which supports the diagnosis of two primary lymphoepithelioma-like carcinomas of the skin.

Discussion

Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare primary cutaneous neoplasm initially described in 1988 by Swanson et al.[6] Since this first report, close to eighty cases have been described in the English literature. LELCS occurs most often in elderly individuals on sun-exposed areas, primarily the head and neck.[2]. However, there has been a report of LELCS occurring on the trunk and upper extremity.[7-9] The incidence occurs equally between men and women.[8] LELCS often presents as a solitary flesh-colored to red, firm papule, plaque, or nodule.[2]The average size is fairly large measuring about 2 to 3 centimeters in diameter.[3] Typically, LELSC is asymptomatic and slowly enlarges over a period of months to years.[8]

On histology, LELCS presents as a dermal proliferation of atypical polygonal epithelioid cells arranged in nests, cords, or sheets surrounded by a peripheral dense lymphocytic infiltrate.[6] Cellular atypia includes vesicular hyperchromatic nuclei and prominent nucleoli with scant amphophilic to eosinophilic cytoplasm.[2] The reactive lymphoid stroma is comprised of small B- and T-lymphocytes, staining positive for CD3 and CD20, with an occasional plasma cell present.[2,8] LELCS generally extends into the reticular dermis with occasional involvement into the subutis and even skeletal muscle.[6,10] LELCS stains positively for pancytokeratin, CK5, CK6, p63 and EMA reactivity likely indicating a neoplasm of epithelial origin.[2,7] In more recent literature, some consider LELCS to be a variant of squamous cell carcinoma (SCC).[2,4,16,17-20] For instance, Wang et al. presented a case of LELCS occurring below a scar from removal of multiple recurrent well-differentiated and subsequent moderately differentiated SCC.[19] However, SCC is typically located in the superficial dermis and maintains connectivity with the epidermis.[4] Lastly, others believe that LELCS is a morphologic pattern as opposed to a distinct clinicopathologic entity.[17,21,22]

Differential

The differential diagnosis is fairly extensive and includes cutaneous metastasis of undifferentiated nasopharyngeal carcinoma or a lymphoepithelioma-like carcinoma of another internal organ, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, Merkel cell carcinoma, melanoma, malignant lymphoma, Hodgkin's lymphoma, cutaneous lymphadenoma, and follicular dendritic cell tumor.[2,4] Histologic features and immunohistochemical staining distinguish LELCS from the possible differential diagnosis.

Figures

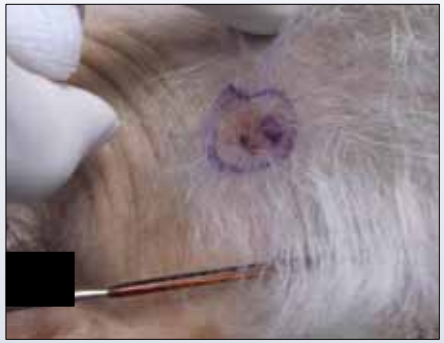


Figure 1

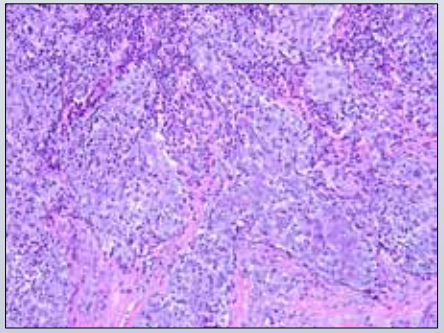


Figure 2

Figure 3

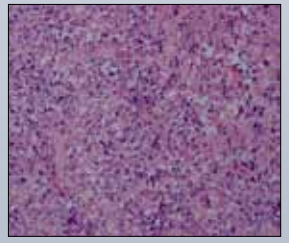


Figure 4

Merkel cell carcinoma (MCC) can present clinically similar to LELCS but will stain positive for neuroendocrine markers such as synaptophysin, neuron-specific enolase, and CK20.[1] In addition, peripheral lymphocytic infiltrate is usually absent in MCC.[2,14]Clarke and Ioffreda report a case in which LELCS demonstrates spindle shaped cells that resemble the spindle cell variant of melanoma.[23] However, unlike LELCS, melanoma is positive for S100 and other neuroectodermal markers such as HMB-45 and Melan-A. LELCS should be distinguished from malignant lymphoma by the absence of atypical lymphocytes in LELCS.[1] Epithelial markers such as epithelial membrane antigen and cytokeratins will react positive in LELCS and negative in malignant lymphoma. LELCS has shown the presence of occasional binucleated cells resembling Reed-Sternberg cells, however Hodgkin lymphoma is negative for cytokeratins and is positive for CD30 and CD15.[1,2,21,23] Basal cell carcinoma will demonstrate neoplastic basophilic cells extending downward from the epidermis whereas LELCS does not typically have an epidermal connection and lacks peripheral palisading. Inflamed poorly differentiated squamous cell carcinoma (SCC) strongly resembles LELCS.[1,19] However, LELCS typically does not involve overlying epidermis and poorly differentiated SCC usually has an area of well-differentiated carcinoma or overlying SCC in situ.[1,3,5]Cutaneous lymphadenoma demonstrates a similar dense lymphocytic infiltrate as LELCS although these lymphocytes appear benign and monomorphic.[1,2]Follicular dendritic cell tumor (FDCT) is similar to LELCS by way of syncytial-appearing plump cells surrounded by reactive lymphoid cells but FDCT stains negative for cytokeratin markers.[2] FDCT will demonstrate positive reactivity to Ki-M4, CD21, and CD35.[2]

Histologically, LELCS is remarkably similar to metastatic lymphoepithelioma of the nasopharynx also known as undifferentiated nasopharyngeal carcinoma.[1,3,22] Epstein-Barr virus (EBV) reactivity is the main distinguishing factor between LELCS and undifferentiated nasopharyngeal carcinoma.[1,2,4,24]In general, LELCS is negative for EBV reactivity whereas undifferentiated nasopharyngeal carcinoma will test positive for EBV.[1,2,4,24] There has only been one reported case of LELCS in a Japanese woman which tested EBV positive yet no related neoplasms were found elsewhere in her body.[22] In situ hybridization for EBER, the most reliable, specific, and highly sensitive method for detecting latent EBV, was used in this case report and yielded a negative result for EBV in our patient.[22,25] Metastatic lymphoepithelioma of the nasopharynx is rare, but aggressive when it does occur.[2,4,6] LELCS secondary to metastasis of undifferentiated nasopharyngeal carcinoma appears to be very rare as there are less than twenty cases currently reported in the literature.[2,6,11] Nonetheless, it is highly recommended to evaluate the patient for possible undifferentiated nasopharyngeal carcinoma by a complete otolaryngologic exam including indirect laryngoscopy of the nasopharynx.[4,26]A review of symptoms is recommended when LELCS is confirmed to exclude metastasis from a variety of internal organ systems.[2,4,5,22] Lymphoepithelioma-like carcinoma can be found in many organs besides the skin including salivary glands, thyroid, thymus, lungs, stomach, kidney, breasts, uterine cervix, prostate, vagina, and urinary bladder.[6,7,16,17,23,27] Histologically, EBV reactivity has been associated only with lymphoepithelioma-like carcinoma of the stomach, salivary glands, lungs, and thymus.[4,7,22,24]

Treatment

The prognosis for patients with LELCS is generally good despite its categorization as a poorly differentiated neoplasm .[2,5,6,22,27]It is a low malignant tumor with rare reports of metastasis to lymph nodes at presentation and to internal organs such as, liver, lung, and bone.[9,27]There are only two reported deaths from metastatic LELCS.[4,6] There are multiple reports of local recurrence after incomplete excision.[6] Therefore, most LELCS are treated by wide local excision or Mohs micrographic surgery to lower the risk of recurrence.[2,28]LELCS and undifferentiated nasopharyngeal carcinoma are both radiosensitive and this treatment modality should be used for recurrent cases, nonsurgical candidates, and those with lymph node metastasis.[3,8]There are also a few reports of perineural invasion, in which Mohs micrographic surgery, radiation, and chemotherapy were used in combination therapy without evidence of recurrence on follow-up evaluation.[3-5,7]

References

1. Spitz JL. Genodermatoses: A clinical guide to genetic skin disorders. 2nd edition. Lippincott Williams & Wilkins; 2004.
2. Elston DM, et al. Requisites in Dermatology: Dermatopathology. Saunders Elsevier; 2009.
3. Bolognia JL, et al. Dermatology. 2nd edition. Mosby Elsevier; 2008.
4. Lassen CB, Lock-Anderson J. Lymphoepithelioma-like carcinoma of the skin: a case with perineural invasion. PRS Global Open 2014;1:3.
5. Gille IM, Miles EF, Mitchell AO. Lymphoepithelioma-like carcinoma of the skin treated with wide local excision and chemoradiation therapy: A case report and review of the literature. Case Rep Oncol Med 2012; 2012:241816.
6. Swanson SA, Cooper PH, Mills SE, Wick MR. Lymphoepithelioma-like carcinoma of the skin. Mod Pathol 1988;1:359-65.
7. Robin P, Perez MI. Lymphoepithelioma like carcinoma of the skin treated by Mohs micrographic surgery. J Am Acad Dermatol 1995;32:814-16.
8. Glueck AS, Rehroozen DS, Cohen JL, Goldberg LH. Lymphoepithelioma-like carcinoma of the skin: a report of two cases treated with complete microscopic margin control and review of the literature. Dermatol Surg 2006;32:1080-4.
9. Hall G, Hanyan A, Azurdia R, Leonard N. Lymphoepithelioma-like carcinoma of the skin: a case with lymph node metastases at presentation. Am J Dermatopathol 2007;29:61-4.
10. Wick MR, Swanson PE, Lelbolt PE, Strickler JG, Cooper PH. Lymphoepithelioma-like carcinoma of the skin with adnexal differentiation. J Cutan Pathol 1991;18:93-102.
11. Luk NM, Yu KH, Choi CL, Yeung WK. Skin metastasis from nasopharyngeal carcinoma in four Chinese patients. Clin Exp Dermatol 2004;29:28-31.
12. Ng KF, Chen TC, Chang PL. Lymphoepithelioma-like carcinoma of the ureter. J Urol 1999;161:1277-8.
13. Gilliam PS, Morgan MB, Snyder MP, Everett MA. Absence of Epstein-Barr virus in lymphoepithelioma like carcinoma of the skin. Polymerase chain reaction evidence and review of five cases. Am J Dermatopathol 1996;5:479-82.
14. Abdelkrim SB, Dhoubi A, Moussa A et al. Merkel cell carcinoma with lymphoepithelioma-like pattern: a case report of an exceedingly rare variant of merkel cell carcinoma with lymph node metastases at presentation. Case Rep Pathol 2013; 2013:751-4.
15. Ko T, Muramatsu T, Shirai T. Lymphoepithelioma-like carcinoma of the skin. J Dermatol 1997;2:104-9.
16. Lee CH, Lee JY, Kim SH, Kim YC, Cho KH. Lymphoepithelioma-like carcinoma of the skin. A case report with immunophenotypic analysis and in situ hybridization for Epstein-Barr virus genome. Am J Surg Pathol 1995;19:1074-80.
17. Lind AC, Bhrat WA, Wick MR. Lymphoepithelioma-like carcinoma of the skin with apparent origin in the epidermis-a pattern or an entity? A case report. Cancer 1999;15:88c96.
18. Cassarino DS, DeRienzo DP, Barr R. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification. J Cutan Pathol 2006;33:191-206.
19. Wang G, Bordeaux JS, Rowe DJ, Honda KS. Lymphoepithelioma-like carcinoma vs inflamed squamous cell carcinoma of the skin. JAMA Dermatol 2014;150:1367-8.
20. Bolognia JL, Jorizzo JL, Rapsni RP, editors. Dermatology. Edinburgh: Mosby, Inc; 2008. 1782-1783. Print.
21. Shek TW, Leung EY, Luk IS, Loong F, Chan AC, Yik YH, et al. Lymphoepithelioma-like carcinoma of the skin. Am J Dermatopathol 1996;6:637-44.
22. Aoki R, Mitsui H, Karada, K et al. A case of lymphoepithelioma-like carcinoma of the skin associated with Epstein-Barr virus infection. J Amer Acad Derm 2010;62(1):81-86.
23. Clarke LE, Ioffreda MD. Lymphoepithelioma-like carcinoma of the skin with spindle cell differentiation. J Cutan Pathol 2005;6:419-23.
24. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol 1995;103:308.

Recognizing Reed Syndrome Case Report and Discussion

Megan Furniss, DO, Greg Delost DO, Michael Mahon, DO

LEARNING OBJECTIVES

Reed Syndrome is a genodermatosis characterized by benign leiomyomas of the skin and uterus. The presentation of the disorder can be subtle, and yet be a herald of risk of aggressive papillary renal cell carcinoma. It is therefore important that providers recognize leiomyomatosis and have awareness of this association.

CASE SUMMARY

A 58 year-old Caucasian woman presented to our dermatology clinic with a complaint of tender, mildly pruritic bumps on her bilateral flanks which erupted 12 years ago after her fourth pregnancy. Further questioning revealed a history of uterine fibromatosis, which necessitated hysterectomy with resultant removal of 42 uterine fibroids. Review of her records from a clinic visit in 2002 revealed that a similar lesions had been biopsied and diagnosed as a leiomyoma.

On exam the patient had clusters of several skin-colored to pink dermal nodules on the bilateral anterior flanks which were mildly tender to touch. Skin surface changes were absent.

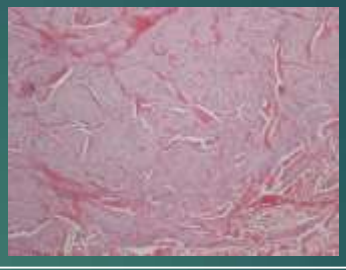
Two skin biopsies were taken; both results were consistent with leiomyomas.

Based on this combination of multiple cutaneous and uterine leiomyomas, the patient was presumptively diagnosed with *leiomyomatosis cutis et uteri*, also known as Reed syndrome, or hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC).

The treatment plan was to obtain appropriate screening for renal pathology, given the high-risk for aggressive renal cell carcinomas in these patients. The patient was sent for a renal US, CT abdomen/pelvis, and labs including a CBC, CMP, and UA. The work-up to date has been negative for internal pathology.

Definitive genetic testing is under consideration.

CLINICAL AND PATHOLOGIC PHOTOGRAPHS



DISCUSSION OF REED SYNDROME

Reed Syndrome is an autosomal dominantly inherited genodermatosis caused by a germline mutation in the fumarate hydratase gene. The cutaneous lesions of RS are solitary or multiple cutaneous leiomyomas, appearing as firm and painful skin-colored or pink to brown papules or nodules up to 2cm in diameter[1]. With an incidence of 85%, cutaneous leiomyomas are mainly found on the trunk and extremities, but can also affect the face[1]. Because cutaneous leiomyomas are rare in the general population, their presence should elicit suspicion of underlying HLRCC with further investigation warranted[1].

The initial cohort study, consisting of two European families with HLRCC, found papillary type II renal tumors in 6 of 19 individuals (32%)[2]. A much larger North American cohort of 95 individuals from 35 families identified a 14% prevalence (13 of 95 patients) of renal tumors in the FH mutation positive carriers[3]. Extrarenal manifestations of HLRCC are quite common with uterine leiomyomas being the most common[2]. In the North American cohort study, 98% of women with cutaneous leiomyomas also had uterine leiomyomas[2]. Furthermore, more than 90% of these women underwent myomectomy or hysterectomy with approximately half of the hysterectomies occurring by the age of thirty[2].

Compared to other hereditary renal tumor syndromes, such as von Hippel-Lindau disease, hereditary papillary renal carcinoma, and Birt-Hogg-Dubé syndrome, renal tumors in patients with HLRCC syndrome are significantly more aggressive, often with early metastasis, despite small primary tumor size[4]. The proposed mechanism of carcinogenesis is that FH is a tumor suppressor, as loss-of-heterozygosity disease models in HLRCC display loss of the wild type allele in cutaneous, uterine, and renal tumors[5].

WORKUP/MANGEMENT

Biopsies of leiomyomas show interlacing fascicles of bland cells with brightly eosinophilic cytoplasm and blunt-ended, cigar-shaped nuclei centered in the reticular dermis, and an absence of mitoses.

Removal of painful or changing lesions to detect malignant transformation to leiomyosarcoma.

Specific guidelines for management do not exist, however current recommendations are:

- Genetic testing by PCR (available through the NIH), or by histopathological staining for the fumarate hydratase defect is imperative
- Referral to gynecology and genetic counselling
- Referral to nephrology for serial monitoring for renal malignancy with labs, CT abdomen/pelvis
- Screening of first degree relatives for the gene defect and renal malignancy

CONCLUSIONS

Recognition of leiomyomatosis presenting to a dermatology clinic is imperative to correctly diagnose and screen Reed Syndrome patients, who are at a high risk of aggressive renal cell carcinoma.

REFERENCES

1. Emer JJ, Solomon S, Mercer S. Reed's Syndrome: A Case of Multiple Cutaneous and Uterine Leiomyomas. J Clin Aesthet Dermatol. 2011; 4(12): 37–42. .

2. Launonen V, Vierimaa O, Kiuru M, Isola J, Roth S, Pukkala E et al: Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci U S A 2001; 98: 3387.

3. Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML et al: Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 2003; 73: 95.

4. Grubb RL, Franks, ME, Toro J, et al. Hereditary Leiomyomatosis and Renal Cell Cancer: A Syndrome Associated With an Aggressive Form of Inherited Renal Cancer. The Journal of Urology. 2007; 177: 2074-2080.

Genetic Skin Disorders, 2nd Edition 2005;10:286

5. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, Leigh I, et al Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet 2002; 30: 406–410.

Cutaneous Rosai-Dorfman Disease: A Case Report

Maren Gaul DO, Timothy Chang MD
Western Reserve Hospital, Dept. of Dermatology, Cuyahoga Falls, OH

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Abstract

Cutaneous Rosai-Dorfman Disease (CRDD) is a rare form of Rosai-Dorfman Disease (RDD) or sinus histiocytosis with massive lymphadenopathy, which has a varied clinical presentation, an unknown etiology, and multiple treatment options which lack efficacy.

We report a case of a 31-year-old African-American female (AAF) who presented with grouped skin-colored and pink papules and plaques within a hyperpigmented patch on her thigh, treated with topical, oral, and intralesional steroids with minimal improvement.

Introduction

Background

- Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a non-Langerhans cell histiocytosis.[1]
- There are two main forms of RDD: One form that affects the lymph nodes and in certain cases the extranodal organs, while the other is purely cutaneous RDD (CRDD).[1]
- CRDD is extremely rare and the etiology is unknown, though a number of viral and immune causes have been postulated.[1]
- Approximately 10% of RDD patients exhibit skin lesions, and in 3% it is contained solely in the skin.[2]
- CRDD presents with median age, 43.5 years, a female predominance (2:1), and most commonly affects Asian and Caucasian individuals.[1]

Diagnosis

- CRDD presents as solitary or numerous papules, nodules, and/or plaques.[1]
- Histopathology reveals emperipolesis, the presence of intact lymphocytes (or less often plasma cells, neutrophils, and red blood cells) within histiocytes.[1-3]
- Histiocytes stain positively for S100 protein, CD4, Factor XIIIa, and CD68 and negatively for CD1a.[1-3]

Case Description

History of Present Illness: A 31-year-old AAF presented with a slowly spreading pruritic rash on her right thigh for approximately 1 year. She had previously seen a dermatologist and was prescribed triamcinolone 0.1% cream and bactroban 2% ointment, though declined a biopsy at that time.

Medical History/Surgical History: Anxiety

Social History: Single, sexually active, nonsmoker, no alcohol or drug use

Family History: Eczema, hypertension

Medications: Triamcinolone 0.1% cream and bactroban 2% ointment

Physical Examination: Well-developed, well-nourished black female in no acute distress, alert & oriented x3, skin type V/VI. Grouped skin-colored to light pink papules and plaques within a hyperpigmented patch on the right medial thigh (Figure 1).

Laboratory Data: CBC w/diff revealed leukopenia

Studies: CT of chest/abdomen/pelvis was wnl. Punch biopsy was negative for fungal, bacterial, or AFB culture.

Biopsy (Figure 2, 3, & 4): The biopsy specimen shows a dense dermal infiltrate of large histiocytes admixed with inflammatory cells composed predominantly of lymphocytes and plasma cells. The histiocytes within the inflammatory infiltrate have vesicular nuclei and abundant eosinophilic cytoplasm. Areas of emperipolesis (intact inflammatory cells within histiocytes) are noted. The large histiocytes are S100+ and are negative for CD1a.

Final Diagnosis: Cutaneous Rosai-Dorfman disease

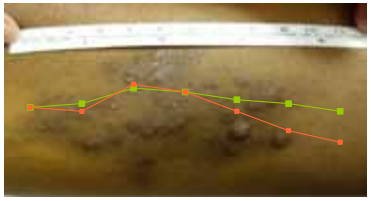


Figure 1. Grouped skin-colored to light pink papules and plaques within hyper pigmented patch on right medial thigh.

Case Description

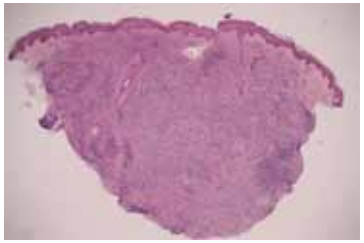


Figure 2. Punch biopsy with dense dermal infiltrate of histiocytes and inflammatory cells at 4x.

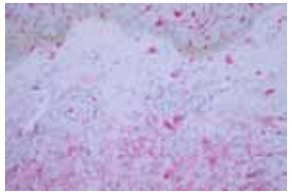


Figure 3. Histiocytes with positive S-100 stain.

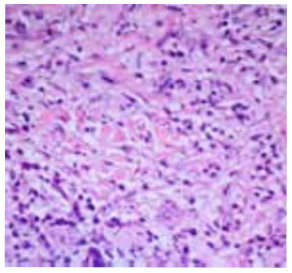


Figure 4. Emperipolesis of inflammatory cells.

Discussion

- Both the clinical and histologic differentials are broad for CRDD. Differential diagnosis includes sarcoidosis, acne vulgaris, lupus vulgaris, granuloma annulare, vasculitis, hidradenitis suppurativa, malignant breast neoplasm, and other histiocytoses.
- The most common site of lesions in CRDD is the face, with eyelids and malar regions frequently involved, followed by the back, chest, thigh, flank and shoulder.[1,3]
- Rarely CRDD may be associated with the involvement of other disorders, including bilateral uveitis, antinuclear antibody positive lupus erythematosus, rheumatoid arthritis, hypothyroidism, lymphoma and HIV infection.[1]
- CRDD may be self-limited, yet surgical excision, cryotherapy, local radiation, topical steroids, laser treatment, dapsone, thalidomide, isotretinoin, imatinib, and methotrexate have all been attempted in various case reports in the literature.[1-7]

Conclusion

- CRDD is an unusual clinical entity with varied lesions
- CRDD follows a benign clinical course, with a possibility of spontaneous remission or various treatments
- Further studies are required to confidently classify the etiology and variance between both RDD and CRDD.

References

1. Fang S, Chen A-J. Facial cutaneous Rosai-Dorfman disease: a case report and literature review. Experimental and Therapeutic Medicine. 2015;9(4):1389-1392. doi:10.3892/etm.2015.2260.
2. James WD, Berger T, Elston D. Andrews' diseases of the skin. 12th ed. Philadelphia (PA): Elsevier; 2015.
3. Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology. 3rd ed. Philadelphia (PA): Elsevier; 2012.
4. Khan A, Musbahi E, Suchak R et al. Cutaneous Rosai–Dorfman disease treated by surgical excision and a review of the literature. Journal of the American Academy of Dermatology. 2015;72(5):AB259.
5. Al Salamah SM, Abdullah M, Al Salamah RA, Al Hadlaq ARA, Al Mogbel E, Al Yahya GM. Cutaneous Rosai-Dorfman disease presenting as a flank swelling. International Journal of Health Sciences. 2014;8(4):434-438.
6. Nadal M, Kervarrec T, Machet MC, et al. Cutaneous Rosai-Dorfman disease located on the breast: rapid effectiveness of methotrexate after failure of topical corticosteroids, acitretin and thalidomide. Acta Derm Venereol. 2015;95(6):758-759.
7. Chen A, Fernedez A, Janik M, et al. Cutaneous Rosai-Dorfman disease. Journal of the American Academy of Dermatology. 2012;66(4):AB48.

Acknowledgements

Timothy Chang MD; Western Reserve Hospital, Graduate Medical Education Department

A Man with Painful Lower Extremity Nodules, Pancreatitis and Polyarthritis

Paul Graham, DO | David Altman, MD | St. Joseph Mercy Ann Arbor, Ypsilanti, MI

Introduction

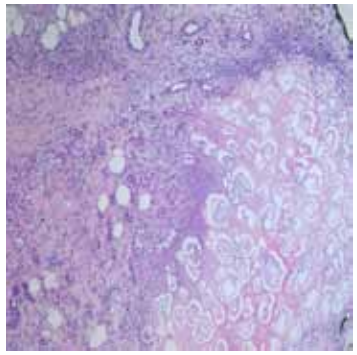
A triad composed of panniculitis, pancreatitis, and polyarthritis is termed in the literature as PPP syndrome. Pancreatic panniculitis is a rare form of subcutaneous fat necrosis associated with underlying pancreatic disease. The etiology of PPP syndrome remains unclear; however, it has been hypothesized that serum trypsin released from the damaged pancreas is responsible for enzymatic destruction of the surrounding subcutis and bone marrow. Patients typically present with mild to absent abdominal symptoms and coexisting joint pain, pitting edema, and subcutaneous nodules.

History

A 69-year-old Caucasian man presented with exquisitely painful nodules and marked edema of his bilateral lower legs. The nodules first appeared nine months ago and exhibited a waxing and waning course. His past medical history was significant for chronic pancreatitis of unknown origin, hypertension, gastroesophageal reflux disease, inflammatory arthritis, and hypercholesterolemia.

Examination

Physical examination revealed multiple 1-3 cm ill-defined, red to brown subcutaneous nodules on the bilateral lower legs and the right inferomedial thigh. Marked erythema and edema of MCP and MTP joints, and bilateral ankles were observed. Diffuse 2+ pitting edema was present in the bilateral lower extremities.



Laboratory and Diagnostic Imaging

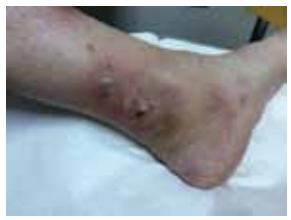
Laboratory results revealed increased amylase (5,250 U/L), lipase (9,197 U/L), ESR (94 mm/h), and CRP (93.5 mg/L). Triglycerides, ANA, and RF were within normal limits. CT scan of the left ankle revealed cortical bony erosion of the calcaneus. Abdominal ultrasound revealed a solitary pseudocyst with coexisting pancreatic ductal dilation.

Histopathology

Punch biopsy of a nodule on the right leg revealed extensive lobular and septal liquefactive adipocyte necrosis with scattered neutrophils and lymphocytes. Aggregates of fine granular basophilic material were observed with prominent adipocyte degeneration and calcification.

Course and Therapy

The patient underwent a pancreaticoduodenectomy (Whipple procedure) with significant improvement in his pancreatic enzymes, lower extremity subcutaneous nodules, and arthritis. He is currently being followed by rheumatology and internal medicine.



Discussion

A triad of pancreatic panniculitis, pancreatitis, and polyarthritis describes an extremely rare entity known as PPP syndrome. Currently, only 25 well-documented cases exist in the literature. Pancreatic panniculitis is a rare form of subcutaneous fat necrosis associated with underlying pancreatic disease. Pancreatic panniculitis has been found in roughly 2-3% of patients with acute or chronic pancreatitis, and pancreatic carcinoma (acinar cell type). Joint disease has been reported in 54-80% of cases, most commonly involving the ankles, knees, wrists, and MCP joints of the hands.

Pancreatic panniculitis in the setting of PPP syndrome commonly presents with ill-defined, red-brown, exquisitely tender, edematous subcutaneous nodules on the lower legs. The subcutaneous nodules may spontaneously ulcerate and exude oily, viscous material as a result of the liquefactive necrosis of adipocytes. Patients with PPP syndrome typically present with mild to absent abdominal symptoms and coexisting joint pain, pitting edema, and subcutaneous nodules.

The exact pathogenesis of PPP syndrome remains unclear. It has been hypothesized that serum trypsin released from the damaged pancreas is responsible for damage to the surrounding subcutis and bone marrow. Intraosseous fat necrosis is responsible for the development of multiple osteolytic bone lesions and endosteal erosions seen on plain radiographs and CT scans. Needle aspiration of the arthritic joints often yields yellow, viscous, purulent fluid with lipid crystals and elevated lipase levels.

Histopathologic findings of pancreatic panniculitis demonstrate lobular subcutaneous inflammation with liquefactive necrosis of adipocytes in the subcutis, leading to the characteristic appearance of “ghost adipocytes”. Ghost adipocytes are cells with absent nuclei containing fine basophilic homogenous material in the presence of fat saponification.

Treatment of PPP syndrome is largely supportive, with a focus on correcting the underlying pancreatic disease. NSAIDs, corticosteroids, and octreotide have been utilized with minimal effectiveness. Plasmapheresis is an effective treatment option in patients with persistent hyperamylasemia and hyperlipasemia. Often reserved for severe refractory disease, a cholecystectomy and/or a pancreatic duct removal have demonstrated success in the management of chronic pancreatitis and panniculitis.

Conclusion

PPP syndrome is an extremely rare diagnosis composed of a triad of pancreatic panniculitis, pancreatitis, and polyarthritis. Adjuvant therapies for PPP syndrome, such as NSAIDs, corticosteroids, plasmapheresis and octreotide, have been used, but definitive treatment requires correction of the primary pancreatic disorder. More importantly, the diagnosis of pancreatic panniculitis could be an early indicator of an occult pancreatic malignancy and should prompt early evaluation with a multidisciplinary approach.

References

1. Arbeláez-Cortés Á, Vanegas-García A, Restrepo-Escobar M, et al. Polyarthritis and pancreatic panniculitis associated with pancreatic carcinoma. J Clin Rheumatol. 2014;20(8):433-436.
2. Borowicz J, Morrison M, Hogan D, et al. Subcutaneous fat necrosis/panniculitis and polyarthritis associated with acinar cell carcinoma of the pancreas: a rare presentation of pancreatitis, panniculitis, and polyarthritis syndrome. J Drugs Dermatol. 2010;9(9):1145-1149.
3. Francombe J, Kingsnorth A, Tunn E. Panniculitis, arthritis and pancreatitis. Brit J Rheum. 1995;34:680-83.
4. Narvaez J, Bianchi M, Santo P, et al. Pancreatitis, panniculitis, and polyarthritis. Semin Arthritis Rheum. 2010;39(5):417-23.

Squamous Cell Carcinoma, Keratoacanthoma-type Within a Tattoo

Elise Grgurich, DO, Nektarios Lountzis, MD, and Stephen Purcell, DO
Lehigh Valley Health Network, Allentown, Pennsylvania

Case Presentation:

Patient: 64 year-old Caucasian male.

History of Present Illness: Patient presents with new growths on his right outer leg that have been present for four months. Lesions appeared within the red ink portion of his tattoo. He admits to burning sensation if touched but denies itching and bleeding. Patient tried using antibiotic ointment which he believes made the lesions larger.

Medical History/Surgical History: Four cutaneous squamous cell carcinomas with two being the keratoacanthoma type, emphysema, hepatitis C, coronary artery disease, myocardial infarction, cerebral vascular accident, tonsillectomy, inguinal hernia s/p herniorrhaphy

Medications: Apixaban, esomeprazole, and tiotropium inhaled

Previous Treatments: Wide local surgical excision and excisional biopsies

Physical Examination: There is a large tattoo comprised predominantly of red ink on the right anterior leg. Within the red portion of the tattoo are four scattered erythematous, crateriform, keratotic papules and nodules ranging in size from 0.6-1.1 cm.

Studies: *Advanced Dermatology Associates, LTD.* (AD15-00774, 1/21/2015) 1. Right inferior lateral lower leg: "Well-differentiated squamous cell carcinoma, keratoacanthoma type, involving the reticular dermis and transected at the base of the specimen."

(AD15-01682, 2/13/2015) 2. Right lateral lower leg, anterior; 3. Right lateral lower leg, proximal posterior; 4. Right lateral lower leg, proximal superior: "Atypical squamous proliferation, consistent with early evolving or regressing well-differentiated, invasive squamous cell carcinoma, keratoacanthoma-type, with adjacent superficial dermal and focal intracorneal red tattoo pigment, completely excised. AFB-Fite, Gram, PAS, and GMS were each performed and were negative for infectious organisms."

Figure 1: Two crateriform, keratotic nodules located within red tattoo pigment on the right lateral lower leg, proximal superior and proximal posterior measuring 8 mm and 9 mm respectively.

Figure 2: A 1.1 cm crateriform, keratotic nodule located within the red pigment of the tattoo on the right lateral lower leg, anterior.

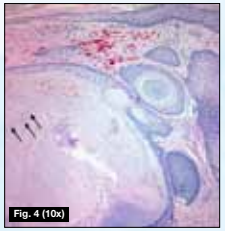


Figure 3: Atypical squamous proliferation consistent with keratoacanthoma. Note the red tattoo pigment embedded in the apex of the cutaneous horn (see arrow).

Figure 4: Atypical cystic squamous proliferation with notable red tattoo pigment in the surrounding dermis and focally embedded in the cutaneous horn (see arrows).

Figure 5: High power view of red tattoo pigment embedded in the apex of the cutaneous horn.

REFERENCES:

1. Kluger N, Minier-Thoumin C, Plantier F. Keratoacanthoma occurring within the red dye of a tattoo. *J Cutan Pathol* 2008;35:504-507.
2. Kluger N, Koljonen V. Tattoos, inks, and cancer. *Lancet Oncol* 2012;13:e161-168.
3. Goldenberg et al. Eruptive squamous cell carcinomas, keratoacanthoma type, arising in multicolor tattoo. *J Cutan Pathol* 2008;35:62-64.
4. Simunovic C, Shinohara M. Complications of decorative tattoos: recognition and management. *Am J Clin Dermatol* 2014;15:525-536.

Discussion:

Keratoacanthoma (KA) is a common keratinizing squamous cell neoplasm characterized by rapid growth and spontaneous involution. Though the origin is not completely understood, ultraviolet light, carcinogenic exposure, genetics, immunosuppression, viral infection and trauma have been associated with development of KA. Tattoo-induced KA is less commonly reported. It typically presents as a rapidly enlarging crateriform nodule most commonly on sun-exposed skin. Clinically the lesion may resemble a viral verruca, squamous cell carcinoma, and mycobacterial or fungal infection.

Histopathologically, KA demonstrates a well-circumscribed, keratin-filled invagination of the epidermis with hyperkeratosis, parakeratosis, and acanthosis. Atypical squamous cells may be present but cellular atypia is less remarkable as the lesion matures. Histopathological differential includes pseudoepitheliomatous hyperplasia, squamous cell carcinoma (SCC), and verrucous carcinoma. Pseudoepitheliomatous hyperplasia is a similar appearing, rapidly growing lesion that is often difficult to distinguish from KA; histopathological correlation is required for diagnosis. A history of rapid growth and development may help distinguish KA and SCC clinically.

Most cutaneous reactions associated with tattoos occur within red ink. A case series of 11 KAs associated with tattoos demonstrated that 82% were within or in close proximity to red ink. Mercuric sulfide (cinnabar), sienna (ferric hydrate), sandalwood, brazilwood, and organic pigments (aromatic azoic compounds) have all been found in red ink. Mercury compounds were eliminated in 1976 because of its potential carcinogenicity. However, some organic colorants (azo compounds) that were classified as carcinogenic remain in current ink products.

Approximately 50 skin cancers in tattoos have been reported in the past 40 years, 23 of which presented as SCC and KA. In the past few years there has been an increase in the incidence of isolated and eruptive KAs within tattoos. Potential mechanisms of induction have been proposed and include trauma from the tattoo procedure, introduction of potential carcinogenic compounds, and sun-exposure. However, with such a low number of reported skin cancers arising in tattoos some consider the association between tattoos and skin cancer coincidental. Despite the elusive pathogenesis of this phenomenon, the presence of intracorneal red tattoo pigment within the squamous proliferations in our specimens raises the possibility that the lesions could represent a reactive form of transepidermal elimination of the tattoo pigment.

Primary management of these lesions includes complete surgical excision. Careful long-term follow-up is recommended to monitor for recurrence or presence of new lesions. Though larger studies are needed to determine the actual causation of skin cancer within tattoos, patient education on the potential health effects of tattooing and implementation of regulations regarding ink manufacturing is necessary in the meantime.

Case Report of Neoadjuvant Use of Vismodegib for Locally Advanced Periorbital Basal Cell Carcinoma: Part I

Lauren Keller, DO, PGY3; Adriana Ros, DO

Palisades Medical Center Dermatology Residency
North Bergen, NJ

Introduction

Basal cell carcinoma accounts for 90% of malignant tumors of the eyelid[1]. Periocular tumors are most often treated surgically with Mohs micrographic technique, or excision with frozen section determination of margins; these approaches are curative in over 90% of cases[1].

The vast majority of basal cell carcinomas have been found to contain pathogenic aberrations within the hedgehog signaling pathway, ultimately resulting in unrestrained proliferation of tumor cells[2]. The smoothened (SMO) protein is a crucial element within this pathway[2]. The small molecule SMO inhibitor vismodegib, administered orally at a dose of 150 mg once daily, has recently expanded treatment strategies for patients with locally advanced basal cell carcinoma. The duration of treatment in published studies has been until disease progression, unacceptable toxicity, or discontinuation of trial[2].

In June 2015, a 12-month update of safety and efficacy of vismodegib in advanced BCC reported a 47.6% objective response rate in patients with locally advanced disease[3]. The median duration of treatment was 12.7 months in this cohort[3]. The most common adverse events that resulted in cessation of treatment were muscle spasm, weight loss, and dysgeusia[3]. 17.3% of patients discontinued treatment due to an adverse event[3].

Here we report the case of a Cacuasian male with locally advanced basal cell carcinoma of the periorbital area, treated with vismodegib in advance of referral for Mohs surgery.

Case Report

A 64 year old Caucasian male with PMH schizoaffective disorder and alcoholism was evaluated by the dermatology consult team for a hemorrhagic plaque of the left lateral canthus and periorbital skin. At the time of his initial evaluation, the patient had been admitted to the inpatient psychiatric service.

The patient reported that the lesion was a "basal cell," and he recalled that it had been biopsied 5 to 7 years ago. However, due to the patient's lack of follow up, the lesion was not treated.

The patient denied changes in vision, and denied restriction of eye movements. He reported that the lesion had slowly enlarged over many years. His primary complaint was that the lesion "bled easily."

Bedside eye exam revealed 20/20 vision with corrective lenses. The patient had worn glasses for many years.

Efforts to obtain the original pathology report from a local dermatologist were unsuccessful. A shave biopsy of the periorbital plaque was done by the dermatology consult team, which yielded the diagnosis of nodular basal cell carcinoma.

Given the involvement of the lateral canthus of the eye, as well as the size of the lesion, surgical treatment was deferred. Vismodegib 150 mg p.o. daily was started as treatment for locally advanced basal cell carcinoma. The planned duration, depending on treatment response and tolerability, was 6 months. Imaging studies and metastatic workup were deferred based on the patient's lack of concerning symptoms.

Within one month of treatment initiation, the lesion contracted in size. The patient reported a decrease in hemorrhagic episodes and friability. He continued to deny visual symptoms and difficulty with eye movement. The patient also denied muscle spasm, decreased taste, and hair loss.

After 2 months of treatment with vismodegib, the patient reported continued improvement and continued to deny new visual symptoms. Review of systems remained negative; the patient did not report any of the common side effects associated with vismodegib. His weight remained stable. Persistent ectropion and inferior distortion of the left lateral canthus was noted on exam, and the patient was referred for ophthalmology evaluation.

Eye exam did not show evidence of visual impairment, and ophthalmology recommended artificial tears as needed for ectropion-related symptoms of dry eye.

Within his third month of treatment with vismodegib, the patient complained of intermittent "muscle cramps" in his thighs and mildly decreased sensation of taste. He stated that his left malar cheek felt "tight." In light of these complaints, the patient was referred to Mohs for definitive surgical treatment. Vismodegib was continued pending surgical evaluation.

Physical Exam Findings

Findings prior to initiation of treatment with vismodegib and during treatment with vismodegib:

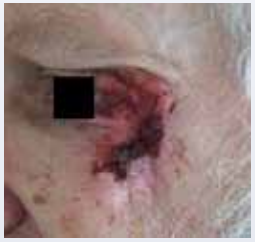


Figure 1: Left lateral canthus and periorbital skin, pre-treatment

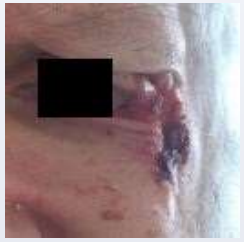


Figure 2: Left lateral canthus and periorbital skin, pre-treatment

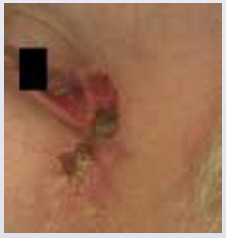


Figure 3: After 1 month of treatment

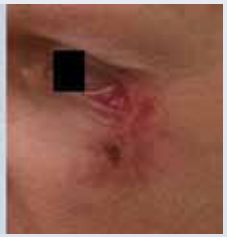


Figure 4: After 2 months of treatment

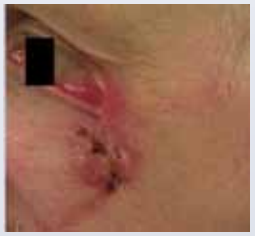


Figure 5: After 3 months of treatment

Discussion

The treatment of basal cell carcinoma involving the eyelid poses challenges both in terms of comesis and functional preservation. Optimally, intervention would occur in an early phase of tumor growth; in this case, neglect led to locally advanced disease. Initiation of vismodegib produced clinical reduction in lesional dimensions and extent of ulceration; however, other considerations arose during the patient's course of treatment.

Notably, the patient reported symptoms of left malar cheek "tightness" as the third month of treatment with vismodegib concluded. On exam, chronic inferior distortion of the left lateral canthus was observed. This clinical picture may be explained by the underlying histologic changes associated with ongoing administration of vismodegib. Maier et al examined basal cell carcinoma tumors using non-invasive imaging techniques between weeks 9-24 of hedgehog pathway inhibitor therapy, followed by biopsy within 1-7 days of imaging[4]. Histopathologically, pseudocystic structures were identified, with rims of basophilic cells and central density of fibrocytes; in later stages, massive fibrosis was found in place of tumor cells[4]. Maier et al note that basal cell carcinoma that is cleared by hedgehog pathway inhibition may be replaced by scar tissue[4]. The formation of fibrosis in the area of tumor regression may therefore present new clinical challenges, such as contractures in cosmetically sensitive areas, or, as in this case, deformation of the eyelid making the cornea more vulnerable to injury or dehydration.

Our patient also reported side effects of muscle cramps and decreased sensation of taste. Recent data from the STEVIE trial, which examined the safety of vismodegib with the secondary endpoint of efficacy, shows a profile consistent with previous studies[5]. STEVIE patients received 150 mg of oral vismodegib on a continuous basis in a 28 day cycle until disease progressed, toxicity became unacceptable, or consent was withdrawn[5]. 468 patients were included in the locally advanced BCC group and 31 were within the metastatic BCC group[5]. The median duration of exposure to vismodegib for patients within the locally advanced basal cell carcinoma group was 36.3 weeks[5]. Most common side effects were muscle spasm in 64% of patients; alopecia in 62%; dysgeusia in 54%; weight loss in 33% [5]. In 9% of patients, muscle spasm led to discontinuation of the drug; 6% discontinued due to dysgeusia; 5% discontinued due to weight loss and 4% discontinued due to alopecia[5]. Fortunately, our patient's symptoms were tolerable and did not necessitate interruption or discontinuation of treatment; however, they did contribute to the decision to facilitate surgical referral following three months of vismodegib.

Furthermore, cost considerations may favor a combined approach, as we recommended for our patient. Current estimations place the cost of vismodegib at $7500 per month, with the surgical treatment of basal cell carcinoma typically costing $2000 or less[1,6]. The experience of Alcalay et al, who report two cases of neoadjuvant vismodegib prior to Mohs surgery, indicates successful surgical result following a six month course of treatment with hedgehog pathway inhibitor[7]. Ally et al, in their open-label study of 11 patients treated with vismodegib preceding Mohs technique for basal cell carcinoma, found that the surgical defect size was reduced by 27% in those patients who took vismodegib for three or more months[8]. Therefore, a three month course of vismodegib followed by prompt Mohs micrographic surgery may result in improved outcomes for patients with cosmetically and functionally sensitive tumors, as well as decrease overall expense of treatment.

At the time of this writing, our patient had completed three months of vismodegib therapy and Mohs surgical referral had been placed, but surgical evaluation was not yet completed. The decision to continue vismodegib in the interim was made, since the side effects were not significantly impacting the patient's quality of life or overall health status.

We await histopathologic findings and final surgical result in order to fully evaluate the success of neoadjuvant vismodegib in this patient's case.

Conclusions and Considerations for Further Study

Vismodegib can be safely used in the setting of locally advanced basal cell carcinoma of the orbital region, and may be successful as a neoadjuvant therapy preceding Mohs micrographic surgery.

Cost considerations and medication side effects may support a shorter duration of treatment with vismodegib, as part of a treatment approach combined with Mohs micrographic surgery after reduction of tumor is achieved.

Available evidence is limited regarding neoadjuvant vismodegib, but current data shows reduced surgical defect size following a minimum of therapy for three months preceding surgical intervention.

Treatment with vismodegib may result in the replacement of tumor with fibrotic tissue, which confers a new clinical challenge.

As noted, further follow-up is required in this case, as the patient has been referred for surgical evaluation at the time of this writing.

References

1. Gill HS et al. Vismodegib for periocular and orbital basal cell carcinoma. JAMA Ophthalmol 2013; 131(12) 1591-1594.
2. Sekulic A et al. Efficacy and safety of vismodegib in advanced basal cell carcinoma. N Engl J Med 2012 Jun 7; 366 (23): 2171-9.
3. Sekulic A et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12 month update of efficacy and safety of vismodegib in advanced BCC. J Am Acad Dermatol 2015 Jun; 72(6):1021-6.
4. Maier T et al. Noninvasive monitoring of basal cell carcinoma treated with systemic hedgehog inhibitors: Pseudocysts as a sign of tumor regression. J Am Acad Dermatol 2014; 71:725-30.
5. Basset-Seguin N et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. Lancet Oncol 2015; 16:729-36.
6. Sobanko JF et al. Vismodegib: Hedgehog pathway inhibitor for locally advanced and metastatic basal cell carcinoma. J Drugs Dermatol 2013; 12 (suppl 10): s154-s155.
7. Alcalay J et al. Vismodegib as neoadjuvant treatment to Mohs surgery for aggressive basal cell carcinoma. J Drugs Dermatol 2015; 14(3):219-221.
8. Ally MS et al. An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high risk basal cell carcinoma. J Am Acad Dermatol 2014; 71:904-11.

Contact

Corresponding author:

Lauren Keller, PGY3
Palisades Medical Center
Dermatology Residency
7600 River Road
North Bergen, NJ
310-980-9580
laurenkeller311@gmail.com

A Rare Case of Segmental Neurofibromatosis

Yuri Kim, DO,* John Moesch, BA,** Frank Don, DO,*** Stanley Skopit, DO, MSE, FAOCD,**** Francisco A. Kerdel, MD,*****

*Dermatology Resident, 2nd year, Larkin Community Hospital/NSU-COM, South Miami, FL; **Medical Student, 3rd year, Philadelphia College of Osteopathic Medicine, Suwanee, GA; ***Dermatologist, Florida Academic Dermatology Center, Coral Cables, FL; ****Program Director, Dermatology Residency Program, Larkin Community Hospital/NSU-COM, South Miami, FL; *****Director of Inpatient Dermatology, Larkin Community Hospital/NSU-COM, South Miami, FL

INTRODUCTION

Segmental neurofibromatosis is a very rare subtype of the neurofibromatoses in which affected individuals have a segmental distribution of neurofibromas or pigmentary changes including café-au-lait macules or axillary freckling. It is an example of somatic mosaicism caused by a post-zygotic mutation in the NF-1 gene. Familial transmission and systemic complications is rare. We report a case of a 42 year old female diagnosed with segmental neurofibromatosis arising on her right neck and shoulder with no family history of neurofibromatosis.

CASE

A 42 year old female with a past medical history only significant for anxiety presented to our dermatology office complaining of "moles" on her right neck extending to her right shoulder. The patient stated that the bigger lesions had been there since birth and approximately ten years ago, smaller lesions erupted in the same region. The patient denied any symptoms including pruritus or pain. She denied any prior treatments. A complete review of systems was negative including any visual, hearing, or neurological complications. The patient denied any family history of neurofibromatosis.

Physical examination showed multiple pink-brown, dome-shaped papules and nodules extending unilaterally from her right lower neck to her right shoulder varying in size from 0.3-0.8 cm (Figure 1, 2). The patient did not have any signs of axillary freckling, café-au-lait macules, or Lisch nodules. An excisional biopsy of her right shoulder was performed. Histologic examination showed a well circumscribed nodule composed of delicate wavy fibrils of neural origin with elongated fibroblasts and some mucoid change in the stroma with a slightly irregular epidermis (Figure 3,4).

CLINICAL PHOTOS

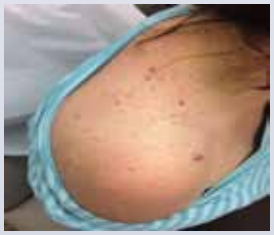


Figure 1- Segmental distribution of neurofibromas

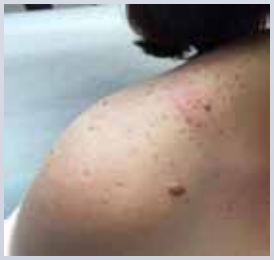


Figure 2- Closer view of segmental distribution of neurofibromas

PATHOLOGY

Figure 3 – Neurofibroma

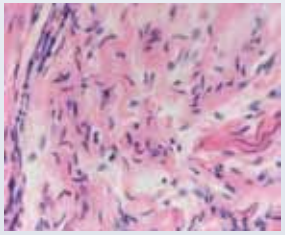


Figure 4- Delicate wavy fibrils of neural origin with elongated fibroblasts

DISCUSSION

Epidemiology and Classification:

Segmental neurofibromatosis (SN) is a rare clinical subtype of the neurofibromatoses. The most recent literature reports only 150 documented cases.[1] The prevalence ranges from .0014 to .002 percent.[2] The first reported cases of segmental neurofibromatosis were published in 1931 by Gammel and in 1956 by Crowe et al.[3] SN became labeled neurofibromatosis type V and was defined as café-au-lait macules and/or axillary freckling, and/or neurofibromas distributed in a single unilateral segment of the body, without midline crossing, family history, or systemic involvement.[3,4] In 1987, Roth observed that the diverse clinical presentations of SN would not fit into the rigid classification system created by Riccardi. He therefore divided SN into four subtypes: true segmental, localized with deep involvement, hereditary, and bilateral.[5]

Genetics:

While neurofibromatosis type I (NF1) is primarily inherited in an autosomal dominant fashion, the majority of SN patients have no consistence pattern of genetic transmission. It is generally considered a non-inheritable disorder. A literature review of 82 cases of SN showed that 93% of patients with SF had no family history.[6] However, exceptions to this rule exist and nine cases of SN transmitted to offspring in a familial pattern have been reported.[1] There has been two case reports of an offspring affected with generalized NF with the history of one of the parents having NF. The large majority of SN cases can be explained by a post-zygotic somatic mutation on the NF-1 gene present on chromosome 17.[7] The somatic mutation occurs during late embryonic development and results in mosaicism. Mosaicism occurs when cells in the body are of more than one genotype.

Somatic mosaicism is not transmitted to offspring because it does not affect gonadal cells. On the contrary, post-zygotic gonadal mosaicism occurs during the early embryonic period in cells that are not terminally differentiated.[8, 9] Gonadal mosaicism is believed to be the origin of the rare cases of familial transmission that can result in offspring with generalized NF-1.

Clinical Presentation:

The clinical presentation of SN is fairly typical between patients. However, rare presentations have been reported in the literature. The largest case review of SN was done by Hager in 1997.[6] He examined the clinical presentation of 82 patients with biopsy proven SN. He found that the median age of onset was 28 years old and that the incidence was higher in women (58%). Out of the 82 patients, 100% had neurofibromas, 26% patients had café-au-lait macules, and 10% had axillary freckling. Most neurofibromas were located unilaterally; however, 5 patients had bilateral neurofibromas. Most patients had only a single dermatome affected. Interestingly, recent case reports have documented patients with SN present on multiple dermatomes.[10] The cervical (38%), thoracic (40%), and lumbar (24%) dermatomes were the most commonly affected regions. Facial involvement is rare but has been reported on several occasions.[1] Fortunately, only 21% of patients had any additional systemic involvement. The most common systemic complaints in this study were painful neurofibromas (7 patients) and pruritic neurofibromas (4 patients). Another clinical finding appreciated in SN patients is an increase in clinical severity during puberty and pregnancy.[2] The increase in severity during pregnancy is directly related to increased activity of progesterone receptors on NF1 tumors cells.[2]

Association with Malignancy:

Recent literature has shown that patients with SN have an increased risk of developing malignant tumors. Ten patients with SN and malignancies have been reported to date. The incidence of malignancies in patients with SN is 5.3%, compared to the 7% life-time risk for cancer in documented in patients with NF1.[11] The two most common malignancies in patients with SN are malignant peripheral nerve sheath tumors and malignant melanoma.[12] This demonstrates the importance of surveillance of patients with SN for any suspicious cutaneous lesions or systemic symptoms.

Treatment:

The management of cutaneous manifestations of SN can provide immeasurable benefit to the patient. Current treatments for cutaneous manifestations of SN are limited and there is presently no consensus on standard therapy.[13] Cutaneous neurofibromas and café-au-lait macules that are bothersome to the patient can be removed. The most common technique to remove neurofibromas is simple surgical excision.[14] This may be time consuming and can result in pain and scarring. Laser ablation and electrocautery has been used on numerous smaller cutaneous neurofibromas, however, reoccurrences can occur.[14] Recent research has showed that CO2 laser treatment for neurofibromas can be effective and provide a high level of patient satisfaction and minimal pain. In one study using Lunmeis 30c CO2 laser, more than 90% of the 106 patients in the study were pleased with the treatment. The drawback to the treatment was a 15% local infection rate and hypertrophic scarring.[15] Another study using a combination of shave excision and laser photothermocoagulation with 1,444 nm Nd:YAG laser showed excellent results. A seven month follow-up showed no visible recurrence of neurofibromas or scars.[13] Similarly, treatment of neurofibromas with electrocautery was effective. Electrocautery allows for quick treatment of numerous lesions with instant hemostasis and minimal thermal damage to surrounding tissue. In one study, all 97 patients treated with electrocautery were satisfied with the results and had minimal scarring.[16]

CONCLUSION

SN is a rare and atypical variant of neurofibromatosis. Our case represents a typical clinical presentation of SN without generalization. The patient denied any familial history of neurofibromatosis or systemic complaints. The patient has one healthy offspring with no signs of neurofibromatosis. Close monitoring is vital for all patients with SN. Additionally, the cutaneous manifestations of SN can inflict emotional distress on patients. Counseling and cosmetic treatments should always be offered to patients. In addition to counseling, our patient had shave removal of the larger neurofibromas and electrocauterization of the smaller lesions with no complications

REFERENCES

1. Jankovic I, Visnjic M, Velickovic M, et al. A unique case of hereditary bilateral segmental neurofibromatosis on the face. An Bras Dermatol. 2012 Jul 7; 87(6): 895-898.

2. Maldonado P, Cudos E, Morel L, et al. Bilateral segmental neurofibromatosis diagnosed during pregnancy. Dermatology Online Journal [Internet]. 2011 [cited 2015 May 6]; 17(5):6. Available from: http://escholarship.org/uc/item/85x550h8.

3. Sobjanek M, Dobosz-Kawalko M, Michajtowski I, et al. Segmental neurofibromatosis. Postep Derm Alergol. 2014 Dec; 6: 410-412.

4. Adigun C, Stein J. Segmental neurofibromatosis. Dermatology Online Journal. 2011[cited 2015 May 6]; 17(10): 25. Available from: http://escholarship/uc/item/8m71w0wh.

5. Roth M, Martines M, James W. Segmental neurofibromatosis. Arch Dermatol. 1987; 123: 917-920.

6. Hager C, Cohen P, Tschen J. Segmental neurofibromatosis: Case reports and review. J Am Acad Dermatol. 1997; 37(5):864-869

7. Ticshert S, Naumann I, Stegmann E, et al. Segmental neurofibromatosis is caused by somatic mutation of the neurofibromatosis type 1 (NF1) gene. Eur J Hum Genet. 2000; 8:455-459.

8. McLimore M, McCaughey C, Vanness E. A case of late-onset Segmental Neurofibromatosis. Wisc Med J. 2014 Apr; 113(2): 72-73.

9. Oguzkan S, Cinibis M, Ayter S, et al. Familial Segmental Neurofibromatosis.J Child Neurol. 2004 Sep 25; 19(5): 392-394.

10. Lee S, Roh S, Kim S. Multiple segmental neurofibromatosis.J Dermatol. 2012 Sep; 39(9): 810-811.

11. Sloan J, Fretzin D, Bovenmyer D. Genetic counseling in segmental neurofibromatosis. J Am Acad Dermtol. 1990 Mar; 22(3): 461-467.

12. Dang JD, Cohen PR. Segmental neurofibromatosis and malignancy.Skinmed.2010 May; 8(3): 156-159.

13. Kim HJ, Lee KG, Yi SM, et al. Successful treatment of multiple cutaneous neurofibromas using a combination of shave excision and laser photocoagulation with a 1,444 nm neodymium-doped yttrium alminmum garnet laser. Dermatol Surg. 2012 Jun; 38 (6): 960-963.

14. Sabantini C, Milani D, Menni F, et al. Treatment of neurofibromatosis type 1. Curr Treat Options Neurol. 2015 Jun; 17(6):26

15. Meni C, Sbidian E, Moreno J, et al. Treatment of neurofibromas with carbon dioxide laser: A retrospective cross-sectional study of 106 patients.Dermatology [Internet]. 2015 Feb 3[cited 2015 May 8]; 230: 263-268. Available from: http://www.karger.com/Article/Pdf/368078

16. Levine SM, Levine E, Taub PJ, et al. Electrosurgical excision technique for the treatment of multiple cutaneous lesions in neurofibromatosis type I. J Plast Reconstr Aesthet Surg. 2008 Aug; 61(8): 958-962.

Necrobiosis Lipoidica: An atypical presentation on the scalp

Pam Kittipongdaja DO[1], Rachel Cetta DO[2],
Nicole Hoxworth MD[3], Stephen Kessler DO[4]

[1]Dermatology Resident, 2nd year, Orlando Dermatology Residency, Orlando, FL
[2]Traditional Rotating Intern, Oakwood Southshore Medical Center, Trenton, MI
[3]Dermatopathologist, Arizona Dermatopathology, Scottsdale, AZ
[4]Program Director, Alta Dermatology/LECOMT, Mesa, AZ

Introduction

Necrobiosis lipoidica (NL) is a type of granulomatous dermatitis that classically appears on the lower extremities, particularly the pretibial surface. However, a few case reports have identified atypical presentation of lesions on the face, penis, trunk, scalp, and upper extremities. The disease has once been called Necrobiosis Lipoidica Diabeticorum as it was thought to be associated with diabetes. NL by itself is the preferred term as only 0.03%-1.2% of patients with diabetes have NL.[1] When NL is presented in an unusual location, other disease entity such as necrobiotic xanthogranula (NXG) should be considered. Histopathologically, NL can look similar to NXG, which also falls into a category of granulomatous reaction pattern. We review the pathologic similarities of these two conditions and discuss treatments for both types of granulomatous dermatitis.

Case report

An 85 year-old Caucasian male presents with a three-month history of nodular lesions on his left frontal scalp. The lesions are completely asymptomatic. His past medical history is significant for rheumatoid arthritis, asthma, irregular heart rhythm, and TIA. His medications include Prilosec, Lasix, Fosamax, synthroid, potassium, aspirin, hydrocodone, and Tylenol.

Physical exam reveals a group of firm, skin-colored nodules about 1 cm in size without epidermal disruption on the left frontal scalp. A 3mm punch biopsy was performed. Histopathology revealed atypical necrobiosis lipoidica with evidence of a kappa light chain restricted atypical plasma cell infiltrate. This finding favors a paraneoplastic necrobiosis lipoidica tissue reaction in the setting of an underlying plasma cell dyscrasia. The case was sent for a consultation to Dr Cynthia Magro at Cornell who recommended a bone marrow biopsy and serum protein electrophoresis (SPEP) for further assessment.

On follow up, patient underwent an SPEP, which reveals no abnormality. He was subsequently referred to an oncologist for further evaluation. Since the biopsy was done, the nodule on the scalp has not grown and no new symptoms were noted. As a result, he decided not to pursue additional testing.

Discussion

Necrobiosis lipoidica (NL) is a rare granulomatous disease. The cause and pathogenesis is not well understood, but many theories have been presented. The most commonly proposed theory involves vascular disturbance with immune complex deposition or microangiopathic changes, which contributes to the development of collagen degeneration and subsequent dermal inflammation.[2,9] The vascular abnormalities seen in NL are thickening of the vessel walls, fibrosis, and endothelial proliferation leading to occlusion in the deeper dermis. These characteristics were more prominent in diabetic patients than nondiabetics.[9] Age of onset is typically around the third decade of life in patients with type 1 diabetes and fourth decade in patients with type 2 diabetes and in nondiabetics.[1] The disease affects more females than males at a 3:1 ratio.[2] Clinically, the lesion begins as multiple, small, firm, red-brown papules that gradually enlarge and coalesce into plaque. Over time these plaques become atrophic and develop central telangiectasias.[6] Although the majority of lesions are painless as a result of associated nerve damage, some lesions can be painful. Ulceration can occur in up to 35% of cases following minor trauma.[1] In addition, there have been reports of squamous cell carcinoma developing within long-standing NL plaques.[2]

NL can have similar appearance to other skin disease, particularly when the lesions occur on less common body sites. We consider necrobiotic xanthogranuloma (NXG) on our differential because of the location of the lesion and the numerous atypical plasma cells infiltrates. NXG typically affects the periorbital area (>80%) but can also occur on the trunk and extremities. The typical presentation consists of multiple, indurated, yellow-brown plaques or nodules.[3] A hallmark feature of NXG is the associated IgG monoclonal gammopathy found in 80% of patients. The most common type of paraproteinemia is IgG-kappa monoclonal gammopathy with IgG-lambda as the runner up. Patients with MGUS and NXG may have an increased risk of developing multiple myeloma and need to be monitored closely. NXG is locally destructive and can affect multiple organ systems.[7] The diagnosis of NXG should prompt a thorough workup for hematologic and lymphoproliferative malignant condition, which typically manifest approximately 2.4 years after development of the skin lesions.[7]

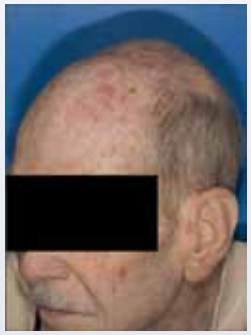
Histologically, both entities display full thickness involvement extending down to the subcutis. NL is described as looking like layers on a cake, having horizontal palisading granulomas interspersed with degenerated pale collagen.[4] Plasma cells can be seen in both entities as well as the presence of lymphoid nodules. NXG generally has broader zones of necrobiosis with granulomatous foci composed of histiocytes, foam cells, and multinucleated giant cells.[5] It is often more cellular with prominent touton and foreign body giant cells. In addition, NXG will commonly display cholesterol clefts in the area of necrobiosis.

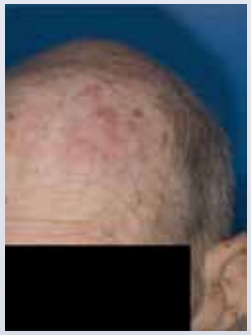
NL is difficult to treat, and there are no established treatment regimens. A multitude of case reports have described the use of several treatments, which include topical and intralesional steroids, calcineurin inhibitors, intralesional infliximab, antimalarials, cyclosporine, TNFα, PUVA, hyperbaric oxygen, and co2 laser.[1] First line treatment is topical and intralesional corticosteroids. The use of corticosteroids should be monitored in diabetic patients especially when used on a large surface area to prevent glucose dysregulation.[1] It should be applied to the active borders of the lesions and not to the atrophic area as this may possibly worsen the atrophy.[1]

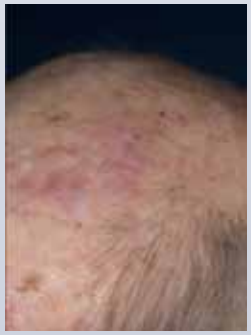
Similar to NL, NXG is also difficult to treat. Some recommendations include topical, lesional, or systemic corticosteroids. Chlorambucil, cyclophosphamide, interferon alpha, antimetabolites, antibiotics, thalidomide, plasmapheresis, and IVIG have also been tried with some success.[7] Surgery is not recommended, as there is a high recurrence rate.[2]

In conclusion, this case demonstrates an unusual presentation of necrobiosis lipoidica on the scalp in the setting of plasma cell dyscrasia. NL and NXG may, perhaps, represent a spectrum of related disease. Therefore, it is important to give a full workup with patients in this type of scenario in case of underlying disease or systemic involvement as there are overlapping histopathologic characteristics.

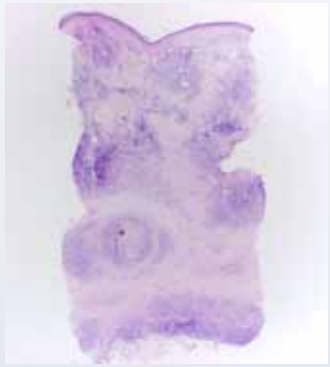
Clinical Photos



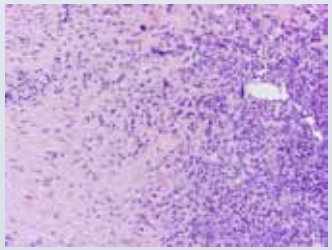




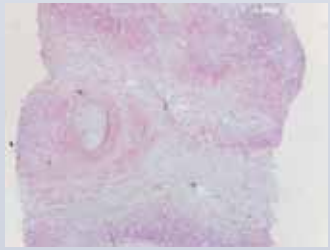
Histopathology



Rectangular punch biopsy showing layers of palisading granulomas interspersed with degenerated pale collagen



The cellular area is infiltrated with numerous plasma cells that are well-differentiated



Immunohistochemical stain showing CD68+ plasma cells

Selected References

1. Reid S, Ladizinski B, Lee K, Baibergenova A, Alavi A. Update on necrobiosis lipoidica: a review of etiology, diagnosis, and treatment options. J Am Acad of Derm. 2013;69(5), 783-791.
2. Bolognia JL, Jorizzo JL, Schaffer JV, ed. Dermatology. 3rd ed. Philadelphia: Elsevier Saunders; 2012. p1566-1568.
3. Finan MC, Winkelmann M. Necrobiotic Xanthogranuloma with paraproteinemia: a review of 22 cases. Medicine (Baltimore). 1986 Nov;65(6): 376-88.
4. Elston DM, Ferringer T. Dermatopathology. 2nd ed. China: Elsevier Saunders; 2014. p174-177.
5. Weedon D. Weedon's Skin Pathology. 3rd ed. China: Churchill Livingstone Elsevier; 2010. p181-183.
6. Brinster NK, Liu V, Diwan AH, McKee PH. Dermatopathology. Philadelphia: Elsevier; 2011. p92,97-98.
7. Rose A, Robinson M, Kamino H, Latkowski J. Necrobiotic xanthogranuloma. *Dermatology Online Journal* [internet]. 2012 [cited 2015 June 14]; 18(12):30. Retrieved from: http://escholarship.org/uc/item/0rr0b85w
8. Muller S.A., and Winkelmann R.K.: Necrobiosis lipoidica diabeticorum. A clinical and pathological investigation of 171 cases. Arch Dermatol 1966; 93: pp. 272-281
9. Sibbald C, Reid S, Alavi A. Necrobiosis Lipoidica. Dermatologic Clinics. 2015; 33(3): 343-60.

Regression of Nevi After Candida Injection for the Treatment of Verruca Vulgaris

Emily Kollmann DO, David Cleaver DO, Lloyd Cleaver DO

Northeast Regional Medical Center, ATSU-KCOM

Abstract

Importance: Many treatments exist for verruca vulgaris. The most common treatment methods are destructive methods that are often painful and treat individual verruca. Thus immune modulators including, Candida immunotherapy, are used to treat persistent recalcitrant and multiple verruca simultaneously.

Observation: Very few serious side effects are reported with Candida immunotherapy including vitiligo and now halo nevi.

Conclusions and Relevance: Physicians need to be aware and discuss side effects with patients receiving Candida immunotherapy.

Introduction

Verruca vulgaris is a viral induced disease frequently seen in children. Treatment is often difficult for both the patient and the physician. Destructive methods such as cryotherapy, cantharidin, laser ablation and excision are used most commonly to treat verruca. Destructive methods are often painful and treat only individual lesions. Methods such as Candida immunotherapy were developed to treat numerous verruca simultaneously with less pain. Candida immunotherapy presumably enhances recognition of the virus by the immune system allowing for distant recognition and clearing (1). It is possible that alerting the immune system to the human papillomavirus could alert the immune system to other entities such melanocytes or nevus cells. Thus, resulting in the onset of vitiligo and halo nevi.

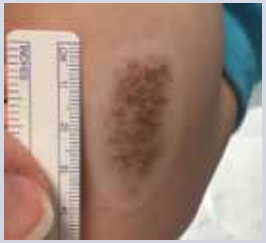


Figure 1 – Regression of her congenital nevus at third visit

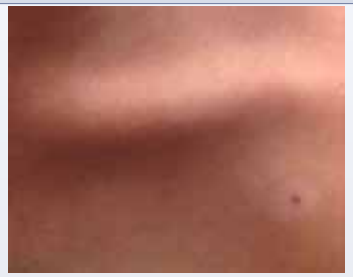


Figure 2 – Regression of nevi at third visit

Case Report

A seven year old female with no significant past medical history presented with a single verruca vulgaris on the left anterior medial malleolus. The lesion was pared with a 15 blade and treated with liquid nitrogen. The lesion was also injected with 0.1 ml of Candida antigen. At the first visit, a normal appearing congenital nevus was also noted on the right distal posterior upper arm measuring 3.5 cm by 1.5 cm. The patient returned for follow up a month later. The verruca vulgaris was treated with a second 0.1 ml Candida antigen injection. Her congenital nevus developed a surrounding area of depigmentation. At her third follow up visit a month later; her verruca was treated with a third Candida antigen injection of 0.1 ml. At this visit, her other benign appearing nevi developed areas of surrounding depigmentation in addition to her congenital nevus seen in Figure 1 and 2. At her fourth follow up appointment one month later, the verruca was again treated with a fourth Candida antigen injection of 0.1 ml. The patient did not return for five months. At that time, the verruca had resolved. The perilesional depigmentation of the congenital nevus remained and the pigmented area had regressed to measure 3.1 cm by 1.2 cm. Similarly, her other small nevi showed perilesional depigmentation and regression. Two of her nevi had completely regressed leaving areas of depigmentation seen in Figure 3. She was seen six months later in which her congenital nevus continued regressing, seen in Figure 4. She also began to develop larger areas of depigmentation in which topical steroids were prescribed to halt the progression.

Discussion

Candida antigen is a commonly used immune modulator used to treat recurrent, recalcitrant or multiple verruca. However, the same immunomodulating technique has been conducted using paramxyovirus and trichophyton. Other immune modulators include imiquimod and contact sensitizers such as diphencyprone and squaric acid dibutyl ester. There are accounts of Candida immunotherapy inducing vitiligo (2). The induction of vitiligo may occur secondary to immune modulators that may induce cytotoxic effects on melanocytes or by revealing occult disease through koebnerization (3, 4, 5). It has also been proposed through a murine model that vitiligo is induced secondary to a local inflammatory response secondary to the trauma of the injection (6). Similarly, the regression of nevi in our patient could be secondary to the induction of cytotoxic effects on the nevus cells as distant nevi began to regress. Thus physicians should educate patients and their parents that regression of nevi and the onset of vitiligo are possible side effects from Candida immunomodulating therapy.

Figure 3 - Complete regression of nevi at fourth visit

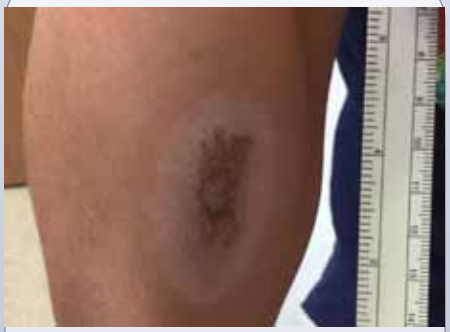


Figure 4 – Regression of her congenital nevus at the sixth visit

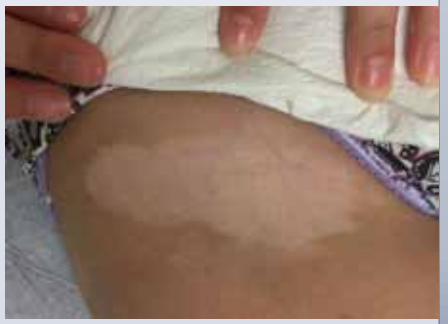


Figure 5 - Depigmented patch from the sixth visit

References

Johnson SM, Roberson PK, Horn TD. Intralesional injection of mumps or *Candida* skin test antigens: a novel immunotherapy for warts. *Arch Dermatol.* 2001; 137:451-455.

Wilmer E, Burkhart C, Morrell, D. Goodbye Warts, Hello Vitiligo: Candida Antigen-Induced Depigmentation. *Ped Dermatol.* 2013; 30(6): e214-e215.

Mashiah J, Brenner S. Possible mechanisms in the induction of vitiligo-like hypopigmentation by topical imiquimod. *Clin Exp Dermatol.* 2008; 33:74-76.

Brown T, Zirvi M, Cosarelis G et al. Vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts. *J Am Acad Dermatol.* 2005; 52:715-716.

Lane C, Leitch J, Tran X et al. Vaccination-induced autoimmune vitiligo is a consequence of secondary trauma to the skin. *Cancer Res.* 2004; 64:1509-1514.

Autoimmune Progesterone Dermatitis

Matthew Laffer, DO; Peter Jajou, DO; Steven Grekin, DO; Jean Holland, MD

Department of Dermatology, Oakwood Hospital Healthcare System, Trenton, Michigan

Case Presentation

History of Present Illness

A 35-year-old Caucasian female presented with a long-standing history of a treatment resistant, relaspsing-remitting urticarial rash diffusely over her entire body. She reported that the lesions had first developed five years prior after discontinuing depo-provera, which she had been taking for the previous 13 years. She noted that the rash would appear (# of days) before her menses and would resolve one to two days after. She also noted that the rash completely resolved during pregnancy and remained absent during lactation, only to recur after discontinuation of breastfeeding. The patient had been treated previously with antihistamines and topical corticosteroids that were ineffective at controlling symptoms, and oral prednisone that was only effective at high doses. She denied any family history of similar conditions. Her medical history was unremarkable and she was not currently on any medications. A review of systems was negative for preceding illness, recent weight loss, or constitutional symptoms.

Work-up

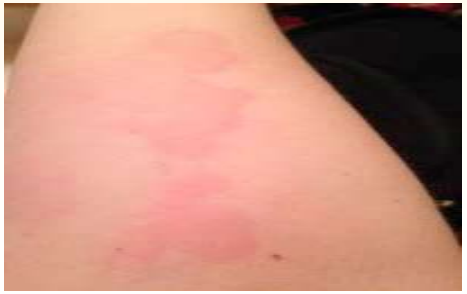
CBC with differential, C3, C4, CH50, and C1Q, TSH, ESR were performed and all laboratory results were within normal limits.

Physical Examination

Physical examination revealed diffuse erythematous wheals involving bilateral flanks and neck and mild swelling of the eyelids.

Course and Therapy

Based on history and clinical examination, a diagnosis of autoimmune progesterone dermatitis was made. The patient was initially given an intramuscular triamcinolone injection that resulted in minimal improvement of the rash. Based on the patient's presumed diagnosis, a trial of oral contraceptives was prescribed. The patient began a daily progestational agent (Mini Pill). With this treatment regimen the patient's condition has been well controlled and limited to one outbreak over the past six months



Discussion

Autoimmune progesterone dermatitis (APD) is a rare disease caused by an autoimmune response to endogenous progesterone.[1] APD primarily occurs in women during their reproductive years, commonly around the luteal phase of menstrual cycle when progesterone levels reach their peak. In rare cases, men being treated with synthetic progesterone preparations have also been reported to also be afflicted.[2] Additionally, reports of familial APD have been described. To date, there have been approximately 60 previously reported cases.[2]

The dermatological features of APD can vary morphologically, but the most commonly described are urticaria, eczema, and erythema multiforme.[3] Other findings have included angioedema, deep gyrate lesions, papulovesicular lesions, targetoid lesions, or anaphylaxis.[1] Often patients with eczematous skin lesions are frequently misdiagnosed with eczematous dermatitis or allergic contact dermatitis, leading to delays in treatment.[4]

The pathogenesis of APD remains unclear. One theory proposes that after exposure to exogenous progesterone, sensitized presenting cells and T helper 2 lymphocytes generate specific IgE antibodies, which then cause skin lesions via a type 1 hypersensitivity reaction as progesterone levels rise. This idea is further supported by findings of eosinophilia in peripheral blood.[4] Positive skin tests and intramuscular challenges to progesterone or its derivatives have provided evidence for a Th2 immune mechanism, with acute and delayed responses consistent with both type I and type IV hypersensitivity reactions.[5] Additionally, reports of the presence of anti-progesterone antibodies suggests other pathogenic mechanisms, including type III hypersensitivity reaction to antigen-antibody complexes that are deposited in the skin, which could induce dermatitis as progesterone secretion increases before and after menstruation.[4] However, this antibody is not detected in all patients, which only partially explains the pathogenesis.[4]

The histological findings of APD may be extremely variable. A dermal perivascular infiltrate composed of mixed lymphocytes and eosinophils is a commonly found pattern, while the immunofluorescence studies are usually negative.[2] Similarly, other reports show inflammatory cell infiltration around follicular and perivascular tissues with increased dermal eosinophils.[4]

The diagnostic criteria for autoimmune progesterone dermatitis proposed by Warin includes: (1) skin lesions related to the menstrual cycle, (2) positive response to intradermal testing with progesterone, and (3) symptomatic improvement after inhibiting progesterone secretion by suppressing ovulation.[6]

A host of treatment options for APD have been reported with varying degrees of success. Autoimmune progesterone dermatitis is not very responsive to antihistamines or corticosteroids.[7] Treatments center on the theme of suppressing ovulation and first line therapy is combined oral contraceptives.[1] GnRH agonists has been reported successful in treatment (Baptist p3). Another therapeutic agent used to suppress ovulation and improve symptoms is tamoxifen.[8] For refractory cases that do not respond to medical management, bilateral oophorectomy has been successful.[9]

References

1. George, R., Shawky Z., Badawy, A. Autoimmune Progesterone Dermatitis: A Case Report, Case Reports in Obstetrics and Gynecology, vol. 2012, Article ID 757854, 2 pages, 2012. doi:10.1155/2012/757854
2. Toms-Whittle, L. M., John, L. H., Griffiths, D. J. and Buckley, D. A. (2011), Autoimmune progesterone dermatitis: a diagnosis easily missed. Clinical and Experimental Dermatology, 36: 378–380. doi: 10.1111/j.1365-2230.2010.03979.x
3. Asai, J., Katoh, N., Nakano, M., Wada, M. and Kishimoto, S. (2009), Case of autoimmune progesterone dermatitis presenting as fixed drug eruption. The Journal of Dermatology, 36: 643–645. doi: 10.1111/j.1346-8138.2009.00723.x
4. Myoung Kyu Lee, Won Yeon Lee, Suk Joong Yong, Kye Chul Shin, Shun Nyung Lee, Seok Jeong Lee, Ji-Ho Lee, Sang-Ha Kim. A Case of Autoimmune Progesterone Dermatitis Misdiagnosed As Allergic Contact Dermatitis. Allergy Asthma Immunol Res. 2011 April; 3(2): 141–144. Published online 2011 February 9. doi: 10.4168/aair.2011.3.2.141
5. Prieto-Garcia A, et al. Autoimmune progesterone dermatitis: clinical presentation and management with progesterone desensitization for successful in vitro fertilization. Fertility and sterility (2011) 95(3): 1121.e9-13. DOI: 10.1016/j.fertnstert.2010.10.038
6. A.P. Warin, "Clinical pathological cases - Case 2", CLIN EXP D, 26(1), 2001, pp. 107-108
7. Stephens CJ, Wojnarowska FT, Wilkinson JD. Autoimmune progesterone dermatitis responding to Tamoxifen. Br J Dermatol. 1989;121:135–137
8. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. Clinical and Molecular Allergy. 2004;2, article no. 10
9. Rodenas JM, Herranz MT, Tercedor J: Autoimmune progesterone dermatitis: treatment with oophorectomy. Br J Dermatol 1998, 139:508-511

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Merkel Cell Carcinoma; A case of a rare disease

Stephanie Lasky, DO
St. John's Episcopal Hospital, Far Rockaway, NY - Dermatology
Program Director- Suzanne Sirota-Rozenberg, DO
DME- Albert Strojan, DO

Introduction:

Merkel cell carcinoma (MCC), also known as neuroendocrine carcinoma, is a rare disease with around 1,500 cases per year in the Unites States. Because MCC is often fatal, diagnosis and immediate treatment are necessary. MCC usually presents in sun-exposed areas, with a small, painless, red-blue colored papule which grows rapidly over weeks and months, with the ability to metastasize. Risk factors include fair skin, sun exposure, age over 65, female gender, and chronic immunosuppression. MCC arises from highly anaplastic cells, that are noted to have similar structure and histological findings to those with neuronal and hormonal function. Although the exact cause of the carcinoma is unclear, recent studies have found a possible link between a polyomavirus found in MCC tissue as a possible cause of the disease. Treatment is determined by the progression of disease at time of diagnosis. Complete surgical excision of the lesion, followed by sentinel lymph node biopsy is the initial treatment. The need for radiation therapy or chemotherapy, are determined on a case by case basis.

Case Study:

My patient was a 90 year old Hispanic female who presented to clinic with a 3 month history of a tender, growing lesion to her left upper extremity. The patient had a past medical history which included diabetes and hypertension, both controlled by medications and followed by her PMD. She denied any fever, weight loss, lethargy or personal/family history of skin cancers. Physical exam showed a red-violaceous "juicy" appearing round nodular plaque to the posterior aspect of the patients left upper arm. No other lesions were noted throughout the rest of the physical exam. There was no lymphadenopathy noted. A shave biopsy of the lesion was done, which showed histology consistent with a merkel cell carcinoma. Pt was referred to an oncologist, and subsequently lost to follow up.

Discussion:

Epidemiology:
Most commonly presents in the elderly population, with an increased female to male ratio. Other risk factors include UV-exposure and fair skin.

Pathogenesis:
MCC is recognized as being a "primary neuroendocrine carcinoma of the skin," due to the similarities noted in this tumor with normal merkel cell findings (as well as other neuroectoderm cells). The merkel cell, is found in the basal layer of the epidermis and is recognized as a receptor touch cell. Recent studies have shown an association between merkel cell carcinoma and a merkel cell polyomavirus (MCV). 80% of patients noted to have MCC, are found to carry the virus, and evidence shows that the MCV plays a caustic role in most MCC. The remainder of cases of MCC without the presence of the MCV, have a different etiology.

Clinical Manifestations:
Although most often found on the head and neck, MCC can also be found in the extremities and buttocks. It most commonly presents as a pink-red to violaceous, firm, dome shaped, nodule with a rapid growth cycle. There is a high risk of recurrence after excision of the lesion. The size of the tumor is a determining factor in patient prognosis; lesions >2 cm have a 51% 5-year survival rate, whereas those lesions <2 cm have a 5-year survival rate of 66%. Lymph node involvement and metastasis further lower the patients' overall 5-year survival rate.

Diagnosis:
Initial diagnosis is done by biopsy of the skin lesion in question. Once the lesion is biopsied, it is looked at under a microscope for distinguishing features specific to a merkel cell carcinoma. Biopsy of a portion, or the entire lesion, is done. In order to determine if there is any spread of cancer cells, a PET or CT scan of the body is done in patients with lesions >2 cm, or with symptoms suggestive of lymph node involvement. Sentinel node biopsy may be done to determine lymph node involvement, and progression of spread.

Pathology:
The MCC tumor presents as a poorly defined mass, noted in the dermis. The mass often infiltrates into the subcutaneous fat, fascia and muscle. The growth pattern most commonly seen is a sheet-like pattern, followed by a nested pattern, and then a trabecular pattern. The growth pattern is composed of monomorphic small blue cells with small amounts of cytoplasm. Nuclear molding, apoptosis, and mitoses are often seen in these cells. Staining for specific neuroendocrine markers, as well as immunohistochemical findings further aid in the diagnosis of MCC. CK20 (a low molecular weight cytokeratin) often stains positive in a perinuclear globule pattern, and markers such as synaphtophysin, chromogranin, and neuron-specific enolase, stain positive as well. PCR can be employed to determine the presence of merkel cell polyomavirus, however false-positive PCR are commonly seen. The presence of p63 expression further shows an increase to the aggressive nature of the tumor.

Treatment:
Initial treatment in MCC is surgical excision. Depending on the tumor stage, radiation therapy and chemotherapy may be indicated. The presence of palpable lymph nodes on physical exam, indicate the need for biopsy of the node. Whereas, non-palpable lymph nodes on exam indicate the needs for wide-local excision with sentinel lymph node biopsy, and further treatment dependent on sentinel node biopsy results.

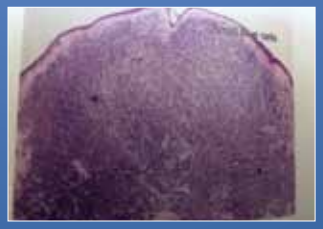
Conclusion:

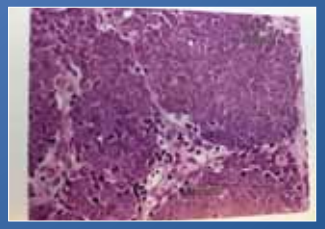
Although a rare disease, the immediate identification of a Merkel Cell Carcinoma is of extreme importance in providing treatment and improving patient prognosis. While the exact cause is unknown, further investigation into a viral etiology is of interest in finding new treatment modalities, and provides new insight into a possible viral-oncologic relationship.

Images:

Left lateral-posterior upper arm

Pathology:





-Small blue cells with minimal amounts of cytoplasm
-Tightly packed nuclei in sheets
-Apoptosis, mitosis also seen
-Usually localized to dermis
-Immunohistochemical stains positive for CK20, CD56, chromogranin, synaptophysin, neurofilament

References

Feng, H. M. Shuda, et al. (2008). "Clonal Integration of a polyomavirus in human Merkel Cell Carcinoma." *Science* 319 (5866); 1096-100.

"Our Viruses-MCV." *Our Viruses-MCV*. Change-Moore Laboratory, 2009. Web. 27 Jan 2015.

Bologna J, Jorizzo J et al. Dermatology. Philadelphia: Elsevier Saunders, 2015.

Elston DM, Ferringer T et al. Dermatopathology Philadelphia: Elsevier Saunders, 2015.

Dermatofibrosarcoma Protuberans: Case Report of a Bednar Tumor

Chelsea Loy DO, Michael Peterson DO, Devin Burr, DO

Aspen Dermatology/OPTI-West

Case Report

A twenty-one year old Caucasian male was referred to our dermatology clinic for evaluation of a 2.5 x 1.4 cm black nodule located on his right anterior arm (Figure 1). The patient and his family were very concerned that he may have malignant melanoma as his maternal grandmother recently died from it. The lesion had been present for three years, and over the past several months had been growing in size. There were no associated symptoms with the lesion, and it previously has not been treated.

An excisional biopsy with 2 cm margins was obtained. Histopathology demonstrated a large asymmetrical deep spindle-cell neoplasm extending into the septa and lobules of the subcutis. Within the dermis, there were interwoven bundles of fibroblastic spindle-cells with plump nuclei in a cartwheel or storiform appearance. There was also intermittent deposits of melanin containing dendritic cells (Figure 2). Immunohistochemical stains were diffusely positive for CD34 (Figure 3), while S-100, MART-1, Factor XIIIa (Figure 4), HMB-45 and AE1/AE3 were all negative. A diagnosis of a pigmented Dermatofibrosarcoma Protuberans, or Bednar tumor, was made. The patient was evaluated by an oncologist and declined radiation treatment. He was tumor free at his 6 month follow up.

Discussion

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue sarcoma that can be locally aggressive, but has a low risk of metastasis. DFSP is considered rare as it causes 0.1% of all malignancies and about 1% of all soft-tissue sarcomas.[1, 2] In the United States, DFSP has an incidence between 0.8 and 4.5 cases per million individuals annually.[1] While DFSP can develop at birth or much later in life, it typically occurs during the third and forth decades.[3] African Americans have a higher incidence of DFSP compared to Caucasians.[4] In a study of 2885 cases over 30 years, DFSP was found in twice as many African Americans than Caucasians, with relatively equal incidence in females and males.[5] DFSP tumors can occur in various locations on the body, but it has a higher propensity to develop on the chest and trunk.[1]

Multiple subtypes of DFSP have been identified including the following: DFSP with areas of giant cell fibroblastoma, DFSP with fibrosarcomatous areas, myxoid, granular, atrophic and sclerotic.[1] The rare pigmented variant of DFSP is known as the Bednar tumor. Bednar tumors predominantly occur in African Americans and account for 1%-5% of all DFSP.[1, 6] The tumor displays spindle cells arranged in a storiform pattern with scattered melanin-bearing dendritic cells causing the tumor to appear blue or black.[1]

The appearance of a DFSP tumor can vary given the slow growth for an extended period before entering a rapid growth phase. In the early stages, DFSP typically presents as an asymptomatic violaceous, red-blue or brown plaque with a firm texture that is generally fixed to the skin, but not underlying tissue.[1] Clinical variations do exist in the preprotuberant stage. If DFSP develops during childhood, it can be morphea-like with a white or brown indurated plaque resembling morphea, morpheaform basal cell carcinoma, scar or dermatofibroma plaque.[7]

DFSP is often associated with a translocation on the 17/22 ring chromosome.[8] The distal long arm of chromosome 17 houses the 17q25 translocation breakpoint, potentially causing an extra copy number and/or poor regulation of an oncogene, a possible contributor to the neoplastic initiation or progression of DFSP.[8]

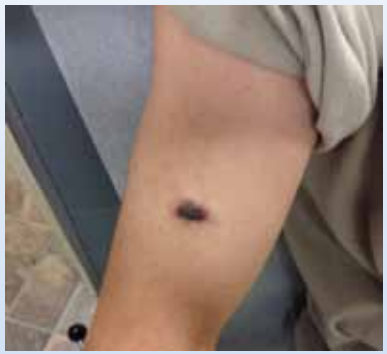


Figure 1. A 2.5 x 1.4 cm black well-circumscribed black nodule.

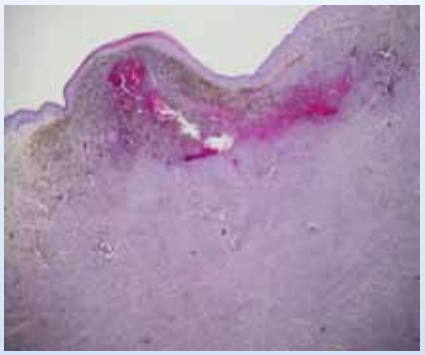


Figure 2. 2x magnification of the asymmetrical spindle-cell neoplasm extending through the dermis into the septa and lobules of the subcutis with intermittent deposits of melanin. (H&E)

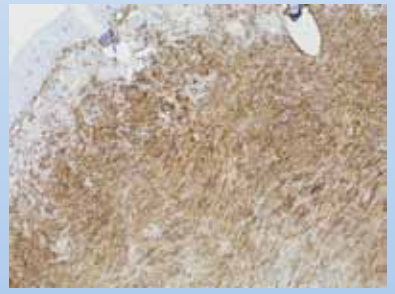


Figure 3. Diffusely positive CD34 stain.

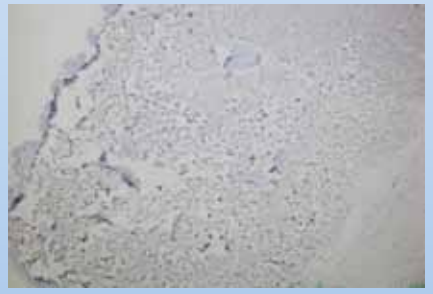


Figure 4. Negative Factor XIIIa stain.

Histologically, the hallmark of DFSP is the arrangement of spindle-shaped fibroblasts in a cartwheel-like, or storiform, pattern around a collagenous center. This appearance is due to the fibroblasts radiating from acellular collagen.[2] The tumor consists of cells with large pleomorphic nuclei and evidence of mitotic figures.[2] DFSP may contain mucin within its fibrous stroma usually below the epidermis, which is typically thin with flattened rete ridges.[1] Immunohistochemical staining classically is positive for CD34 and negative for Factor XIIIa, while dermatofibromas stain positive for Factor XIIIa and negative for CD34 thus aiding in the diagnosis.[1]

There are multiple treatment options available for DFSP. Wide surgical excision has been considered the treatment of choice for local DFSP.[2] Over time, determining adequate surgical margins has varied. Given its high recurrence rate, clinicians agree that the first resection should have sufficient surgical margins, anywhere from 3-5 cm.[1,2] The tumor has a high tenacity for invading localized tissue as histology studies have shown that DFSP displays tentacle-like growth into lateral normal collagen bundles and into deep fascia and muscle.[2] Mohs micrographic surgery (MMS) has been found to be a useful treatment option of DFSP with more supportive data compared to wide local excision.[2]

Radiation therapy has also been used as a treatment choice for DFSP. Occasionally it has been used as a primary treatment option, but it is more often used as an adjuvant therapy following surgery.[9]

Imatinib is considered the gold standard for locally advanced or metastatic DFSP.[1, 9] It can be used as a primary treatment or prior to surgery to decrease tumor burden.[9] The toxicity is typically minimal with the most common side effects being dyspepsia, nausea, vomiting, and myelosuppression.[1] With proper treatment DFSP can be successfully managed. The relative 5 and 15-year survivals for DFSP were 99.2% and 97.2% respectively, with minimal variation in survival among race and sex.[7]

Conclusion

In conclusion, although DFSP is considered a rare malignancy, clinicians should be aware of its variants and be knowledgeable of its treatments and workup. Even more rare is a Bednar variant of DFSP, as seen in our patient. When properly treated and with plenty of patient counseling, the prognosis of DFSP is quite good.

References

1. Llombart B, Serra-Guillén C, Monteagudo C, López Guerrero JA, Sanmartín O. Dermatofibrosarcoma protuberans: a comprehensive review and update on diagnosis and management. Semin Diagn Pathol. 2013 Feb; 30(1):13-28.

2. Gloster HM Jr. Dermatofibrosarcoma protuberans. J Am Acad Dermatol. 1996 Sep;35(3 Pt 1):355-74; quiz 375-6. Review. Erratum in: J Am Acad Dermatol 1997 Apr;36(4):526.

3. Marcus JR, Few JW, Senger C, Reynolds M. Dermatofibrosarcoma protuberans and the Bednar tumor: treatment in the pediatric population. J Pediatr Surg. 1998 Dec;33(12):1811-4.

4. Rouhani P, Fletcher CD, Devesa SS, Toro JR. Cutaneous soft tissue sarcoma incidence patterns in the U.S. : an analysis of 12,114 cases. Cancer. 2008 Aug 1;113(3):616-27.

5. Criscione VD, Weinstock MA. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. J Am Acad Dermatol. 2007 Jun;56(6):968-73. Epub 2006 Dec 1. PubMed PMID: 17141362.

6. Sirvent N, Maire G, Pedeutour F. Genetics of dermatofibrosarcoma protuberans family of tumors: from ring chromosomes to tyrosine kinase inhibitor treatment. Genes Chromosomes Cancer. 2003 May;37(1):1-19.

7. Stivala A, Lombardo GA, Pompili G, Tarico MS, Fraggetta F, Perrotta RE. Dermatofibrosarcoma protuberans: Our experience of 59 cases. Oncol Lett. 2012 Nov;4(5):1047-1055.

8. Naeem R, Lux ML, Huang SF, Naber SP, Corson JM, Fletcher JA. Ring chromosomes in dermatofibrosarcoma protuberans are composed of interspersed sequences from chromosomes 17 and 22. Am J Pathol. 1995 Dec; 147(6):1553-8.

9. Miller SJ, Alam M, Andersen JS, Berg D ,et al; National Comprehensive Cancer Network. Dermatofibrosarcoma protuberans. J Natl Compr Canc Netw. 2012 Mar;10(3):312-8.

Necrolytic Acral Erythema: a diagnostic hint to HCV

Bridget McIlwee DO[1], Joseph Susa DO[2], Stephen Weis DO[1]

[1]University of North Texas Health Science Center, Forth Worth, TX; [2]Cockerell Dermatopathology, Dallas, TX

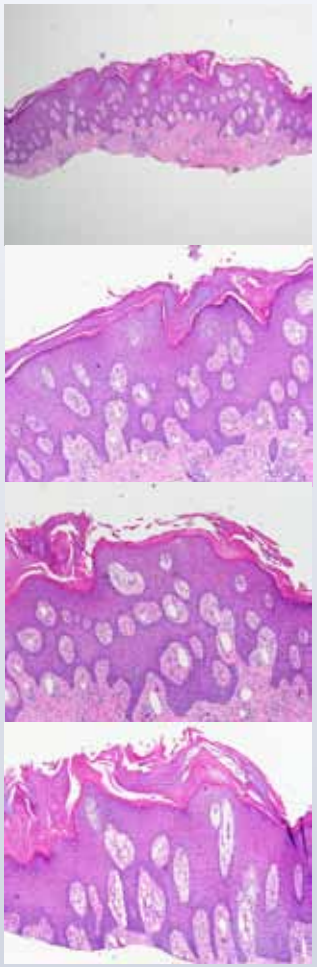
HISTORY

A 50-year-old diabetic Hispanic female with a history of untreated hepatitis C virus infection (HCV) and cirrhosis presented with a burning, minimally pruritic eruption on her lower legs for 2 years (Figures 1-3). She was treated unsuccessfully for psoriasis with calcipotriol and triamcinolone 0.1% ointment. She had then self-treated the areas with several unidentified creams, Vaseline, triple antibiotic ointment, Epsom soaks, rubbing alcohol, hydrogen peroxide, and scrubbing with a loofah.

PHYSICAL EXAM

Figures 1-3: On the bilateral lower legs are dusky, erythematous scaly plaques with small superficial erosions and a surrounding halo of hypopigmentation. The plaques extend from above the lateral malleoli to the dorsal feet.

HISTOPATHOLOGY



Figures 4-7: Histopathology showed a spongiotic psoriasiform dermatitis with an infiltrate of lymphocytes and histiocytes in the dermis. There was overlying hyperkeratosis with focal parakeratosis without neutrophils. There was also slight pallor of the superficial epidermis and a decreased granular cell layer with focal dyskeratosis..

LABORATORY DATA

Histopathology consistent with necrolytic acral erythema (figures 4-7).Serum laboratory results were within normal, with exception of following abnormals (normal reference range):

- Albumin 2.6 g/dL (3.6-5.1)
- ALP 143 U/L (33-130)
- ALT 44 U/L (6-29)
- AST 56 U/L (10-35)
- Platelets 41,000 plt/uL (150,000-400,000)
- HCV antibodies – *reactive*
- Serum zinc:
  - Measurement A: 34 mcg/dL(60-130)
  - Measurement B: 39mcg/dL (60-130)

CLINICAL COURSE

Zinc sulfate supplementation was initiated at 220mg orally twice per day and increased incrementally until a dosage of 440mg orally three times per day (1320mg daily) was reached.

At follow up, 1 month after initiation of zinc supplementation, the patient exhibited clinically notable improvement of rash. She reported decreased pruritus in lesional areas.

DISCUSSION

Necrolytic acral erythema (NAE) is a rare condition first described in 1996. Clinically, the disease can resemble psoriasis, acrodermatitis enteropathica, and necrolytic migratory erythema. Its failure to respond to topical corticosteroids and acral distribution – commonly the dorsal feet – may be helpful in making this clinical distinction.

The pathogenesis of NAE is poorly understood, but the vast majority of NAE cases occur in patients with active hepatitis C.

DISCUSSION, *continued*

HCV seropositivity and serum zinc levels appear to be important disease factors as NAE improvement or resolution has occurred with zinc supplementation and antiviral treatment of HCV. Cirrhosis patients without HCV do not develop NAE. The degree of HCV-induced liver damage is directly correlated with the severity of NAE.

NAE is almost certainly underdiagnosed, as there are currently fewer than five published case reports of NAE from within the US. The prevalence of NAE in HCV patients has been estimated at 1.7%. However, NAE reinforces the role of dermatologists in diagnosing systemic illness as one study cited 87% of patients presenting with NAE as having no prior knowledge of their HCV-positive status. Earlier diagnosis of NAE and therefore HCV could potentially improve patients' quality of life and reduce morbidity and mortality.

REFERENCES

1. Abdallah MA, et al. Necrolytic acral erythema: a cutaneous sign of hepatitis C virus infection. J Am Acad Dermatol 2005; 53:247-51.
2. El Darouti M et al. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. Int J Dermatol 1996; 35:252-56.
3. Fielder LM et al. Necrolytic acral erythema: case report and review of the literature. Cutis. 2008;81(4):355-60.
4. Gusau et al. Zinc status in chronic liver disease; studies in Nigerian patients. West Afr J Med. 1990;9(4):245-51.
5. Khanna VJ et al. Necrolytic acral erythema associated with hepatitis C: effective treatment with interferon alfa and zinc. Arch Dermatol. 2000;136(6):755-7.
6. Ko HM et al. Morphologic features of extrahepatic manifestations of hepatitis C virus infection. Clin Dev Immunol. 2012;2012:740138.
7. Patel U, et al. Necrolytic acral erythema. Dermatol Online J. 2010;16(11):15.
8. Raphael BA, et al. Low prevalence of necrolytic acral erythema in patients with chronic hepatitis C virus infection. J Am Acad Dermatol. 2012;67(5):962-8.
9. Xu J et al. Analysis of serum and urinal copper and zinc in Chinese northeast population with the prediabetes or diabetes with and without complications. Oxid Med Cell Longev. 2013;2013:635214.

CALCIPHYLAXIS: A CASE REPORT AND REVIEW OF THE LITERATURE

Shannon McKeen, DO, PGY-3; Mark A Kuriata, DO, FAOCD

MSUCOM/Lakeland Regional Medical Center

ABSTRACT

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare condition characterized by exquisitely painful necrotic ulcerations in patients with end-stage renal disease (ESRD) undergoing dialysis.[1,2] Risk factors associated with the disease include dialysis treatment, warfarin use, disturbances in calcium-phosphate metabolism leading to an elevated calcium-phosphorus product, hyperparathyroidism, diabetes, female gender, Caucasian race, obesity and inflammatory conditions.[1-8] Our understanding of the complex pathophysiology of this rare disease entity is evolving as the number of reported cases increases. Recent reports suggest two phases in the development of calciphylaxis, beginning with medial calcification and stenosis of small arteries followed by thrombus formation, luminal obstruction and tissue infarction.[5] Early lesions present with indurated violaceous mottling, similar to livedo reticularis, with painful erythematous to violaceous nodules in areas of increased adipose content and progress to exquisitely tender black necrotic eschars.[5] Although the gold standard for diagnosis is obtaining a biopsy specimen, this is controversial as the trauma of the biopsy may exacerbate the patient's condition. Mortality rate for calciphylaxis is extremely high, reaching 80% in some reports, and is usually due to secondary infection progressing to septicemia.[7] Awareness of this condition and early recognition is key in initiating therapeutic intervention. Treatment of these patients is multifaceted and involves wound care, pain control, correcting underlying laboratory abnormalities as well as sodium thiosulfate.[2-9] We present a case of calciphylaxis in its advanced stages to illustrate the disease process and its potential devastating complications. We hope to raise awareness of calciphylaxis in hopes of prompting earlier recognition with improved clinical outcomes.

CASE PRESENTATION

Our patient is a 68-year-old Caucasian male with a past medical history significant for end-stage renal disease requiring hemodialysis three times a week, atrial fibrillation on warfarin, congestive heart failure and ischemic cardiomyopathy who was admitted as an inpatient for rectal bleeding in the setting of a supra-therapeutic INR. Upon admission, the patient was noted to have painful, necrotic wounds on the anterior thighs for which Dermatology was consulted. The patient reported the wound being present for six weeks prior to presentation which began after his dog jumped onto his legs. The patients' primary care physician referred him to the wound care clinic. The patients wound care consisted of cleansing the area with Betadine, applying Xeroform and covering the wounds with an ABD pad secured with Kerlix. The wounds are exquisitely painful and his pain has not been controlled with oral narcotic medications. The patient had been ambulatory until one week prior to admission, when his lower extremity pain precluded him from ambulation. The patient was started on warfarin six months prior to his presentation and was bridged appropriately on a prior inpatient admission. Upon admission, the patient had a white blood cell count of 9.7 and a serum calcium of 10.1. The patient did not have a serum phosphorus or parathyroid hormone level drawn. The patient was started on intravenous narcotic pain medication without resolution of his lower extremity pain and a Pain Management Consult was placed. On physical examination, the patient was noted to have a 10.5 x 9.0 cm and a 9.0 x 4.5 cm painful black irregular thick necrotic eschar surrounded by tender violaceous border on the right anterior thigh and left anterior thigh, respectively. There were multiple indurated plaques with retiform purpura on the lower extremities. Two punch biopsies of lesional skin were obtained showing focal calcified small blood vessels within the deep adipose tissue and ischemic tissue necrosis of the epidermis and fat. At the time the biopsy results were obtained, the patient and his family chose to have the patient placed in hospice care. The patient expired several days after joining the hospice program.

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is rare condition characterized by exquisitely painful necrotic ulcerations in patients with end-stage renal disease (ESRD) on dialysis.[1,2] Although the majority of patients with calciphylaxis are on either peritoneal dialysis or hemodialysis, there have been reported cases in patients without renal disease, referred to as non-uremic calciphylaxis.[2-4] Risk factors associated with the disease include dialysis treatment, warfarin use, disturbances in calcium-phosphate metabolism leading to an elevated calcium-phosphorus product, hyperparathyroidism, diabetes, female gender, Caucasian race, obesity and inflammatory conditions.[1-8] The prevalence of calciphylaxis is estimated to be 1-4% of patients with end-stage renal disease (ESRD).[1,2,8,9]

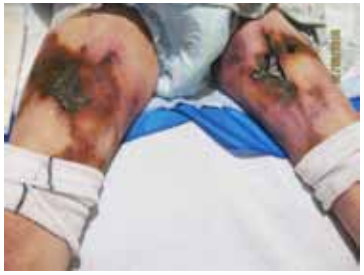


Figure 1: Large black, necrotic eschars located on the bilateral thighs

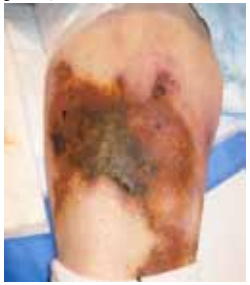


Figure 2: 10.5 x 9.0 cm tender black, necrotic eschar with irregular borders surrounded by a violaceous, dusky hue

Figure 3: 9.0 x 4.5 cm irregular, black necrotic eschar with surrounding violaceous mottling; note Betadine from prior wound care

PATHOPHYSIOLOGY AND DIAGNOSIS

Our understanding of the complex pathophysiology of this rare disease entity is evolving as the number of reported cases increases. Dialysis can alter the pro- and anti-calcification factors which favors medial calcification of the small arteries. Calcium and phosphate levels are increased due to their impaired metabolism in patients with chronic kidney disease. An increase in the calcium-phosphate product ($Ca^{+2} \times PO_4$) increases the risk of vascular ossification. Chronic kidney disease will decrease fetuin A levels, inhibitor of vascular ossification-calcification, produced by the liver which in turn increases the risk of calcification.[5] Rather than simply causing passive deposition of calcium in vessels as previously hypothesized, vascular smooth muscle cells differentiate into an osteochondrocyte phenotype which leads to production of calcium-phosphate nanocrystals and calcification.[5] Of importance, matrix GLA protein (MGP) is found in the extracellular matrix and actively inhibits bone morphogenetic protein (BMP)-2 which is involved in osteogenesis. Activation of MGP is dependent on γ-carboxylation which is a Vitamin K dependent reaction.[5] Decreased Vitamin K activity, as seen in patients taking warfarin, allows for decreased activity of MGP and increased ossification.[5,8] Endothelial cells undergo intimal hyperplasia along with varying degrees of necrosis. Endothelial necrosis then leads to vascular thrombosis.[5] Although there is a strong association with dialysis, the low prevalence rates in patients with ESRD suggest two phases in the development of calciphylaxis.[5] In the first phase, medial calcification and stenosis of small arteries occur leading to primary lesions which appear clinically as indurated violaceous mottling, similar to livedo reticularis, with exquisitely tender erythematous to violaceous nodules concentrated in areas with increased adipose content. Phase two is characterized by thrombus formation, luminal obstruction and tissue infarction producing painful black necrotic eschars within the existing primary lesions.[5]

Although the gold standard for diagnosis is obtaining a biopsy specimen, this is controversial as the trauma of the biopsy may exacerbate the patient's condition. Histopathologic findings in calciphylaxis include medial calcification of small arteries with intimal hyperplasia, small vessel thrombosis, endovascular fibrosis, tissue ischemia and possible panniculitis.[1-3,8] Other modalities to help suggest the diagnosis of calciphylaxis include biochemistry, plain radiographs of soft tissues, mammography and bone scintigraphy with Tc99m. Laboratory abnormalities that can be seen in calciphylaxis include an elevated serum phosphorus, increased calcium-phosphorus product, hyperparathyroidism and hypercalcemia.[1-3,5]

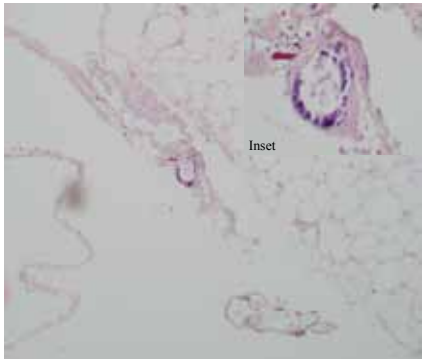


Figure 4: Focal calcification of a blood vessel within the deep adipose tissue (see inset for magnification)

TREATMENT OPTIONS

Calciphylaxis treatment is multifaceted and involves wound care, pain control, correcting underlying laboratory abnormalities as well as sodium thiosulfate.[2-9] Wound care should aim to keep the lesions clean and prevent infection, as sepsis is the leading cause of mortality in these patients. Debridement of wounds with an overlying eschar is contraindicated because it can exacerbate existing lesions. Case reports have shown improvement in patients treated with hyperbaric oxygen.[2] Pain control is a difficult task in calciphylaxis patients and often requires narcotic pain medications. Fentanyl is preferred over morphine because morphine has been associated with hypotension and decreased tissue perfusion leading to potential worsening of the patient's condition.[2] Efforts to correct underlying abnormalities in calcium, phosphate and parathyroid hormone (PTH) should be initiated. Calcium supplements, Vitamin D analogs and calcium-based phosphorus binders should be discontinued. A non-calcium-based phosphorus binder should be started. Calcinet, a calcimimetic, is used to suppress PTH levels with downstream effects on calcium and phosphorus. If medical therapy does not control PTH, a parathyroidectomy may be considered.[2-5] Sodium thiosulfate (STS) has classically been known as an antidote for cyanide poisoning, but was first used in 2004 for the treatment of calciphylaxis. Since that time, numerous case reports have shown its efficacy and safety profile which have made it a forerunner in calciphylaxis management.[6] STS chelates calcium and is eliminated via biliary excretion. In addition to calcium chelation, STS has anti-oxidant and vasodilatory properties.[2,4,5,6] The most commonly used regimen for STS is 25gm IV three times a week administered at the end of dialysis. Case reports have shown complete clearance in three months on average.[2,5,6] A case series presented multiple lesions of calciphylaxis that were successfully treated with intralesional STS. In the reported cases, STS 250mg/mL was injected into the active violaceous border of the lesions of interest.[7] Multiple intralesional injections were required for resolution. Injections were well-tolerated with the most common complaint being pain at the site of injection.[7] As indicated above, the management of calciphylaxis is complex. These patients warrant close monitoring with a multi-disciplinary approach.

DISCUSSION

I feel our patient's case demonstrates the decreased awareness of this devastating condition in a specific patient population. The patient's wounds were located on the thighs, rather than the medial and lateral malleoli as seen with typical lower extremity wounds. His pain was out of proportion to the physical exam and should prompt further work-up in a patient not responding to traditional wound care. Incorporating multiple specialties for evaluation of these wounds may have led to an earlier diagnosis of the condition. Treating these lesions with the various options discussed above may have halted the progression of the wounds and prevented the patient from joining the hospice program. Dermatologists as a specialty have a duty to raise awareness of conditions such as calciphylaxis. Recognition of this condition in its early stages can allow for comprehensive care with a multi-disciplinary approach leading to improved morbidity and mortality rates.

REFERENCES

1. Hayashi M. Calciphylaxis: Diagnosis and Clinical Features. Clin Exp Nephrol. 2013 Aug;17(4):498-503.
2. Yerram P, Chaudhary K. Calcific Uremic Arteriolopathy in End Stage Renal Disease: Pathophysiology and Management. Ochsner J. 2014 Fall;14(3):380-5.
3. Tamayo-Isla RA, Cuba de la Cruz M. Calciphylaxis in end-stage renal disease prior to dialytic treatment: a case report and literature review. Int J Nephrol Renovasc Dis. 2015 Feb 13;8:13-8.
4. Erdel BL, Juneja R, Evans-Molina C.A Case of Calciphylaxis in a Patient with Hypoparathyroidism and Normal Renal Function. Endocr Pract. 2014 Jun;20(6):e102-5.
5. Oliveira TM, Frazao JM. Calciphylaxis: from the disease to the diseased. J Nephrol. 2015 Apr 3.
6. Yu Z, Gu L, Pang H, Fang Y, Yan H, Fang W. Sodium Thiosulfate: An Emerging Treatment for Calciphylaxis in Dialysis Patients. Case Rep Nephrol Dial. 2015 Mar 13;5(1):77-82.
7. Strazzula L, Nigwekar SU, Steele D, Tsiaras W, Sise M, Bis S, Smith GP, Kroshinsky D. Intralesional Sodium Thiosulfate for the Treatment of Calciphylaxis. JAMA Dermatol. 2013 Aug;149(8):946-9.
8. Saifan C, Saad M, El-Charabaty E, El-Sayegh S. Warfarin-Induced calciphylaxis: a case report and review of literature. Int J Gen Med. 2013 Aug 9;6:665-9.
9. Carter T, Ratnam S. Calciphylaxis: A Devastating Complication of Derangements of Calcium-Phosphorus Metabolism – A Case Report and Review of the Literature. Nephrol Nurs J. 2013 Sep-Oct;40(5):431-5

A Case of Mycosis Fungoides In An Elderly Male

Irina Milman D.O.[1], Marcus Goodman D.O. FAOCD.[2]

[1] PCOM/North Fulton Hospital Medical Campus, Roswell, GA
[2] Residency Program Director, PCOM/North Fulton Hospital Medical Campus, Roswell, GA

INTRODUCTION

Mycosis fungoides is the most common form of cutaneous T cell lymphoma.

Cutaneous lymphomas are a heterogeneous group of non-Hodgkin lymphomas of T- and B-cell origin. This is a case of an 89-year male who was diagnosed and managed as a case of eczema; however, further investigations confirmed a diagnosis of Mycosis fungoides. This condition could be difficult to diagnose in the elderly population due to the variety or possible presentations and subtleties of histopathological correlation in the early stage.

Case Report

89-year-old male presented to our practice with a painful and pruritic eruption that has been treated by his primary care physician for the last year. Patient stated that a biopsy was performed and a diagnosis of eczema was made. He was treated with triamcinolone acetonide 0.1% ointment twice daily with only slight improvement of his symptoms. Upon review of his records, we discovered that a shave biopsy had been done, which showed a predominantly chronic inflammatory infiltrate and spongiosis, most consistent with an acute allergic or irritant contact dermatitis.

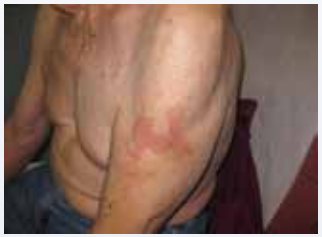
Patient's other medical conditions included high blood pressure, hyperlipidemia as well as coronary artery disease. He had no prior history of dermatologic disease. Examination revealed an elderly male in no acute distress and good spirits. The patient was found to have a diffuse eruption consisting of erythematous polycyclic plaques with slight scale on both of his upper extremities, abdomen, trunk, lower extremities, and groin. (Figure 1) Mild bilateral lymphadenopathy was discovered on exam.

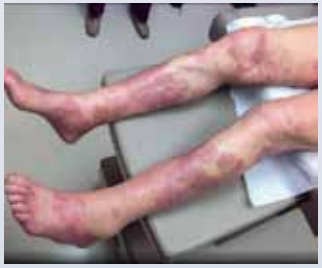
Two separate 3mm punch biopsies were performed at the time of his presentation. Both revealed an intraepidermal collection of atypical mononuclear cells with associated mild spongiosis and adjacent superficial predominantly lymphoid infiltrate consistent with cutaneous t-cell lymphoma. Further gene rearrangement studies confirmed the diagnosis of mycosis fungoides. Patient was referred to hematology-oncology for peripheral blood flow cytometry and CT imaging of the chest abdomen and pelvis. No lymph nodal enlargement by CT criteria was identified. Peripheral blood flow cytometry revealed no clonal population of T-cells. His disease was deemed primary cutaneous T-cell lymphoma staged 2A due to presence of nonmalignant bilateral inguinal lymphadenopathy. Patient has been treated with mechlorethamine hydrochride 0.016% gel and clobetasol propionate 0.05 ointment with good response. His pruritus has significantly improved since therapy was implemented.

Discussion

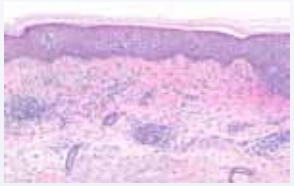
Primary cutaneous lymphomas represent a heterogeneous group of T- and B-cell lymphomas. Mycosis fungoides (MF), which is generally indolent in behavior, and Sezary syndrome (SS), an aggressive and leukemic variant, comprise approximately 53% of all cutaneous T-cell lymphomas (CTCL).[1]

Clinical Pictures

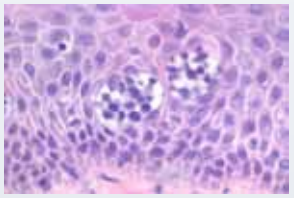




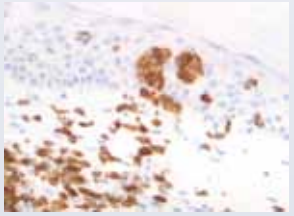
Histopathology



atypical mononuclear cells with associated mild spongiosis and adjacent superficial predominantly lymphoid infiltrate



intraepidermal collection of atypical mononuclear cells



Immunohistochemical staints showing CD4 + T-cells

Immunohistochemical staints showing CD3+ T-cells

Discussion

The incidence of CTCL has risen since 1973, with an annual age-adjusted incidence of 6.4 to 9.6 cases per million people in the United States [4]

Mycosis fungoides is mostly disease of the elderly with a median age at diagnosis of 55 to 60 years and a male: female ratio of 2:1. [1,5,7]

However, mycosis fungoides has also been seen in younger populations, including children. [5,6,7] Approximately 70% of patients with mycosis fungoides are white. African Americans, Hispanics, and Asians making up 14%, 9%, and 7% of mycosis fungoides cases in the United States, respectively. [19] Patients with both mycosis fungoides and Sezary syndrom are at a highly increased risk of developing a second lymphoma, in particular Hodgkin lymphoma and the CTCL subtype lymphomatoid papulosis, as well as nonhematologic malignancies. [4,7,14]

Mycosis fungoides classically is a very slowly progressive disease. It evolves slowly over years, sometimes decades and frequently has a relapsing course. Classic clinical presentation includes multiple, well defined, often pruritic erythematous patches distributed in non-sun exposed "bathing suit" areas, including the breasts, buttocks, lower trunk, and groin. These patches may evolve to infiltrative plaques and tumors, and all 3-lesion types can be seen concomitantly. [1,7] Hypopigmented lesions are a rare presentation of mycosis fungoides, most often seen in children, adolescents, and dark-skinned individuals. [7,19]

MF is characterized by the presence of lymphocytes that express a T cell helper phenotype (CD4+). These cells also express CD45RO, a marker of mature memory T cells. [7,16] CD8+ cytotoxic/suppressor T cell immunophenotype can be seen in rare cases, usually hypopigmented MF.[7,9,10]

For early stage MF when the disease is confined to the skin, topical skin-directed therapies are first-line treatments. Topical corticosteroids, topical nitrogen mustard (mechlorethamine hydrochride), topical retinoids (topical bexarotene), phototherapy, and total skin electron beam therapy are the mainstay of skin directed therapies. [18]

Oral bexarotene, interferon, histone deactylase inhibitors (vorinostat and romidepsin), extracorporal photopheresis, monoclonal antibody agent alemtuzumab and chemotherapy are used for more extensive or recalcitrant disease. [18]

Selected References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105:3768-85
2. Crowley JJ, Nikko A, Varghese A, Hoppe RT, Kim YH. Mycosis fungoides in young patients: clinical characteristics and outcome. J Am Acad Dermatol 1998; 38:696-701.
3. Sarah I. Jawed, Patricia L. Myskowski, MD, Steven Horwitz, MD, Alison Moskowitz, MD, and Christiane Querfeld, MD, PhD. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) Part I. Diagnosis: Clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatology 2014; 70:14 -205e1-e16.
10. Nikolaou VA, Papadavid E, Katsambas A, Stratigos AJ, Marinos L, Anagnostou D, et al. Clinical characteristics and course of CD81 cytotoxic variant of mycosis fungoides: a case series of seven patients. Br J Dermatol 2009;161:826-30.
18. Sarah I. Jawed, BA, Patricia L. Myskowski, MD, Steven Horwitz, MD, Alison Moskowitz, MD, and Christiane Querfeld, MD, PhD Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) Part II. Prognosis, management, and future directions 2014; 70:223e1-e17

Hypohidrotic ectodermal dysplasia Case Report and Discussion

Summer Moon, DO; Sean Stephenson, DO

McLaren OAKLAND

LEARNING OBJECTIVES

Hypohydrotic ectodermal dysplasia (HED) refers to a group of disorders that share the following features: sparse or absent hair; absent or peg-shaped teeth; and decreased ability to sweat. HED is a life-long disease therefore it's essential early on to educate the parents on ways to prevent and control hyperpyrexia.

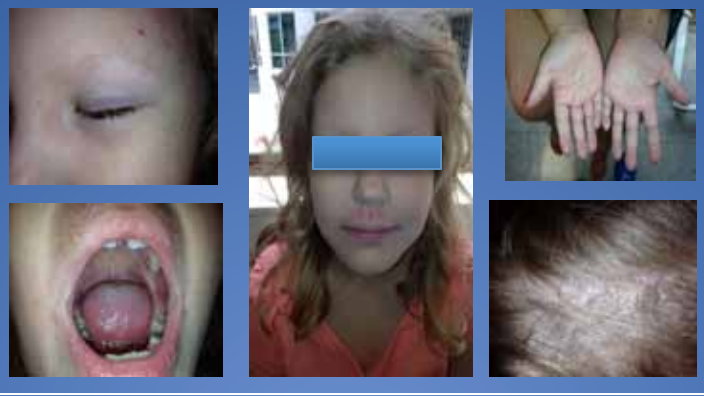
CASE SUMMARY

An 8 year-old Caucasian female presented with a chief complaint of decreased sweating, frequent skin infections and eczema since birth. Patient complained of "red-scabbed" areas on the face and extremities and heat intolerance with minimal sweat production.

Physical examination revealed diffuse pallor with erythematous patches on bilateral cheeks and scattered impetiginized, excoriated papules and plaques on the philtum, wrists, ankles and anticubital fossa with moderate lichenification. Examination of patient's scalp revealed blonde hair with thick chalky adherent scale. Sparse eyebrows, minimal body hair and hypodontia were also observed.

We began treating patients impetiginized eczema with triamcinolone 0.1% cream and mupirocin 2% ointment. Bleach baths twice weekly, wet wraps and daily topical emollients were encouraged. A referral to genetics was encouraged for further work up of presumed anhidrotic ectodermal dysplasia as there is a strong family history of the disease. Handouts were provided, and we continue to follow the patient for the development of any additional disease manifestations.

CLINICAL PHOTOS



DISCUSSION OF NBCIE

Hypohydrotic ectodermal dysplasia (HED), also known as anhidrotic ectodermal dysplasia or Christ–Siemens–Touraine syndrome refers to a group of disorders that share the following features: sparse or absent hair; absent or peg-shaped teeth; and decreased ability to sweat. The most common form is X-linked inherited occurring in approximately 1 in 10 000 live-born males, but both autosomal dominant and autosomal recessive inheritance patterns have been documented. It is likely that our patient has the X-linked or autosomal dominant variant. HED affects the developing nail, hair follicle and eccrine gland through a genetic defect in ectodysplasin signal transduction pathway. In the X-linked form of HED ectodysplasin A, which is secreted by epithelial cells, is defective. In the autosomal dominant and recessive forms ectodysplasin-A receptor (EDAR) is the underlying defect. Signaling errors ultimately translate into the nucleus with the help of NF-κB and result in aplasia, hypotonia or dysplasia of these structures.

Clinically newborns present encased in a collodion-like membrane or with skin scaling. Scalp hair may be absent, sparse, or when present is typically blonde. Body hair is sparse to absent. Newborns are unable to sweat and often present with pyrexia of unknown origin. Eczema, periorbital wrinkling, and hyperpigmentation are common. Nails are usually unaffected, but hypodontia, anadontia, and/or conical teeth are common. Patients may also have saddle nose, everted lips and frontal bossing. Female patients with the X-linked form have variable involvement due to the random nature of X- inactivation presentations.

WORKUP/MANGEMENT

Prenatal diagnosis by skin biopsy through fetoscopy would show absent pilosebaceous units. Post-natal skin biopsy of palmar skin reveals a lack of eccrine units.

Antipyretics and external methods of cooling such as ice packs, wet T-shirts and cooling vests are important. Daily use of topical emollients should be recommended.

CONCLUSIONS

HED is a life-long disease therefore it's essential early on to educate the parents on ways to prevent and control hyperpyrexia.

Multidisciplinary care is often required for the treatment of upper respiratory symptoms, dental complications, and atopy. Referral to the National Foundation for Ectodermal Dysplasias is also an important aspect of care. Gene and protein therapy for HED is on the horizon.

REFERENCES

1. Mikkola ML: Molecular aspects of hypohidrotic ectodermal dysplasia. Am J Med Genet A 2009;149A: 2031-2036.
2. Headon DJ, Emmal SA, Ferguson BM, et al. Gene defect in ectodermal dysplasia implicates a death domain adapter in development. Nature 2001;414:913-916.
3. Gaide O: Gene therapy and protein therapy of ectodermal dysplasias: a perspective. Am J Med Genet A 2009;149A:2042-2044.
4. Bolognia JL, Jorizzo JJ, Schaffer JV, et al. Dermatology, 3rd Edition 2012;63:984-985.
5. Spitz JL, Genodermatoses: A Clinical Guide to Genetic Skin Disorders, 2nd Edition 2005;10:286

Erythrodermic Dermatomyositis

Huyenlan Nguyen, DO, Joshua Levin, MD and Stephen M. Purcell, DO
Lehigh Valley Health Network, Allentown, Pennsylvania

Case Presentation:

Patient: 50 year-old Caucasian male.

History of Present Illness: This patient presented with a 15-week history of a rash over his entire body. The rash is associated with pruritus and edema. Prior treatments include prednisone, hydroxyzine, cetirizine, famotidine, and triamcinolone with some improvement. He reports odynophagia, unintentional 10 pound weight loss within the last 3-4 months, and occasional difficulty lifting both arms. He denied nausea, vomiting, headaches, changes in urinary patterns, and back pain.

Medical History/Surgical History: Hypothyroidism, sleep apnea, inguinal hernia repair

Family History: Hypertension, amyotrophic lateral sclerosis

Medications: Levothyroxine

Previous Treatment: Prednisone, hydroxyzine, cetirizine, famotidine, triamcinolone 0.1% ointment

Current Treatment: Prednisone, hydroxychloroquine, mycophenolate mofetil, clobetasol 0.05% ointment

Physical Examination: Generalized erythematous patches on the extensor surfaces of the upper extremities and most of the trunk. There is confluent erythema and edema of the lower extremities with sparing of the popliteal fossa and lateral feet. Scaly erythematous papules and patches on the dorsal hands with distinct flat-topped papules over the PIP and DIP joints and dorsal toes. Erythema and edema on face, ears, and the upper eyelids. There is hyperkeratosis and prominent telangiectatic vessels in the proximal nail folds with ragged cuticles. There is a palpable 1cm lymph node in the right axilla. Genitals are spared. No muscle weakness on initial exam.

Laboratory Data: (9/19/2014) Creatinine kinase 1148 (<351), AST 104 (<41), ALT 57 (<56), Aldolase 16.3 (1.5-8.1), ANA negative; (7/17/14) UA, urine porphyrins, serum complement, ACE, ESR, CRP, HLB-27 and creatine kinase WNL. Anti-thyroglobulin Ab 42 (0-40), anti-thyroid peroxidase Ab 337(0-34); (05/24/14) CMP, uric acid, RF, ESR, TSH and CBC WNL except lymphocyte count 0.79(1.2-4.8)

Studies: MRI brain, CT scan of head/neck, chest, and abdomen were negative for underlying malignancy (10/10/14). Colonoscopy, endoscopy (10/2/14), PFT (10/14/14), and left inguinal node biopsy (9/30/14) were negative for malignancy.

Biopsy: *CBL Path* (D14NY1-0234678, 08/15/14) Left 3rd finger dorsal DIP, right knee: Interface dermatitis. "Mild acanthosis and patchy parakeratoisis with sparse perivascular infiltrate". Left arm- Punch DIF: Granular deposition of IgG in epidermis and C3 in BMZ.

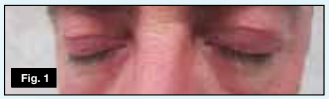


Figure 1: Heliotrope rash.

Figure 2: Erythema of the hands with Gottron's papules along the DIP joints and ragged cuticles.

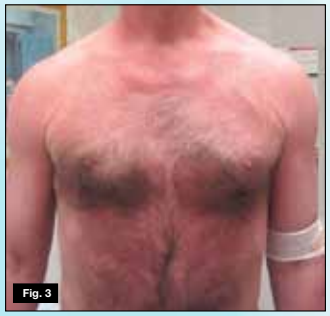


Figure 3: Erythroderma of the neck and trunk.

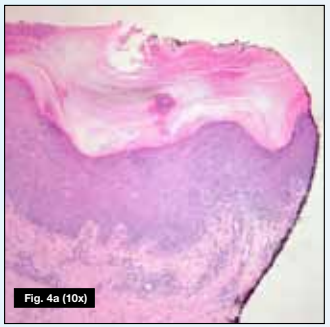


Figure 4a: Magnification 10x- Mild acanthosis and patchy parakeratosis with sparse perivascular infiltrate.

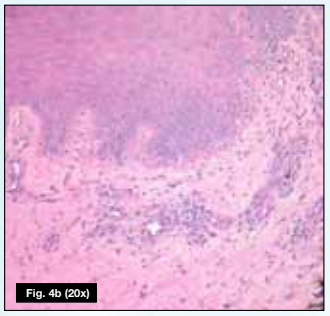


Figure 4b: Magnification 20x.

Discussion:

Dermatomyositis (DM) is an autoimmune systemic disease that can involve the skin, musculoskeletal, gastrointestinal, cardiac and pulmonary systems. Pathognomonic cutaneous features include the heliotrope rash and Gottron's papules. Gottron's papules are flat-topped erythematous papules and plaques typically found on joints of the hands and elbows. Poikiloderma, malar erythema, periungual telangiectasia, and photosensitivity are other common characteristic findings. Dystrophic and ragged cuticles, known as Samitz sign, can be observed. Proximal muscle weakness may occur before, during, or after the presence of cutaneous findings. Systemic manifestations can present as arthralgia, arthritis, dyspnea, dysphagia, arrhythmia, and dysphonia.

Laboratory studies may yield an elevated creatine kinase, aldolase, aspartate aminotransferase or lactic dehydrogenase due to myositis. A positive antinuclear antibody result is common but not diagnostic. Several myositis-specific antibodies have been identified but are not routinely used in diagnosis. They may, however, aid in the classification of DM subtypes for prognosis. Anti-Mi-2 antibody is highly specific and is associated with acute-onset classic DM with a relatively good prognosis. Anti–Jo-1 antibodies are more common in patients with polymyositis and can be associated with interstitial lung disease, Raynaud phenomenon, and arthritis. Juvenile onset DM has the best prognosis for survival, while paraneoplastic DM has the worst prognosis. A malignancy work up should be performed in all patients with adult onset DM. Multiple associated malignancies have been reported, including ovarian and breast cancer in women and lung cancer in men.

Erythroderma is an uncommon presentation of DM and can be associated with an underlying malignancy. Documented cases include erythrodermic DM associated with gastric cancer, liver cancer, and adenocarcinoma. Our patient with erythrodermic DM has had a negative malignancy work up to date. After 3 months on mycophenolate mofetil, hydroxychloroquine, prednisone, and topical clobetasol, he has cleared significantly. He occasionally experiences musculoskeletal pain but no longer experiences weakness.

Laboratory studies, malignancy work up, referral to appropriate specialists, and treatment to control cutaneous and muscle disease are important in the management of DM. Treatment options include topical and systemic corticosteroids, antimalarial agents, and immunomodulators. Systemic corticosteroids has been first line in the treatment of muscle disease. Methotrexate, mycophenolate mofetil, or azathioprine can be used as steroid-sparing agents. Sun avoidance and sun protection are important to avoid further exacerbations of skin disease.

REFERENCES:

1 Iorizzo LJ 3rd, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. *J Am Acad Dermatol.* Jul 2008;59(1):99-112.

2 Kim SW, Kang YS, Park SH, et al. A case of Erythrodermic Dermatomyositis Associated with Gastric Cancer. *Ann Dermatol* 2009;21(4):435-9.

3 Nousari H, Kimyai-Asadi A, Spegman D. Paraneoplastic dermatomyositis presenting as erythroderma. *J Am Acad Dermatol* 1998;39:653-4.

Abdominal Pain: A Unique Presentation of Neurofibromatosis-1

Brandon Nickle DO (PGY-3) *,Blaze Emerson MS**, Kimberly Hull DO***, Jacqueline Thomas DO*** Leeor Porges DO****, Carlos Nousari MD*****

Dermatology Resident PGY-3, Broward Health Medical Center/NSUCOM* OMS-IV, NSUCOM** Dermatologist, Fort Lauderdale, FL*** Dermatology Resident PGY-4, Broward Health Medical Center/NSUCOM**** Program Director Broward Health Medical Center/NSUCOM*****

ABSTRACT

Neurofibromatosis type 1 (NF-1) is a common autosomal dominant neurocutaneous disorder affecting 1 in 3000 people. It often presents with a myriad of cutaneous features including, neurofibromas, Lisch nodules, café-au-lait macules, axillary freckling, and plexiform neuromas (PFN). Many other non-cutaneous manifestations have been observed in NF-1. Gastrointestinal (GI) stromal tumors, malignant peripheral nerve sheath tumors, and adenocarcinoma are commonly found in the GI tract of NF-1 and can manifest as a complaint of abdominal pain. Here we present a unique case of NF-1 with an initial presenting symptom of abdominal pain caused by PFN located outside the gastrointestinal tract.

CASE PRESENTATION

A 17-year-old female was admitted for investigation of non-radiating abdominal pain in the right upper quadrant. The patient did not have a significant medical history or family history of NF-1; however, her mother was found to have multiple café au lait macules. Physical examination revealed numerous café-au-lait macules on her limbs **(Fig. 1)** and torso, axillary freckling and three subcutaneous nodules were noted on the neck and face. Further inspection revealed bilateral Lisch nodules **(Fig. 2).**

Cervical MRI revealed PNF's from the foramen magnum to T1 extending into the neuroforamen bilaterally. Imaging studies of the cervical, thoracic, and lumbar regions revealed innumerable tumors around the margins of multiple transverse processes, posterior ribs, and neural foramen. Plexiform neurofibromas were also found extending into the retropertieum, pelvis, and illiopsoas muscles. Imaging of the bowel was negative for gastrointestinal tumors **(Fig. 3)(Fig.4)**

No signs of cord compression or neurological symptoms were found although countless neurofibromas were located. Other structural symptoms such as disc atrophy, intramedullary signal abnormality, or hemorrhage were not present. The chief complaint of abdominal discomfort was likely caused by PNF's compressing structures in the abdomen since gastrointestinal tumors were not found on MRI or esophagogastroduodenoscopy (EGD) with biopsy.

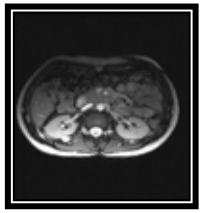
There was no acute neurosurgical intervention warranted. It was recommended that she have an MRI of the cervical/thoracic/lumbar-spine in 1 year, or sooner if she should have any acute changes. The patient was released from the hospital and is being followed by dermatology, ophthalmology, and neurosurgery services.

CLINICAL PHOTOS

Figure 1 - Large café au lait patch noted on the left lateral thigh

Figure 2 - Lisch nodules

RADIOGRAPHICAL DATA



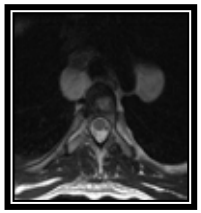


Figure 3 (Left) and Figure 4 (Right)- Numerous plexiform neurofibromas noted in the pelvis and thoracic region on MRI

TABLES

Diagnostic criteria for NF1 NIH consensus development conference 1988[4]
6 or more café au lait macules: >5mm in diameter in pre-pubertal and >15 mm in post-pubertal individuals. For each lesion the longest diameter is measured.
2 or more neurofibromas of any type or one plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic Glioma
Two or more Lisch nodules
Bony dysplasia +/- pseudoarthrosis
First degree relative with NF1
*At least 2 of the clinical features must be present to make the diagnosis of NF1

Table 1- NIH diagnostic criteria for NF-1[9]

Cutaneous Manifestations and Common Age of Onset for Patients with Neurofibromatosis Type 1	
Cutaneous Manifestations	**Age of Onset**
Café-au-lait spots	Birth through age 12
Axillary freckling and Lisch nodules	Ages 3-adolescence
Subcutaneous and cutaneous neurofibromas	Adolescence

Table 2-Cutaneous manifestations and common age of presentation of NF-1 [9]

DISCUSSION

Abdominal complaints related to NF-1 tumors are fairly common; however, the etiology of this condition is often due to gastrointestinal tumors which are reported in 2-25% of NF-1 patients.[1,2] Visceral and gastrointestinal tumors are often asymptomatic but may appear as pain, palpable masses, GI bleeding, vessel compression, or bowel occlusion.[12] Patients with NF-1 can present with a wide variety of abdominal tumors including phaeochromocytomas, gastrointestinal stromal tumors (GISTs), malignant peripheral nerve sheath tumors (MPNSTs), and PFNs. This patient is unusual because the abdominal distress was caused by plexiform neurofibromas (PFNs) located outside of the GI tract. Our case highlights the importance of timely identification and management of NF-1 patients in order to properly monitor tumors for malignant progression.

Neurofibromatosis is a common condition with a reported incidence of approximately 1 in 3000.[1,2,3] The diagnostic criteria originally established by the NIH in 1988 (see Table 1) has been shown to be very specific and sensitive in correctly diagnosing NF-1 patients in early childhood, however many patients, are not diagnosed until adolescence or early adulthood.[4,5] Specific dermatological manifestations of NF-1 include café au lait patches, skin freckling, hypopigmented macules, Lisch nodules, and cutaneous and plexiform nodules, most of which were present in our patient. (Table 2)

As with our patient, many NF-1 patients are only identified through incidental imaging from a seemingly unrelated and somewhat unusual complaint.[6] Exotic presentations of NF-1 have been reported in the literature and range from signs of spinal cord compression, incontinence due to tumor growths in the bladder, breathing difficulties, epigastric pain, and gastric outlet obstruction.[3,7,8,9,10,11]

REFERENCES

1. Bakker JR, Haber MM, Garcia FU. Gastrointestinal neurofibromatosis: an unusual cause of gastric outlet obstruction. Am Surg 2005;71(2):100-5.
2. Rastogi R. Intra-abdominal manifestations of von Recklinghausen's neurofibromatosis. Saudi J Gastroenterol 2008;14(2):80-2.
3. Rastogi R. Gastric outlet obstruction due to neurofibromatosis: an unusual case. Saudi J Gastroenterol 2009;15(1):59-61.
4. National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis. Arch Neurol 1988;45(5):575–8.
5. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 2000;105(3 Pt 1):608-14.
6. Schorry EK, Crawford AH, Egelhoff JC, Lovell AM. Thoracic tumors in children with neurofibromatosis-1. Am J Med Genet 1997;74(5):533–537.
7. Krishna KK, Agarwal PA, Jain MM. Neurofibromatosis type I presenting with urinary retention and lung collapse. J Clin Neurosci 2004;11(4):423-4.
8. Leonard JR, Ferner RE, Thomas N, Gutmann DH. Cervical cord compression from plexiform neurofibromas in neurofibromatosis 1. Journal of neurology, neurosurgery, and psychiatry. 2007;78(12):1404-6.
9. Shonnard KM, Jelinek JS, Benedikt RA, Kransdorf MJ. CT and MR of neurofibromatosis of the bladder. J Comput Assist Tomogr 1992;16(3):433-8.
10. Setabutr D, Perez MR, Truong MT, Senders CW, Rubinstein BK. Neurofibromatosis of the larynx causing stridor and sleep apnea. Am J Otolaryngol 2014;35(5):631-5.
11. Leung VK, Lee SW, Yuen NW, Kung NN, Loke TK. Epigastric pain in a patient with neurofibromatosis type 1. Hong Kong Med J 2005;11(3):213-5.
12. Stone MM, Weinberg B, Beck AR, Grishman E, Gertner M. Colonic obstruction in a child with von Recklinghausen's neurofibromatosis. J Pediatr Surg. 1986;21(8):741-3.
13. Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. Pediatrics. 2009;123(1):124-33.
14. Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis: clinical and population study in south east Wales. Brain 1988;111:1355–81.
15. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. Cancer Res. 2002;62(5):1573-7.
16. Ferner RE, Huson SM, Thomas N, Moss C, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44(2):81-8.
17. Korf BR. Diagnostic outcome in children with multiple cafe au lait spots. Pediatrics 1992;90:924–7.
18. Cavallaro G, Crocetti D, Pedulla G, Giustini S, et al. Retrocaval mass in patient with von Recklinghausen disease: case report. G Chir 2012;33(1-2):26-30.
19. Korf BR. Plexiform neurofibromas. Am J Med Genet 1999;89(1):31-7
20. Dugoff L, Sujansky E. Neurofibromatosis type 1 and pregnancy. Am J Med Genet 1996;66:7-10.
21. Inoue M, Mitsudomi T, Osaki T, Oyama T, et al. Malignant transformation of an intrathoracic neurofibroma in von Recklinghausen's disease. Scand cardiovasc J 1998;32(3):173-5.
22. Tucker T, Wolkenstein P, Revuz J, Zeller J. Association between benign and malignant peripheral nerve sheath tumors in NF1. Neurology 2005;65(2):205-11.
23. Woodruff JM. Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. Am J Med Genet 1999;89(1):23-30.
24. Thakkar SD, Feigen U, Mautner VF. Spinal tumours in neurofibromatosis type 1: an MRI study of frequency, multiplicity and variety. Neuroradiology 1999, 41(9):625–629.
25. Chung CJ, Armfield KB, Mukherji SK, et al. Cervical neurofibromas in children with NF-1. Pediatr Radiol 1999, 29(5):353–356.

Cutaneous Diseases from the Peruvian Amazon Jungle

Mayha Patel, DO, Donna Tran, DO, David C. Horowitz, DO

Western University of Health Sciences, Dermatology Department, California

INTRODUCTION

In early August 2015 myself, a fellow resident and our Program Director traveled to Peru for a medical mission which consisted of two main projects serving as the focus: the Iquitos Medical Campaign and the Amazon River Campaign. We arrived in Lima, where we spent three days becoming acquainted with the new environment and culture. Two of those days were spent touring a medical school and then a teaching hospital in Lima. We then flew to Iquitos where we spent the majority of the next four days providing medical care and education to locals from the surrounding areas. Iquitos is situated beautifully on the base of the Amazon in the shadows of the great Andes mountains. We had patients travel from all across the region to meet us in Iquitos. Some even came from over 14 hours away (on foot!) over the Andes to reach us. For most patients, those four days of clinic are an annual sojourn that provide relief and healing.

We then ventured down the Amazon on a medically-stocked river boat, called The Amazon Queen IQ17051 where we traveled down the river making medical stops at various villages. We provided medical care on the boat to the Amazonian people and were named 'The River Docs.' The impovished Amazonian people don't have access to medical care as their villages were very isolated from the nearest town. In addition, their living conditions were very simple. They were given one solar panel per hut that would light one lightbulb. They built small canoes that would allow them to visit nearby villages and also allow them to fish and provide food for their families.

Our goal was to treat our patients condition and then educate them about prevention and recurrence. We highlight some of the interesting and common but unique presentations of various cases from our medical mission.

Our clinic in Iquitos

Seeing patients on the Amazon Queen

Severe burn patient treated with normal saline and silver sulfadiazine

DISCUSSION

A total of over 370 dermatology cases were seen by our team; of which 270 were seen in Iquitos, Peru and 100 were seen at the various villages in the Amazonian Jungle.

The Amazon River originates in Peru and exists as a world of mystery and grandeur. Its towering forest and rushing waters harbor such an incomparable diversity of life that scientists are still working to classify it all: 2,000 species of fish, more than those in the Atlantic Ocean; 4,000 species of birds, including 120 hummingbirds; 60 species of reptiles such as the caiman and anaconda, the world's largest non-poisonous snake; and mammals such as the marmoset, anteater, tapir, capybara, and pink dolphin. At its widest point in Brazil, the mighty Amazon River is 40 miles across. Oceangoing vessels can sail the 2,300 miles from the Atlantic Ocean upriver to Iquitos, Peru's major port on the Upper Amazon. In both Iquitos, Peru and the Amazonian villages the predominant cases were infectious, followed by inflammatory diseases and then pigmentary diseases. The hot and humid environment we believe was the leading cause of the majority of infectious cases.

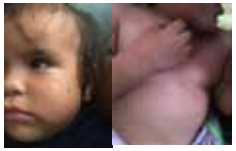
Table 1 highlights the estimated number of cases by disease category in Iquitos and the Amazonian Jungle.

Table 1. Summary of Cases

Disease Category	Diagnosis	No. Cases
Benign neoplasms	Giant cell tumor of tendon sheath	1
	Digital myxoid cyst	1
	Acrochordon	4
	Seborrheic keratosis	40
	Prurigo nodularis	10
	Benign self healing histiocytosis	1
Malignant neoplasms	Basal cell carcinoma	2
Infectious	Tinea corporis	60
	Tinea manuum	55
	Tinea cruris	25
	Tinea capitis	10
	Tinea versicolor	50
	Onychomycosis	40
	Candida	15
	Impetigo	24
	Paronychia	11
	Verruca vulgaris	4
	Herpes zoster	1
Infestations	Arthropod assault	30
	Scabies	5
	Cutaneous larva migrans	1
Congenital	Linear epidermal nevus	2
Inflammatory	Psoriasis	6
	Eczema	20
	Dishydrotic eczema	15
	Contact dermatitis	20
	Seborrheic dermatitis	30
	Lichen simplex chronicus	28
Pigmentary	Dermal nevus	2
	Halo nevus	1
	Lentigo	19
	Melasma	20
	Postinflammatory hyperpigmentation	17
	Pityriasis alba	3
	Nevus anemicus	1
	Vitiligo	3
Other	Neurodermatitis	20
	Acne vulgrais	5
	Miliaria crystallina	2
	Lichen amyloidosis	15
	Rosacea	20
	Pyoderma faciale	1
	Actinic pruritus	28
	Drug reaction	1
	2nd degree burn	2
	Keratoderma	1
Unknown	Leishmaniasis*	1

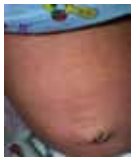
Scabies in an infant boy

Basal Cell carcinoma **Basal cell Carcinoma**



Benign Self-healing histiocytosis

Herpes zoster x 2 days duration. Treated with Acyclovir and Calamine lotion



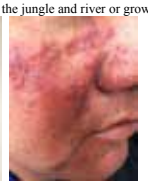
Miliaria crystallina

Tineas Capitus **Tinea Versicolor** **Tinea Facei** **Tinea Corporis**

DISCUSSION

It was interesting to discover that the Amazonian people were actually healthier in terms of systemic diseases than the people of Iquitos, the nearest large town in Peru. This was due to the processed food and unhealthy diet the people of Iquitos eat while those in the amazon eat fish, rice, fruits and vegetables all found in the jungle and river or grown on their land.

Leishmaniasis



Pyoderma Faciale

Psoriasis

SUMMARY

- Of the over 300 cases that were seen in Iquitos and the Amazon, the most common were infectious followed by inflammatory and then pigmentary disorders.
- The Mayor of Iquitos welcomed us very graciously as we arrived at our clinic location in Iquitos, Peru and upon our departure we established a site for continuing medical care in Iquitos, Peru.
- It is important to note the significance of awareness in the prevention of skin disease in the Peruvian people.
- We learned to be creative mixing various creams in small tubs as we had limited medical supplies and medicines available.
- We were able to treat each patients skin disease temporarily however in order to prevent the disease form returning we educated the patients on healthy skin practices.
- We are rejuvenated and inspired to learn and continue to help others.

The Amazon Queen boat

First Clinic day in the Amazon Jungle

Some of the Amazon Jungle children

The River Docs

References

1. Tyring, S. Lupi, O. Hengee, U. Tropical Dermatology. 1edition. 2014
2. Schaller, K. Colour Atlas of Tropical Dermatology and Venerology. 2000

Folliculotropic Mycosis Fungoides with Large Cell Transformation

Rosanne Paul, DO[1]; Ashley Feneran, DO[1]; Kevin D. Cooper, MD[1]

University Hospitals Case Medical Center/Case Western Reserve University School of Medicine Cleveland, OH, USA

Department of Dermatology[1]

History

A 71-year-old Caucasian female presented in 2007 with a persistent, solitary, asymptomatic lesion on the left preauricular cheek for one month. An outside biopsy was consistent mycosis fungoides (MF), folliculotropic variant (FMF). Disease persisted despite trials of topical bexarotene, oral bexarotene with nitrogen mustard, peg-interferon alfa-2b with oral bexarotene, and vorinostat combined with NB-UVB and topical steroids

A new lesion on the right chin developed in 2007 and a punch biopsy was consistent with tumor stage MF. Brentuximab was initiated for 8 doses with partial response, later discontinued due to worsening peripheral neuropathy. A lower dose of vorinostat was re-introduced in combination with NB-UVB and topical steroids and the patient remained with adequate disease control until reevaluation in March 2015.

Physical Examination

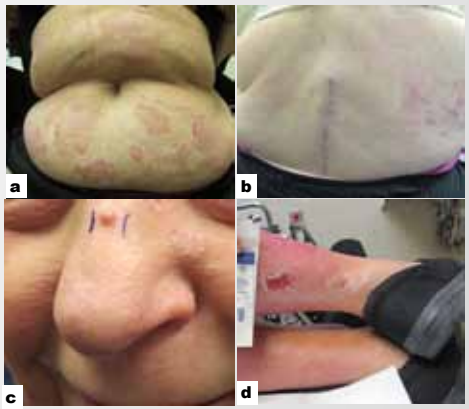


Figure 1 – **(a)** Initial presentation abdomen and **(b)** back; **(c)** Large cell tranformation on the mid nasal bridge and **(d)** right leg.

Clinical Course

In March 2015, a new lesion developed on the nasal bridge. Biopsy was consistent with transformed large cell lymphoma. Due to persistence of disease on the face, vorinostat was discontinued and the patient was restarted on topical nitrogen mustard ointment. One month later, a new, draining lesion developed on the right posterior leg and biopsy confirmed large cell transformation of mycosis fungoides. The legs were treated palliatively with a short course of radiation therapy with improvement.

Discussion

• Cutaneous T-cell lymphoma (CTCL) describes a group of neoplasms of skin-homing T cells.

• The most common subtype of CTCL is mycosis fungoides (MF).

• FMF is a distinct variant of MF and is characterized by the presence of folliculotropic infiltrates that often spare the epidermis.

•Patients with FMF may present with follicular papules, acneiform lesions, plaques and occasionally tumors classically involving the face, neck and upper trunk.

•Staging is not helpful in patients with FMF, and even when the face alone is involved they should be considered as having tumor stage disease.

• FMF is often refractory to standard treatments and is associated with a worse prognosis. Combination therapy with interferon-α, retinoids, local radiotherapy or total skin electron beam (TSEB) are often initiated, however complete remission is rare.

•Large cell transformation (LCT) is definitively diagnosed histologically and is defined by the presence of CD30- or CD30+ large cells. To be considered CD30+, there should be staining of at least 25% of the cells with CD30.

• LCT is associated with a poor prognosis. Studies have shown that MF and LCT have a common clonal origin.

•The risk factors involved in LCT are largely unknown. One group demonstrated that expression of CD25 may identify patients that are at risk for LCT.

• The median survival is 37 months for LCT versus 163 months of those with classic MF.

•Recently, Herrmann et al. analyzed 14 patients with LCT to guide a dermatologist to what should prompt biopsy for suspected LCT. Three major categories were defined:

- (1) LCT occurring as a new, solitary nodule within a long-standing classic MF patch or plaque
- (2) LCT occurring as an abrupt onset of multiple pink scattered nodules without spontaneous resolution
- (3) LCT occurring within a new or enlarging tumor. In each of the cases the primary morphological lesion was a nonspecific erythematous papule..
- . None of these patients were noted to have the folliculotropic variant of MF.

•There are no small or large studies of folliculotropic MF with LCT, but there are several case reports.

- In one case, a patient with FMF with LCT was treated with electron beam irradiation and oral bexarotene with remission.
- Similar results were seen in this case.

Histopathology

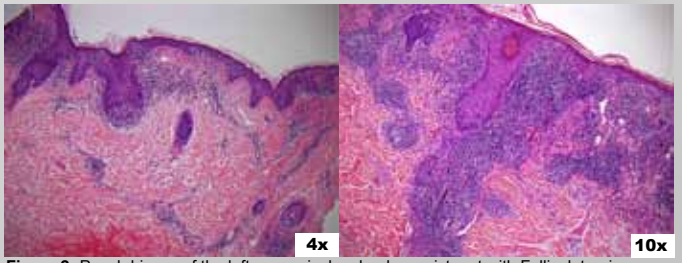


Figure 2- Punch biopsy of the left pre-auricular cheek consistnent with Folliculotropic Mycosis Fungoides

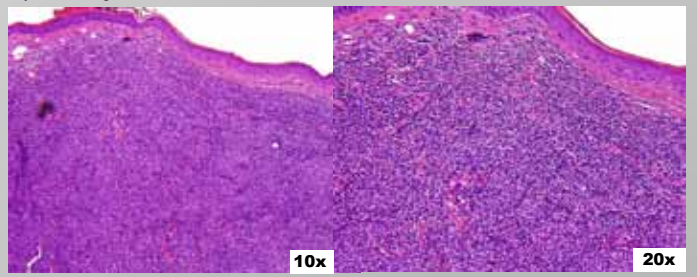


Figure 3 – Punch biopsy of the Mid Nasal Bridge revealing LCT.

Laboratory

- ANA, ENA panel negative
- Initial CBC with diff WNL, now with low hemoglobin and elevated MCV, with normal B12 and Folate levels
- Initial CMP notable for elevated glucose, now CMP with mild elevation in BUN and Cr, 24 and 0.97, respectively
- LDH Initially elevated and now WNL
- Initial and repeat CTs of the chest, abdomen and pelvis negative

References

1. Herrmann, J.L., et al. "Recognizing large-cell transformation of mycosis fungoides." *Journal of American Academy of Dermatology* (2012): 665-72. *PubMed*. Web. 12 Aug. 2015. <http://www.ncbi.nlm.nih.gov/pubmed/22261416>.
2. Mitteldorf, C., et al. "Folliculotropic mycosis fungoides with CD30+ large cell transformation in a young woman: beneficial effect of bexarotene." *Britis Journal of Dermatology* 156.3 (2006): 584-85. *PubMed*. Web. 16 Aug. 2015. <http://www.ncbi.nlm.nih.gov/pubmed/17300259>.
3. Willemze, Rein. "Cutaneous T-Cell Lymphoma." *Dermatology*. By Jean L. Bolognia, Joseph L. Jorizzo, and Julie V. Schaffer. 3rd ed. Vol. 2. N.p.: Elsevier, n.d. 2017-26. *ClinicalKey*. Web. 16 Aug. 2015. <https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780723435716001202>.

Aplasia Cutis Congenita Type V: a case report and review of the literature

Benjamin M. Perry, DO, PGY-3; Cory Maughan, DO

Western University of Health Sciences- Silver Falls Dermatology

Abstract

Aplasia cutis congenita is a relatively rare congenital anomaly that most commonly occurs as a solitary cutaneous defect on the scalp. Depth of involvement varies and involvement of deeper calvarium and dural structures can be seen in more severe cases. Multiple classification systems have been devised with the Frieden Classification System being the most widely adopted. Using this system, we describe a patient that developed Type V aplasia cutis congenita (ACC) with associated fetal papyraceous. The child healed remarkably well with application of petrolatum impregnated gauze and topical silver sulfadiazine twice daily for approximately 4 weeks. The child was noted to have no significant contractures or complications at 6 months and 1 year follow-up exams.

Case

A 37w4d male was born to a G8P5 mother after a complicated, monochorionic twin pregnancy. At 16 weeks gestation mother experienced fetal demise of one fetus. The surviving fetus developed hydrops fetalis and severe anemia requiring a fetal blood transfusion. At the time of delivery the male infant was noted to have significant absence of skin on the lateral torso and vertex scalp (Image 1). There was also apparent stellate scarring on the elbows, knees and hips. This was presumed to have been areas of aplasia cutis that had begun the healing process in utero. The remaining open wounds on the torso were initially dressed with petrolatum impregnated gauze and then a regimen of topical silver sulfadiazine was implemented (Image 2). The parents applied these dressings twice daily for approximately 4 weeks. At two weeks postpartum the infant developed a fever of unknown origin. Bacterial cultures from the healing wounds were taken and returned negative. At 4-8 weeks postpartum the areas of involvement demonstrated significant healing (Image 3). No significant contractures or complications were noted with routine exams at 6 months, 12 months and 2 years (Image 4).

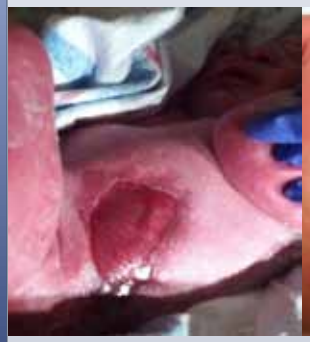


Image 1- Large defect on the lateral torso

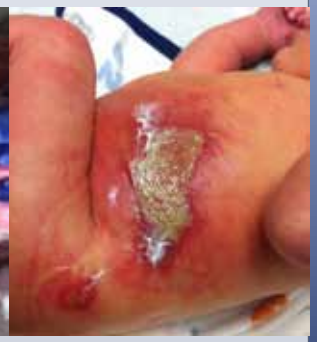


Image 2- Healing at 1 week old with conservative wound care

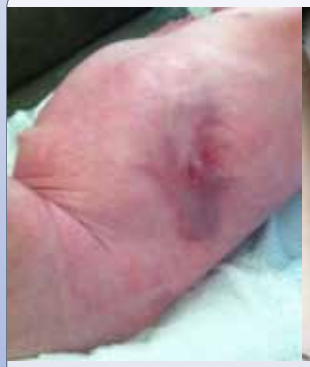


Image 3- At 2 months old, defect has nearly closed

Image 4- At 2 years old, well formed scar without contracture or restrictions in mobility.

Background

Aplasia cutis congenita (ACC) involves the congenital absence of a localized or widespread area of skin occurring in approximately 1-3 out of every 10,000 live births. It is most commonly observed in the scalp (84% of cases,[1] 86% of solitary lesions[2]) but can affect any part of the body. It is was first described by Cordon in 1767 and later by Campbell in 1826.[3,4,5] Typically a clinical diagnosis with findings of single or multiple circular, oval, linear, stellate or rhomboidal defects with varied depth from upper dermis down to dura in 15-30% of cases.[6] Mortality rates ranging from 20% to 55% have been reported in association with large areas of scalp involvement, often secondary to sagittal sinus hemorrhage, surgical complications, or associated congenital defects.[1] ACC has been reported to occur in approximately 1-3 out of every 10,000 live births.[7] The most widely used system to classify ACC was developed by Frieden (Table 1).[2] Using this system, the patient discussed above was diagnosed with type V aplasia cutis congenita with fetus papyraceus.

Group/Subtype	Clinical Features
1	Scalp aplasia cutis congenita without multiple anomalies
2	Scalp aplasia cutis congenita with associated limb abnormalities
3	Scalp aplasia cutis congenita with associated epidermal and organoid nevi
4	Aplasia cutis congenita overlying embryologic malformation
5	**Aplasia cutis congenita w/ associated fetus papyraceus or placental infarcts**
6	Aplasia cutis congenita associated with epidermolysis bullosa
7	Aplasia cutis congenita localized to extremities without blistering
8	Aplasia cutis congenita caused by specific teratogens
9	Aplasia cutis congenita associated with malformation syndromes

Table 1- Freiden Classification for Aplasia Cutis Congenita[2]

Discussion

In contrast to the other types of Aplasia cutis congenita, type V most commonly affects the trunk and is often symmetric (Table 2).[1,8] ACC with fetus papyraceus is typically observed in association with monochorionic twin pregnancies (95% of cases).[1] It has been noted that if demise occurs prior to 14 weeks gestation, ACC typically will develop on the trunk versus the extremities with fetal demise after 14 weeks.[8,9] Following twin fetal demise, some believe that an ensuing transient hypovolemia leads to ischemia of watershed areas of the skin[4,10] while others have suggested that thrombi formation in the setting of disseminated intravascular coagulation of the dying fetus embolizes to the healthy twin.[9] An exact pathogenesis has not been proven but it is almost certain that a transient vascular process is responsible for the clinical findings observed in type V ACC.

Body Area	Percent Affected
Flank	70%
Buttock/Thighs	60%
Abdomen	33%
Scalp	26%
Axilla/arms	21%
Back	16%

Table 2- Type V ACC distribution[1,8]

One of the greatest risks in type V ACC, is neonatal development of infection. As a result, early intervention is directed towards minimizing this risk. Depending on the size of the defect, treatment using surgery (skin grafts or flaps) or conservative wound care is often employed. Surgical risks include potentially fatal hemorrhage, infection, and anesthesia complications. Supportive wound care caries risk of hemorrhage, sagittal sinus thrombosis, wound bed necrosis, and infection. Because both carry significant risk of complications a definitive consensus for treatment has yet to be achieved. Most experts agree that conservative wound care is appropriate in the majority of cases with size of defect and location the most important factors to consider. In general, skin grafting is often reserved for defects larger than 2-4 cm; particularly with scalp defects.[4,11] One review of 11 cases of type V ACC associated with twin loss demonstrated successful reepithelialization and later scar formation in 10 of the cases.[9] In the remaining case, skin graft became necessary due to the development of bacteremia.[9] Conservative wound care has found similar success in other cases including our patient.

As a result, we feel that any treatment algorithm for type V ACC should rely on conservative wound care and infection prevention with more invasive methods utilized if complications arise. A basic regimen could include sequential application of silver sulfadiazine, petrolatum gauze, dry gauze and a self-adherent wrap with dressing changes twice daily.[9] Use of antibiotic ointment can be considered in place of silver sulfadiazine for any concern of toxicity with close monitoring for fungal overgrowth.[9] Antibiotics (topical or IV) should be reserved for signs that are suggestive of infection. Due to the risk for infection or significant electrolyte disturbances with conservative care, it is imperative to monitor closely until reepithelialization has occurred. Surgical intervention should primarily be considered in cases of refractory fluid loss, stalled epithelialization, and infection.[9]

References

1. Chan RK, Liu AS, Rogers GF. Aplasia cutis congenita of the trunk associated with fetus papyraceous. Journal of Craniofacial Surgery 2012; 23(4): 995-997.
2. Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. Journal of the American Academy of Dermatology 1986; 14(4):646-660.
3. Starcevic M, Sepec MP, Zah V. A case of extensive aplasia cutis congenita: a conservative approach. Pediatric dermatology 2010; 27(5): 540-542.
4. Browning JC. Aplasia cutis congenita: approach to evaluation and management. Dermatologic therapy 2013; 26(6):439-444.
5. Cordon M. Extrait d'une lettre au sujet de trois enfants de la même mère nés avec partie des extrémités dénuée de peau. J Med Chir Pharm 1767; 26:556-557.
6. Silberstein E, Pagkalos VA, Landau D, Berezovsky AB, Krieger Y, Shoham Y, Levy A, Rosenberg L, Silberstein T. Aplasia cutis congenita: clinical management and a new classification system. Plast Reconstr Surg. 2014; 134(5):766e-774e.
7. Martinez-Regueira S, Vazquez-Lopez ME, Somoza-Rubio C, Morales-Redondo R, Gonzalez-Gay MA. Aplasia cutis congenital in a defined population from northwest Spain. Pediatr Dermatol. 2006; 23:528–532.
8. Schaffer JV, Popiolek DA, Orlow SJ. Symmetric truncal aplasia cutis congenita following multifetal reduction of a sextuplet pregnancy. The Journal of pediatrics 2008; 153(6):860-863.
9. Morrow D, Schelonka R, Krol A, Davies M, Kuang A. Type V aplasia cutis congenita: case report, review of the literature, and proposed treatment algorithm. Pediatr Dermatol. 2013;30(6):e208-13.
10. Klein RQ, Robinson DM, Lieber CD, Antaya RJ. Symmetric aplasia cutis congenita associated with fetus papyraceus: report of two cases. Pediatr Dermatol. 2011;28(4):467-9.
11. Kuang F, Zhang Z, Chen B, Zhao Y, Li XJ. Combined conservative and surgical management for aplasia cutis congenita: a case report and review of the literature. Wounds 2014;26(9):273-9.

Metastatic Potential of Microcystic Adnexal Carcinoma

Jennifer S. Peterson, DO, PGY-3, Angelo A. Petropolis, MD, Amy Weierman, PA-C, Vernon T. Mackey, DO

Advanced Desert Dermatology & Cochise Dermatology, Peoria & Sierra Vista, AZ

ABSTRACT

Microcystic adnexal carcinoma is a rare adnexal neoplasm, with significant morbidity due to extensive subclinical extension, and an infrequent but demonstrated potential for regional as well as distant metastasis.

We present the case of a 58-year old female with a seven-month history of a slowly enlarging growth on her chin. Punch biopsy was performed and the specimen identified as sclerosing sweat duct carcinoma, a histologic variant of microcystic adnexal carcinoma.

The tumor demonstrated perineural invasion, and primary excision by Mohs surgery produced a large final defect requiring complex reconstruction. The patient was subsequently found to have multiple lymph node metastases with extracapsular extension and lymphovascular invasion. She underwent a modified neck dissection and completed a course of adjuvant chemoradiation.

This case highlights the insidious nature of microcystic adnexal carcinoma, which warrants a high index of suspicion in any patient presenting with a solitary sclerotic facial plaque.

HISTORY OF PRESENT ILLNESS

A 58-year old Caucasian female presented with a seven-month history of a slowly enlarging growth on her chin. She first observed this lesion in photos of herself as a shiny, reflective area of skin. She denied any associated pain, numbness, or tingling.

Past medical history significant for allergic rhinitis, eczema, hypertension, nephrolithiasis, cholelithiasis, and gastroesophageal reflux disease. Surgical history was non-contributory.

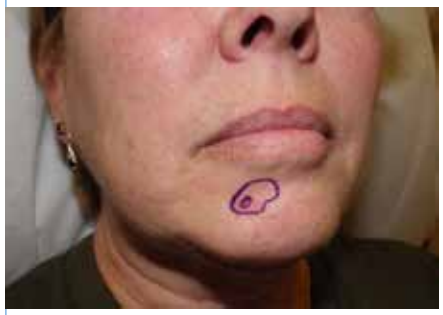
Family history significant for cancer deaths in maternal grandmother (rectal), mother (uterine), and pancreatic (maternal uncle).

The patient is retired from 20 years of military service, and married with two children. She admitted to social alcohol use, and denies tobacco or recreational drug use.

Current medications include dexlansoprazole, montelukast, and cetirizine. She is allergic to penicillins.

PHYSICAL EXAMINATION

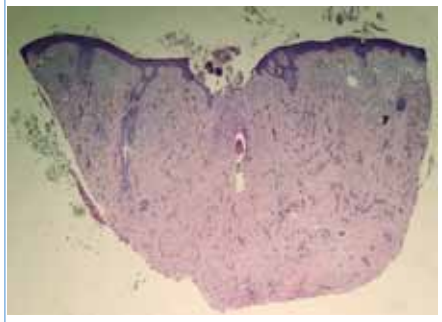
Physical examination revealed an ill-defined, erythematous, waxy, indurated, sclerotic plaque without significant epidermal changes on the right inferior medial lower cutaneous lip, measuring 1.8 by 1.0 cm in diameter.



The clinical differential diagnosis included morphea or other localized scleroderma, morpheaform basal cell carcinoma, infiltrative basal cell carcinoma, desmoplastic squamous cell carcinoma, and microcystic adnexal carcinoma.

PATHOLOGY

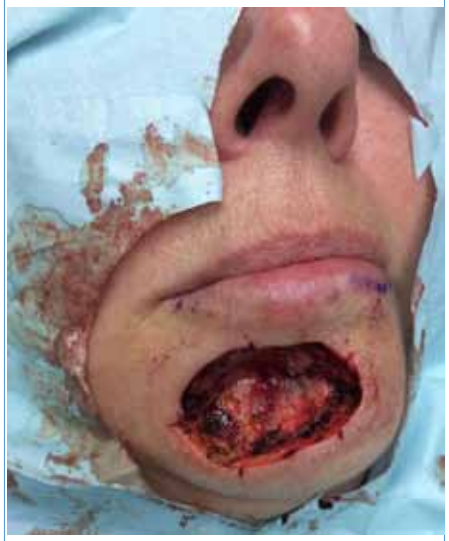
A 3-mm punch biopsy was performed, which demonstrated a dermal tumor composed of deeply infiltrative aggregates of basaloid epithelial cells with ductal differentiation. The proliferation was highlighted by EMA and CK7, while failing to stain with CEA or BerEP4.



The diagnosis was thus established of sclerosing sweat duct carcinoma. This entity is synonymous with microcystic adnexal carcinoma (MAC) from a clinical perspective. The distinction, where recognized, is purely histologic: sclerosing sweat duct carcinoma consists of monophasic sweat duct-like structures, whereas MAC demonstrates a biphasic pattern of ductal and pilar differentiation with superficial follicular keratinization.[1]

MANAGEMENT & CLINICAL COURSE

The patient was referred for primary resection by Mohs surgery, with plan for reconstructive repair to follow. The tumor was cleared in four stages and exhibited perineural invasion. The resulting defect ultimately required more complex reconstruction than originally anticipated; this was performed by a head and neck oncologic surgeon.



The patient was subsequently referred to an oncologist for further staging and consideration of adjuvant therapy. Staging PET/CT revealed two fluorodeoxyglucose-avid deep cervical lymph nodes in the right neck on staging PET scan. Excisional biopsies of both nodes were positive for adenocarcinoma.

A right modified neck dissection was performed, which demonstrated five additional lymph nodes positive for poorly differentiated metastatic carcinoma, favor adenocarcinoma, many with extracapsular extension and lymphovascular invasion.

The patient completed a course of chemoradiation, with electron beam radiation therapy of 63 Gy in 35 fractions to the tumor bed and neck bilaterally and concomitant chemotherapy with weekly carboplatin and paclitaxel.

She recovered well from these interventions, but was lost to follow up three months later after moving cross-country to be with her husband.

DISCUSSION

Microcystic adnexal carcinoma is a rare adnexal neoplasm that classically presents as a firm, slow-growing plaque on the lip of a middle-aged Caucasian female.[2]

Despite its relatively indolent appearance, MAC routinely exhibits extensive subclinical extension, with reticular dermal infiltration and perineural invasion. In one study detailing 26 MAC cases, final Mohs surgery defect size averaged six times larger than clinical tumor size. [3]

The locally aggressive behavior of MAC does not, however, typically translate to potential for regional or distant metastasis. The first documented case of lymph node metastasis was published in 1995[4], and to date fewer than 20 cases of lymph node or distant metastases have been reported.

Furthermore, a 2010 retrospective analysis of National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) data regarding MAC identified 223 patients, of which only three had lymph node involvement and one had distant metastasis. [5]

Our case illustrates a common clinical presentation of MAC with an uncommon progression to metastatic disease. The insidious nature of MAC may belie timely diagnosis, and given its propensity for local tissue destruction and potential for metastasis, this diagnosis should remain high on the differential diagnosis when evaluating any patient with a solitary sclerotic plaque, particularly on the face.

REFERENCES

1. Elston DM. Sweat gland neoplasms. In: Elston DM, Ferringer T, eds. *Dermatopathology*, 2nd ed. Amsterdam: Elsevier Limited; 2014:93-95.
2. McCalmont TH. Adnexal Neoplasms. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*, 3rd ed. Vol 2. Amsterdam: Elsevier Limited; 2012:1846.
3. Thomas CJ, Wood GC, Marks VJ. Mohs micrographic surgery in the treatment of rare aggressive cutaneous tumors: the Geisinger experience. *Dermatol Surg*. 2007; 33:333.
4. Bier-Laning CM, Hom DB, Gapany M, et al. Microcystic adnexal carcinoma: management options based on long-term follow-up. *Laryngoscope*. 1995; 105:1197.
5. Yu JB, Blitzblau RC, Patel SC, et al. Surveillance, Epidemiology, and End Results (SEE) database analysis of microcystic adnexal carcinoma (sclerosing sweat duct carcinoma) of the skin. *Am J Clin Oncol*. 2010; 33:135.

Rapidly Progressive Erythroderma Caused by Pityriasis Rubra Pilaris

Dustin Portela DO*, Dana Burandt BS**, Steve Grekin DO***

*Dermatology Resident, Oakwood Southshore Medical Center, **OMS III Michigan State University, *** Program Director
Dermatology Residency Oakwood Southshore Medical Center

Abstract

We present the case of a 50-year-old male who developed rapidly progressive erythroderma as a complication of pityriasis rubra pilaris (PRP), requiring hospital admission. The initial eruption developed following a sunburn. Following hospital discharge the patient has experienced a protracted course of erythroderma, which was treated with cyclosporine and acitretin as well as topical corticosteroids. We briefly review the various classifications of PRP as well as potential treatment options and prognosis.

Introduction

Erythroderma is a generalized redness to the skin with or without scaling. It can be a manifestation of many common primary disorders of the skin including psoriasis, atopic dermatitis, or drug reactions; or less common disorders such as cutaneous lymphoma or pityriasis rubra pilaris. Potential complications of erythroderma include peripheral edema, hypothermia, electrolyte imbalance, and high output heart failure. Prompt identification of the underlying disorder and treatment of erythroderma can prevent many complications and potentially be life saving.

Case Presentation

A 50-year-old Caucasian male presented with a three-day history of mildly pruritic erythematous papules and patches progressing from his head to his chest and upper arms after experiencing a sunburn during work. He also complained of redness to his hands and feet. The rash began two months earlier as a single, red, scaly patch on his scalp, which appeared after a mushroom hunting excursion. He had treated the patch with a mid potency topical corticosteroid prescribed by his primary physician with a presumptive diagnosis of psoriasis. The patient had a family history significant for psoriasis, but no other skin disorders. His past medical history was significant for hypertension, controlled with atenolol. A review of systems was negative for constitutional symptoms at his initial presentation.

Physical examination revealed a well appearing male with brightly erythematous, hyperkeratotic, follicular-based papules and scaly patches coalescing on the scalp, face, chest, and upper extremities (Figure 1). Examination of his hands and feet revealed erythema and hyperkeratosis of the palms and soles (Figure 2).

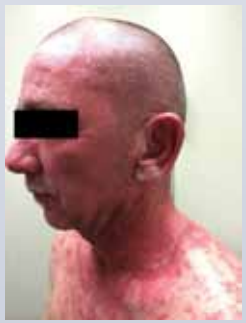


Figure 1

Clinical differential diagnosis included erythrodermic psoriasis, pityriasis rubra pilaris, and drug induced phototoxicity.

Initial laboratory evaluation was within normal limits and included complete blood count with differential, comprehensive metabolic panel, and urinalysis.

Two 4mm punch biopsies were obtained and revealed elongation of rete ridges, hyperkeratosis and confluent parakeratosis. There was a mild superficial perivascular lymphocytic and neutrophilic infiltrate as well as the presence of extravasated red blood cells. PAS stain was negative for fungi and colloidal iron stain was negative for mucinosis. A diagnosis of pityriasis rubra pilaris was rendered.

At the initial visit, the patient was started on triamcinolone 0.1% cream and instructed to follow up in two days to review his biopsy results. Initial follow-up revealed progressing erythroderma in a cephalic to caudal direction with islands of spared skin as well as more extensive hyperkeratosis of the palms and soles with fissuring and marked edema. At this time, he was started on oral cyclosporine and acitretin. Despite these medications the erythroderma progressed and he developed 3+ pitting edema of the lower extremities. He was admitted to the hospital for fluid and electrolyte management. During the hospitalization, his laboratory abnormalities included a mild hypoalbuminemia and hypoproteinemia. Following hospital discharge, the patient's dose of cyclosporine had been progressively tapered, and the dose of acitretin had been increased. The patient remained erythrodermic, but had experienced much less scaling, and the fissuring to his palms and soles had resolved. He continued to experience moderate pruritus and difficulty in body temperature regulation.

Discussion

Pityriasis rubra pilaris (PRP) is an uncommon, chronic skin condition of unknown etiology. It is characterized by hyperkeratotic follicular papules and palmoplantar keratoderma. The coalescence of papules bordered by uninvolved skin creates the appearance of "islands of sparing" between salmon-colored, scaling plaques. Progression to erythroderma is a potential complication.

PRP affects approximately 2.5 per million of the population and does not differ based on race or gender. There is a bimodal distribution for age of onset, including childhood for familial cases and the fifth or sixth decade for acquired cases[1,2].

The Griffiths' classification scheme describes six different types of PRP, differing in clinical presentation, lesion distribution, course, and duration (Table 1). The majority of patients are Type I, "classic adult," with generalized distribution and a cephalocaudal progression. In addition to the cosmetic and functional implications of the tight scales of the scalp and face, the waxy, thickened skin of the soles and palms can crack resulting in painful fissures. The onset is acute and 80% resolve within a three-year period[3].

Table 1

Clinical Type	Name	% of PRP Patients	Features
I	Classic adult	55%	Generalized distribution, cephalic to caudal spread, red- orange plaques with "islands of sparing", Perifollicular keratotic papules, waxy palmoplantar keratoderma
II	Atypical adult	5%	Generalized distribution, areas of eczematous dermatitis with ichthyosiform scale on legs, keratoderma with coarse lamellated scale, occasional alopecia
III	Circumscribed juvenille	25%	Focal distribution, elbows and knees show erythema & follicular papules, prepubertal onset
IV	Classic juvenille	10%	Generalized distribution with clinical findings similar to Type I, onset in first 2 years of life or in adolescence
V	Atypical juvenille	5%	Generalized distribution with follicular hyperkeratosis and erythema, scleroderma-like changes of hands and feet, onset in first few years of life
VI	HIV-associated follicular syndrome		Generalized distribution with findings similar to Type I, can occur in association with acne conglobata and hidradenitis suppurativa in HIV-infected individuals

Griffith's classification scheme of pityriasis rubra pilaris. Adapted from Bolognia, 3rd Ed. Fig. 9.9 p 164

While the pathogenesis of PRP remains uncertain, abnormal vitamin A metabolism, specifically a deficiency of retinol binding protein, and human immunodeficiency virus (HIV) have been studied as possible causes. Autoimmune diseases, sunburn, infections, and malignancies are linked as trigger factors; however, most cases occur without an inciting event[4].

The familial type of PRP, Type V, follows an autosomal dominant mode of inheritance, early age of onset, incomplete penetrance, and variable expression. In a recent study, Fuchs-Telem et. al. showed that mutations in CARD14, which regulates inflammatory processes through nuclear factor kappa B (NF-kB) and is strongly expressed in the skin, cause familial PRP[5].

Treatment

There is no universally effective treatment for PRP and some cases may even demonstrate resistance to both systemic and topical therapies[6]. A lack of thorough research comparing current treatment options exists due to the rarity of the condition. Traditionally, retinoids, methotrexate, or cyclosporine are used as systemic therapy. Topical emollients, corticosteroids, and keratolytics supplement the oral treatment. Biologic medications against psoriasis, such as tumor necrosis factor (TNF) antagonists, may have value in treating PRP, given the histological and clinical similarities between the two diseases[1,4,7].

Conclusion

Pityriasis rubra pilaris is an uncommon chronic skin condition, which can potentially lead to erythroderma. The majority of PRP patients will present as adults with a generalized eruption beginning on the head and neck, which then generalizes in a caudal direction. Unique features include "islands of sparing" and a waxy palmoplantar keratoderma. Although the etiology is unknown most patients presenting with classic symptoms will experience resolution within three years. There are no universally successful treatments and the patient approach must be individualized.

References

1. Petrof G, Almaani N, Archer CB, Griffiths, WAD, Smith CH. A systematic review of the literature on the treatment of pityriasis rubra pilaris type 1 with TNF-antagonists. J European Acad Derm Venerology 2013; 27:131-135
2. Griffiths WA. Pityriasis Rubra Pilaris – An Historical Approach. 2. Clinical features. Clin Exp Dermatol. 1976; 1:37–50.
3. Griffiths WAD. Pityriasis Rubra Pilaris. Clin Exp Dermatol. 1980; 5:105-12
4. Klein A, Landthaler M, Karrer S. Pityriasis Rubra Pilaris: A Review of Diagnosis and Treatment. Am J Clin Dermatol. 2010; 11:157-70
5. Fuchs-Telem D, Sarig O, Van Steensel M et al. Familial Pityriasis Rubra Pilaris Is Caused by Mutations in CARD14. Am J Hum Genet. 2012; 91:163-70.
6. Müller H, Gattringer C, Zelger B et al. Infliximab Monotherapy as First-line Treatment for Adult-onset Pityriasis Rubra Pilaris: Case Report and Review of the Literature on Biologic Therapy. J Am Acad Dermatol. 2008 Nov; 59(5): S65-70.
7. Ivanova K, Itin P, Haeusermann P. Pityriasis Rubra Pilaris: Treatment with Biologics - A New Promising Therapy? Dermatol. 2012; 224(2):120-5
8. Wood GS, Reizner G. Dermatology. 3rd ed. Elsevier Saunders; 2012. Chapter 9, Other Papulosquamous Disorders; p. 157-69

Scarring alopecia of the scalp from sarcoidosis: A case report

Laura F. Sandoval[1], D.O., Jonathan S. Crane[2,3], D.O.

[1]Sampson Regional Medical Center, Dermatology Resident, PGY-3, Clinton, NC, [2]Sampson Regional Medical Center, Dermatology Residency Program Director, Clinton, NC, [3]DermOne, Wilmington, NC

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Introduction

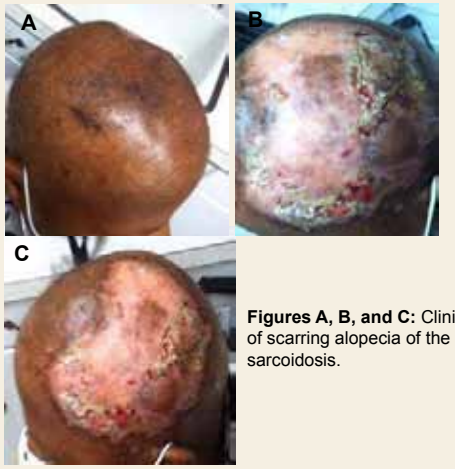
- Sarcoidosis is a systemic disease that can involve the skin in 25% of patients, however, cutaneous sarcoidosis of the scalp is uncommon.[1]
  - A 2012 review of literature identified 39 cases of sarcoidosis induced alopecia, which included both scarring and non-scarring cases.[2]
- Cutaneous sarcoidosis has been referred to as the great imitator of other skin diseases and is often a diagnosis of exclusion. Sarcoidosis alopecia similarly has been mistaken for discoid lupus erythematosus or other scarring alopecia, as well as, necrobiosis lipoidica.[3-5] Infectious causes of granulomas on histopathology must also be ruled out.

Case

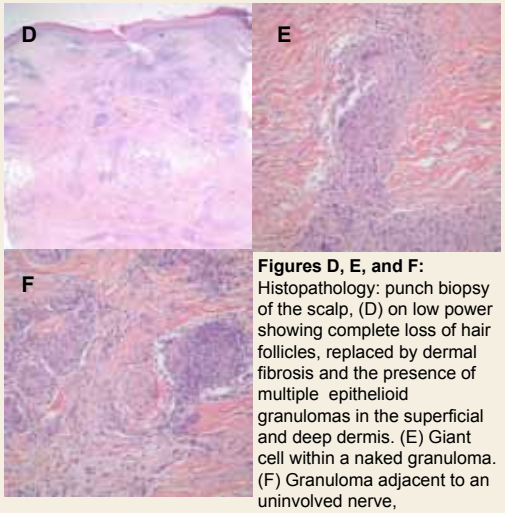
- A 51 year-old African American female presented for evaluation of "infection of the scalp". She had previously been treated with cephalexin and topical mupirocin without significant improvement.
- On physical exam, there was alopecia of the entire scalp, except for a few areas of thin patchy hair, and loss of follicular openings.(Figure A) There were large hypertrophic plaques and areas of superficial erosions overlying a smooth, shiny, hypopigmented patch covering the left side of the scalp.(Figures B & C) There were also scattered small hyperpigmented papules and plaques on the remainder of the scalp.
- On further history, patient stated she had a long history of hair loss, not previously worked-up. The current lesions ("infection") had been present for approximately 2 years, gradually worsening. She also had a past diagnosis of systemic sarcoidosis with pulmonary involvement, but she had not received medical care for many years. In addition, she had a recent diagnosis of breast carcinoma.
- A 4-mm punch biopsy was obtained from the left parietal scalp. Differential diagnosis included: discoid lupus erythematosus, sarcoidosis, lichen planopilaris, however a secondary infection (fungal or bacterial) or malignancy such as squamous cell carcinoma were also considered.
- Histopathology showed no hair follicles, the dermis replaced by fibrosis, and the presence of multiple epithelioid granulomas.(Figures D & E) The findings were consistent with a scarring alopecia due to granulomatous inflammation consistent with sarcoidosis.
- Pending pathology results, the patient was started on topical clobetasol ointment, with significant improvement after one month. Given the severity of disease, systemic treatment was recommended. After discussion with the patients' oncologist, it was decided that prednisone would be initiated. Once her cancer treatment was complete, the plan was to switch to hydroxychloroquine or methotrexate, however patient was lost to follow-up.

Discussion

- We report a case of sarcoidosis presenting as severe scarring alopecia.
- Scarring alopecia of the scalp from sarcoidosis is rare and usually presents as a few patches of hair loss resembling discoid lupus erythematosus, however, rarely is diffuse scarring alopecia reported.[3,6]
- A review of literature showed that sarcoidosis of the scalp is predominately in females and African Americans and is often associated with systemic involvement.[2,7] Therefore, a diagnosis of cutaneous sarcoidosis of the scalp alone warrants a work-up for systemic disease. Patients should also have a full skin exam since involvement of other skin sites are usually present with sarcoidosis of the scalp.[2,7] In our patient cutaneous sarcoidosis was limited to the scalp.
- Sarcoidosis of the scalp can be difficult to treatment. Treatment options include: topical, oral, and intralesional corticosteroids, immunosuppressive agents such as azathioprine and methotrexate, and hydroxychloroquine, with oral prednisone most frequently providing improvement.[2,6-9] While treatment may successfully halt progression of disease, if may not result in hair regrowth.



Figures A, B, and C: Clinical presentation of scarring alopecia of the scalp from sarcoidosis.



Figures D, E, and F: Histopathology: punch biopsy of the scalp, (D) on low power showing complete loss of hair follicles, replaced by dermal fibrosis and the presence of multiple epithelioid granulomas in the superficial and deep dermis. (E) Giant cell within a naked granuloma. (F) Granuloma adjacent to an uninvolved nerve, differentiating sarcoidosis from tuberculoid leprosy.

References

1. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;336:1224-1234.
2. House NS, Welsh JP, English JC, III. Sarcoidosis-induced alopecia. *Dermatol Online J* 2012;18:4.
3. Henderson CL, Lafleur L, Sontheimer RD. Sarcoidal alopecia as a mimic of discoid lupus erythematosus. *J Am Acad Dermatol* 2008;59:143-145.
4. Harman KE, Calonje E, Robson A, Black MM. Case 1. Sarcoidosis presenting as a scarring alopecia resembling necrosis lipoidica. *Clin Exp Dermatol* 2003;28:565-566.
5. Andersen KE. Systemic sarcoidosis with necrobiosis lipoidica-like scalp lesions. *Acta Derm Venereol* 1977;57:367-369.
6. La PM, Vincenzi C, Misciali C, Tosti A. Scalp sarcoidosis with systemic involvement. *J Am Acad Dermatol* 2008;59:S126-S127.
7. Katta R, Nelson B, Chen D, Roenigk H. Sarcoidosis of the scalp: a case series and review of the literature. *J Am Acad Dermatol* 2000;42:690-692.
8. Golitz LE, Shapiro L, Hurwitz E, Stritzler R. Cicatricial alopecia of sarcoidosis. *Arch Dermatol* 1973;107:758-760.
9. Smith SR, Kendall MJ, Kondratowicz GM. Sarcoidosis--a cause of steroid responsive total alopecia. *Postgrad Med J* 1986;62:205-207.

Costs Associated with Melanoma in the United States

Tanasha Simela, DO, MS, Adriana Ros, DO
Dermatology Residency Program, Palisades Medical Center

Background

It is estimated that melanoma is responsible for 8,790 deaths in the US annually. There is significant cost associated with melanoma. These cancerous growths result from un-repaired DNA damage to skin cells, which triggers mutations that lead skin cells to multiply rapidly and form malignant tumors. While the incidence of melanoma is well documented in the scientific literature the associated inpatient cost is not well documented.

Study Design

The study was conducted using data from the National Inpatient Sample (NIS) which is part of the Healthcare Cost and Utilization Project (HCUP) .

Methods

The 2012 Health Care Utilization Project Nationwide Inpatient Sample (HCUP-NIS) data was used to identify, track and analyze the national trend of those patients admitted with a diagnosis of melanoma. Inpatient stays for melanoma were identified by The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). A range of ICD-9 codes 172.-172.9 reflect those assigned to diagnoses and procedures associated with melanoma.

Results

In 2012, there were a total of 3,130 inpatient discharges with a diagnosis of melanoma in the US. The greatest associated mean cost was accrued by ICD 9 code 172.2, melanoma of the ear, which was closely followed by melanoma of the face. ICD 9 code 172.6, which represents melanoma of the arm, had the lowest associated mean cost.

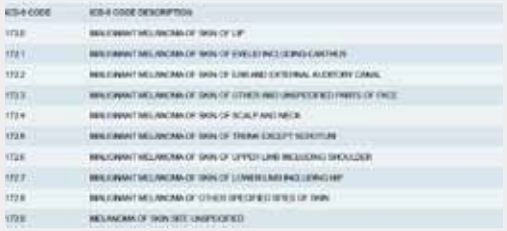


Figure 1.

Table 1.

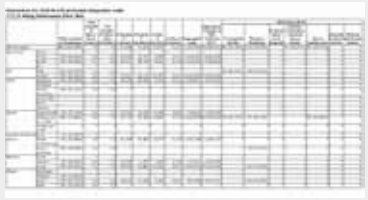


Table 2.

Discussion

There is considerable resource utilization associated with melanoma in the United States. In our study we found that the overwhelming majority of patients admitted with a diagnosis of melanoma regardless of region were insured by a government-sponsored program. With the current focus on reducing government spending, the allocation of healthcare dollars is under constant review. Melanoma prevention and early detection may reduce the number of melanoma-related hospitalizations and may improve clinical outcomes and reduce costs. This review summarizes the economic burden associated with melanoma with a focus on the US healthcare system.

References

1. National Inpatient Sample (NIS) beginning with 2012 data: The study examined regional cost differences for melanoma using discharge data from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality.
2. Tsao, Hensin, Gary S. Rogers, and Arthur J. Sober. "An estimate of the annual direct cost of treating cutaneous melanoma." Journal of the American Academy of Dermatology 38.5 (1998): 669-680.
3. Kirsner, Robert S., Doris G. Yang, and Francisco A. Kerdel. "Dermatologic disease accounts for a large number of hospital admissions annually." Journal of the American Academy of Dermatology 41.6 (1999): 970-973

A Complicated Case of Acute Parotitis

Anna Slobodskya DO
St. John's Episcopal Hospital, Far Rockaway, NY Dermatology
Suzanne Sirota-Rozenberg DO, Program Director Albert Strojan DO, DME

Introduction:

Acute bacterial suppurative parotitis is most commonly caused by Staphylococcus aureus and is often polymicrobial. Many times parotitis occurs in chronically ill elderly patients. The diagnosis is made when the characteristic clinical findings are present including pre and post-auricular swelling, pain, and trismus. Purulent drainage may be present at the opening of the duct of Stensen. Acute suppurative parotitis requires prompt aggressive treatment to prevent respiratory compromise and other complications. Treatment is generally a 10-14 day course of broad spectrum intravenous antibiotics. In recurrent cases of parotitis, a parotidectomy may be considered

Case Report:

An 83 year old female with a PMH of Alzheimer's dementia, schizoaffective disorder, NIDDM and HTN presented to the ED from a nursing home with a two day history of right sided facial swelling. Due to her dementia and confused mental status, a history was unable to be obtained from the patient. Per nursing home records, the patient had swelling that had gotten progressively worse over the past two days, with a noted fever of 103F. Her other vitals signs were stable and she was able to follow commands.
Clinical presentation was significant for erythema and edema to the right side of the face from the pre-auricular region to the right side of the mouth, with diffuse tenderness to palpation and trismus. The facial nerve was determined to be intact. Purulent discharge was expressed from her right Stensen's duct. The remained of the physical and otolaryngologogical exam was unremarkable. Diagnostic interpretation of a CT of the head showed an abnormally enlarged right parotid gland and thickened Stensen's duct. The patient received IV Vancomycin, Clindamycin and IV fluids. Her treatment also included warm compresses and frequent parotid massage. She was transferred to the ICU to monitor for respiratory compromise. 48 hours into antibiotic treatment, her swelling was not markedly improved. An abscess had formed and subsequently was incised and drained. Wound culture results showed MRSA and Candida albicans infection. Fluconazole was added to the patient's treatment regimen. The patient was successfully treated and discharged after 14 days of treatment with instructions to take oral Fluconazole for a total of four weeks of treatment. At follow-up examination, the parotitis had resolved.

Discussion:

Epidemiology:
Acute suppurative parotitis predominantly affects the elderly patients, the majority of whom are debilitated by systemic disease and dehydrated. Diabetes, alcoholism, autoimmune disorders such as Sjogren's disease, poor oral hygiene, malnutrition, decrease in salivary flow secondary to medications (such as diuretics, anticholinergics, antihistamines), postsurgical dehydration, and ductal obstruction are some of these predisposing risk factors.
Many of the risk factors for acute suppurative parotitis and MRSA overlap, and include old age, multiple co-morbidities, hospital admission and residence in a nursing home.

Clinical Manifestations:
The most common clinical manifestation of acute suppurative parotitis is the onset of an indurated, warm, erythematous swelling of the pre and postauricular areas that extends to the angle of the mandible. This is usually a unilateral swelling, although there have been a few cases of bilateral parotitis. The area above the swelling is extremely tender, and patient may have complaint of extreme pain, trismus, and dysphagia. Symptoms may be exacerbated by meals. Intraorally, Stensen's duct may appear erythematous or inflamed and purulent material may be expressed from its orifice. Due to the dense fibrous nature of the parotid fascia, a fluctuant quality is usually not observed. Additionally compression of the facial nerve as it passes through the gland may occur.

Microbiology:
•Staphylococcus aureus is the most common pathogen
•Microbiology is quite variable and often polymicrobial
•Other pathogens include streptococci, gram-negative bacilli and anaerobes
•Diabetic patients have increased susceptibility to oral yeast carriage. This may be due to decreased salivary flow or increased levels of salivary glucose. A review of the literature revealed only a handful of cases where Candida was isolated in a parotid abscess.

Diagnostic Evaluation and Imaging:
•Patient with the above clinical presentation
•An elevated amylase (in the absence of pancreatitis)
•Purulent discharge should be collected for a Gram stain and culture. If there is no purulent discharge from Stensen's duct, extra-oral needle aspiration of the swollen gland should be performed
•Ultrasonography, CT scan, and MRI are the common radiology imaging used
  •CT scan with IV contrast is often the first radiologic evaluation of choice due to its ability to enhance the different soft tissue densities within the gland

Treatment:
•Hydration and Antibiotics.
  • Initial antibiotic therapy should be based on the expected microbiology and host factors. Therapy should be directed against Staphylococcus aureus (including MRSA in nosocomial and nursing home patients), oral aerobes and anaerobes. Therapy should be administered for 10-14 days in uncomplicated cases
•Any cause of salivary stasis such as certain medications should be stopped
•Attempts should be made to increase salivary flow.
  • applying warm compress to the area
  • massaging the gland
  • maximizing oral hygiene
  •irrigating the mouth and giving the patient lemon drops to increase salivation
•Surgical incision and drainage - if the patient does not improve in 48 hours
•Piliocarpine can be used to stimulate salivary flow

Complications:
Progression of the swelling can lead to many complications. The infections can spread to the deep fascia of the head and neck. Increase in swelling of the neck can cause respiratory obstruction. Additionally, septicemia, osteomyelitis of the adjacent facial bone, and facial nerve palsy are all possible complications.

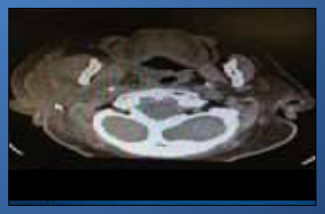
Images:


Lab Values:

CBC: WBC-17.1 Hgb-11.9 Hct-33.4 Plt- 190
CMP: Na-134 K-4.3 Cl-95 HCO3-30 BUN-19 Crea-0.77 Gluc- 204 Amylase - 40
Wound Culture/Gram Stain: Methicillin resistant Staphylococcus Aureus , Candida Albicans
Blood Culture: No growth

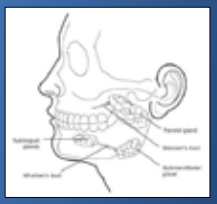
CT Findings:

Marked , and diffuse cutaneous and subcutaneous edema diffusely, including the temporalis muscle, the overlying scalp. The edematous soft tissues extend laterally and caudally, through the peri-auricular soft tissues and tapering towards the supraclavicular region. There is thickening of the platysma muscle and right submandibular gland. Anterior triangle lymph nodes, are borderline enlarged. The epicenter is the right parotid gland, which is diffusely swollen, including the superficial and deep portion. The gland is abnormally dense. There is diffuse thickening of Stensen's duct, but without calculi. Asymmetric thickening of the parapharyngeal fat planes, deep portion of the parotid gland, the right lateral pharyngeal wall, from the soft palate to the base of the tongue, without airway obstruction.

Conclusion:

Acute suppurative parotitis can be seen in various clinical settings. MRSA parotitis is largely a disease of the elderly with a high mortality. It is important to diagnose these patients early and initiate appropriate therapy. A culture of parotid drainage fluid (via pus expression or needle aspiration) and blood cultures is necessary. Empirical antibiotics should cover *S.* aureus (including MRSA if risk factors exist) and anaerobes, pending susceptibility results. Drainage is usually only required if an abscess forms. This case illustrates the importance of considering Candida Albicans in the differential diagnosis of diabetic patients.
Adequate hydration, proper oral hygiene, and blood glucose control are effective measures at preventing reoccurrence.



References:

1. AJ, McCaffrey TV. Inflammatory disorders of the salivary glands. In: Cummings CW, Flint PW, Harker LA, Haughey BH, Richardson MA, Robbins KT et al., eds. Cummings: Otolaryngology: Head and Neck Surgery, 4th edn. Philadelphia: Elsevier Mosby, 2005:1323–9
2. Brook I. Acute bacterial suppurative parotitis: microbiology and management. J CraniofacSurg 2003;14: 37–40
3. Fattahi TT, Lyu PE, Van Sickels JE. Management of acute suppurative parotitis. J Oral MaxillofacSurg 2002;60: 446–8
4. Smith DR, Hartig GK. Complete facial paralysis as a result of parotid abscess. Otolaryngol Head Neck Surg 1997;117: 114–17
5. Tan, VES. Parotid Abscess: A Five Year Review. The Journal of Laryngology& Otology 2007;121: 872-79

Epidermolysis Bullosa Acquisita with Extensive Mucocutaneous Involvement

Brittany P. Smirnov, DO (PGY-3)[1], Alexis Stephens, DO (PGY-4) [1], Elyse Julian, DO (PGY-1)[2], Carlos H. Nousari, MD[3]

1) Dermatology Resident, Department of Dermatology, Broward Health Medical Center 2) Traditional Rotating Intern, Broward Health Medical Center 3) Program Director, Department of Dermatology, Broward Health Medical Center, Graduate Medical Education Department, Fort Lauderdale, FL 33316

BACKGROUND

First described by Elliot in 1895, epidermolysis bullosa acquisita (EBA) is a rare heterogeneous autoimmune bullous disease of cutaneous and mucosal tissue.[1] Autoimmune bullous diseases can be subdivided into two main categories: pemphigus, demonstrating autoantibodies targeting desmosomal antigens, and pemphigoid, or subepidermal diseases demonstrating autoantibodies to hemidesmosomal antigens (figure 1c).[2,3,4] A subepidermal bullous dermatosis, EBA results from the formation of IgG autoantibodies (figure 1b) targeting type VII collagen (C7) within the anchoring fibrils attaching the epidermis to the dermis.[3] As a result, patients present with skin fragility, cutaneous and mucosal blisters, milia, nail loss, erosions and chronic scarring. [3]

A rare disease, EBA is estimated to develop in only 1 per every five million individuals.[2] With no reported gender predilection and primarily affecting adults, EBA's mean age of onset is 40-50 years, although it has been reported in children and the elderly.[5] Though rare, EBA has been reported in association with Crohn's disease, systemic lupus erythematosus (SLE), and drug-exposure such as penicillamine. Not only is the diagnosis of EBA complicated by its rarity, it is further convoluted by a variable clinical presentation that closely mimics those of other subepidermal blistering diseases.[5] Clinically, EBA is divided into a trauma-induced or mechanobullous variant and an inflammatory subtype. Here we present a case of EBA, initially misdiagnosed as bullous pemphigoid, with extensive mucocutaneous involvement.

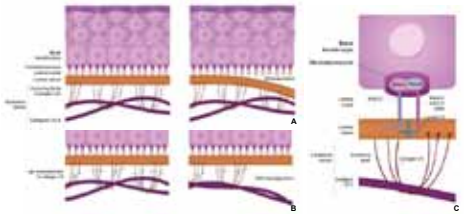


Figure 1. Graphic representation of the normal components basement membrane zone (a) and the cleavage plane location of salt-split skin, through the lamina lucida (a). Below, a depiction EBA IgG autoantibodies targeting collagen VII, a component of anchoring fibrils, resulting in a subepidermal, and specifically, sub-lamina densa cleavage in EBA (b). Above right, a depiction of the components of hemidesmosomal units in the BMZ and their interaction with the lamina densa and sublamina densa (c).

CASE PRESENTATION

A 63 year old Jamaican male presented with a 4-month history of a severe generalized cutaneous bullous eruption with intraoral lesions, accompanied by pruritus, dysphagia, odynophagia, epistaxis, loss of teeth, and changes in vocal quality. Patient reported previous hospitalization 4 months prior for similar blistering skin rash and was discharged home with a diagnosis of bullous pemphigoid, on a long-term prednisone taper, finishing three days before re-presentation. Patient denied any nausea, vomiting, abdominal pain, or penicillamine exposure.

Dermatologic examination revealed multiple tense and ruptured bullae on an erythematous base involving the head, trunk, extremities, and acral surfaces on a background of mottled pink and light-tan hypopigmented patches (Figure 2). Oral examination revealed multiple tense and ruptured bullae of the tongue, gingiva, and buccal mucosa (Figure 3) with ulcerations of the inferior left labial mucosa, not extending past the vermillion border, with positive mucocutaneous nikolsky sign and no evidence of ocular involvement. Laboratory workup for SLE was negative with comprehensive metabolic panel, and complete blood count negative save for a mild normocytic, normochromic anemia.

CLINICAL IMAGES

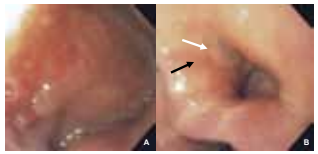


Figure 4 (above). Tense, and denuded bullae on the background of mottled pink hypopigmented patches, with milia, of extremities, trunk, hands, lateral face, tense bullae involving lingual and buccal mucosa, associated with dental loss.

Figure 5 (left). Upper endoscopy demonstrated intra-esophageal bullae and ulcerations of mucosa (a), and bullae (white arrow) and erosions (black arrow) of epiglottis (b). subsequent laryngoscopy confirmed bullae involving aeryepiglottic folds as well (not pictured).

PATHOLOGY

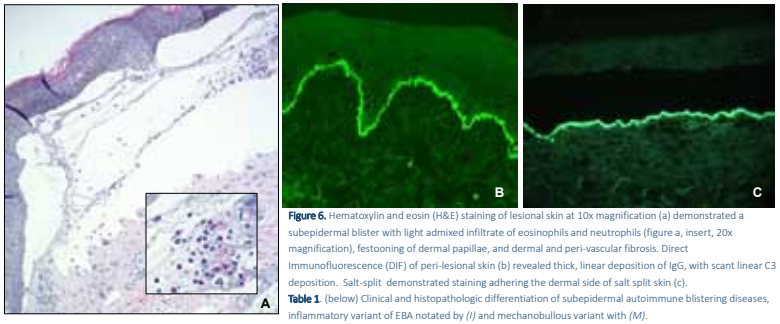


Figure 6. Hematoxylin and eosin (H&E) staining of lesional skin at 10x magnification (a) demonstrated a subepidermal blister with light admixed infiltrate of eosinophils and neutrophils (figure a, insert, 20x magnification), festooning of dermal papillae, and dermal and peri-vascular fibrosis. Direct Immunofluorescence (DIF) of peri-lesional skin (b) revealed thick, linear deposition of IgG, with scant linear C3 deposition. Salt-split demonstrated staining adhering the dermal side of salt split skin (c).

Table 1. (below) Clinical and histopathologic differentiation of subepidermal autoimmune blistering diseases, inflammatory variant of EBA notated by *(I)* and mechanobullous variant with *(M)*.

Disease	Clinical differentiation	Histopathologic differentiation
EBA	+scarring +milia +cutaneous and mucocutaneous involvement +erythematous blister base (I) +pruritus (I)	+ fibrosis +subepidermal blister +pauci-cellular (M) +PMNs and Eos (I) DIF: linear IgG, scant C3 salt-split: dermal staining
Bullous Pemphigoid (BP)	-Scarring -milia +pruritus +cutaneous involvement -mucocutaneous involvement (MC involvement rare) +erythematous blister base	- Fibrosis, +subepidermal blister, +Eos sometimes PMNs, DIF: thick linear IgG and C3, salt-split: epidermal staining
BSLE	+ANA, +history of lupus -mucocutaneous involvement	Histologically almost identical
Linear IgA Bullous Dermatosis(LABD)	-scarring (rare) -mucocutaneous involvement +erythematous blister base +typical targetoid appearance (esp drug-induced)	-fibrosis +subepidermal blister +PMNs and Eos DIF: linear IgA
Mucous Membrane Pemphigoid (MMP)	+scarring -cutaneous involvement (usually very limited) +mucocutnaeous involvement (extensive)	+ perivascular and dermal fibrosis +subepidermal blister *biopsy specimen c/w mucocutaneous sites
Porphyria Cutanea Tarda (PCT)	+milia -scarring +photodistributed +dorsal hands -erythematous blister base (non-inflammatory) -mucocutaneous involvement	+pauci-cellular +subepidermal blister +caterpillar bodies DIF: linear and peri-vascular staining

DISCUSSION

Pathogenesis:

The pathogenesis of EBA is due to circulating and tissue-bound IgG reactive to collagen VII (C7) (Figure 1b), a common target antigen with bullous systemic lupus erythematosus (BSLE). The target antigen, C7, is a comprised of three 145-kDa alpha-chains with central collagenous triple helixes, a 145-kDa amino terminal non-collagenous domain (NC1), and a 34-kDa carboxy-terminal non-collagenous domain (NC2).[3] IgG autoantibody destruction of C7 results in disruption of anchoring fibrils and consequent separation at the dermal epidermal junction (figure 1b).[4] When injecting C7 reactive IgG antibodies into laboratory mice the mice develop an EBA-like blistering disease, thus confirming the IgG antibodies targeting C7 as primary pathogenic agent in the development of EBA.[5]

Diagnosis:

Distinguishing EBA from its more common counterparts remains a clinical and histologic challenge, reinforcing the importance of both routine H&E staining, as well as DIF. Ensuring diagnostic accuracy when addressing autoimmune bullous diseases requires clinicians utilize both clinical and histopathologic information (table 1). Clinically EBA, can look identical to BP, especially the inflammatory subtype in earlier stages, with the exception of scarring, milia formation, and occasionally extensive mucocutaneous involvement. Histopathologically, it can be differentiated by fibrosis (figure 6a), and specific patterns of DIF and salt-split skin (figure 6b, 6c).

TREATMENT & MANAGEMENT

Due to severity of disease and extent of involvement (>90%) a combination multi-target immunosuppressive regimen was selected including:

- Solumedrol 1mg/kg daily
- Mycofenolate Mofetil 1,500 mg twice daily
- Rituximab 1mg/kg IV on day 1 and day 15 (Rheumatoid Arthritis protocol)
- IVIG 2gm/kg total dose, given IV over 3 days

With both cutaneous and mucocutaneous involvement, EBA patients must continue to follow regularly with all specialties corresponding to organ systems affected, including dermatology, ophthalmology, gastrointestinal specialists, dentistry, otolaryngology, and pulmonology.

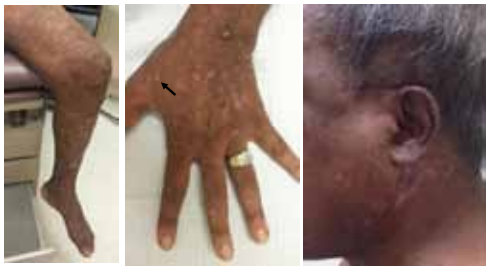


Figure 7. Clinical response 3 months after multi-target immunosuppressive therapy including Solumedrol, IVIG, Rituximab, Mycofenolate mofetil. Residual tan hypopigmented patches and milia (black arrow), no active bullae or erythematous patches or plaques.

REFERENCES

1. Elliot FI. Two cases of epidermolysis bullosa. J Cutan Genitour Diseases 1895; 13: 10-18.
2. T. Hashimoto, N. Ishii, C. Ohata, M. Furumura. Pathogenesis of epidermolysis bullosa acquisita, an autoimmune subepidermal bullous disease. J Pathol. 2012; 228(1):1-7.
3. M. Chen, G.H. Kim, L. Prakash, D.T. Woodley. Epidermolysis bullosa acquisita: autoimmunity to anchoring fibril collagen. Autoimmunity. 2012; 45(1):91-101.
4. N. Ishii, T. Hamada, T. Dainichi et al., Epidermolysis bullosa acquisita: what's new? Journal of Dermatology, 2010; 37 (3):220-230.
5. A. Barreiro-Capurro, J.M. Mascaro-Galy, P. Iranzo. Retrospective study of the clinical, histologic, and immunologic features of epidermolysis bullosa acquisita in 9 patients. Actas Dermosifiliogr. 2013; 104(10):904-914.
5. Gupta R, Woodley DT, Chen M. Epidermolysis bullosa acquisita. Clin Dermatol. 2012 2012 Jan-Feb;30(1):60-9.

Marijuana: An Underreported Cause of Fixed Drug Eruption & Review of Cutaneous Manifestations of Illicit Drug Use

Palm Beach Consortium for Graduate Medical Education

Palms West Hospital
St. Lucie Medical Center
University Hospital & Medical Center
West Palm Hospital

Christina Steinmetz-Rodriguez, D.O. PGY IV Dermatology Fellow,
Brent Schillinger, M.D.
PBCGME/West Palm Hospital, West Palm Beach FL

BACKGROUND

First described by Burns in 1889 and subsequently five years later termed "eruption erythemato-pigmentee fixe" by Brocq, the designation "fixed drug eruption (FDE) " represents one of the most common types of drug eruptions whose incidence continues to increase over the years relative to other drug eruptions.[1,2,3] The most characteristic finding of FDE are lesions that recur at the same anatomic sites upon repeated exposure to an offending agent.[3] A large number of drugs, including barbituates, penicillin, sulfonamides, tetracyclines, bismuth and iodides have been linked as the cause of FDE[4]. However, marijuana use remains an underreported cause of FDE. As legalization of marijuana in the United States becomes more widespread, it is important for clinicians to recognize and be familiar with the cutaneous manifestations of marijuana use. Because drug abuse carries a negative stigma, patients are not always immediately forthright in reporting this history. By both recognizing cutaneous signs and routinely inquiring a history of illicit drug use, dermatologist can be the first to recognize signs of illicit drug use in patients resulting in earlier treatment for patients.

CASE DESCRIPTION

Presentation & History:

A 32-year-old Hispanic male presented to the dermatology clinic with:

- Recurring hyperpigmented patches on his face over the past year that were transient
- Lesions would erupt in the same location on his face each time on a monthly basis and resolve in 6 to 7 days
- Denied any prior medical history and reported no medication use including over-the-counter medications.

Pertinent Physical Exam Findings:

- Well-defined 2 cm circular hyperpigmented patch over his right zygoma with mild scaling at the periphery (Figure 1).
- Two 0.5 cm hyperpigmented macules bilaterally on the lower lip, and a 1 cm macule in the philtral ridge (Figure 2).

Histology:

- Shave biopsy of the zygomatic lesion revealed interface vacuolar changes with dermal melanophages and some eosinophils, as well as near full thickness epidermal necrosis (Figures 3 and 4)
- PAS stain failed to reveal any dermatophytes. However, the PAS did reveal normal thickness of the epidermal basement membrane consistent with fixed drug eruption.

Clinical Course:

- After the biopsy results returned, a careful review of the patient's medical history revealed that each episode was produced by the same event –recreational use of marijuana.
- A short course of class 5 topical corticosteroid therapy resulted in complete resolution of the lesions and patient was advised to abstain from marijuana.

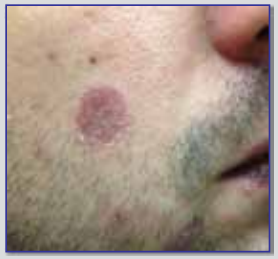


Figure 1

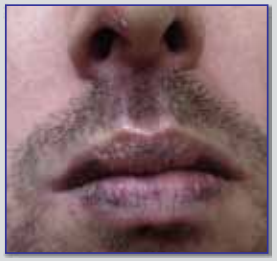


Figure 2

Table 1: Clinical Variations of Fixed Drug Eruptions (FDE)[3,5]

Type	Presentation	Known Causes
Pigmenting FDE	Lesions heal with residual hyperpigmentation	Barbituates, penicillin, NSAIDs sulfonamides, tetracyclines, bismuth and iodides
Erythema multiforme-like fixed drug eruption	Lesion with three zones: central dusky purpura, an elevated, edematous, pale ring and surrounding erythema	Mefenamic acid
Toxic epidermal necrolysis-like fixed drug eruptions	Widespread, bullous lesions	NSAIDs
Linear fixed drug eruptions	Multiple lesions that are distributed linearly; may follow Blaschko's lines or nerve root distribution	Trimethoprim
Wandering fixed drug eruption	Involved sites do not flare with each exposure and activity does not always appear at the same with each recurrence	Acetaminophen
Non-pigmenting fixed drug eruption	Lesions do not leave any residual hyperpigmentation and appear uniformly red	Pseudoephedrine hydrochloride, tetrahydrozoline, contrast media, betahistine, etodolac
Bullous fixed drug eruption	Subepidermal blister that heals without scarring	Aminophenzone, antipyrine, barbituates, clotrimoxazole, tremithoprim, sulfamethoxazole, diazepam, mefenamic acid, acetaminophen, phenaoane, phenylbuzone, piroxicam, sulfadizine, sulfathiazole

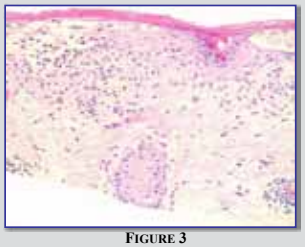


Figure 3

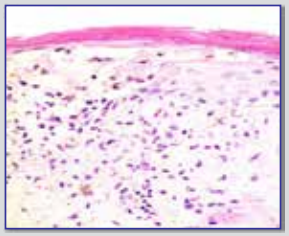


Figure 4

Table 2: Cutaneous manifestations of illicit drug use[8]

Illicit Drug	% of Americans using > 12 yrs old	Clinical Manifestations
Cannabis (marijuana, pot, weed)	7.5%	Contact urticaria, cannabis arteritis, skin aging
Cocaine/Crack (coke, C, snow, flake, blow)	0.6%	Nasal septal perforation, "snorter warts," halitosis, madarosis, frequent lip smacking, bullous erythema multiforme, "crack hands," scleroderma, Henoch-Schonlein purpura, vasculitis due to levamisole
Ecstasy (elephants, Scooby snacks, Molly, love drug)	0.4% (includes LSD and ecstasy)	"Ecstasy pimples", guttate psoriasis
Methamphetamines (speed, meth, chalk, ice, crystal, crank, glass)	0.2%	"meth mites," "meth mouth," xerosis, weight loss, premature aging
Heroin (smack, H. ska, junk)	0.1%	Track marks, sooting tattoos, cellulitis, candida folliculitis, transcutaneous botulism, pseudoaneurysms, granuloma formation, pruritis, fixed drug eruption, puffy hand syndrome, tourniquet hyperpigmentation

DISCUSSION

Fixed Drug Eruptions:

Drug eruptions are one of the most common cutaneous disorders encountered by dermatologists, representing 2 to 3% of all dermatological issues.[3] FDE is a form of drug allergy that presents as single, or multiple round, sharply demarcated dusky red lesions several centimeters in diameter that occur at the same sites after each administration of the inciting drug.[5] Pruritis and burning are often associated symptoms. The average age of onset is approximately 30 years old and the most commonly implicated medication is trimeothoprim-sulfamethoxazole.[5,6] Between the time when the individual is first exposed to the medication and development of the first lesion, a variable refractory period can exist for a week, months or even years.[5] With subsequent exposure, lesions appear within thirty minutes to eight hours. Most commonly, the lesions heal with residual hyperpigmentation. However, other types of FDE have been reported (Table 1). Our patient, presented with the classic pigmented FDE.

While generally only a solitary lesion appears on first exposure, repeated administration of the medication can lead to new lesions or an increase in size of the original lesions.[5] Although they can occur anywhere on the skin, FDE's most commonly occur on the glans penis, lips, palms, soles and groin area.[5] Overall, the legs are most commonly affected in women and the genitalia are most commonly affected in men.[1]

Histological examination displays two possible scenarios depending on when the biopsy was done. In lesions that are only one to two days old, hydropic degeneration of basal keratinocytes with dyskeratotic cells in the epidermis and exocytosis of mononuclear cells are seen.[3] Healed hyperpigmented lesions often demonstrate pigmentary incontinence revealing dermal melanophages with little perivascular infiltration of inflammatory cells.[3] To identify the culprit of the FDE, provocation tests can be done with the patch test being the most commonly used method as long as it is placed over a previously involved site and the patient is not in the refractory period.[3] Challenging a patient with an oral provocation test has been associated with generalized bullous lesions in some cases.[5] In our case, we did not re-challenge the patient with the suspected drug due to legal concerns. Treatment consist of cessation of suspected drug with the use of topical steroids and systemic anthistamines.[3] Extensive lesions or those with bullae may require systemic corticosteroids.[3] Post-inflammatory hyperpigmentation can be treated with hydroquinone bleaching creams.[5]

Cutaneous manifestations of illicit drug use:

In 2013, an estimated 24.6 million individuals aged 12 or older were current illicit drug users, representing over 9% of the population in the United States (US).[8] Dermatologist may be the first to recognize drug abuse in select patients allowing for earlier intervention and treatment as often the vascular and cardiac manifestations are internal and thus, cannot be readily seen by clinicians outside of dermatology. Table 2 outlines some of the cutaneous manifestations of illicit drug use.

CONCLUSION

So far this is the first case report, which describes fixed drug eruption elicited by recreational marijuana use. With 19.8 million current users in the United States and the growing rate of use associated with legislature changes, questions regarding patient's recreational drug use should be included in the patient's history.[8] By recognizing the cutaneous findings of illicit drug use, dermatologist can stand on the forefront of early recognition before the devastating effects of drug abuse succumbs a patient.

REFERENCES

1. Pai VV, Bhandari P, Kikkeri NN, Athanikar SB, Sori T. Fixed drug eruption to fluconazole: a case report and mini-review of literature. Indian J Pharmacol. 2012;44(5):643-645.
2. Brocq, L. Eruption erythemato-pigmentee fixe due a l'antipyrine. Ann Dermatol Venereol. 1894;5:308–313.
3. Lee AY. Fixed drug eruptions. Incidence, recognition and avoidance. Am J Clin Dermatol. 2000;1(5):277-285.
4. Stritzler C, Kopf AW. Fixed drug eruption caused by 8-chlorotheophylline in Dramamine with clinical and histologic studies. J Invest Dermatol. 1960;34:319-330.
5. Gendermalik SB, Galeckas KJ. Fixed drug eruptions: a case report and review of literature. Cutis. 2009;84(4):215-219.
6. Ozkaya-Bayazit E, Bayazit H, Ozarmagan G. Drug related clinical pattern in fixed drug eruption. Eur J Dermatol. 2000;10(4):288-291.
7. Liu SW, Lien MH, Fenske NA. The effects of alcohol and drug abuse on the skin. Clin Dermatol. 2010;28(4):391-399.
8. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. SAMHSA: Rockville (MD); 2014.

Radiation induced eruptive keratoacanthomas

Kevin Svancara DO, 2nd year Dermatology Resident

Advanced Desert Dermatology/ Midwestern University

Introduction

Keratoacanthomas (KA) are common skin tumors that most often appear on sun exposed areas of fair skinned adults. They are commonly found on the face, forearm and hands[1]. KAs are often described as pseudotumors due to their ability to grow rapidly and histologically appear identical to squamous cell carcinoma (SCC)[2]. Debate exists over the classification of KAs with some physicians describing them as a distinct, follicular based tumors following a benign course. Others describe the lesions as an abortive malignant form of SCC that rarely can be aggressive[1]. Histologically, they can be indistinguishable from one another[2]. However, an overall histological picture along with clinical findings can aid in the diagnosis[2]. Multiple causes of KAs have been reported in the literature including UV exposure, trauma, chemical exposures, drug exposures and genetics[1,3]. KAs are treated in multiple ways including most often surgery, electrodesiccation and curettage (ED&C), and occasionally radiation in poor surgical candidates or cosmetically sensitive areas[4-6]. We present a case demonstrating eruptive KAs, three weeks after a large KA was treated on the lower extremity with superficial radiation.

Initial KA of the lower extremity treated with radiation

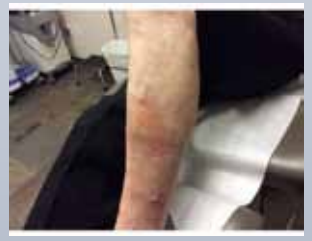
Multiple biopsy proven KAs, three weeks after treatment with radiation. Each lesion was injected with 0.2 cc of fluorouracil 50mg/ml

Case Report

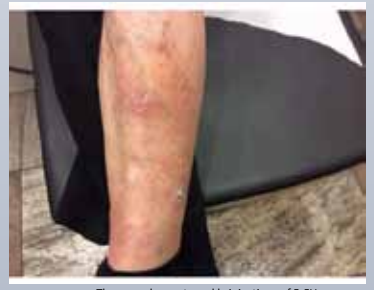
An 87 year male presented to the clinic with a large hyperkeratotic, erythematous, and scaly nodule of the lower extremity. The lesion was biopsied and was found to be a squamous cell carcinoma (SCC) KA type. All treatment options were discussed including surgery, ED&C, and superficial radiation. Due to the size of the lesion and risk of poor wound healing on the lower extremity the patient was referred for superficial radiation treatment. He was treated with HDR Brachytherapy at a dose of 45 gray over several days. The patient stated that days after the radiation treatment was completed he developed five erythematous, hyperkeratotic papules near the treated area. The lesions were biopsied and found to be consistent with KAs. Treatment options were again discussed, which were now limited considering the recently treated area with radiation. The patient was treated with weekly injections of fluorouracil 50mg/ml at 0.1-0.3 ccs per lesion. The patient's KAs showed improvement after one week and appeared to be resolved within 3 weeks of treatment. Further follow up will be required to assess any evidence of recurrence.

Discussion

KAs are often viewed as abortive malignancies, which rarely progress into an invasive SCC[1]. However, their histologic similarity to SCC often leads dermatologists to treat them as such[5]. This patient demonstrates an uncommon effect of eruptive KAs secondary to superficial radiation therapy. KAs have been known to develop from trauma to UV exposed areas, however, few articles have reported KAs appearing secondary to radiation[1]. Shaw demonstrated a case of eruptive KAs after receiving megavoltage x-ray and electron beam therapy, which improved after a six month course of isotretinoin[7]. Robertson presented a case of exacerbation of multiple KAs in a patient with Ferguson-Smith disease after receiving radiation[8]. One further case was noted by Bashir of a patient developing eruptive KAs after receiving radiation to treat a SCC, which resolved with oral acitretin[9]. This patient had a history of multiple SCCs, but no personal or family history of KAs to suggest the autosomal dominant condition of Ferguson-Smith disease. Considering the patient's recent treatment with superficial radiation, the treatment options were limited. Previously radiated skin is noted to have poor surgical wound healing with surgery and once a region is radiated, cannot receive a second treatment[10]. When recurrence or eruptive KAs occur post radiation, this can limit options. The patient was treated with fluorouracil injections, which acts as an antimetabolite inhibiting RNA synthesis and its metabolites inhibiting DNA synthesis[11]. Multiple small studies have demonstrated intralesional fluorouracil curing KAs with 96% clearance after 3-6 weekly injections[11].



One week after 5-FU injections



Three weeks post weekly injections of 5-FU

Conclusion

We propose that intralesional injections ,such as fluorouracil, be considered prior to radiation for large cancers and cancers in cosmetically sensitive areas. Occasionally first line treatments such as surgery, and ED&Cs may not the best options due to risks of poor wound healing and post radiated skin complications. While intralesional injections for cutaneous skin cancers have been used for years, they are often underutilized by dermatologists[11]. By choosing intralesional fluorouracil, the cure rate is excellent and leaves more options for future treatments, should new cancers develop in close proximity. Our patient demonstrates a rare potential side affect of superficial radiation leading to eruptive KAs and the usefulness of intralesional fluorouracil for treatment.

Works Cited

1. Schwartz, R. Keratoacanthoma. J Am Acad Dermatol. 1994; 30(1): 1-19.

2. Cribier B, Asch P, Grosshans E. Differentiating squamous cell carcinoma from keratoacanthoma using histopathological criteria. Is it possible? A study of 296 cases. Dermatology. 1999;199(3):208.

3. Pattee SF, Silvis NG, Keratoacanthoma developing in sites of previous trauma: a report of two cases and review of the literature. J Am Acad Dermatol. 2003; 48(2): 35.

4. Donahue B, Cooper JS, Rush S. Treatment of aggressive keratoacanthomas by radiotherapy. J Am Acad Dermatol. 1990;23(3 Pt 1):489-93.

5. Sarabi K, Selim A, Khachemoune A. Sporadic and syndromic keratoacanthomas: diagnosis and management. Dermatol Nurs. 2007; 19(2): 166-170.

6. Donahue B, Cooper JS, Rush S Treatment of aggressive keratoacanthomas by radiotherapy. J Am Acad Dermatol. 1990;23(3 Pt 1):489-93.

7. Shaw JC, Storrs FJ, Everts E. Multiple keratoacanthomas after megavoltage radiation therapy. J Am Acad Dermatol. 1990; 5(2): 1009-1011.

8. Robertson SJ, Bashir SJ, Pichert G, Robson A, Whittaker S. Severe exacerbation of multiple self-healing squamous epithelioma (Ferguson-Smith disease) with radiotherapy, which was successfully treated with acitretin. Clin Exp Dermatol. 2010 Jun;35(4): 100-102

9. Bashir S, Calonje E, Barlow, E. Eruptive keratoacanthomas following radiotherapy. J Am Acad Dermatol. 2009; 60(3): 192.

10. Bolognia, J, Jorizzo J, Schaffer J. Dermatology: Third Edition. Elsevier Limited 2012.

11. Good LM· Miller MD, High WA. Intralesional agents in the management of cutaneous malignancy: a review. J Am Acad Dermatol.2011 Feb;64(2):413-22.

12. Sarabi K, Selim A, Khachemoune A. Sporadic and syndromic keratoacanthomas: diagnosis and management. Dermatol Nurs. 2007; 19(2):166-170

Contact: Kevin Svancara DO PGY3

drsvancara@addermatology.com

Neoadjuvant Targeted Therapy for Locally Advanced Orbital Basal Cell Carcinoma: A Case Presentation and Discussion

Madeline Tarrillion, DO,* Jennifer DePry, DO,** Jeremy Bordeaux, MD,**, Jenifer Lloyd, DO*

*University Hospitals Regional Medical Center, Cleveland, OH, **University Hospitals Case Medical Center, Cleveland, OH

INTRODUCTION

Vismodegib was FDA-approved in January 2012 for metastatic basal cell carcinoma and locally advanced basal cell carcinoma.[1] The latter is characterized by large tumor size, multiple lesions, or locally recurrent disease not appropriate for surgical treatment.[2] Vismodegib is an antagonist of the hedgehog pathway, which has been found to be activated in basal cell carcinoma leading to cellular proliferation.[2] Vismodegib may serve an important role in the future treatment of metastatic and locally advanced basal cell carcinoma. We present a case of locally advanced orbital basal cell carcinoma where Vismodegib was used as neoadjuvant therapy to assist in shrinking the tumor prior to surgery in the efforts of sparing the eye.

CASE PRESENTATION

The patient is a 56 year-old man, who presented with a 2x3x4cm ulcerated plaque with a pink raised border involving the left medial canthus, and upper and lower eyelids (Figure 1). A biopsy of the left lower eyelid demonstrated a nodular proliferation of atypical basaloid cells within the dermis with peripheral nuclear palisading, stromal mucin, tumor-stromal clefting, and focal ulceration consistent with nodular basal cell carcinoma (Figure 2). An MRI of the brain, sinuses and orbits with and without contrast revealed abnormal soft tissue along the anteromedial aspect of the left orbit, extending over the proximal left nasofrontal region with no evidence of paranasal sinus involvement or intracranial metastatic disease.

The patient was referred for Mohs micrographic surgery consultation. Treatment options were discussed, including Mohs micrographic surgery at that point, which would likely sacrifice the eye, targeted therapy alone with Vismodegib, and neoadjuvant therapy with Vismodegib followed by Mohs micrographic surgery.

We initiated Vismodegib 150mg/day with the plan that the patient would remain on Vismodegib until the tumor stopped responding or the patient could no longer tolerate the side effects of the medication. At that point, surgery could be performed potentially reducing the surgical defect and hopefully preserving the eye.

The patient completed 11 months of Vismodegib with decrease in tumor size and improvement of ulceration (Figure 3, 4). Throughout the treatment period, the patient experienced dysgeusia (disturbance of taste), alopecia, fatigue, nausea, and significant weight loss. After 11 months of treatment, the patient could no longer tolerate the side effects, and Vismodegib therapy was discontinued.

A month later, the patient obtained an ocular infection complicated by a severe corneal ulcer, and the patient underwent an orbital exenteration with paramedian forehead flap. The patient is currently healing well six months after surgery, and is planning on reconstruction with prosthetic rehabilitation in the near future.

DISCUSSION

Most basal cell carcinomas contain alterations in the hedgehog signaling pathway resulting in its activation and uncontrolled proliferation of cells. Most commonly, 90% of basal cell carcinomas are due to loss of function of the tumor suppressor gene PATCHED (PTCH1), which inhibits the signaling activity of smoothened (SMO). There also can be an activating mutation in smoothened in 10% of basal cell carcinomas.[3] Smoothened activates the Hedgehog pathway through downstream activation of GLI1.[4] Vismodegib is the first, FDA approved, small-molecule, Hedgehog pathway inhibitor. It inhibits smoothened (SMO), thereby preventing downstream signaling of the pathway.[3]

Vismodegib is FDA-approved for the treatment of adults with metastatic or locally advanced basal cell carcinoma, when it is inoperable or when surgery is inappropriate. In a phase II trial of Vismodegib, patients with metastatic and locally advanced BCC showed response rates of 30% and 43% respectively. Response was defined as a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration if present at baseline.[1]

In several studies of Vismodegib use, multiple side effects were commonly experienced, including muscle spasms or cramps, alopecia, dysgeusia (alteration of taste), weight loss, fatigue, nausea, decreased appetite, and diarrhea. While these adverse effects were generally regarded as minor, the necessary chronic use of Vismodegib and, therefore, the persistent side effects commonly led patients to discontinue therapy.[1] These chronic adverse effects potentially limit the long term use of Vismodegib.

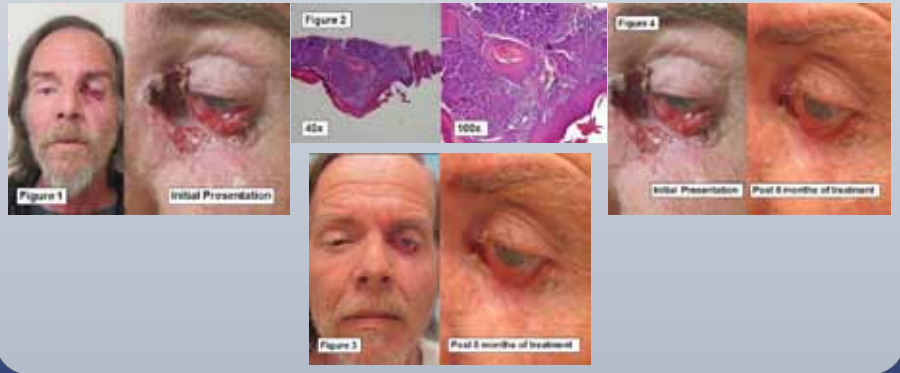
Other limitations hindering the chronic use of Vismodegib include the possibility of tumor skip areas (persistent tumor in clinically "cured" skin), acquired resistance, increase risk of squamous cell carcinomas, and cost-efficacy due to the average monthly cost of $7500 per month.[4]

With the development of Vismodegib, there have been a few case reports and a small clinical trial evaluating neoadjuvant targeted therapy followed by surgery. This small clinical trial found that Vismodegib needed to be used for at least 3 months to elicit a response. It found that Vismodegib use reduced the surgical defect area by 27% for the 11 patients that underwent surgery following Vismodegib. Finally, it showed that clinically resolved lesions do not necessarily correlate with histologic cure.[5]

Another study was performed in seven patients with periocular and orbital basal cell carcinoma where the mean treatment duration was 11 weeks, and two patients demonstrated complete clinical regression, two patients demonstrated greater than 80% partial clinical regression, two patients demonstrated less than 35% partial clinical regression, and one patient progressed. However, two patients developed new squamous cell carcinomas at uninvolved sites.[4]

There are currently multiple treatment options for locally advanced basal cell carcinoma, including surgery, targeted therapy, and neoadjuvant therapy followed by surgery.[4] Surgery remains the mainstay of treatment for locally advanced basal cell carcinomas with a much higher cure rate compared to the response rates of Vismodegib.[1] However, there are limitations to surgery. For example, cases could potentially be inappropriate for surgery due to compromise of function or cosmesis, multiple recurrences or low likelihood of surgical cure.[5] As in our case, surgery at the initial presentation would have sacrificed the patient's eye; therefore, neoadjuvant therapy was attempted to ideally shrink the tumor and spare the eye.

PHOTOS



CONCLUSION

Vismodegib may serve an important role in the future treatment of metastatic and locally advanced basal cell carcinoma. However, due to Vismodegib's new and exciting development, there potentially may be cases of Vismodegib use where surgery may have been indicated. Inappropriate use of Vismodegib could potentially place the patient at increased risk without an increased benefit compared to surgical treatment.

Vismodegib's ideal treatment duration, long-term side effects, and cost effectiveness, as well as potential for causing resistance, residual skip lesions and squamous cell carcinoma remain unknown and warrant further investigation. These current limitations of Vismodegib may discourage its future use.

REFERENCES

1. Rudin C. Vismodegib. Clin Cancer Res. 2012 Jun 15;18(12):3218-22.

2. Yin V, Pfeiffer M, Esmaeli B. Targeted Therapy for Orbital and Periocular Basal Cell Carcinoma and Squamous Cell Carcinoma. Ophthal Plast Reconstr Surg. 2013 Mar-Apr;29(2):87-92.

3. Chang A, Solomon J, Hainsworth J, Goldberg L, McKenna E, Day B, Chen D, Weiss G. Expanded access study of patients with advanced basal cell carcinoma treated with Hedgehog pathway inhibitor, vismodegib. J Am Acad Dermatol. 2014 Jan;70(1):60-9.

4. Gill H, Moscato E, Chang A, Soon S, Silkiss R. Vismodegib for Periocular and Orbital Basal Cell Carcinoma. JAMA Ophthalmol. 2013 Dec;131(12):1591-4

5. Ally M, Aasi S, Wysong A, Teng C, Anderson E, Bailey-Healy I, Oro A, Kim J, Chang A, Tang J. An investigator-initiated open-label clinical trial of Vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. J Am Acad Dermatol. 2014 Nov;71(5):904-911.

CONTACT INFORMATION

Madeline Tarrillion, DO
University Hospitals Case Medical Center
Department of Dermatology
11100 Euclid Avenue, LKS 5028
Cleveland, OH 44106
Phone: 216-844-5794
Fax: 216-844-8993
Madeline.tarrillion@uhhospitals.org

Acquired Elastotic Hemangioma: A Case Report of Multiple Lesions Following Progesterone Therapy

Nicole Tillman, D.O.*, Stephen J Plumb, D.O.*, David Cleaver, D.O.*, Lloyd Cleaver, D.O.*

*Northeast Regional Medical Center, ATSU-KCOM

INTRODUCTION

Acquired elastotic hemangioma is a relatively newly described cutaneous lesion that presents as an erythematous, well defined, asymptomatic plaque on sun damaged skin of upper extremities. Characteristically it is described as a slow growing, solitary lesion, without history of trauma. We report a unique case of acquired elastotic hemangioma in which the patient presented with multiple lesions following initiation of progesterone therapy

CASE REPORT

A 57-year-old woman presented for evaluation of multiple, asymptomatic, erythematous plaques on her arms bilaterally. The patient denied prior trauma to the areas. She noted the onset of the first plaque correlated with initiating progesterone therapy. The lesions slowly became more numerous over five years. Her medical history was notable for hypertension and rosacea. Her family history was unremarkable.

Physical examination revealed seven erythematous, well-defined, nontender, slightly elevated, nonblanching plaques on her arms bilaterally (Figures 1 and 2). The lesions ranged in size from 0.5 cm to -3 cm, with the largest lesion on the right lower forearm.

Based on the clinical presentation and history, our initial differential diagnosis included Kaposi's sarcoma, targetoid hemosiderin hemangioma, and pupura annularis telangiectoides. A punch biopsy was performed for histologic examination with hematoxylin and eosin (H and E) staining. The biopsy revealed solar elastosis in the epidermis with thin walled vessels in the upper dermis (Figure 3). No cytologic atypia or mitotic figures were seen. Inflammation was absent. Despite the multiplicity of lesions, a diagnosis of acquired elastotic hemangioma was favored. Due to the benign nature, no further treatment was warranted. Following discontinuation of progesterone therapy, new lesions stopped occurring and some lesions showed mild regression.

FIGURE 1

FIGURE 2

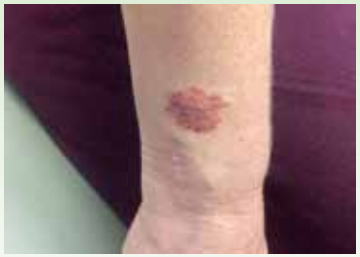
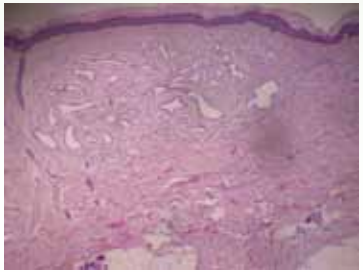


FIGURE 3



DISCUSSION

Acquired elastotic hemangioma was first described in 2002 as a clinicopathologic variant of an acquired hemangioma.[1] This lesion classically occurs in middle aged or elderly women, however, one report showed a slight male predominance.[2] An acquired elastotic hemangioma presents as an irregularly shaped, well defined, non-blanching, erythematous to violaceous plaque. Generally the lesions are asymptomatic, but occasionally they can be painful.[1] The lesion is usually solitary and very slow growing. The plaques have a predilection for sun damaged skin and are most commonly seen on the dorsal aspect of the forearms, but may also be found on the lower lip, shoulder, nose, and neck.[2] Clinically the lesion may be confused with a superficial basal cell or Bowen's disease.[1]

Histologically, an acquired elastotic hemangioma shows several characteristic features. The classic finding is a band-like proliferation of capillary blood vessels arranged parallel to the epidermis and confined to the superficial dermis. [3] A zone of non involved papillary dermis separates the capillaries from the epidermis. The epidermis is unremarkable or atrophic. Solar elastosis is present surrounding the capillaries. Mitotic figures, cellular atypia, spindle cell proliferation, red cell extravasation, hemosiderin deposition and fibrosis is not seen.[4] Scant lymphocytic infiltrate may be present, but is typically absent.[1,2]

Immunohistochemically, the endothelial cells strongly express CD31 and CD34.[1,2,4] Alpha smooth muscle actin-positive (SMA) pericytes surround the vascular channels. Acquired elastotic hemangioma was initially thought to be a true vascular tumor, however research has recently proposed a lymphatic origin after noting expression of D2-40.[2] Proliferating markers Ki-67 and MPM2 stain only a few nuclei of the endothelial cells of the vessels.[1,4]

The histopathological differential diagnosis includes Kaposi's sarcoma (patch stage), acquired tufted angioma, and targetoid hemosiderotic hemangioma. Kaposi's sarcoma histologically exhibits jagged, vascular spaces lined by thin endothelial cells with a lymphoplasmacytic infiltrate, and red blood cell extravasation. The promontory sign, thin walled vessels surrounding preexisting capillaries and adnexal

DISCUSSION CONTINUED

structures, is a characteristic finding for Kaposi's sarcoma. An acquired tufted angioma shows a "cannon-ball" histopathological pattern with multiple lobules of capillary tufts scattered in the dermis and subcutaneous fat. A targetoid hemosiderotic hemangioma displays dilated vascular spaces in the superficial dermis, lined by prominent hobnail endothelial cells and anastomosing collagen bundles with hemosiderin deposits.[1] None of these entities show band-like capillaries arranged along the superficial dermis with solar elastosis characteristically seen in acquired elastotic hemangioma.

The etiology is not completely understood, but the finding of solar elastosis supports the role of long-term sun exposure as an inciting cause. In most cases, there is no history of previous trauma. Since the lesions in our case occurred following progesterone therapy, the question arises of hormonal influence in developing acquired elastotic hemangiomas. This possible correlation has not been described by previously published reports on elastotic hemangiomas, however estrogen has been reported as an inciting factor for targetoid hemosiderotic hemangiomas.[6]

CONCLUSION

Acquired elastotic hemangiomas are benign, asymptomatic plaques seen on sun damaged skin. Treatment is unnecessary, but excision of solitary lesions has been successful without local recurrence.[1] Our case of seven lesions, arising following initiation of progesterone, makes this acquired elastotic hemangioma presentation atypical and unique.

REFERENCES

Requena L, Kutzner H, Mentzel T. Acquired elastotic hemangioma: A clinicopathologic variant of hemangioma. *J Am Acad Dermatol.* 2002;47:371-376.

Martorell-Calatayud, A, Balmer N, Sanmartin O, Diaz-Recuero JL, Sangueza OP. Definition of the features of acquired elastotic hemangioma reporting the clinical and histopathological characteristics of 14 patients. *J Cutan Pathol.* 2010;37:460-464.

Goh SGN, Calonje E. Cutaneous vascular tumors: an update. *Histopathology.* 2008;52:661-673.

Tong PL, Beer TW. Acquired elastotic hemangioma: ten cases with immunohistochemistry refuting a lymphatic origin in most lesions. *J Cutan Pathol.* 2010;37:1259-1260.

Sangueza OP. Update on vascular neoplasms. *Dermatol Clin.* 2012;30:657-665.

Cleaver JL, Cleaver NJ, Cleaver LJ. Targetoid hemosiderotic hemangioma: a case report of multiple asymptomatic lesions. *Cutis.* 2013;92: 91-93.

A Woman with an Urticarial Eruption, Fevers, Arthralgias and Hearing Loss

SAINT JOSEPH MERCY HEALTH SYSTEM

Monica Van Acker, DO | David Fivenson, MD | St. Joseph Mercy Ann Arbor, Ypsilanti, MI

Introduction

Muckle-Wells Syndrome (MWS) also known as hereditary periodic fever syndrome is a rare autosomal dominant disease caused by a heterozygous mutation on chromosome 1q44 affecting the NLRP3 (CIAS1) gene which encodes the protein cryopyrin. This protein serves as a scaffold for assembly of the NALP3 inflammasome complex. This complex is responsible for the activation and amplification of the proinflammatory cytokines IL-1β and IL-18, which induce and maintain inflammation. Hyperactivity of cryopyrin in MWS can be demonstrated clinically by episodic fevers, inflammation, hearing loss and kidney damage.

History

A 35-year-old Caucasian woman presented with redness of the eyes and a transient pruritic rash on her bilateral upper extremities, chest and back. These clinical findings and associated arthralgias, oral ulcers and low-grade fevers had been present for approximately 20 years. She admitted to new onset hearing loss with associated tinnitus. The urticaria was transient and lasted roughly 24 hours. There was no history of angioedema. The patient reported a family history of similar symptoms present in her brother, mother and grandmother.

Examination

Physical examination revealed well-circumscribed, blanchable, erythematous, edematous papules and plaques on her bilateral upper extremities, chest and back. Additionally, her sclerae were injected bilaterally without associated discharge. No oral ulcers were identified.

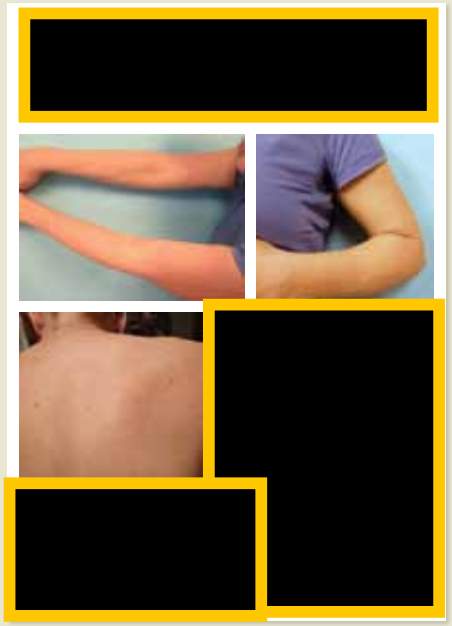
Laboratory

Laboratory evaluation included an elevated CRP at 1.4 (normal<0.5) and an elevated thyroid peroxidase antibody at 108 (normal<9) with a normal CBC, CMP, ANA, hepatitis B antigen, hepatitis C antibody, TSH, free T4 and anti-thyroglobulin antibody. Protein electrophoresis revealed beta-gamma bridging and increased IgA.

Course and Therapy

The patient was treated with cyclosporine ophthalmologic drops and colchicine 0.6 mg twice daily. She was referred to genetics for further evaluation and confirmation of her condition.

Buondonna I. Muckle-Wells Syndrome. Flipper e nuvola. Flipper.diff.org.12/7/2012.



	Cryopyrin-Associated Periodic Syndrome (CAPS)		
	FCAS Familial Cold Autoinflammatory Syndrome	MWS Muckle-Wells Syndrome	NOMID Neonatal-Onset Multisystemic Inflammatory Disease
Frequency of fever and/or rash	Usually daily symptoms with circadian rhythm	Variable; rare to daily symptoms with circadian rhythm	Variable; usually rare fever and daily rash
Joint Movement	Arthralgia	Arthralgia, arthritis	Arthralgia, arthritis, overgrowth arthropathy
Neurological Involvement	None	None	Chronic aseptic meningitis (headache, possible mental delay)
Eye Involvement	Conjunctive	Conjunctive, uveitis	Uveitis, papillary edema, possible optic neuritis
Deafness	No	Frequent (60-70%)	Frequent (>60%)
Amyloidosis	No	Frequent (~25%)	Frequent (~25%)
Inheritance	Autosomal dominant	Autosomal dominant (typical) or de novo (rare)	De novo (Typical) or autosomal-dominant (rare)

Increasing Disease Severity

Benedicte N, Prieur A and Quartier dit Marie P. Cryopyrinopathies: update on pathogenesis and treatment. Nat Clin Pract Rheumatol. 2008;4:481-489.

Discussion

Muckle-Wells Syndrome is classified on a spectrum amongst two other cryopyrin associated periodic syndromes (CAPS) caused by the same NLRP3 mutation: familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory disease (NOMID). These three interlukin-1 autoinflammatory disorders or cryopyrinopathies have a prevalence of 1 in 360,000 individuals. FCAS demonstrates the least severity, as its inflammatory component does not typically cause permanent damage. In contrast, NOMID demonstrates the worst severity causing permanent inflammatory damage throughout most areas of the body including joints, brain, ears and eyes. MWS falls in between these two variants in terms of severity.

With roughly 135 cases of MWS reported, diagnostic criteria have not been established, creating difficulty in proper diagnosis. However, clinical features well described in MWS include recurrent urticaria, episodic fevers and sensorineural deafness. Additionally, patients may present with conjunctivitis, episcleritis, abdominal pain, myalgias, arthralgias, digital clubbing, chronic fatigue, and headaches. Severe presentations exhibit papilledema, optic atrophy or chronic meningitis. Males may demonstrate sterility. Symptoms occur spontaneously or in response to stress, temperature change or fatigue. Renal amyloidosis resulting in proteinuria and chronic renal insufficiency will occur in 25% of patients.

Two clinical variants can be seen in MWS. These include inflammatory and organ disease phenotypes. The inflammatory type is often seen in children experiencing episodic fevers and abdominal pain while the organ disease type is primarily observed in adults experiencing chronic fatigue with sensorineural hearing loss.

In the laboratory evaluation of MWS patients, elevated levels of CRP, ESR, serum amyloid protein and IL-6 are characteristic. Genetic analysis confirms the diagnosis of MWS through identification of the NLRP3 gene mutation.

Cryopyrin hyperactivity contributes to increased levels of IL-1, which is responsible for the promotion of inflammation in MWS. Anakinra, an IL-1 receptor antagonist, canakinumab, a monoclonal IL-1 antibody, and rilonacept, an IL-1 signaling blocker have shown remarkable efficacy in decreasing inflammatory markers, reversing amyloidosis and improving hearing loss in MWS.

Conclusion

In conclusion, Muckle-Wells Syndrome is a rare autosomal dominant cryopyrinopathy. The classic triad of recurrent urtiaria, episodic fever and sensorineural deafness can identify patients with this condition. Early recognition and utilization of IL-1 receptor antagonists is key for symptomatic treatment and prevention of further amyloidosis and hearing loss progression.

References
1. Dode C, Le Du N, Cuisset L, et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. Am J Hum Genet. 2002;70:1498-1506.
2. Hoffman HM, Mueller JL, Broide DH, et al. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nature Genetics. 2001;29(3):301-305.
3. Kuemmerle-Deschner JB, Koltschev A, Ummenhofer K, et al. Hearing loss in Muckle-Wells syndrome. Arthritis Rheum. 2013;65:824-831.
4. Kummerle-Deschner JB, Tyrrell PN, Reess F, et al. Risk factors for severe Muckle-Wells syndrome. Arthritis Rheum. 2010;62:3783-3791.
5. Maksimovic L, Stinnemann J, Caux F, et al. New CIAS1 Mutation and Anakinra Efficacy in Overlapping of Muckle-Wells and Familial Cold Autoinflammatory Syndromes. Rheum. 2008;47(3):309-310.

DEPARTMENT OF INTERNAL MEDICINE SAINT JOSEPH MERCY ANN ARBOR

A Man with Pruritic Nodules on the Face, Trunk, and Extremities

SAINT JOSEPH MERCY HEALTH SYSTEM

Jennifer Vermeesch, DO | James Ramirez, MD | Ann LaFond, MD | St. Joseph Mercy Ann Arbor

Introduction

Cutaneous B-cell lymphomas represent a group of lymphomas derived from B-lymphocytes in different stages of differentiation. The skin can be the site of primary or secondary involvement of B-cell lymphomas. Primary cutaneous B-cell lymphomas (PCBCL) are cutaneous B-cell lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. The World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues recognizes five distinct PCBCL subtypes:

- Primary Cutaneous Follicle Center Lymphoma (PCFCL).
- Primary Cutaneous Marginal Zone Lymphoma (PCMZL).
- Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCDLBCL-LT).
- Diffuse Large B-Cell Lymphoma NOS.
- Intravascular Diffuse Large B-Cell Lymphoma.

The diffuse large B-cell lymphoma NOS category includes less common provisional entities with insufficient evidence to be recognized as distinct diseases at this time. EBV-positive diffuse large B-cell lymphoma is a rare subtype in this group.

History

An 84-year-old man with a past medical history significant for prostate cancer successfully treated with radiation therapy in 2008, presented with a five-month history of a pruritic eruption on the arms, legs, back, neck, and face. The patient denied any constitutional symptoms and review of systems was otherwise negative. The patient was taking prednisone, which alleviated his pruritus, but the lesions persisted.

Examination

Physical examination revealed multiple pink to erythematous papules and subcutaneous nodules on the face, neck, back, and upper and lower extremities. No cervical, supraclavicular, axillary, or inguinal lymphadenopathy was present.

Laboratory

A peripheral blood smear showed a population of circulating CD10 positive T-helper lymphocytes suspicious for a T-cell lymphoproliferative process. A bone marrow biopsy was performed and did not show evidence of B-cell lymphoid neoplasia, but did show atypical lymphoid aggregates composed of CD4 and CD10 positive T-cells, which were identical to the abnormal population in the peripheral blood. Peripheral blood T-cell rearrangement and JAK2 were negative.

Histopathology

Punch biopsies of representative lesions of the upper back and right arm revealed diffuse and nodular infiltrates of atypical lymphoid cells with scattered centroblasts and immunoblasts. Immunohistochemical staining demonstrated CD79, MUM-1, and EBV-encoded RNA positivity among the neoplastic cells. The Ki-67 proliferative index was >90%. The neoplastic cells were negative for CD5, CD10, CD20, CD21, CD30, CD56, CD123, CD138, PAX5, C-MYC, BCL-2, BCL-6, cyclin D1, TCL-1A, and TDT. PCR showed a clonal B-cell population.

Course and Therapy

Based on clinical and histologic findings, a diagnosis of primary cutaneous EBV-positive diffuse large B-cell lymphoma was made. The patient was started on CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy for the treatment of this aggressive cutaneous lymphoma, which resulted in clinical improvement of his lesions. Clinical follow-up and monitoring in conjunction with this treatment will likely be of benefit in determining the clinical significance of the T-cell findings.

Discussion

EBV-positive diffuse large B-cell lymphoma was initially described in 2003 by Oyama et al and was included as a provisional entity in the 2008 WHO classification system as a rare subtype of the diffuse large B-cell lymphoma NOS category. It is defined as an EBV-positive monoclonal large B-cell proliferation that occurs in immunocompetent patients over 50 years old. EBV is a human herpesvirus that demonstrates tropism for lymphocytes and survives in human hosts by establishing latency in B-cells. Under normal immune conditions, the proliferation of EBV-infected B-cells is prevented by cytotoxic T cells; therefore, it has been postulated that EBV-positive DLBCL of the elderly might be caused by age-related senescence of the immune system.

EBV-positive DLBCL is more common in Asia than in Western countries and there is a slight male predominance. A majority of patients present with extranodal disease at the time of diagnosis and the skin is the most common extranodal site of involvement. Rare cases of primary cutaneous involvement have also been described. Cutaneous manifestations include erythematous papules and subcutaneous nodules. Other sites of extranodal involvement include the lungs, oral cavity, pharynx, GI tract, and bone marrow. However, it is an aggressive lymphoma and prognosis is poor irrespective of the primary site of involvement.

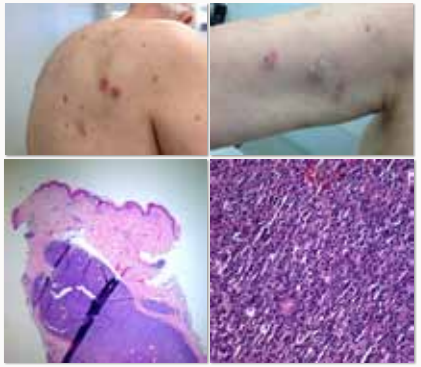
Two morphologic subtypes can be seen on histology. The polymorphic pattern is characterized by a broad range of B-cell maturation along with admixed reactive cells (lymphocytes, histiocytes, and plasma cells). The monomorphic or large-cell pattern is characterized by monotonous sheets of large transformed B-cells. However, many cases show both histologic patterns and these morphologic variants do not impart any clinical or prognostic significance. Regardless of the histologic subtype, the neoplastic cells express pan B-cell antigens (CD19, CD20, CD79a, and PAX-5) as well as MUM1, BCL2, and EBER. Cases with plasmablastic features show weak or absent CD20 (as in our patient). Detection of EBV by in situ hybridization is required for the diagnosis.

Workup of a suspected cutaneous lymphoma should include a complete history and physical exam, lab studies, and relevant imaging evaluation. In addition, a bone marrow biopsy and aspirate should be performed in all cutaneous lymphomas with intermediate to aggressive clinical behavior. Accurate staging evaluation is integral to confirm the absence of extracutaneous involvement and to provide prognostic and anatomic information for the appropriate selection of treatment.

Primary cutaneous lymphomas tend to have different clinical behaviors and prognoses compared to histologically similar systemic lymphomas, and therefore require different therapeutic strategies. EBV-positive DLBCL has an aggressive clinical course with median survival of 2 years. Patients with EBV-positive DLBCL have a poorer overall survival and treatment response when compared to patients with EBV-negative diffuse large B-cell lymphomas. No standard treatment exists, but R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), which is the standard treatment for PCDLBCL-LT may provide a survival benefit. However, further studies are required to determine optimal treatment strategies.

Conclusion

Although rare, EBV-positive DLBCL is an important entity to consider when evaluating a patient with a suspected primary cutaneous lymphoma. Workup to rule out an underlying systemic lymphoma with labs, imaging, and bone marrow biopsy is critical. Prognosis is poor and treatment is difficult, as standard treatment protocols have yet to be determined.



References

1. Castillo JJ, Beltran BE, Miranda RN, et al. Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: what we know so far. Oncologist. 2011;16:87-96.
2. Eminger LA, Hall LD, Hesterman KS, et al. Epstein-Barr virus: Dermatologic associations and implications. J Am Acad Dermatol. 2015;72:21-34.
3. Fink-Puches R, Wolf IH, Zalaudek I, et al. Treatment of primary cutaneous B-cell lymphoma with rituximab. J Am Acad Dermatol. 2005;52:847-853.
4. Kempf W, Sander C. Classification of cutaneous lymphomas – an update. Histopathology. 2010;56:57-70.
5. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110:479-484.
6. Kodama K, Massone C, Chott A, et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. Blood. 2005;106:2491-2497.
7. Ok CY, Papathomas TG, Medeiros LJ, et al. EBV-positive diffuse large B-cell lymphoma of the elderly. Blood. 2013;122:328-340.
8. Oyama T, Ichimura K, Suzuki R, et al. Senile EBV+ B-cell lymphoproliferative disorders: a clinicopathologic study of 22 patients. Am J Surg Pathol. 2003;27:16-26.
9. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. Clin Cancer Res. 2007;13:5124-5132.
10. Suarez AL, Pulitzer M, Horowitz S, et al. Primary cutaneous B-cell lymphomas. J Am Acad Dermatol. 2013;69:329.e1-13.
11. Willemze R, Jaffe ES, Cerroni L, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768-3785.

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An unusual presentation of erythema elevatum diutinum with underlying hepatitis B infection

Jessica Vincent DO[1], Adeline Kikam DO[2], Kelly Tyler MD[3], Sara Peters MD[3], Ryan Kirkland MD[4], Benjamin Kaffenberger MD[3]

[1]OhioHealth O'bleness Hospital, Athens, Ohio, [2]Firelands Regional Medical Center, Sandusky, Ohio, [3] Ohio State University Medical Center, Columbus, Ohio,
[4]Dermatologists of Greater Columbus, Columbus, Ohio

Abstract

Erythema Elevatum Diutinum (EED) is a rare chronic cutaneous small vessel vasculitis of unclear pathogenesis. Classically, lesions present as symmetric red to purple plaques, papules and nodules overlying joints. First-line therapy is with dapsone. We report a case of EED with widespread lesions involving the hands, extensor extremities and trunk. Multiple biopsies showed concentric intradermal perivascular inflammation with dermal fibrosis and leukocytoclastic vasculitis suggesting EED in various stages of evolution. An extensive workup was positive for underlying hepatitis B infection. Our case represents the clinicopathologic spectrum on which EED can present and emphasizes the importance of searching for an underlying etiology.

Case Report

A 57-year-old white male presented complaining of burning and stinging red nodules on the dorsum of his hands for about 1 year. He also admitted to an episodic rash over the lower legs and bilateral flanks of 7 years duration. He was briefly treated with an oral prednisone taper and topical corticosteroids including triamcinolone 0.1% cream and clobetasol 0.05% cream without improvement.

On exam were deep red to violaceous discrete nodules and plaques with overlying hyperkeratosis involving all distal and proximal interphalangeal joints of the hands and extensor elbows (Figure 1). On the bilateral posterior arms, anterior legs and periumbilical area were deeply erythematous papules and plaques with background hyperpigmentation (Figure 3). Across his low back and bilateral flanks were erythematous papules with central hemorrhagic crusting (Figure 5).

Pertinent laboratory findings included a positive hepatitis B surface antigen with hepatitis B DNA value 4313876 IU/mL (reference range <10 IU/mL) and a HBV quantitative PCR value of 6.64 units (reference range <1.00 unit).

An additional infectious workup was negative for hepatitis C, streptococcus, syphilis, tuberculosis and HIV. A complete blood count, complete metabolic panel, urinalysis, complement, cryoglobulins and serum protein electrophoresis were within normal limits. Autoimmune serologies were negative including anti-nuclear antibody, rheumatoid factor, anti-Sjogren's-syndrome-related antigen A and B, anti-cyclic citrullinated peptide, anti-Smith, anti-neutrophilic cytoplasmic antibodies. Peripheral blood immunophenotyping, lactate dehydrogenase, quantitative immunoglobulins, and age appropriate cancer screens did not demonstrate evidence for malignancy underlying his disease.

Three 4-mm punch biopsies were performed from the left 5th digit, left posterior arm, and left flank (Figures 2, 4 and 6, respectively). The constellation of clinical findings together with the histopathologic changes represented EED in various stages of evolution. The patient was started on dapsone 100mg daily and referred to the Infectious Disease service for treatment of the chronic hepatitis B, however, he was subsequently lost to follow up.

Figures

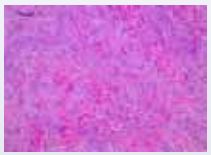


Figure 1 (left). Deep red firm plaques and nodules overlying the distal and proximal interphalangeal joints

Figure 2 (right). Punch biopsy of the left 5th digit showed intradermal vascular proliferation forming a concentric, "onion skin" pattern in a background of increased fibrosis. (H&E, original magnification x20)

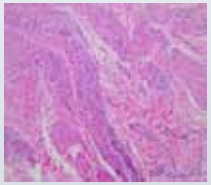


Figure 3 (left). Red to violaceous papules and nodules scattered over posterior arms with background hyperpigmentation

Figure 4 (right). Punch biopsy of the left posterior arm showed intradermal vascular proliferation on a background of increased fibrosis. (H&E, original magnification x20)

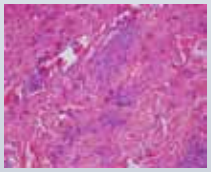


Figure 5 (left). Scattered erythematous papules with central hemorrhagic crusting of left flank

Figure 6 (right). Punch biopsy of the left flank showed leukocytoclastic vasculitis. (H&E, original magnification x20)

Discussion

Erythema elevatum diutinum represents a rare form of chronic cutaneous small vessel vasculitis. The disease classically presents as firm, fixed red-brown to violaceous papules, plaques and nodules affecting the extensor extremities.[1] Lesions are most commonly found symmetrically overlying joints of the hands, feet, elbows and knees as well as the Achilles tendon and buttocks.[2] Less common locations have been described including palms and soles, face,[3, 4] trunk[5] and periauricular region.[1] Our patient was unique as in addition to typical lesions of EED, he presented with crusted papules on the flanks and violaceous papules of the lower legs and periumbilicus.

Originally associated with *Streptococcus* as isolated from EED lesions,[6,2] additional infectious etiologies include viral hepatitis,[7,8,9] HHV-6[10] and HIV.[1,11] Hepatitis B and C are well-known to be associated with EED, however, only previously reported in patients with concomitant HIV infection.

Discussion (con't)

While the precise pathogenesis of EED remains unknown, it has been suggested that a complement cascade initiated by immune-complex deposition in post-capillary venules induces a leukocytoclastic vasculitis.[12,13] Chronic antigenic exposure or high antibody levels[14] in the face of infections, autoimmune disease or malignancy may incite this immune-complex reaction. Skin lesions seen in association with hepatitis reflect circulating immune-complex deposition in vessel walls causing destruction. It has been postulated that the duration of immune complexemia may be sufficient to account for the differences in the type of vascular injury seen in acute versus chronic infection.[15]

EED may present on a histopathologic spectrum of LCV, as manifested in our patient. Early lesions show predominantly polymorphonuclear cells with nuclear dust pattern in a wedge-shaped infiltrate with fibrin deposition in the superficial and mid-dermis.[2,16] Later lesions show vasculitis in addition to dermal aggregates of lymphocytes, neutrophils, fibrosis and areas of granulation tissue. The fibrosis may be dense and comprised of fibroblasts and myofibroblasts.[17] Newly formed vessels within the granulation tissue have been postulated to be more susceptible to immune-complex deposition, thus potentiating the process.[1,18]

Spontaneous resolution of EED may occur, albeit after a prolonged and recurrent course of up to 5-10 years.[19] Treatment of the underlying cause, when identified, remains paramount. First-line therapy includes dapsone, shown to be effective in reducing lesion size to complete resolution in 80% of the 47 cases in the literature reviewed by Momen and colleagues.[20]

Conclusion

Our case exemplifies the clinicohistologic spectrum on which EED can present. The constellation of clinical findings was histologically confirmed to be manifestations of the disease in various stages of evolution. When typical lesions of EED present along with cutaneous findings in less common locations, performing multiple biopsies can be helpful. The clinician should retain a high index of suspicion for an underlying etiology and perform a complete work-up for infection, malignancy or autoimmune disease.

References

1. Gibson LE, el-Azhary RA. Erythema elevatum diutinum. *Clinics in Dermatology*. 2000; 18(3):295-299.
2. Wilkinson SM, English JS, Smith NP, Wilson-Jones E, Winkelmann RK. Erythema elevatum diutinum: a clinicopathological study. *Clin Exp Dermatol*. 1992;17(2):87-93.
3. Barzegar M, Davatchi CC, Akhyani M, Nikoo A, Daneshpazhooh M, Farshnejad K. An atypical presentation of erythema elevatum diutinum involving palms and soles. *Int J Dermatol*. 2009;48:73–75.
4. Futei Y, Konohana I. A case of erythema elevatum diutinum associated with B-cell lymphoma: a rare distribution involving palms, soles and nails. *Br J Dermatol*. 2000;142:116–119.
5. Ben-Zvi GT, Bardsley V, Burrows NP. An atypical distribution of erythema elevatum diutinum. *Clin Exp Dermatol*. 2014;39:269–270.
6. Weidman FD, Besancon JH. Erythema elevatum diutinum. Role of streptococci, and relationship to other rheumatic dermatoses. *Arch Dermatol Syphilol*. 1929;20:593-620.
7. Fakheri A, Gupta SM, White SM, Don PC, Weinberg JM. Erythema elevatum diutinum in a patient with human immunodeficiency virus. *Cutis*. 2001;68:41–42.
8. Kim, H. Erythema elevatum diutinum in an HIV-positive patient. *J Drugs Dermatol*. 2003;2(4):411-2.
9. Revenga F, Vera A, Muñoz A, De la Llana FG, Alejo M. Erythema elevatum diutinum and AIDS: are they related? *Clin Exp Dermatol*. 1997;22:250–251.
10. Drago F, Semino M, Rampini P, Lugani C, Rebora A. Erythema elevatum diutinum in a patient with human herpesvirus 6 infection. *Acta Derm Venereol*. 1999;79(1):91-2.
11. Muratori S, Carrera C, Gerami A, Alessi E. Erythema elevatum diutinum and HIV infection: a report of five cases. *Br J Dermatol*. 1999;141(2):335-338.
12. Haber H. Erythema elevatum diutinum. *Br J Dermatol* 1955;67:121–145.
13. Katz SI, Gallin JL, Hertz KC, Fauci AS, Lawley TJ. Erythema elevatum diutinum: skin and systemic manifestations, immunologic studies, and successful treatment with dapsone. *Medicine (Baltimore)* 1977;56:443–455.
14. Walker KD, Badame AJ. Erythema elevatum diutinum in a patient with Crohn's disease. *J Am Acad Dermatol* 1990;22:948-952.
15. Popp, JW, Harrist, T, Dienstag, JL, Bhan, AK, Wands, JR, LaMont, JT, Mihm, MC. Cutaneous vasculitis associated with acute and chronic hepatitis. *Arch Intern Med*. 1981;141:623-629.
16. Yiannias JA, el-Azhary RA, Gibson, LE. Erythema elevatum diutinum: a clinical and histopathologic study of 13 patients. *J Am Acad Dermatol*. 1992;26(1):38-44.
17. Lee AY, Nakagawa H, Nogita T, Ishibashi Y. Erythema elevatum diutinum: An ultrastructural case study. *J Cutan Pathol*. 1989;16(4):211–217.
18. LeBoit PE, Yen TS, Wintroub B. The evolution of lesions in erythema elevatum diutinum. *Am J Dermatopathol*. 1986;8(5):392-402.
19. Soubeiran E, Wacker J, Hausser I, Hartschuh W. Erythema elevatum diutinum with unusual clinical appearance. *J Dtsch Dermatol Ges*. 2008;6(4):303-305.
20. Momen SE, Jorizzo J, Al-Niaimi F. Erythema elevatum diutinum1. a review of presentation and treatment. *J Eur Acad Dermatol Venereol*. 2014;28(12):1594-1602.

Severe Adult-Onset Atopic Dermatitis: Investigating the Pathogenic Role of *Malassezia spp.* and Anti-Fungal Treatment in Refractory Disease - A Case Report

Tyler O. Vukmer DO[1]
Adriana Ros DO FAOCD[1]
Palisades Medical Center, North Bergen NJ

Abstract

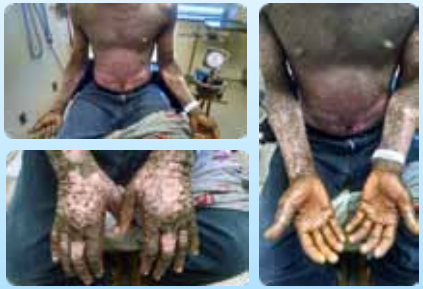
Atopic Dermatitis (AD) is a common inflammatory dermatosis characterized by pruritus and a cyclic clinical course. It's estimated prevalence in industrialized countries has tripled over the last 30 years, affecting 15-30% of children and up to 10% of adults[1]. AD is one part of the 'Atopic Triad', along with allergic rhinitis and asthma. The pathogenesis and clinical course of AD is likely multifactorial with defective barrier function (fillagrin deficiency/mutation), allergic, and infectious processes implicated[1,2]. Specifically, *Malassezia spp.* yeasts have been demonstrated to have a pathogenic role in at least some cases of AD. Circulating anti-Malassezia antibodies are only seen in patients with AD[3]. Antibody titers have been correlated to severity in several studies[1,2,3,4].

We report the case of an otherwise healthy 37 year old African American patient with severe, disfiguring AD of 19 years duration. The patient presented to our dermatologic clinic an intensely pruritic and cosmetically disfiguring dermatitis. Physical exam revealed a diffuse inflammatory dermatosis with lichenfication, thickening, and dispigmentation involving > 80% BSA and non-tender axillary/inguinal adenopathy. The psycho-social impact for this patient was severe; the disfigurement had made employment virtually impossible, and interpersonal relationships suffered greatly.

Various topical corticosteroids (triamcinolone 0.1% ointment, hydrocortisone 2.5% cream), as well as topical calcineurin inhibitors (tacrolimus 0.1% ointment) failed to improve the condition over a one year course, and oral cyclosporine therapy was initiated at 100mg twice daily, in addition to the topicals. Minimal improvement was seen over another year on this combination. At this point, other etiologies and therapeutic strategies for the dermatosis had to be considered. Laboratory testing was ordered (**Table 1**).

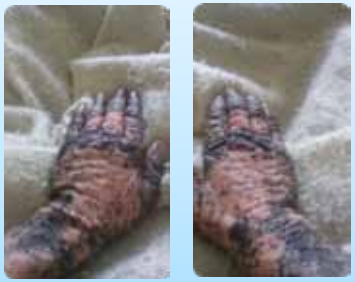
Clinical Images 10/2014

Prior to initiation of cyclosporine 100mg BID



Clinical Images 7/2015

After 12 months of cyclosporine 100mg qd and 1 month of terbinafine 250mg qd



Clinical Images 8/2015

2 months after initiation of terbinafine 250mg qd

Table 1

Selected Laboratory Values

IgE: 24311 (H)

Malassezia Mix-IgE: 11.30 kU/L **(H)**

- **Reference Ranges**
  - <0.10 - Negative
  - 0.1-0.34 - Equivocal/Borderline
  - 0.35-0.69 - Low Positive
  - 0.70-3.49 - Moderate Positive
  - 3.50-17.49 - High Positive
  - 17.50-49.99 - Very High Positive
  - >50.00 - Very High Positive

CBC
- WBC - 5.8
- HGB - 12.3
- HCT - 38.0
- PLT - 232

CMP
- Na - 140
- K - 3.7
- Cl - 105
- CO2 - 26.7
- BUN - 6
- Creat - 1.0
- GLU - 73

ANA: Neg.

Blood Culture: Neg.

ESR: 14

Lymph Node Biopsy: Reactive lymph node with paracortical hyperplasia consistent with dermatopathic lymphadenopathy.

The possibility of an allergy-mediated process was supported by the elevated serum IgE level (in the 24,000kU/L range; ref. range <114kU/L), and the suspected role of *Malassezia spp.* commensurate yeast was confirmed by ImmunoCAP allergen-specific IgE testing (11.30; ref. range <0.35).

The regimen was then changed to oral terbinafine 250mg daily, cyclosporine 100mg daily, and the topicals previously mentioned. Within one month the patient reported significant improvement in pruritus, diffuse softening of the skin, and repigmentation.

Clinical improvement continues to be seen today.

References

1. Glatz M. Et. al. The Role of Malassezia spp. in Atopic Dermatitis. J Clin Med 2015. Jun; 4(6): 1217-1228.
2. Sugita T. Et. al. Atopic Dermatitis and Skin Fungal Microorganisms. "Atopic Dermatitis - Disease Etiology and Clinical Management. Editors: Esparaza-Gordillo J. Dekio I.
3. Zhang E. Et. al. Anti-Malassezia-Specific IgE Antibodies Production in Japanese Patients with Head and Neck Atopic Dermatitis: Relationship between the Level of Specific IgE Antibody and the Colonization Frequency of Cutaneous Malassezia Species and Clinical Severity. J Allergy. 2011; Dec. 29.
4. Gioti A. Et. al. Genomic Insights into the Atopic Eczema-Associated Skin Commensal Yeast *Malassezia sympodialis*. MBio. 2013 Han22; 4(1).

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Ritz Carlton Battery Park
New York, NY
March 30 - April 3, 2016

2016 Annual AOCD Fall Meeting
Loews Santa Monica Beach Hotel
Santa Monica, CA
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2017 Annual AOCD Spring Meeting
Ritz Carlton Atlanta
Atlanta, GA
March 29 - April 2, 2017