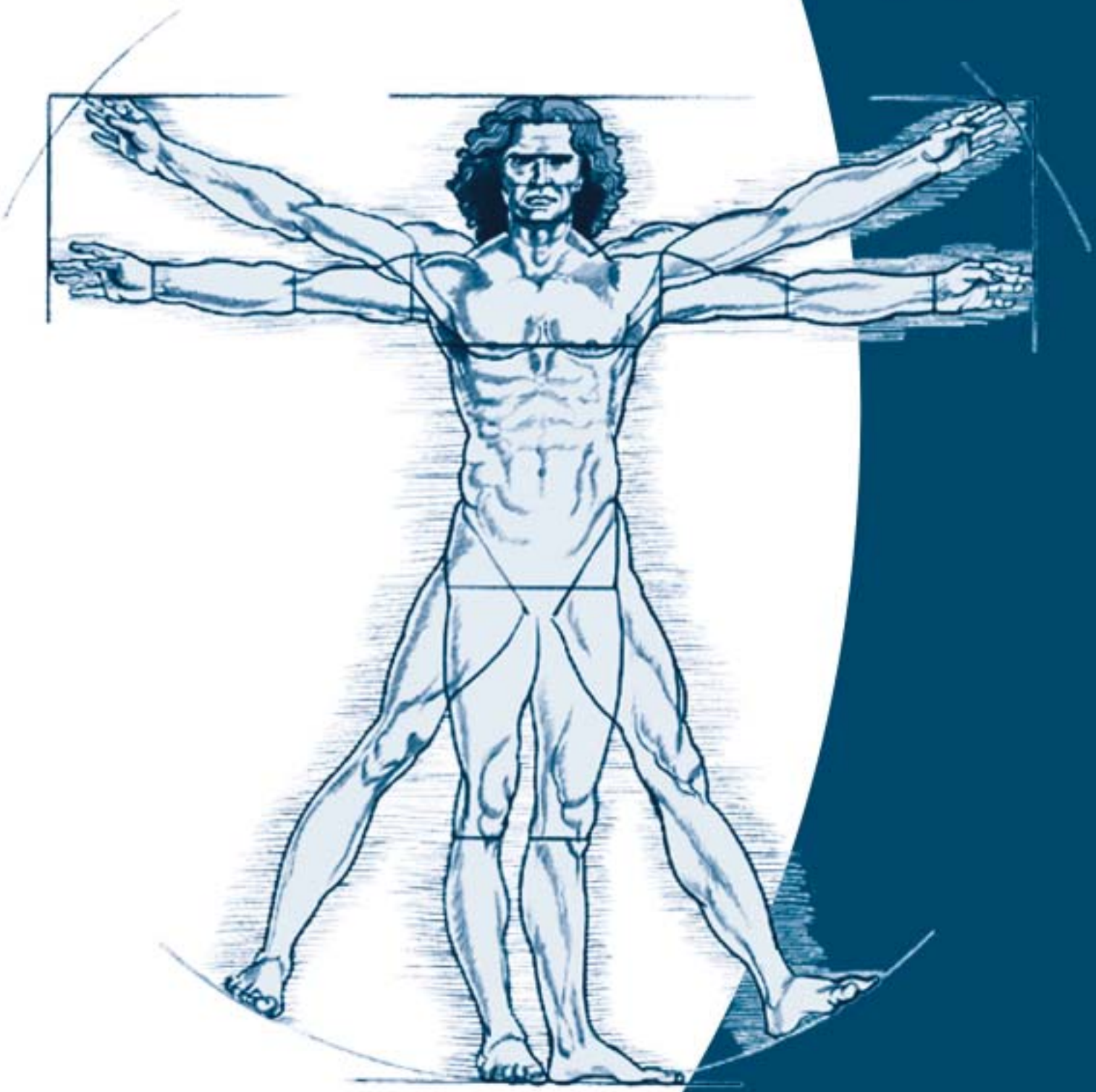
Journal of the American Osteopathic College of Dermatology

AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY · AOCD · FOUNDED 1968 ·



Journal of the American Osteopathic College of Dermatology

AOCD • 1501 E. Illinois • Kirksville, MO 63501
800-449-2623 • FAX: 660-627-2623
www.aocd.org

Printed by: Stoyles Graphics Services, Mason City, IA 50401
Journal of the American Osteopathic College of Dermatology

VOLUME 5 , NUMBER 1 FEBRUARY 2006

Journal of the American Osteopathic College of Dermatology

CONTENTS

Volume 5 , Number 1 February 2006

Journal of the American Osteopathic College of Dermatology

Contents continued...

Letter From The JAOCD Editors

Jay S. Gottlieb, D.O.

Stanley E. Skopit, D.O.

James Q. DelRosso, D.O.

This is the 5th issue of the JAOCD. We have had a lot of interest in our journal from various industries. Many of these inquiries have come from companies that wish to advertise to our membership, while other inquiries have come from companies asking how they can become involved with our journal. All of this is exciting and very complimentary to what we have been working so hard and long to accomplish. Every industry and every physician that looks at any issue of the JAOCD, quickly recognizes and realizes that we are not just another dermatology journal. We are all about the dermatology resident, the future of dermatology!

Currently, I am in discussion with various publishing companies that have interest in working with us to make our journal better and more widely distributed. I have also discussed outsourcing much of the review process. Our members will be asked to do peer review and to help bring the JAOCD to an even a more prestigious level.

We will continue to strive to make the JAOCD a journal that all dermatologists can look forward to receiving on a regular basis. We are committed to maintaining our position as a journal for residents. We will be widely known as a journal 'for and by residents'. We will emphasize education for residents. I plan to add resident members to our Editorial Review Board in the next six months. These members are the future of dermatology and our college.

I continue to be amazed at the unwavering support of our extended family, the Founding Sponsors of the JAOCD. These six companies continue, without hesitation or reservation, to support our efforts. We have developed a long and mutually beneficial relationship with each one of our sponsors. We look forward to developing an even closer and stronger commitment to each of them. Our deepest thank you continues to go to Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services, Novartis Pharmaceuticals Corporation, Medicis-The Dermatology Company and 3M Pharmaceuticals who have continued to make the financial commitment to see that our journal succeeds. Without their support, the JAOCD would have remained a dream and never would have become a reality.

Get more information about the JAOCD at www.aocd.org or e-mail us at jaocd@aol.com.

Fraternally yours in Dermatology,

Jay S. Gottlieb, D.O., F.O.C.O.O. (Chief Editor)
Stanley E. Skopit, D.O., F.A.O.C.D. (Co-Editor)
James Q. Del Rosso, D.O., F.A.O.C.D. (Associate Editor)

Letter from the President of the AOCD

Richard Miller, DO, FAOCD, President

Greetings

I would like to thank you for allowing me the honor of representing you this next year as President of the AOCD. As a longstanding AOCD executive committee member, I have had the opportunity to observe and participate in many of the functions of our college. In doing so, I have endeavored to become familiar with the requirements necessary for the continued successful growth of our college.

Our college is experiencing remarkable growth. Our membership has doubled in the last ten years and will most likely double again in the next ten years. As our numbers and thereby our strength increase, we can also expect an increase in corporate involvement and financial support. With these increasing numbers comes a degree of power. This is acutely evident to the pharmaceutical companies and ancillary businesses which support our specialty. These added resources will augment funding for resident training and research. Thus, it is important that we attract all potential members, retain current members and impress upon future members as to why the AOCD should play an important role in their career. Attracting all potential members to join our college will ensure our future place in the field of dermatology. My goal is to reach out to those Osteopathic Dermatologists who have not joined or have departed from our college.

As physicians today, we are asked to join a myriad of organizations. The AOCD is an organization by and for the Osteopathic Dermatologist and is singularly concerned with those issues and problems that are unique to our profession. It is currently the only dermatologic organization that is able to certify our graduate members. It is the controlling force that ensures the quality training necessary to develop and instruct our residents. Biannual Scientific seminars are developed exclusively by Osteopathic Dermatologists allowing our residents, members and guest faculty a forum to present lectures of varied topics. The college has developed avenues for certification in Dermatopathology and Mohs surgery and will be responsible for recertification that will be required in the future.

I would hope that most of us would maintain our AOCD membership purely out of gratification for the ability to practice our specialty. Unfortunately, I know that there are members and potential members that may not feel a connection or appreciation for what they have received thus far. They have no motivation to participate in the organization or share their knowledge or talent. As president of the AOCD, I would like to bring our members back to the original focus of this organization. I ask you to support this organization by volunteering for one of our committees or by adding whatever unique talent you have that will help to enhance and improve the AOCD. As a group we have a vast wealth of knowledge and experience that we should share. This is our organization which will continue to improve with your contributions. I challenge each and every one of you to get involved and give in some way to the enhancement of our college.

In the past, the AOCD has been instrumental in developing informative brochures (What is an Osteopathic Dermatologist?), posters and marketing campaigns promoting the AOCD and our foundation. These past accomplishments are only a small part of what could be achieved. Although we are a relatively small group, we have unlimited potential. As an organization, the AOCD can make a tremendous impact on the future of our profession. Please feel free to contact me by phone at 727-841-8505 or via email at rmiller.aocd@gmail.com. I look forward to hearing from you with your concerns and ideas.

Richard A. Miller, D.O., F.O.D.
President
American Osteopathic College of Dermatology

For the temporary treatment of moderate to severe glabellar lines in patients 18 to 65 years of age

Trusted tool of aesthetic artistry

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in patients 18 to 65 years of age.

Important Safety Information: BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation. There have been rare reports of adverse events involving the cardiovascular system. Serious and/or immediate hypersensitivity reactions have been reported rarely. These reactions include anaphylaxis, urticaria, soft-tissue edema, and dyspnea.

The most common adverse events following injection include blepharoptosis and nausea. Less frequently occurring (<3%) adverse reactions include facial pain, erythema at the injection site, paresthesia, and muscle weakness. Patients with neuromuscular disorders such as ALS, myasthenia gravis, or Lambert-Eaton syndrome may be at increased risk of serious adverse events.

Please see brief summary of full prescribing information on following page.

BOTOX® Cosmetic
Botulinum Toxin Type A

By prescription only

BOTOX® COSMETIC (Botulinum Toxin Type A) Purified Neurotoxin Complex

INDICATIONS AND USAGE

BOTOX® COSMETIC is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

CONTRAINDICATIONS

BOTOX® COSMETIC is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS

BOTOX® and **BOTOX® COSMETIC** contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® COSMETIC**.

Do not exceed the recommended dosage and frequency of administration of **BOTOX® COSMETIC.** Risks resulting from administration at higher dosages are not known.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined. If such a reaction occurs further injection of **BOTOX® COSMETIC** should be discontinued and appropriate medical therapy immediately instituted.

Pre-Existing Neuromuscular Disorders

Caution should be exercised when administering **BOTOX® COSMETIC** to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX® COSMETIC**. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Dysphagia

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

Cardiovascular System

There have also been rare reports following administration of **BOTOX®** of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

Human Albumin

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General:

The safe and effective use of **BOTOX® COSMETIC** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX® COSMETIC** must understand the relevant neuromuscular and/or orbital anatomy of the area involved, as well as any alterations to the anatomy due to prior surgical procedures and avoid injection into vulnerable anatomic areas. Caution should be used when **BOTOX® COSMETIC** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Reduced blinking from **BOTOX® COSMETIC** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of **BOTOX®** for in the treatment of blepharospasm, one case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Caution should be used when **BOTOX® COSMETIC** treatment is used in patients who have an inflammatory skin problem at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart as these patients were excluded from the Phase 3 safety and efficacy trials.

Needle-related pain and/or anxiety may result in vasovagal responses, (including e.g., syncope, hypotension) which may require appropriate medical therapy.

Injection intervals of **BOTOX® COSMETIC** should be no more frequent than every three months and should be performed using the lowest effective dose (See Adverse Reactions, Immunogenicity).

Information for Patients

Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech or respiratory disorders arise.

Drug Interactions

Co-administration of **BOTOX® COSMETIC** and aminoglycosides[1] or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Pregnancy: Pregnancy Category C

Administration of **BOTOX® COSMETIC** is not recommended during pregnancy. There are no adequate and well-controlled studies of **BOTOX® COSMETIC** in pregnant women. When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of **BOTOX® COSMETIC** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification.

In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX® COSMETIC**.

If the patient becomes pregnant after the administration of this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations that have been observed in rabbits.

Carcinogenesis, Mutagenesis, Impairment of fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX® COSMETIC**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and testicular atrophy or an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **BOTOX® COSMETIC** is administered to a nursing woman.

Pediatric use: Use of **BOTOX® COSMETIC** is not recommended in children.

Geriatric use

The two clinical studies of **BOTOX® COSMETIC** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, the responder rates appeared to be higher for patients younger than age 65 than for patients 65 years or older. (See: CLINICAL STUDIES)

There were too few patients (N=3) over the age of 75 to allow any meaningful comparisons.

ADVERSE REACTIONS

General:

BOTOX® and **BOTOX® COSMETIC** contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® COSMETIC**.

The most serious adverse events reported after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, pneumonia, and/or other significant debility. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. (See: WARNINGS). New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, a report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

In general, adverse events occur within the first week following injection of **BOTOX® COSMETIC** and while generally transient may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema and/or bleeding/bruising may be associated with the injection.

Glabellar Lines

In clinical trials of **BOTOX® COSMETIC** the most frequently reported adverse events following injection of **BOTOX® COSMETIC** were headache*, respiratory infection*, flu syndrome*, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site*, paresthesia* and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months or longer.

(* incidence not different from Placebo)

The data described in Table 4 reflect exposure to **BOTOX® COSMETIC** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® COSMETIC** in the improvement of the appearance of glabellar lines (See: CLINICAL STUDIES). Adverse events of any cause were reported for 44% of the **BOTOX® COSMETIC** treated subjects and 42% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX® COSMETIC** treated arm than in placebo (3% vs. 0).

In the open-label, repeat injection study, blepharoptosis was reported for 2% (8/373) of subjects in the first treatment cycle and 1% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not be predictive of rates observed in practice.

TABLE 4.

	Percent of Patients Reporting Adverse Events	
Adverse Events by Body System	**BOTOX® Cosmetic (N=405) %**	**Placebo (N=130) %**
Overall	44	42
Body as a Whole Pain in Face	2	1
Skin and Appendages Skin Tightness	1	0
Digestive System Nausea Dyspepsia Tooth Disorder	3 1 1	2 0 0
Special Senses Blepharoptosis	3	0
Musculoskeletal System Muscle Weakness	2	0
Cardiovascular Hypertension	1	0

Adverse Events Reported at Higher Frequency (>1%) in the BOTOX® COSMETIC Group Compared to the Placebo Group

Immunogenicity

Treatment with **BOTOX® COSMETIC** may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments with **BOTOX® COSMETIC** by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX® COSMETIC** has not been well studied.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting the lowest effective dose given at the longest feasible intervals between injections.

Rx Only

Based on package insert 71711US13S revised January 2005

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612

Reference:

1. Wang YC, Burr DH, Korthals GJ, Sugiyama H. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. *Appl Environ Microbiol* 1984; 48:951-955.

Cutaneous Alternaria Infection in a Patient with Waldenström Macroglobulinemia

Benjamin E. Adams D.O*, Lloyd J. Cleaver D.O., F.A.O.C.D.**
**2nd year Dermatology Resident, Northeast Regional Medical Center, Kirksville, Missouri*
***Program Director of Department of Dermatology, Northeast Regional Medical Center, Kirksville, Missouri*

ABSTRACT

The following is a case of cutaneous alternariosis, in an 82 year-old male with a history of Waldenström macroglobulinemia and hypogammoglobulinemia. Initially the patient presented with a nodule on his left foot, and later subcutaneous nodules on his right thigh. Alternaria was isolated from tissue cultures, and fungal organisms were observed on histology from both locations. The patient was subsequently treated with oral itraconazole, and surgical excision.

Summary:

The following is a case of cutaneous alternariosis, in an 82 year-old male with a history of Waldenström macroglobulinemia and hypogammoglobulinemia. Initially the patient presented with a nodule on his left foot, and later subcutaneous nodules on his right thigh. Alternaria was isolated from tissue cultures, and fungal organisms were observed on histology from both locations. The patient was subsequently treated with oral itraconazole, and surgical excision.

Introduction:

Alternaria species are pigmented (also known as dematiaceous or phaeoid) filamentous fungi, which are well-known soil saprophytes and plant pathogens that infrequently cause infection in humans. They are characterized by the presence of an olive-brown or black pigment in the cell wall and macroconidia with muriform septation. The genus Alternaria has a worldwide distribution and is commonly isolated from soil, air, and plants. This species of fungus can often be a contaminant and is an uncommon cause of disease in man. The clinical spectrum of disease caused by Alternaria includes the following: hypersensitivity pneumonitis, granulomatous lung disease, bronchial asthma, paranasal sinusitis with and without osteomyelitis, allergic sinusitis and rhinitis, keratitis, peritonitis, and cutaneous and subcutaneous deep-tissue infection. Alternaria infections are most common in immunosuppressed or transplant recipients, and are frequently a consequence of an exogenous inoculation from a traumatic event.[2]

Case Report:

An 82 year-old white male presented to the dermatology clinic with a one month history of a non-healing sore on his left foot. The patient denied any local trauma to the area or any unusual exposures. The patient had a history of Waldenström macroglobulinemia and hypogammoglobulinemia, and was followed on a regular basis by his oncologist. He had completed a course of fludarabine two years previously, and was currently treated with IVIG.

On examination he had a 1.3 x 1.1 cm red slightly ulcerated nodule at the base of the fifth digit of his left foot (Fig. 1). Due to the rapidity of growth and the clinical appearance of the lesion, an excisional biopsy was performed. The differential diagnosis included: adnexal tumor, basal cell carcinoma, squamous cell carcinoma, dermatofibroma, dermatofibrosarcoma protuberans, and foreign body reaction. Histology revealed an ulcerated lesion with a dense underlying proliferation of histiocytes with multinucleated giant cells, with admixed acute and chronic inflammation (Fig. 2). A silver methenamine stain showed fungal elements including broad septate hyphae (Fig. 3).

The diagnosis of a deep fungal infection was made, and the patient was started on oral terbinafine; however, he was unable to continue treatment due to appearance of hives and desquamation of his palms after initiating therapy. The nodule recurred on his left foot and a punch biopsy was performed and sent for culture as well as histology. Histopathology again showed large numbers of fungal elements with branching septate hyphae admixed with an inflammatory infiltrate. The culture isolated an Alternaria species. The patient was then started on pulse-dosing of oral itraconazole 200 mg daily for seven days a month for four months.

Subsequently, one month after initial presentation for the nodule on his left foot, the patient developed two subcutaneous nodules on his right lower thigh. The largest of these nodules measured 1.8 x 1.8 cm. The nodules were non-tender to palpation and had a soft rubbery consistency. The largest of these nodules was excised and was culture positive for an Alternaria species. Histology showed necrotic granulomas with a neutophilic infiltrate. Futhermore, a methenamine silver strain revealed septate branching hyphae with bulbous ends. The patient had no lympadenopathy or other systemic complaints such as fever, fatigue, or weakness.

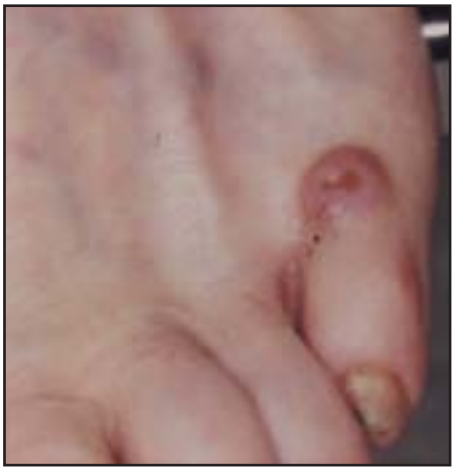


Figure 1
Lesion at base of 5th digit of left foot.

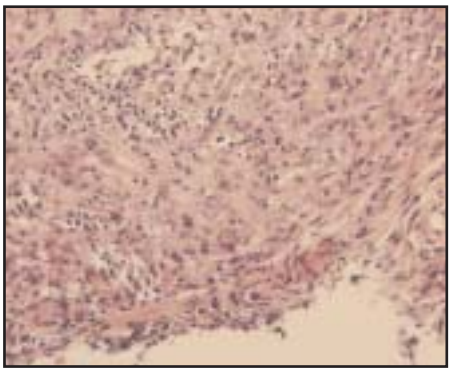


Figure 2
Proliferation of histiocytes with multinucleated giant cells, with admixed acute and chronic inflammation. H&E 200X

Due to the patient's immune status, and multiple foci of infection, an infectious disease specialist was consulted. The patient was then started on oral itraconazole 200 mg daily for six months. In addition, the remaining nodule on the patient's right thigh was excised, and it also was culture positive for Alternaria. The patient is cur-

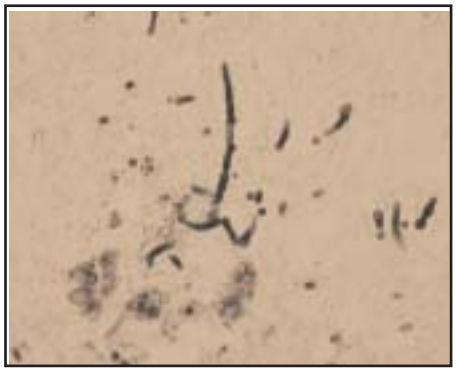


Figure 3
Fungal elements including broad septate hyphae. Methenamine silver stain 400X

rently in his third month of treatment with itraconazole and has had clinical improvement at the excision sites. Additionally, the patient has not developed any new nodules.

Discussion:

The denomination phaeohyphomycois indicates a heterogenous group or rare fungal diseases caused by dematiaceous fungi. Alternaria is one of a group of approximately 30 fungal genera involved in these infections. Although there have been more than 80 species of Alternaria identified, only 8 have been involved in human infections. The most common species seen in human disease are A alternata, A tenuissima, A chartarum, A longipes, A infectoria, A chlamydospora, A stemphyloides, and A dianthicola.

The majority of Alternaria infections are cutaneous in nature, and generally associated with an immunocompromised host. With respect to the pathogenesis of cutaneous alternariosis, two possible routes of infection are distinguished. In the exogenous variant, the condition results from the traumatic inoculation of fungal elements (e.g. after injury by a plant spine) or develops after colonization of pathologically altered skin. In the endogenous variant, inhalation of fungal conidia and subsequent systemic spread eventually result in secondary cutaneous involvement. Some authors have also defined a "dermatopathic" cutaneous alternariosis, consisting of secondary colonization by Alternaria of a pre-existing lesion, such as steroid-treated eczema of the face. Development of disease seems to be related to a spontaneous or induced immunodeficiency of the host. Examples of immunocompromised states associated Alternaria infection include: solid-organ transplant recipients, Cushing's syndrome, patients receiving chemotherapy for lymphoma, myeloproliferative syndrome,9 autoimmune blistering diseases, and AIDS. Investigation of the literature reveals that in nearly half of the reported cases, oral steroids play the major pathogenic role in the occurrence of cutaneous alternariosis. It has been postulated that cutaneous fragility induced by corticosteroids my increase the risk of percutaneous inoculation from the environment.

As the population of immunocompromised patients grows, clinicians are likely to encounter more cases of cutaneous alternariosis. Therefore, recognition of Alternaria as a potential opportunistic pathogen is important for the differential diagnosis of dermatologic lesions. The clinical manifestations of cutaneous alternariosis vary greatly. Lesions can appear as shallow-based nonhealing ulcers that evolve from nodules, subcutaneous noninflammatory cysts, verrucous-like lesions, or erythematous, confluent, scaly patches resembling eczema. The lesions usually develop on exposed sites or boney prominences such as the feet, knees, legs dorsum of the hands, and occasionally on the face. The most common presentation is a solitary asymptomatic reddish-brown to purplish papule, nodule, or plaque which may subsequently ulcerate. Histologically, variation of the host response and of the morphological appearance of hyphae in tissue creates the potential for diagnostic confusion. A mixed inflammatory dermal infiltrate (neutrophils, lymphocytes, and plasma cells) is typically seen with or without giant cells and histiocytes. Microabscesses or well-formed granulomas may also be present. A recent article has concluded that suppurative granulomas are most common in lesions of more than three months duration.[2] The epidermis may be uninvolved or may show hyperplasia, neutrophilic infiltration with microabcess formation, erosion, or ulceration. Fungal morphology is pleomorphic, ranging from globose cells to distorted hyphae with variable frequency of septation and branching.

The observation of characteristic large round-to-oval, thick walled retractile inclusion structures within the histiocytes or neutrophils is a characteristic histopathologic feature of fungus infection and a morphologic hallmark that may permit a suggestion of the diagnosis.[2]

Due to the ubiquitous nature of Alternaria in the environment, diagnosis requires the combination of a positive tissue culture, histologic evidence of fungal elements, and clinical correlation in order to distinguish between contamination, colonization, and pathogenicity.[20] In addition to being readily isolated from the environment, Alternaria is frequently cultured from the skin surface. Botticher found that Alternaria spp. comprised 15% of all fungi cultured from over 2,000 specimens in patients with superficial mycoses. However, in most instances the Alternaria sp. was not the only fungus isolated and was probably not the primary pathogen. Alternaria shows rapid growth on Sabourand dextrose agar, and colonies are usually apparent within 5 days. It forms dark grayish to grayish-green colonies that later turn black, often with a white rim.

Treatment of cutaneous alternariosis is not well standardized and currently much controversy exists. It is recommended that immunosuppression be reduced if possible, and surgical excision of localized lesions be performed. Much improvement even complete resolution has been seen after tapering of oral corticosteroids, even without any interruption in the administration of other chemotherapeutic agents.[20] Alternaria species are sensitive to oral itraconazole, amphotericin B,[15] fluconazole,[12] miconazole, terbinafine, and ketaconazole;[10] however, the degree of sensitivity is variable. Resistance to flucytocine and griseofulvin has been seen.[15] Recent reports consider itraconazole to be as effective as, if not superior to amphotericin B. In view of the lower toxicity and easier administration of itraconazole, some authors feel that it represents the first-line drug for alternariosis and other phaeohyphomycosis. Several months of therapy are often needed, and it is recommended to treat for several months after achieving a clinical resolution. Even with prolonged treatment relapses often occur, and long-term clinical follow-up is advised.

Conclusion:

Herein we reported a case of cutaneous alternariosis in a patient with Waldenström macroglobulinemia. Waldenström macroglobulinaemia is a distinct clinicopathological disorder characterized by a monoclonal lymphoplasmacytic neoplasm accompanied by an increased serum monoclonal immunoglobulin M. Patients with Waldenström macroglobulinemia have an increased risk of opportunistic infections because of baseline immunodeficiency such as low concentrations of uninvolved immunoglobulins, chemotherapy-related neutropenia, and T-cell dysfunction induced by purine nucleoside analogues. Our patient had been treated two years previously with the nucleoside analogue fludarabine, and it is unknown if this contributed to his Alternaria infection. We are hopeful that prolonged treatment with itraconazole combined with surgical excision will provide resolution of this infection.

References

1 Anaissie EJ, Bodey GP, Pinaldi MG. Emerging fungal pathogens, Eur J Clin Microbiol Infect Dis 1989:8:323-30.

2 Gilaberte M, Bartralot R, Torres JM, Reus FS, Rodriguez V, Alomar A, Pujol RM. Cutaneous alternariosis in transplant recipients: Clinicopathologic review of 9 cases, J Am Acad Dermatol 2005:52(4):653-9.

3 De Bievre C. Les Alternaria pathogenes pur L;homme: mycologie epidemiologique. J Mycol Med 1991:1:50-8.

4 Wiest PM, Wiese K, Jacobs MR, et al. Alternaria infection in a patient with acquired immunodeficiency syndrome: case

report and review of invasive Alternaria infections, Rev Infect Dis 1987:9:799-803.
5 McGinnis MR, Hilger AE. Infections caused by black fungi. Arch Dermatol 1987:123:1300-2.
6 Lyke KE, Miller NS, Towne L, Merz WG. A Case of Cutaneous Ulceratrive Alternariosis: Rare Association with Diabetes Mellitus and Unusual Failure of Itraconazole Treatment, Clin Infec Diseases 2001:32:1178-87.
7 Male O, Pehamberger H. Secondary cutaneous mycoses caused by Alternaria species. Hautarzt 1986:37:94-101.
8 Repiso T, Martin N, Huguet P, et al. Cutaneous alternariosis in a liver transplant recipient. Clin Infect Dis 1993:16:729-730.
9 Viviani MA, Tortorano AM, Laria G, et al. Two new cases of cutaneous alternariosis with a review of the literature. Mycopathologica 1986:96:3-12.
10Guerin V, Barbaud A, Duquenne M, et al. Cushing's disease and cutaneous alternariosis, Arch Intern Med 1991:151:1865-8.
11 Rovira M, Martin P, Martin-Ortega E, et al. Alternaria infection in a patient receiving chemotherapy for lymphoma. Acta Haematol 1990:84:98-100.
12 Machet MC, Stephanov E, Esthve E, et al. Alternariose cutanie surenant au cours de l'evolution d'un pemphigus traiti: a propos de 2 cas. Ann Pathol 1994:14:186-191.
13 Weist PM, Weise K, Jacobs MR, et al. Alternaria infection in a patient with acquired immunodeficiency syndrome: Case report and review of the invasive alternaria infections. Rev of Infect Dis 1987:4:799-803.
14 Machet L, Jan V, Machet MC, et al. Cutaneous alternariosis: role of corticosteroid-induced cutaneous fragility. Dermatology 1996:193:342-344.
15 Iwatsu T. Cutaneous alternariosis. Arch Dermatol 1988:124:1822-25.
16 Weitzman I. Saprophytic molds as agents of cutaneous and subcutaneous infection in the immunocompromised host. Arch Dermatol 1986:122:1161-1168.
17 Palencarova E, Jesenska Z, Plank L, et al. Phaeohyphomycosis caused by Alternaria species and Phaeosclera dematioides Sigler, Tsuneda and Carmichael. Clin Exp Dermatol 1995:20:419-22
18 Pec J, Palencarova E, Plank L, et al. Phaeohyphomycosis due to alternaria spp. And Phaeosclera dematioides: a histopathological study. Mycosis 1996:39:217-21.
19 Romano C, Valenti L, Miracco C, et al. Two cause of cutaneous phaeohyphomycosis by Alternaria alternata and Alternaria tenuissima. Mycopathologia 1197:137:65-74.
20 Junkins JM, Beveridge RA, Friedman KJ, et al. An unusual fungal infection in an immunocompromised oncology patient. Arch Dermatol 1988:124:1421-6.
21 Botticher WW. Alternaria as a possible human pathogen. Sabouraudia. 1966:4:256-258.
22 Romero ML, Siddiqui AH. Diagnosis Cutaneous alternariosis. Clinical Infect Dis. 2000:30:174-5.
23 Machet L, Machet MC, Maillot F, et al. Cutaneous alternariosis in a patient treated with a corticosteroid enema. Axta Derm Venerol. 1995:75:328-9.
24 Lanigan SW. Cutaneous alternaria infection treated with itraconazole. Br J Dermatol. 1992:127:39-40.
25 De Moragas JM, Prats G, Verger G. Cutaneous alternariosis treated with miconazole. Arch Dermatol. 1981:117:292-294.
26 Altomare GF, Capella GL, Boneschi V, Viviani MA. Effectiveness of terbinafine in cutaneous alternariosis. Br J dermatol. 2000:142:840-41.
27 Sharley KP, Graybill JR, Rinaldi MG, et al. Itraconazole treatment of phaeohyphomycosis. J Am Acad Dermatol. 1990:23:577-86.
28 Ghobrial IM, Gertz MA, Fonseca R. Waldenström macroglobulinemia. The Lancet-Oncology. 2003:4:11.

What are the Biologics? A Review for the Non Dermatologist

Ty Hanson, D.O.*, John Hibler, D.O.**

**Resident, Ohio University College of Osteopathic Medicine, O'Bleness Memorial Hospital Athens, Ohio.*

***Dermatology Program Director of Ohio University College of Osteopathic Medicine and O'Bleness Memorial Hospital. Clinical Assistant Professor West Virginia School of Osteopathic Medicine.*

With an increasing number of patients presenting to medical care providers with a broader array of new medications it is difficult to keep up with these new drugs and their associated side effects, drug to drug interactions, and relative and absolute contraindications. Most clinicians probably ask the patient what a particular medication they are taking is used for, or they look up the medication in a physician's desk reference or similar book. Fortunately, most of these newer medications are much more efficacious and carry a bigger safety profile with fewer drug to drug interactions. This is certainly true of the largest and most exciting new class of pharmaceuticals in the field of dermatology.

This new class, the biologics, is currently being used throughout the United States for the treatment of psoriasis and psoriatic arthritis. Traditionally, the treatments of psoriasis include products non dermatologists would easily recognize. These include topicals like corticosteroids, dovenex, tazoratene, and tar products. Also, oral immunosuppressive agents like methotrexate and cyclosporine have been used broadly, despite an established history of serious side effects. In this light, biologics are a welcome alternative to dermatologists and patients alike.

The National Psoriasis Foundation reports that psoriasis is a common condition affecting 2.1% of adults. The prevalence of psoriasis approaches 4.5 million people. Approximately 1 million Americans have psoriatic arthritis. The incidence of psoriasis is between 150,000 to 260,000 new cases per year[1].

Psoriasis affects patients without respect to gender, age, ethnicity nor socioeconomic status. It is estimated that 56 million work hours per year are lost because of psoriasis. Not only does psoriasis cause people to miss work but the cost of treating the condition approaches three billion dollars annually[1].

In his third edition text on Immunodermatology, Mark Dahl MD, theorized that above anything else, T cells were the perpetrators of psoriasis along with the immune system[2]. Since that text's publication in 1996 much headway has been achieved in the understanding of the pathogenesis of psoriasis, so much so that it is now accepted that psoriasis is an auto-immune disease[3,4,5]. However, the exact origin or psoriasis and psoriatic arthritis have not been established. In 1983 Bos et al. reported that most of the inflammation in psoriasis was due to partially activated CD4+ and CD8+ T cells[6]. Also these cells express CD45RO on their surface which indicates that they are of effector/memory status[7,8]. Most of these dermal infiltrating cells also express markers such as interleukin-2 and HLA-DR[6]. This immunologic behavior of psoriasis was supported by what dermatologists had observed clinically. The benefits of anti-T cell therapies including cyclosporine, which inhibits interleukin-2 and interferon-gamma by T lymphocytes, can dramatically cause a complete remission of psoriasis that sadly returns when the medication is discontinued[2].

T-cells participate in several ways in the development of psoriasis. A psoriatic plaque is created in what is thought by three different steps by these T-cells. The first step is activation of T cells by an unknown antigenic peptide. Then next step is the migration of T cells into lesional skin. Finally, there is a release of cytokines by activated T cells in the skin which leads to the typical psoriatic phenotype[5].

New medications are needed because of the adverse effects of the older medications. According to a National Psoriasis Foundation survey, only 26% of patients samples were satisfied with their current treatment[9]. And a survey done in the United Kingdom revealed that 44% of respondents preferred systemic therapy to topical treatment[10]. These findings help explain why the biologicals have found such a warm welcome in the marketplace.

The Biologicals: Background Information

The biologicals are engineered proteins that modify immune reactions. Some examples are: antibodies, fusion proteins, and recombinant cytokines. The "biological response modifiers" are made to work in the pathways involved in the process of psoriasis such as T cell activation, interaction of antigen-presenting cells, and the production of cytokines5.

Biologicals are divided into three groups: monoclonal antibodies, fusion proteins, and cytokines. The nomenclature of the biologicals has been set by convention. At first glance the generic names may seem very odd. None of the names seem to end in the same way like most drug classes such as the proton pump inhibitors or ACE inhibitors. The reasoning is behind the nature of the protein. If it is a chimeric monoclonal then the name ends with -zimab. Humanized monoclonals end with -zumab. Human monoclonal antibodies end with -umab. And finally, receptor antibody fusion proteins end with -cept[5].

There are several biologics currently in use; however, this article will discuss the three main drugs most used. These three are Alefacept (Amevive), Etanercept (Enbrel), and Efalizumab (Raptiva). The first of these to be approved was Alefecept. As one can tell from the name, it is a fully human fusion protein consisting of two extra cellular domains of leukocyte function-associated antigen type 3 bound to the Fc portion of human IgG1[11]. Alefecept is designed to block the interaction for the activation of T-cells that is important in the development of psoriasis. It accomplishes this by binding to CD2 and blocking co stimulatory signaling[12]. A secondary effect of the drug is selectively inducing apoptosis of these T cells by local macrophages and natural killer cells[11,12].

Alefacept can be dosed as either an IM injection, which is the most common, or IV push. 80% of U.S. dermatologists prefer the IM route[11]. Injections are 15mg once a week for 12 weeks. While the FDA has approved this medication for a single course it is now becoming common to initiate a second twelve week course after a twelve week intermittent period. One of the good things about Alefecept is its ability to yield clinical remissions with an average of over 7 months post treatment with equally satisfactory results with retreatment[11,12]. However, this comes with a slow onset of action, with optimal results appearing about 18 weeks after the first injection12. These are the reasons why Alefacept is the first biological with FDA approval as a potential first line therapy for moderate to severe psoriasis in patients who are candidates for any systemic therapy or phototherapy.

The safety profile of Alefacept appears to be superb. Unlike its traditional predecessors there seems to be no problems with any of the internal organs. Amevive does lower CD45RO(+) T-cells[11]. This brings up the concern of immunosupression and infections. However, in trials there was no difference between Alefecept and placebo

with regard to infections. Recommended monitoring includes CD4 counts. Alefacept should not be administered with CD4 counts less than 250/ul. If CD4 counts are below this level for 4 consecutive weeks Amevive should be stopped. Although this is a very safe and effective medication it should be used judiciously in patients with systemic cancer or chronic infections[11,12].

The next biologic is not only used in psoriasis but is the only drug approved for the treatment of psoriatic arthritis. Etanercept is a fully human fusion protein of the p75 receptor for tumor necrosis factor alpha and the Fc portion of human IgG[13]. This particular drug binds and inactivates TNF in the tissue and helps to prevent its work in the pathogenesis of psoriasis and psoriatic arthritis. The exciting thing about Etanercept is its apparent disease modifying properties. It seems to prevent the progressive bony degeneration seen in psoriatic arthritis[11].

Etanercept is dosed as a single 25 mg injection given subcutaneously twice per week. However, a more practical dose of 50 mg twice weekly is now being used with 50 mg used once weekly for maintenance. It is FDA approved for treatment of juvenile rheumatoid arthritis but is being used off label in pediatric patients with psoriasis at a dose of 0.8mg/kg biweekly[13]. With over 250 thousand patients be treated with Etanercept safety is well established. As with Alefacept, there appears to be no internal organ toxicity. Also, there is no recommended lab monitoring. However, most dermatologists will obtain a PPD before treatment because of the concern of TNF blockade and re-activation of tuberculosis. Some dermatologists also order baseline and quarterly complete blood counts, metabolic profiles, and antinuclear antibodies when using any of the biologic agents[13]. There are a few very rare effects seen with Etanercept that are not all understood with respect to causality. These are progression of demyelinating disease, worsening of congestive heart failure, susceptibility to infections, and drug associated lupus erythematosis[11]. As of now there are no limitations to length of therapy or total dosage of the medication.

Efalizumab is a humanized monoclonal antibody directed against CD11a which is a subunit of leukocyte function-associated antigen type 1 (LFA-1)[14]. This is the primary ligand for intercellular adhesion molecule-1 (ICAM-1)[11]. The interaction of Efalizumab helps to block T-cell activation and migration into the skin. After being administered efalizumab saturates available CD11a binding sites on T cells[15,16]. However, this effect is reversible with CD11a binding sites returning to pretreatment levels withing 10 days of efalizumab clearing the circulation[17]. Dosing is 1 to 2 mg/kg per week given subcutaneously. As with the other biologicals discussed there appears to be no problems with systemic toxicity[18,19]. Eight patients (0.3%) in controlled trials evaluating efalizumbab developed thrombocytopenia (platelet counts less than 52,000) while on therapy. Causality can not be made because the small number. Therefore, the package insert recommends checking platelets monthly for the first three months, and then quarterly[14,20]. The most commonly reported side effects are flu-like symptoms after the first few doses[14]. As with Etanercept, most dermatologists obtain a PPD before treatment. Psoriasis will usually flare upon discontinuation of efalizumab. However, because of its safety it will hopefully be used as continuous therapy.

Although all three of these medications are unique they all have several things in common with one another. First is price. The monthly cost of alefacept is $3,300, etanercept $720, and efalizumab $1100. Certainly these prices are quite prohibitive to most. However, when one figures in the cost of multiple office visits, the minimum of monthly lab monitoring, liver biopsies and likelihood of serious side effects from the traditional treatments, the cost seems to even out. Pregnancy and safety in lactation are additional issues they relatively have in common. Alefacept is category B in pregnancy and safety in lactation is unknown or controversial. Etanercept is category B in pregnancy and considered unsafe in lactation. Efalizumab is category C in pregnancy due to reduced ability for offspring to generate an antibody response several months after birth in mice. Safety is unknown or controversial in lactation[14]. Finally, it is recommended that vaccination with acellular, live, and live-attenuated agents not be used in patients receiving these medications[14].

Conclusions

In conclusion, this new series of therapies is a welcome addition to the treatment of psoriasis. Not only are they efficacious but their safety is excellent. The future probably will bring more and more of these medications not only to the field of dermatology but to all specialties. A physician in primary care may not feel comfortable treating their patients with systemic methotrexate or cyclosporine but could quite easily use these medications with relative confidence.

References:

1. National Psoriasis Foundation, Psoriasis, Treatment Options and Patient Management, Psoriasis Consensus Meeting, 2002; 1
2. Dahl, MV: Clinical Immunodermatology. 3rd ed. St. Louis, MO: Mosby, 1996: 301-315
3. Bos JD, De Rie MA, The pathogenesis of psoriasis: immunological facts and speculations. Immunology Today 1999: 20: 40-46
4. Kupper TS. Immunologic targets in psoriasis. N Engl J Med 2003: 349: 1987-1990
5. De Rie MA, Goedkoop AY, Bos JD, Overview of psoriasis, Dermatologic Therapy 2004, 17: 341-349
6. Bos JD, Hulsebosch HJ, Krieg SR, Bakker PM, Cormane RH. Immunocompetent cells in psoriasis. In situ immunophenotyping by monoclonal antibodies. Arch Dermatology 1983: 275: 181-189
7. Bos JD, Hagenaars C, Das PK, Krieg SR, Voorn WJ, Kapsenberg ML. Predominance of ÅgmemoryÅh T cells (CD4+, CDw29+) over ÅgnaiveÅh T cells (CD4+, CD45R+) in both normal and diseased human skin. Arch Dermatol 1989: 281: 24-30
8. Morganroth GS, Chan LS, Weinstein GD, Voorhees JJ, Cooper KD. Proliferating cells in psoriatic dermis are comprised primarily of T cells, endothelial cells, and factor XIIIa+ perivascular dendritic cells. J Invest Dermatol 1991: 96: 333-340
9. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The Impact of Psoriasis on Quality of Life. Results a 1998 Natl Psoriasis Foundation Patient Membership Survey. Arch Dermatol 2001: 137: 280-284
10. Richards HL, Fortune DG, OÅfSullivan TM, Main CJ, Griffiths CEM. Patients with psoriasis and their compliance with medication. J Am Acad Dermatol 1999: 41: 581-583
11. Camisa C, Handbook of Psoriasis 2nd ed. Malden MA, Blackwell, 2004: 328-336
12. Hodak E, David M. Alefacept: a review of the literature and practical guidelines for management. Dermatol Ther, Vol 17, 2004, 383-392
13. Gottlieb AB. Etanercept for the treatment of psoriasis and psoriatic arthritis. Dermatol Ther, Vol 17, 2004, 401-408
14. Leonardi CL. Efalizumab in the treatment of psoriasis. Dermatol Ther, Vol 17, 2004, 393-400
15. Bauer RJ, Dedrick RL, White ML, Murray MJ, Garovoy MR. Population pharmacokinetics and pharmacodynamics of the anti-CD11a antibody hu1124 in human subjects with psoriasis. J Pharmacokinet Biopharm 1999: 27 (4): 397-420
16. Gottlieb AB, Krueger JG, Bright R, et al. Effects of administration of a single dose of humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. J Am Acad Dermatol 2000: 42 (3): 428-435
17. Papp K, Bissonnette R, Krueger JG, et al. The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. J Am Acad Dermatol 2001: 45 (5): 665-674
18. Gottlieb AB, Gordon KB, Koo J, et al. Long-term efalizumab treatment maintains clinical benefit in patients with moderate to severe plaque psoriasis: Updated findings from an open-label trial. Poster presented at: Summer Academy 2003 of Am Assoc of Dermtol Acad; July 25-29, 2003; Chicago, IL.
19. Lebwohl M, Papp KA, Tyring S, et al. Continued Treatment with Subcutaneous Efalizumab is Safe: Pooled Results from Two Phase III Trials. Poster presented at the Annual Meeting of the Am Acad of Dermatol, July 31-August 4, 2002. New York, NY.
20. Raptiva (efalizumab) package insert. South San Francisco, CA: Genentech, Inc., October 2003.

Capillary Hemangiomas Which Mimic Kaposi's Sarcoma: A Novel Classification System

Erik Austin, D.O., M.P.H.*, Bill V. Way, D.O., FAOCD**

**2nd Year Resident, Northeast Regional Medical Center, Kirksville College of Osteopathic Medicine, Department of Dermatology – Texas Division, Duncanville, Texas*

***Program Director and Adjunct Professor, Northeast Regional Medical Center, Kirksville College of Osteopathic Medicine, Department of Dermatology – Texas Division, Duncanville, Texas*

ABSTRACT

Due to the proliferation of AIDS and its related cutaneous manifestations, vascular lesions have been studied in detail and more intensively than previously. This paper discusses the most common vascular lesions that need to be considered in the differential diagnosis of Kaposi's sarcoma, with special emphasis on capillary hemangiomas that may mimic Kaposi's sarcoma, both histologically and clinically.

Up to this point, capillary hemangiomas have been mentioned singularly in the differential diagnosis of Kaposi's sarcoma; however, capillary hemangiomas have not been brought together into one classification system in order to showcase their histopathologic similarities and differences and to contrast each entity with Kaposi's sarcoma.

This paper seeks to provide a new conceptual integration of the four capillary hemangiomas, which should prove to be helpful in the differential diagnosis of Kaposi's sarcoma.

Introduction

The primary objective of this paper is to discuss vascular lesions, especially those capillary hemangiomas that may mimic Kaposi's sarcoma. Since the vascular entities that "masquerade" as Kaposi's sarcoma have not yet been integrated into one classification system in the available literature; an ancillary objective is to fill a void in the existing literature. This paper will begin with a review of Kaposi's sarcoma, then follow that with a discussion of those entities which need to be considered in differential diagnosis.

I. Kaposi's Sarcoma

This vascular neoplasm was first described by Kaposi in 1872 under the name of "idiopathic multiple pigmented sarcoma of the skin."[1] The skin is the most common site, but other organ systems may be affected.

A. Clinical Setting

The classic European form of Kaposi's sarcoma (KS) is an uncommon disease that generally affects individuals greater than 50 years of age of Jewish, Italian, Mediterranean, or African ancestry.[2,3] Typically, the process is confined to the lower extremities in these patients, although over time the lesions may increase in number and arise proximally. Kaposi's sarcoma lesions evolve through stages as patches, plaques, and nodules; clinical lesions of varying stages are often present in a single patient. Lesions may gradually coalesce, and nodules may eventually ulcerate. Importantly, the clinical course of the classic form is relatively indolent.[1]

AIDS-associated or epidemic Kaposi's sarcoma occurs in homosexual men, predominantly; who comprise 95% of all cases.[1] In this variety, the lesions of KS appear clinically as red, violaceous, or purple macules, papules, plaques, and nodules. The disease may manifest on any skin surface, or involve the lungs or gastrointestinal tract. In this group, extensive lymph and visceral involvement may occur as well. All but very rare cases have serologic antibody titers to the AIDS virus, type 1. Importantly, AIDS-associated KS is a more aggressive variant of the disease.[1]

B. Histopathologic Features

Histopathologically, lesions associated with Kaposi's sarcoma are usually described according to their stage at presentation. At patch-stage, KS presents as a proliferation of small, irregularly shaped, angular vascular spaces lined by a single layer of flattened or plump endothelial cells.[4] A variable, predominantly lymphocytic perivascular infiltrate is present and contains a variable number of plasma cells. There are subtle vascular changes, the earliest of which is a proliferation of miniature or irregular jagged blood vessels around normal or ectatic dermal blood vessels and about adnexal structures.[4] The newly formed vessels may protrude into a vascular lumen or surround and partially isolate normal dermal structures (this is referred to as the "promonotory sign"). There are other useful diagnostic criteria at this stage that have been amply addressed by various investigators.[1-6]

Plaque-stage lesions of Kaposi's sarcoma show further progression of the neoplastic process, filling the entire dermis and involving the superficial subcutaneous tissue. The neoplastic process is more cellular, and a more dense inflammatory infiltrate is present.[5] Erythrocytes both within and outside of vascular spaces are numerous, and phagocytized erythrocyte break-down products, including hemosiderin and eosinophilic "hyalin globules," are often present. The most characteristic feature of this stage is the presence of a significant spindle cell component. Between spindle cells, it is of note that irregular, cleft, or slit-like spaces are formed, creating new, angulated vascular channels that contain small numbers of erythrocytes. As stated, hemosiderin deposits and hyaline globules within proliferating spindle cells are more prominent than in patch-stage Kaposi's sarcoma. These cytoplasmic inclusions stain positively for PAS; because of their relative specificity, they are particularly helpful in the recognition of Kaposi's sarcoma.[6]

Nodular lesions of Kaposi's sarcoma show a further proliferation of spindle cells into intersecting fascicles and sheets. The spindle cells show a degree of cytologic atypia (mild to moderate). Irregular spaces occur between all bundles and represent attempts at vascular formation. Nuclear pleomorphism, atypia, and atypical mitotic figures are obvious at this stage.[4]

According to Barnhill,[1] variable immunohistochemical results have been obtained but endothelial cells of early Kaposi's sarcoma are usually negative for factor VIII-related antigen and weakly positive for Ulex europaeus lectin 1. The spindle cells of nodular lesions of Kaposi's sarcoma display only patchy reactivity for factor VIII-related antigen and show diminished reactivity for Ulex europaeus lectin 1. In addition, all forms of KS are thought to be induced by human herpes virus-8, therefore, HHV-8 may be demonstrated by immunoperoxidase staining and may be of utility in the diagnosis of Kaposi's sarcoma.

The clinical entities to be distinguished in the differential diagnosis of Kaposi's sarcoma are discussed in the ensuing sections (i.e., Sections II and III).

II. Capillary Hemangiomas which Mimic Kaposi's Sarcoma: A Novel Classification System

With the increase in incidence of the Acquired Immune Deficiency Syndrome (AIDS), there has been enhanced interest in and study of vascular tumors because Kaposi's sarcoma, a cutaneous manifestation of AIDS, has increased in incidence and therefore specific vascular tumors are important to include in the differential diagnosis of Kaposi's sarcoma.

Hunt and Santa Cruz[7] discuss vascular entities in general terms and utilize the following categorization: (1) Benign vascular lesions, for example: ectasias/telangiectasias and capillary hemangiomas, (2) Lesions with borderline or indeterminate status, for example: Kaposi's sarcoma, and (3) Malignant vascular lesions, such as angiosarcoma.

This paper is concerned primarily with benign vascular lesions, especially the capillary hemangiomas, which mimic Kaposi's sarcoma.

While a number of investigators have pointed out singular clinical entities which mimic Kaposi's sarcoma, such as targetoid hemosiderotic hemangioma,[8,9] microvenular hemangioma,[10,11] pyogenic granuloma,[12-16] or acquired tufted angioma,[17,18] this paper has sought to integrate all of these entities conceptually.

A novel categorization schema is proposed below, wherein the four capillary hemangiomas are categorized according to the presence or absence of lobular structures. It is hoped that this conceptual hypothesis presented below will engender additional research into the similarities and differences between these lesions:

A. *Non-lobular* Capillary Hemangiomas
   1. Targetoid Hemosiderotic Hemangioma (aka Hobnail Hemangioma)
   2. Microvenular Hemangioma

B. *Lobular* Capillary Hemangiomas
   1. Pyogenic Granuloma
   2. Progressive Capillary Hemangioma (aka Acquired Tufted Angioma).

A detailed description of each of the capillary hemangiomas follows below, utilizing the newly proposed classification system.

A. Non-Lobular Capillary Hemangiomas which Mimic Kaposi's Sarcoma

1. Targetoid Hemosiderotic Hemangioma (aka Hobnail Hemangioma)

In making the differential diagnosis of Kaposi's sarcoma, one needs to heavily consider the uncommon vascular tumors referred to as capillary hemangiomas, both non-lobular and lobular. Of the non-lobular capillary hemangiomas, Santa Cruz and Aronberg, [8] in 1988, described 8 cases of targetoid hemosiderotic hemangioma as a new and distinct vascular disorder. In 1990, Rapini and Golitz[9] presented a single case of targetoid hemosiderotic hemangioma. Since that time, the literature is replete with examples of this entity, which is also known as "hobnail hemangioma."

Targetoid hemosiderotic hemangioma is one of the histologic simulants of Kaposi's sarcoma and knowledge of its clinicopathologic features is critical in avoiding misdiagnosis. Targetoid hemosiderotic hemangioma typically presents as a solitary annular violaceous to purple papule, 2 to 3 mm in diameter, with a surrounding pale rim and a more peripheral ecchymotic ring which gives it its targetoid appearance.[9] The histology of targetoid hemosiderotic hemangioma varies depending on the age of the patient, or duration of the lesion. The earliest finding is a proliferation of widely dilated and irregular, thin-walled vascular lumina in the superficial dermis. The endothelial cells are flat to epithelioid; there is a "hobnail appearance," with epithelioid cells often protruding into the vascular lumina. Later, lesions show a collapsed lumina and spindle cells appear. The endothelial cells stain positively for CD31, weakly for factor VIII-related antigen, and strongly with Ulex europaeus lectin 1.

2. Microvenular Hemangioma

Another non-lobular capillary hemangioma, the microvenular hemangioma, has been described by Hunt, Santa Cruz, and Barr. [10] Five additional cases were added to the literature by Aloi and colleagues.[11] Microvenular hemangiomas present clinically as relatively small purple to red lesions (approximately 1 cm), typically on the extremities of young adults. Histologically, there is a pattern of irregular, branching vessels with inconspicuous lumina and lack of cellular atypia.

Microvenular hemangioma has a fairly distinctive histologic appearance, although there is some resemblance to early Kaposi's sarcoma.[1] Also, the venular differentiation is similar to that which may sometimes be seen in late stages of tufted angioma and targetoid hemosiderotic hemangioma. Early Kaposi's sarcoma can be excluded by clinical setting, along with the absence of angulated, irregular vascular spaces enveloping preexisting dermal blood vessels; plasma cells; hyaline (eosinophilic) globules; and any spindle cell population.[1]

B. Lobular Capillary Hemangiomas which Mimic Kaposi's Sarcoma

1. Pyogenic Granuloma

Lobular capillary hemangioma (aka pyogenic granuloma) is a common vascular lesion once considered to be secondary to pyogenic infection, or arising as granular tissue in response to trauma. At present, it is best understood as a lobular capillary hemangioma because of its lobular architecture on low-power magnification.[12-16] It typically appears as a solitary, rapidly growing, dark red, exophytic, raised or polypoid, vascular lesion, with frequent superficial ulceration.[1] Many lobular capillary hemangiomas arise without cause and others are in association with trauma, pregnancy, or retinoid therapy; the common sites are fingers, face, and oral cavity. Histopathologically, lobular capillary hemangiomas evolve through three distinct phases. First, there is a compact vascular proliferation of solid, largely unopened vascular structures. Later, these structures evolve into a multilobular arrangement with regular appearing lumina. In the final stage, there is a progressive development of pericytic cells.

Immunohistochemically, vimentin stains all the endothelial cells; and any spindle-cell proliferation will mark for muscle-specific actin collagen type IV and will likely be pericytic.[1] Lobular capillary hemangioma has features that link it with tufted hemangioma.

2. Progressive Capillary Hemangioma (aka Acquired Tufted Angioma)

Wilson-Jones and Orkin[17] described the acquired tufted angioma, also known as progressive capillary hemangioma or angioblastoma. Historically, these entities have been regarded as similar or identical, with the differences viewed as purely semantic. Yet, Padilla et al.[18] have made the case that this lesion should be considered a distinct clinicopathologic entity.

Acquired tufted angioma is certainly related to the pyogenic granuloma (lobular capillary hemangioma) and peripheral satellite nodules resembling pyogenic granulomas have been observed.[1]

Clinically, acquired tufted angioma arises as slowly enlarging erythematous macules and plaques that often have a deep component and typically occur on the neck and upper trunk of children and young adults.

Histopathologically, the hallmark of this hemangioma is the presence of small, cellular, capillary tufts dispersed as "cannonballs" throughout the dermis. The tufts tend to be larger in the middle to lower dermis.

Immunoreactivity for CD31, CD34, factor VIII-related antigen and Ulex europaeus lectin is best seen in endothelial cells of larger, well-formed vascular channels. Ulex europaeus lectin also outlines the capillaries of the vascular tufts, but except for occasional dilated lumina within these tufts, there is little or no staining for factor VIII-related antigen. The progressive nature of acquired tufted angioma may involve consideration of a low-grade

angiosarcoma or Kaposi's sarcoma. The most likely differential diagnosis is with pyogenic granuloma; although the vascular lobules are very similar, the scattered nature of acquired tufted angioma is fairly characteristic.

III. Other Vascular Lesions in the Differential Diagnosis of Kaposi's Sarcoma

A. Benign

1. Acro-angiodermatitis. Also known as statis dermatitis, angiodermatitis or pseudo-Kaposi's sarcoma, acro-angiodermatitis is a reactive vasoproliferative condition.[19-22] The vessels of acro-angiodermatitis are arranged in a lobular pattern; have round, regular contour; are centered in the papillary dermis; and show no tendency to localize around preexisting dermal structures. In contrast, Kaposi's sarcoma shows a haphazard arrangement of slit-like vascular spaces around dermal structures. The inflammatory infiltrate of Kaposi's sarcoma is more pronounced than that of acro-angiodermatitis and contains more plasma cells.

2. Bacillary Angiomatosis. This disorder, which is also known as epithelioid angiomatosis, typically occurs in patients with AIDS, and in this setting, the clinical appearance may be mistaken for Kaposi's sarcoma, especially because of bacillary angiomatosis' highly vascular features.[23-25] The most helpful features in differential diagnosis and for recognizing bacillary angiomatosis are the presence of neutrophils and the interstitial, finely granular aggregates. Silver stains, and, if needed, electron microscopy may be used to detect the bacilli and confirm the diagnosis. Bacillary angiomatosis may show lobular aggregates of blood vessels but lacks the well-organized lobular architecture that characterizes the pyogenic granulomas.

3. Benign Lymphangioendothelioma. This is a rare entity that can offer diagnostic difficulty in distinguishing it from low-grade angiosarcoma and the lymphangioma-like form of Kaposi's sarcoma.[26,27] It mimics patch-stage Kaposi's sarcoma. The caveat is that the clinical setting is important and that a diagnosis of benign lymphangioendothelioma should not be established on a small biopsy in the absence of clinical history.[1]

4. Spindle Cell Hemangioma. Still, there is yet another category of benign vascular lesion which mimics Kaposi's sarcoma, which is known as spindle cell hemangioma. First discovered in 1986, Weiss and Enzinger[28] described this unique vascular lesion as a low-grade gliosarcoma having features of both cavernous hemangioma and Kaposi's sarcoma. Additional cases of spindle cell hemangioma were reported by Scott and Rosai[29] in 1988 and their findings showed that there was insufficient evidence to view spindle cell hemangioma as a low-grade angiosarcoma; rather, it appears that spindle cell hemangioma is a non-neoplastic, reactive vascular proliferation, associated with malformed blood vessels and repeated cycles of recanalization after thrombosis.[30,31] Spindle cell hemangioma is not a capillary hemangioma and falls into a distinct category, yet it too mimics Kaposi's sarcoma.

B. Borderline

1. Kaposiform Hemangioendothelioma. Also known as hemangioma with Kaposi's sarcoma-like features, this lesion is an exceedingly rare vascular tumor occurring almost exclusively in childhood and involving the soft tissue and skin.[32] The differential diagnosis includes Kaposi's sarcoma, capillary hemangioma, spindle cell hemangioma, and acquired tufted angioma.

C. Malignant

1. Angiosarcoma. Also known as malignant hemangioma or lymphangiosarcoma, this lesion is a rare, malignant endothelial tumor that arises in skin, soft tissues, breast, bones, liver, and other viscera.[33-39] Kaposi's sarcoma displays dissection of dermal collagen by newly formed vascular channels similar to that of angiomatous-appearing and lymphangiomatous-appearing areas of angiosarcoma.[1] Angiosarcoma (AS) has a predominant spindle cell pattern and may mimic plaques and nodules of Kaposi's sarcoma. Features of distinction include the identification of more angiomatous areas in angiosarcoma and a degree of cytologic atypia exceeding that observed in even florid nodules of Kaposi's sarcoma.[1] Along with various important characteristics, the clinical context is also helpful in differential diagnosis, since AS is often confined to the head and neck of elderly individuals or unilaterally to a lymphedematous upper extremity, while KS often does not involve such anatomic sites in older individuals.[1]

IV. Conclusion

Due to the proliferation of AIDS and its related cutaneous manifestations, vascular lesions have been studied in detail and more intensively than previously. Through such investigation, Kaposi's sarcoma has been increasingly characterized; yet, more time needs to be spent on the differential diagnosis of a wide array of related dermatopathologic entities.

This paper has discussed the most common vascular lesions that need to be considered in the differential diagnosis of Kaposi's sarcoma, with special emphasis on the capillary hemangiomas that may mimic Kaposi's sarcoma, both histologically and clinically. This paper has sought to provide a new conceptual integration of the relevant clinical entities.

While a number of investigators have pointed out singular entities which mimic Kaposi's sarcoma, that is, while there has been discussion of each single type of capillary hemangioma, such as targetoid hemosiderotic hemangioma,[8,9] microvenular hemangioma,[10,11] pyogenic granuloma,[12-16] or acquired tufted angioma,[17,18] this paper has sought to integrate all of these entities into one paper and to integrate them conceptually by looking at the presence or absence of a lobular architecture in the structural histopathology of these clinical entities.

A novel categorization schemata has been introduced; this integration should prove to be helpful in the differential diagnosis of Kaposi's sarcoma.

Further, it is hoped that the conceptual hypothesis presented herein will engender additional research into the similarities and differences of the capillary hemangiomas and related vascular neoplasms.

V. References

1. Barnhill RL, editor. Textbook of Dermatopathology, 1st ed. New York: McGraw-Hill, 1998:539-591.
2. Cox FH, Helwig EB. Kaposi's sarcoma. Cancer 1959;12:289-298.
3. Center for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections: Special report, Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. N Engl J Med 1982;306:248-252.
4. Maloney ME, Torres A, Hoffman TJ, Helm KF, eds. Surgical Dermatopathology. Malden, MA: Blackwell Science, Inc., 1999: 379-381.
5. Cockerell CJ. Histopathological features of Kaposi's sarcoma in HIV infected individuals. Cancer Surg 1991;10:73-89.
6. Murphy, GF. Dermatopathology: A Practical Guide to Common Disorders. Philadelphia: W.B. Saunders Co., 1995;284-288.
7. Hunt SJ, Santa Cruz DJ. Acquired benign and "borderline" vascular lesions. Dermatol Clinic 1992;10:97-112.
8. Santa Cruz DJ, Aronberg J. Targetoid hemosiderotic hemangioma. J Am Acad Dermatol 1988;19:550-558.
9. Rapini RP, Golitz LE. Targetoid hemosiderotic hemangioma. J Cutan Pathol 1990;17:233-235.
10. Hunt SJ, Santa Cruz DJ, Barr RJ. Microvenular hemangioma. J Cutan Pathol 1991;18:235-240.
11. Aloi F, Tomasini C, Pippione M. Microvenular hemangioma. Am J Dermatopathol 1993;15:534-538.
12. Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: The underlying lesion of pyogenic granuloma: A study of 73 cases from the oral and nasal mucous membranes. Am J Surg Pathol 1980;4:471-479.
13. Cooper PH, McAllister HA, Helwig EB. Intravenous pyogenic granuloma: A study of 18 cases. Am J Surg Pathol 179;3:221-228.
14. Cooper PH, Mills SE. Subcutaneous granuloma pyogenicum: Lobular capillary hemangioma. Arch Dermatol 1982;118:30-33.
15. Braunstein Wilson B, Greer KE, Cooper PH. Eruptive disseminated lobular capillary hemangioma (pyogenic granuloma). J Am Acad Dermatol 1989;21:391-394.
16. Strohal R, Gillitzer R, Zonzits E, Stingl G. Localized vs. generalized pyogenic granuloma: A clinicopathologic study. Arch Dermatol 1991;127:856-861.
17. Wilson-Jones E, Orkin M. Tufted angioma (angioblastoma): A benign progressive angioma, not to be confused with Kaposi's sarcoma or low-grade angiosarcoma. J Am Acad Dermatol 1989;20:214-225.
18. Padilla RS, Orkin M, Rosai J. Acquired "tufted" angioma (progressive capillary hemangioma): A distinctive clinicopathologic entity related to lobular capillary hemangioma. Am J Dermatopathol 1987;9:292-300.
19. Strutton GF, Weedon D. Acro-angiodermatitis. A stimulant of Kaposi's sarcoma. Am J Dermatopathol 1987;9:85-

89.
20. Kolde G, Worheide J, Baumgartner R, Brocker EB. Kaposi-like acro-angiodermatitis in an above-knee amputation stump. Br J Dermatol 1989;120:575-580.
21. LeBoit PE. Lobular capillary proliferation. The underlying process in diverse benign cutaneous vascular neoplasms and reactive conditions. Semin Dermatol 1989;8:298-310.
22. Marshall ME, Hatfield ST, Hatfield DR. Arteriovenous malformation simulating Kaposi's sarcoma (pseudo-Kaposi's sarcoma). Arch Dermatol 1985;121:99-100.
23. Cockerell CJ, LeBoit PE. Bacillary angiomatosis: A newly characterized, pseudoneoplastic, infectious, cutaneous vascular disorder. J Am Acad Dermatol 1990;22:501-512.
24. Koehler JE, Quinn FD, Berger TG, et al. Isolation of Rochalimaea species from the cutaneous and osseous lesions of bacillary angiomatosis. N Engl J Med 1992;327:1625-1631.
25. Koehler JE, Glaser CA, Tappero JW. Rochalimaea henselae infection: A new zoonosis with the domestic cat as reservoir. JAMA 1994;271:531-535.
26. Wilson-Jones E, Winkelmann RK, Zachary CB, Reda AM. Benign lymphangioendothelioma: Report of 2 cases. J Am Acad Dermatol 1990;23:229-235.
27. Mehregan DR, Mehregan AH, Mehregan DA. Benign lymphangioendothelioma: Report of 2 cases. J Cutan Pathol 1992;19:502-505.
28. Weiss SW, Enzinger FM. Spindle cell hemangioendothelioma: A low-grade angiosarcoma resembling a cavernous hemangioma and Kaposi's sarcoma. Am J Surg Pathol 1986;10:521-530.
29. Scott GA, Rosai J. Spindle cell hemangioendothelioma: Report of seven additional cases of a recently described vascular neoplasm. Am J Dermatopath 1988;10:281-288.
30. Fletcher CD, Beham A, Schmid C. Spindle cell hemangioendothelioma: A clinicopathological and immunohistochemical study indicative of a non-neoplastic lesion. Histopathology 1991;18:291-30.
31. Pellegrini AE, Drake RD, Qualman SJ. Spindle cell hemangioendothelioma: A neoplasm associated with Maffuci's syndrome. J Cutan Pathol 1995;22:173-176.
32. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood: An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol 1993;17(4):321-328.
33. Holden CA, Spittle MF, Jones EW. Angiosarcoma of the face and scalp, prognosis and treatment. Cancer 1987;59:1046-1057.
34. Offori TW, Platt CC, Stephens M, Hopkinson GB. Angiosarcoma in congenital hereditary lymphoedema (Milroy's disease)—diagnostic beacons and a review of the literature. Clin Exp Dermatol 1993;18:174-177.
35. Mark RJ, Tran LM, Sercarz J, et al. Angiosarcoma of the head and neck: The UCLA experience 1955 through 1990. Arch Otolaryngol Head Neck Surg 1993;119:973-978.
36. Girard C, Johnson WC, Graham JH. Cutaneous angiosarcoma. Cancer 1970;26:868-883.
37. Fletcher CD, Beham A, Bekir S, et al. Epithelioid angiosarcoma of deep soft tissue: A distinctive tumor readily mistaken for an epithelial neoplasm. Am J Surg Pathol 1991;15:915-924.
38. Rosai J, Sumner HW, Kostianovsky M, Perez-Mesa C. Angiosarcoma of the skin: A clinicopathologic and fine structural study. Hum Pathol 1976;7:83-109.
39. McWilliam LJ, Harris M. Granular cell angiosarcoma of the skin: Histology, electron microscopy and immunohistochemistry of a newly recognized tumor. Histopathology 1985;9:1205-1216.

Confluent and Reticulated Papillomatosis- A Case Report and Review of the Literature

Darron D. DiGiulio, D.O.*, Marvin S. Watsky, D.O.**

**3rd year resident St. John's Episcopal Hospital- South Shore Far Rockaway, NY*

***Dermatology Residency Program Director St. John's Episcopal Hospital- South Shore Far Rockaway, NY 11691*

ABSTRACT

Confluent and Reticulated Papillomatosis (CRP) was first described by Gougerot and Carteaud in 1927. This entity presents with hyperpigmented hyperkeratotic papules and plaques with a tendency for central coalescence, and peripheral fading into normal skin forming a reticulated network. Its etiology is unknown with theories including a disorder of keratinization and an abnormal host response to Pityrosporum. Treatment modalities include oral antibiotics and retinoids with variable response. We present a patient whom was initially treated for Pityriasis (tinea) versicolor but through lack of response to systemic antifungal therapy and subsequent biopsy, a diagnosis of CRP was made. This paper will review the clinical presentation, pathophysiology, biopsy findings, and treatment of this entity through a review of the literature.

History

A 20 year old hispanic female presented with a complaint of a mildly pruritic brown rash for approximately 1.5 years. The patient first noticed the lesions on the mid-chest, then noted subsequent spread to the neck, back, abdomen, arms, and legs. She had received multiple treatments from her family physician including oral ketoconazole, topical ciclopirox cream, and 12% lactic acid lotion without improvement. There was no family history of similar lesions. Past medical history was significant only for asthma treated with albuterol. The patient reported no drug allergies, and review of systems was unremarkable.

Physical Exam

Examination revealed 0.5-1.5cm brown scaly papules and plaques mainly of the chest, back, and abdomen with involvement of the neck, arms, and legs to a lesser degree. The lesions were confluent in the intermammary region and faded peripherally on the abdomen, lower back, and extremities forming a reticulated pattern (Figures 1, 2, 3). Intertriginous areas were spared, and no oral lesions were noted.

Evaluation and Course

After Wood's lamp and KOH examinations did not reveal fluorescence nor evidence of hyphae or spores respectively, a 4mm punch biopsy was obtained. Differential diagnosis included CRP, pityriasis versicolor, Darier's disease, and digitate dermatosis. Findings revealed hyperkeratosis, papillomatosis, and acanthosis with a sparse superficial perivascular lymphocytic infiltrate. Periodic acid-Schiff stain did not reveal evidence of fungus.

With a diagnosis of CRP the patient was placed on minocycline 100mg bid. Subsequently, calcipotriene cream 0.005% then tretinoin cream 0.025% were added with mild improvement after 4 months. Consideration was given to isotretinoin but the patient did not wish to pursue this treatment modality.

Discussion

Symptoms

First described by Gougerot and Carteaud in 1927[1] as one of the primary papillomatoses, CRP is usually an asymptomatic dermatosis of unknown etiology.[2] The majority of cases are sporadic though familial cases have been reported in the literature.[3,4]

Onset typically occurs in adolescence or early adulthood[5] with a mean age of 21 years old.[6] It has a gender and racial predilection occurring 2.5x and 2x more often in women and blacks respectively.[7]

The primary lesion as described by Gougerot and Carteaud is a 1-2mm red papule that turns gray then brown attaining a size of 4-5mm.[8] Initial sites of involvement include the intermammary,11 interscapular,[12] and epigastric regions.[8] The papules then increase in number and merge, becoming confluent centrally[2,8] forming a rhomboid pattern with the long axis running cephalocaudally.[13] There is also peripheral centrifugal spread9 with fading of the lesions into normal skin forming a reticulate pattern, hence the name CRP.[10] Areas of this peripheral extension may include the face and neck,[10] axilla,[7] abdomen, and extremities though to a lesser extent.[15] Accentuation of skin folds of the neck and axilla has been observed, 6 and no oral lesions are noted.[2] Lesions are usually asymptomatic with pruritis occurring occasionally.[10] In short, CRP classically presents with multiple brown, scaling papules and plaques in mainly a seborrheic distribution[16] with confluence centrally and reticulation peripherally.

Pathophysiology

The etiology of CRP is unknown though several theories exist on its pathogenesis. As CRP is sensitive to retinoids and calcipotriene, a disorder of keratinization has been suggested.[12,13,17,18,19,20,21] This was first proposed by Meischer when he observed response to vitamin A.[22] Further support comes from electron microscope studies which show an increase in transitional cells between the stratum corneum and granulosum.[15,4] This finding suggests premature keratinization and has been associated with ichthyotic disorders4 which are also responsive to retinoids. There is also alteration of cornified cell structures and an increased number of Odland bodies, also supportive of a defect in keratinization.[23] Marked expression of keratin 16 (K16), seen in squamous epithelia undergoing hyperproliferation or abnormal differentiation,[4] has also been observed in lesions of CRP.

Pityrosporum yeasts, classified in the genus Malassezia using newer taxonomy, are part of the normal skin microflora and may cause superficial skin infection under certain conditions.[24] Whether CRP is due to an abnormal host response to P. orbiculare is unclear and controversial.[10,15] Reasons supportive of this theory include the occasional presence of the yeast in lesions of CRP,[2,25,13,1,11,26] and its close clinic resemblance to pityriasis versicolor[4,27] which is caused by the fungus. Further support comes from the responsiveness of CRP to topical and systemic antifungal agents,[15,13,28] though this can be variable.[11]

Factors that argue against the role of Malassezia (older term Pityrosporum) as the cause of CRP include the fact that the organism is a common nonpathogenic part of the normal skin microflora in the yeast form.[29] It's presence in lesions of CRP does not prove a causal relationship[30] as the majority of lesions are free of the organism.[2] Further, antifungal agents are not effective in the majority of cases[30] and the efficacy of one such agent, selenium sulfide, may be more from its keratolytic than antifungal properties.[11]

Other proposed causes and associations include an endocrine imbalance,[31] bacterial infection,[22] induction by UV light,[35] and a

clinical variant of amyloid cutis as amyloid has been noted in skin lesions.[33,34] Perhaps stemming from its clinical and histological resemblance to acanthosis nigricans, the endocrine abnormalities that have been linked to CRP include insulin resistance, thyroid dysfunction, menstrual irregularities, and obesity.[2] However, no single hormone abnormality is detected consistently, and the evaluation is usually negative with the majority of patients free of disease.[11,36]

As antibiotics have also been used successfully in its treatment, it has been postulated that CRP may be triggered by bacterial infection.[32] Staphylococcus may be isolated from lesions of keratinizing disorders,[32] and staphylotoxin may affect keratinization via induction of inflammatory cytokines such as TNFa.[37] In those with a genetic predisposition, CRP may be triggered by an abnormal response to staph toxins or Malassezia colonization.

Histopathology

The main histologic findings include hyperkeratosis, papillomatosis,[2] thinning of the granular layer,[10] and acanthosis (Figures 4 and 5). Acanthosis tends to be mild and focal, limited to the "valleys" between elongated papillae.[29] Papillomatosis is low set or may be absent.[25] Other findings that may be present include a sparse superficial perivascular lymphocytic infiltrate,[2] basal layer hyperpigmentation[5] and focal atrophy of the malphigian layer.[14,5] Histologic differential diagnosis includes some epidermal nevi along with acanthosis nigricans, though the latter lacks mild dilation of superficial dermal blood vessels and beading of elastic fibers that may be seen in lesions of CRP.[14]

Diagnosis

The criteria for diagnosis originally described by Gougerot and Carteaud is based on lesion morphology, configuration, site of initial manifestation, distribution, and presence of concomitant manifestations.[1,8] This is demonstrated by the finding of red-brown scaly hyperkeratotic papules and plaques initially in the midline of the chest and/or upper back that coalesce centrally and fade peripherally. Absence of fungus by means of Wood's lamp, KOH exam,[5,11] and PAS stain also coincide with the diagnosis. The biopsy findings of hyperkeratosis, papillomatosis, and acanthosis are supportive not diagnostic as similar findings can be seen in acanthosis nigricans and epidermal nevi.[25]

Differential Diagnosis

The main differentials in the diagnosis of CRP are pityriasis versicolor and acanthosis nigricans. Pityriasis versicolor presents similarly with brown scaly lesions in a similar age of onset and distribution as CRP, though there is no reticulation[2] and typically no acral involvement.[21] Diagnosis is confirmed with fluorescence on Wood's lamp, and KOH exam showing the characteristic hyphae and spores of Malassezia in the so-called spaghetti and meatballs pattern.[24] Biopsy does not reveal papillomatosis.

The site of onset and presence of a reticulated pattern are probably the most important clinical criteria in differentiating acanthosis nigricans from CRP.[6] Acanthosis nigricans is characterized by hyperpigmented velvety plaques that typically begin in the axilla and posterior neck, and involve the intertriginous areas.[21] There is frequent association with endocrinopathy,[2] and mucous membranes may be involved. CRP typically begins in the midline chest or back, spares the intertriginous areas, and does not involve the oral mucosa.

Pseudoacanthosis nigricans presents identically as acanthosis nigricans with velvety hyperpigmented plaques in intertriginous areas. It is a direct result of obesity which leads to papillomatosis via sweating, maceration, and friction. By definition, there are no associated endocrinopathies and the condition improves with weight loss.[2,8,6]

Other differentials in the diagnosis of CRP include nummular and confluent papillomatosis,[8] Darier's disease, pseudoatrophoderma colli,[8,11] epidermodysplasia verruciformis,[8] dyskeratosis congenita,[7] Dowling-Degos disease and noninflammatory epidermal nevi.[5]

Treatment

With regards to treatment, it is difficult to judge efficacy as the disease is relatively rare and its natural history is not completely understood. CRP can be resistant to therapy with no single agent uniformly successful in providing long term relief. Agents reported to be successful include antibiotics, retinoids, vitamin D3 analogs, and antifungal agents.

Response of CRP to antibiotics was first noted in 1965.[38] One of the most commonly reported antibiotics to be effective is minocycline, a lipophilic synthetic derivative of tetracycline. In a study by Montemarano et al using 50mg bid for 6 weeks, all 9 patients responded including 4 who cleared and 3 who were left only with residual pigmentary changes. Recurrence rate was 33% at an average follow-up time of 11 months with all patients responding to re-treatment.[39]

Though unknown, possible mechanisms of action on the pathogenesis of CRP include minocyclines' antibiotic or immunomodulatory actions including anti-inflammatory and anti-proliferative properties.[39,40,41] Minocycline can reduce or inhibit lymphocyte transformation, collagenase, lipase, and free-fatty acids in sebum. In cultured keratinocytes IL1a and TNF are inhibited.[42] It also suppresses leukocyte chemotaxis[43] and blocks protein/DNA synthesis which results in decreased epidermal proliferation.[44] According to Poskitt and Wilkinson, it is these latter properties that may be responsible for its benefit in CRP.[40] Other antibiotics found effective include azithromycin,[32,45] clarithromycin,[32] and erthromycin.[32,46] The observation that different antibiotics result in clearance when little inflammation is seen clinically or histologically raises another possibility that CRP is triggered by a bacterial infection that is responsible for epidermal proliferation.[32]

Retinoids are vitamin A analogs and effect cell differentiation and proliferation via intracellular nuclear receptors that regulate gene expression.[47] They are effective in many dermatologic conditions including disorders of cornification.[48] Both topical and systemic retinoids have been used in CRP and their responsiveness suggests disordered keratinization.[9] Topical tazarotene, an acetylenic retinoid with b/g RAR specificity9 that normalizes epidermal differentiation49 has been successful as has tretinoin cream50 and gel.[13,36] Systemic retinoids are also reported effective though should be considered second line after antibiotics due to a greater side effect profile. Specific agents used have included vitamin A,[6] etretinate,[17] and isotretinoin.[20,21] In one study when combined with lactinol lotion, isotretinoin at a dose of 1mg/kg for 14-18 weeks resulted in complete response with no recurrence of lesions after 18 months of follow-up.[20]

The vitamin D3 analog calcipotriol may be useful in disorders of epidermal hyperproliferation12 as it is a potent regulator of cell differentiation, and inhibitor of cell proliferation in keratinocytes.[51] It reduces markers of abnormal keratinization[52,53] such as suprabasilar expression of K16.[12] Its beneficial effect in CRP was first noted by Kurkenoglu et al[18] and supported by other case reports.[12,19]

Lastly, antifungal agents have been effective in some patients. These include selenium sulfide,[11,13] propylene glycol,[28] and ketoconazole.[54] Selenium sulfide is worth noting in regards to the controversial role of Pityrosporum in CRP. It has both antifungal and keratolytic properties and this latter effect may explain its effectiveness as most patients with CRP do not have Pityrosporum13,[11] as was previously discussed.

Course and Prognosis

The course of CRP is unpredictable and subject to exacerbations and remissions,11 though spontaneous resolution can occasionally occur.[13] Temporary or partial resolution followed by recurrence and progression of disease after cessation of treatment is commonly reported.[27]

Conclusion

CRP should be considered in the differential diagnosis of hyperpigmented scaly lesions involving seborrheic distributions. Commonly used agents effective in treating the dermatosis include antibiotics and retinoids. The therapeutic response to multiple agents suggests that this entity is a reactive pattern to a variety of endogenous and/or exogenous agents that have yet to be clearly defined.

References

1. Gougerot H and Carteaud A. Papillomatose pigmentee innominee, Bull Soc Franc Derm Syph 1927;34:719-21.
2. Pierson D, Bandel C, Ehrig T, and Cockerell. Benign Epidermal Tumors and Proliferations. In: Bolognia JL, Jorizzo JL, Rapni RP, et al, editors. Dermatology. Philadelphia: Elsevier 2003. p.1717-1718.
3. Henning JP, DeWit RFE. Familial Occurrence of CRP. Arch Dermatol. 981;117:809-10.
4. Inaloz HS, Uzeri KY, and Patel GK. Familial CRP. Arch Dermatol. 2002;138:276-7.
5. Berger CM. Clinical Pathological Challenge. CRP of Gougerot and Carteaud. Am J Dermatopathol. 2003 Apr;25(2)179-80.
6. Hamilton D, Tavafoghi V, et al. CRP of Gougerot and Carteaud. JAAD 1980 May;2(5):401-10.
7. El-Tonsy MH, El-Benhawi MO, et al. CARP. JAAD 1987 Apr;16(4):893-4.
8. Palomeque FE, Hairston MA. CRP of Gougerot and Carteaud. Arch Dermatol 1965 Jul;92(1):49-51.
9. Bowman PH, Davis LS. CARP: Response to Tazarotene. JAAD 2003;48:580-1.
10. Barnette DJ, Yeager JK, et al. A progressive asymptomatic hyperpigmented papular eruption. CARP of Gougerot and Carteaud. Archives of Derm 1993 Dec;129(12):1608-12.
11. Nordby CA, Mitchell AJ. CRP Responsive to selenium sulfide. Int J Dermatol 1986 Apr:25(3):194-9.
12. Gulec AT, Seckin D. CRP: Treatment with topical calcipotriol. British Jour Dermatol 1999 Dec;141(6):1150-1.
13. Schwartzberg JB, Schwartzberg HA. Response of CRP of Gougerot and Carteaud to topical tretinoin. Cutis 2000 Oct;66(4):291-3.
14. Weedon D. Skin Pathology. NY: Pearson Professional Limited; 1997. p.575-576.
15. Lee SH, Choi EH, et al. CRP: A clinical, histopathological, and electron microscope study. J Dermatol 1991 Dec;18(12):725-30.
16. Fuller JC, Hay RJ. CRP of Gougerot and Carteaud clearing with minocycline. Clinical and Experimental Dermatology. 1994 Jul;19(4):343-5.
17. Bruyhzeel-Koomen CAFM, DeWit RFE. CRP successfully treated with aromatic etretinate. Arch of Derm 1984;120:1236-7.
18. Kurkcuoglu N, Celebi CR. CRP: Response to topical calcipotriol. Dermatology 1995;191:341-2.
19. Carrozzo AM, Gatti S, Ferranti G, et al. Calciprotriol treatment of CRP (Gougerot-Carteaud syndrome). J Eur Acad Dermatol Venereal 2000 Mar;14(2):131-3.
20. Solomon BA, Laude TA. Two patients with CRP: Response to oral isotretinoin and 10% lactic acid lotion. JAAD 1996;35(4):p.645-6.
21. Lee MP, Stiller MJ, et al. CRP: Response to high dose oral isotretinoin therapy and reassessment of epidermiologic data. JAAD 1994;31:327-31.
22. Miescher G. Erythrokeratodermia papillaris et reticularis. Dermatologica 1954;108:303-14.
23. Jimbow M, Talpash O, Jimbow K. CRP: clinical, light, and electron microscope studies. Int J Dermatol 1992;31:480-3.
24. Gupta AK, Batra R, et al. Skin diseases associated with malassezia species. JAAD 2004;51:785-98.
25. Mutasim DF. CRP without papillomatosis. JAAD 2003;49:1182-4.
26. Yesudian P, Kamalam S, Razack A. CRP (Gougerot-Carteaud). An abnormal host reaction to Malassezia Furfur. Acta Derm Venereal 1973;53(5):381-4.
27. Sau P, Lupton GP. Reticulated truncal pigmentation. Archives of Derm 1988 Aug;124(8):1272-5.
28. Broberg A, Faergemann. A case of CRP (Gougerot-Carteaud) with an unusual location. Acta Derm Venereal 1988;68(2):158-60.
29. Maize J, Metcalf J. Metabolic Diseases of the Skin. In: Elder D, Elenitsas R, Jaworsky C, Johnson B, editors. Lever's Histopathology of the Skin. Philadelphia:Lippincott-Raven; 1997:p395.
30. Chang SN, Kim SC, et al. Minocycline treatment for CRP. Cutis 1996 Jun; 57 (6):454-7.
31. Watkins D, Lockwood J. CRP. Arch Dermatol 1957;76:648.
32. Jang HS, Oh CK, et al. Six cases of CRP alleviated b various antibiotics. JAAD 2001;44: 652-5.
33. Groh V, Schnyder UW. Nosologie der papillomatosis papuleuse confluente et reticulee (Gougerot-Carteaud). Hautarzt 1983;34:81-86.
34. Groh V, Schnyder UW. Papillomatosis papuleuse confluente et reticulee Gougerot-Carteaud: a further form of skin amyloidosis? Dermatologica 1981;162:118-23.
35. Vassileva S, Pramatarov K, et al. Ultraviolet light-induced CRP. JAAD 1989; 21:413-4.
36. Nagy R, Fairfield JC. CRP. Cutis 1982 Jan;29(1):48-50.
37. Katayama I, Yokozeki H, et al. Oral minocycline improved keratosis follicularis squamosa (Dohi) and reticulated disorders: bacterial factors are possibly involved in aberrant keratinization. J Dermatol 1994;21:604-8.
38. Carteaud A. Un cas de papillomatose papuleuse confllluente et reticulee de Gougerot et Carteaud, completement blanchie par antibiotiques. Bull Soc Franc Dermatol Syphiligr. 1965;72:396-7.
39. Montemarano A, Hengge M, et al. CRP: Response to minocycline. JAAD 1996;34:253-6.
40. Poskitt L, Wilkinson JD. Clearance of CRP of Gougerot and Carteaud with minocycline. Brit J Dermatol 1993 Sept;129(3):351-3.
41. Puig L, DeMoragas J. CRP of Gougerot and Carteaud: Minocycline deserves trial before etretinate. Arch of Dermatol 1995;131:109-10.
42. Dreno B, Celerier P, et al. In vivo modulation of epidermal inflammatory cytokines (IL-1a, IL-6 and TNF-a) by minocycline. J Invest Dermatol 1993;101:407.
43. Humbert P, Treffel P, et al. The tetracyclines in dermatology. JAAD 1991;25:691-7.
44. Roberts S, Lachapelle J. CRP (Gougerot and Carteaud) and Pityrosporum orbiculare. Br J Dermatol 1969;81:841-5.
45. Grurer E, Zamolo G, et al. Treatment of CRP with azithromycin. Clin Exp Dermatol1998;23:191.
46. Baalbaki SA, Natarajan S, et al. CRP: treatment with antibiotics. J Dermatol Treat1995;6:13-15.
47. Kuenzli S, Saurat JH. Retinoids. In: Bolognia JL, Jorizzo JL, Rapni RP, et al, editors. Dermatology. Philadelphia. Elsevier;2003. p1991-3.
48. Peck G, DiGiovanna J. The Retinoids. In: Freedberg IM, Eisen AZ, Wolff K, et al, editors. Fitzpatrick's Dermatology in General Medicine. NY:McGraw-Hill;1995. p2810-3.
49. Esgleyes-Ribot T, Chandraratna, et al. Response of psoriasis to a new topical retinoid, AGN 190168. JAAD 1994;30:581-90.
50. Kagi MK, Trueb, et al. CRP associated with atopy. Successful treatment with topical urea and tretinoin. Br J Dermatol 1996 Feb;134(2):381-2.
51. Kragballe K. Non-calciotropic vitamin D3 analog stimulates differentiation and inhibits proliferation of cultured human keratinocytes. J Invest Dermatol 1988;91:383.
52. Gerritsen MJP, Rulo HFC, et al. Topical treatment of psoriatic plaques with 1,25-dihydroxy vitamin D3; a cell biological study. Br J Dermatol 1993;128:666-73.
53. Gerritsen MJP, Boezman JBM, et al. The effect of tacalcitol (1,24(OH)2D3) on cutaneous inflammation, epidermal proliferation, and keratinization in psoriasis: a placebo controlled double-blind study. Br J Dermatol 1994;131:57-63.
54. Kellet JK, Macdonald RH. CRP. Archives of Dermatol 1985;121:587-8.

Class I Strength[1]

PRESERVATIVE FREE

- An FDA-approved, super-potent fluocinonide formulation
- Demonstrated Class I Strength[1]
- QD or BID dosing options*
- An elegant cream alternative to ointments, gels, lotions, and foams

Vanos™
(fluocinonide)
cream 0.1%

Available in 60 g and 30 g tubes.

Safety Information

The most commonly reported side effects were headache, burning at the application site, nasopharyngitis and nasal congestion. Because of potential HPA axis suppression, treatment should not exceed two weeks or 60 grams per week. Reversible HPA axis suppression may occur with potential glucocorticosteroid insufficiency after withdrawal of treatment. Twice daily two-week treatment demonstrated HPA axis suppression in two out of 18 adults. VANOS should not be used on the face, groin, or axillae; in patients under 18 years; or for the treatment of rosacea or perioral dermatitis.

Blue man is a symbolic representation—not intended to portray actual results.

Reference

1. VANOS (fluocinonide) prescribing information. Medicis Pharmaceutical Corporation

* Twice daily application has been shown to be more effective in achieving treatment success.

MEDICIS
The Dermatology Company®

VANOS™

(fluocinonide) Cream, 0.1%

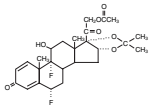
Rx Only

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

DESCRIPTION

VANOS™ (fluocinonide) Cream, 0.1% contains fluocinonide, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Fluocinonide has the chemical name 6 alpha, 9 alpha-difluoro-11 beta, 21-dihydroxy-16 alpha, 17 alpha-isopropylidene-dioxypregna-1, 4-diene-3,20-dione 21-acetate. Its chemical formula is $C_{26}H_{32}F_2O_7$ and it has a molecular weight of 494.58.

It has the following chemical structure:



Fluocinonide is an almost odorless white to creamy white crystalline powder. It is practically insoluble in water and slightly soluble in ethanol.

Each gram of VANOS™ Cream contains 1 mg micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, carbopol 980 NF, diisopropanolamine, and citric acid USP.

CLINICAL PHARMACOLOGY

The exact mechanism of action of topical corticosteroids, such as fluocinonide, in the treatment of psoriasis is not known. However, topical corticosteroids are thought to be effective primarily because of their anti-inflammatory, anti-pruritic, and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachadonic acid. Arachadonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Vasoconstrictor studies performed with VANOS™ Cream, 0.1% in healthy subjects indicate that it is in the super-high range of potency as compared with other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

Application of VANOS™ Cream, 0.1% twice daily for 14 days in 18 adult patients with plaque-type psoriasis (10-50% BSA, mean 19.6% BSA) showed demonstrable HPA axis suppression in 2 patients (with 12% and 25% BSA) where the criterion for HPA axis suppression is a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin ($ACTH_{1-24}$).

Treatment of patients with VANOS™ Cream for more than 2 weeks at a time is not recommended, and only small areas should be treated at any one time due to the increased risk of HPA-axis suppression (See **PRECAUTIONS**).

HPA axis suppression has not been evaluated in psoriasis patients who are less than 18 years of age.

CLINICAL STUDIES

A double masked, vehicle controlled, randomized study of VANOS™ Cream was conducted in patients with plaque-type psoriasis. Patients with 2% to 10% body surface area involvement at baseline applied either VANOS™ Cream or Vehicle Cream to all affected areas either once daily (*qd*) or twice daily (*bid*) for 14 consecutive days.

The primary measure of efficacy was the proportion of patients whose psoriasis lesions cleared or almost cleared at the end of treatment. The results are presented in the table below as patients cleared or almost cleared at Week 2 with once or twice daily application of VANOS™ Cream.

	VANOS™ Cream, *once daily* (n=107)	Vehicle, *once daily* (n=54)	VANOS™ Cream, *twice daily* (n=107)	Vehicle, *twice daily* (n=55)
Patients cleared	0 (0)	0 (0)	6 (6%)	0 (0)
Patients achieving treatment success*	19 (18%)	4 (7%)	33 (31%)	3 (6%)

* Cleared or almost cleared

No efficacy studies have been conducted to compare VANOS™ (fluocinonide) Cream, 0.1% with any other topical corticosteroid product, including fluocinonide cream 0.05%.

INDICATIONS AND USAGE

VANOS™ (fluocinonide) Cream, 0.1%, is a corticosteroid indicated for treatment of plaque-type psoriasis affecting up to 10% body surface area (BSA). Use in patients under 18 years of age is not recommended because safety has not been established (See **PRECAUTIONS–Pediatric Use**.)

Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 60 g/week because the safety of VANOS™ Cream for longer than 2 weeks has not been established and because of the potential for the drug to suppress the-hypothalamic-pituitary-adrenal (HPA) axis. Therapy should be discontinued when control of psoriasis has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS

VANOS™ Cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using cosyntropin ($ACTH_{1-24}$) stimulation testing. Patients should not be treated with VANOS™ Cream for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA-axis suppression.

If HPA-axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Application of VANOS™ Cream, 0.1% twice daily for 14 days in 18 adult patients with plaque-type psoriasis (10-50% BSA, mean 19.6% BSA) showed demonstrable HPA axis suppression in 2 patients (11%).

HPA axis suppression has not been evaluated in psoriasis patients who are less than 18 years old. Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See **PRECAUTIONS–Pediatric Use**.)

If irritation develops, VANOS™ Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of VANOS™ Cream should be discontinued until the infection has been adequately controlled.

VANOS™ Cream should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for the Patient: Patients using VANOS™ Cream should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or unintended effects:

1) VANOS™ Cream is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2) VANOS™ Cream should not be used for any disorder other than that for which it was prescribed.
3) The treated skin area should not be bandaged or otherwise covered or wrapped, so as to be occlusive unless directed by the physician.
4) Patients should report to their physician any signs of local adverse reactions.
5) Other corticosteroid-containing products should not be used with VANOS™ Cream without first talking to the physician.
6) If no improvement is seen in 2 weeks, the patient should be instructed to contact a physician. The safety of the use of VANOS™ Cream for longer than 2 weeks has not been established.

Laboratory Tests The cosyntropin ($ACTH_{1-24}$) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of fluocinonide.

Fluocinonide revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames test and an *in vitro* chromosomal aberration assay in human lymphocytes). However, fluocinonide was positive for clastogenic potential when tested in the *in vivo* mouse micronucleus assay.

Pregnancy Category C: Teratogenic Effects: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies in pregnant women. Therefore, VANOS™ Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA-axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA-axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to cosyntropin ($ACTH_{1-24}$) stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: Clinical studies of VANOS™ Cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious.

ADVERSE REACTIONS

In clinical trials, a total of 443 patients with atopic dermatitis or plaque-type psoriasis were treated once daily or twice daily with VANOS™ Cream for 2 weeks. The most commonly observed adverse events in these clinical trials were as follows:

Adverse Event	VANOS™ Cream, *once daily* (n=216)	VANOS™ Cream, *twice daily* (n=227)	Vehicle Cream, *once* or *twice daily* (n=211)
Headache	8/216 (3.7%)	9/227 (4.0%)	6/211 (2.8%)
Application Site Burning	5/216 (2.3%)	4/227 (1.8%)	14/211 (6.6%)
Nasopharyngitis	2/216 (0.9%)	3/227 (1.3%)	3/211 (1.4%)
Nasal Congestion	3/216 (1.4%)	1/227 (0.4%)	0
Unspecified Application Site Reaction	1/216 (0.4%)	1/227 (0.4%)	3/211 (1.4%)

No other adverse events were reported by more than 1 subject receiving active treatment. The incidence of all adverse events was similar between the active treatment groups and the vehicle control groups.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Systemic absorption of topical corticosteroids has produced hypothalamic-pituitary-adrenal (HPA) axis suppression manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

OVERDOSAGE

Topically applied VANOS™ Cream can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Apply a thin layer of VANOS™ Cream once or twice daily to the affected skin areas as directed by a physician. Twice daily application has been shown to be more effective in achieving treatment success after 2 weeks of treatment (See **CLINICAL STUDIES).**

Treatment with VANOS™ Cream should be limited to 2 consecutive weeks, and amounts greater than 60 g/week should not be used.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

HOW SUPPLIED

VANOS™ (fluocinonide) Cream, 0.1% is supplied in aluminum tubes as follows:

30 g (NDC 99207-525-30)

60 g (NDC 99207-525-60)

Store at controlled room temperature: 15° to 30°C (59° to 86°F).

Manufactured for:
MEDICIS, The Dermatology Company®
Scottsdale, AZ 85258

Manufactured by:
Patheon, Inc.
Mississauga, Ontario
Canada L5N 7K9

Made in Canada

U.S. Patent 6,765,001

Prescribing information as of February, 2005.

MEDICIS
The Dermatology Company®

Treatment of Lichen Amyloidosis with Narrow-Band Ultraviolet B Phototherapy

Sami Abbasi, DO*, Kimball Silverton, DO, SL Husain Hamzavi, MD PhD***, and Iltefat Hamzavi, MD******

**Resident Department of Dermatology, Genesys Regional Medical Center, Grand Blanc, MI*

***Silverton Skin Institute, Grand Blanc, MI*

****Hamzavi Dermatology, Port Huron Medical Center*

*****Faculty Department of Dermatology, Wayne State University, Detroit, MI, Faculty Department of Dermatology, Henry Ford Hospital, Detroit, MI*

ABSTRACT

This manuscript describes two cases of lichen amyloidosis, a persistent, pruritic disorder typically affecting the anterior legs. Phototherapy utilizing narrow-band ultraviolet B has been used to treat many diseases of the skin, but reports of its use to treat lichen amyloidosis are lacking and no report has shown histologic clearance of disease. We describe two cases of lichen amyloidosis successfully treated with narrow-band ultraviolet B phototherapy and provide evidence of histologic clearance.

CASE 1

A 74-year-old Caucasian male presented with a history of a pruritic rash on his lower extremities over the last 7 months. Examination revealed multiple erythematous bilateral pretibial and thigh papules. Subsequent biopsy demonstrated eosinophilic deposits in the papillary dermis and stained pale blue with acid-orcein-Giemsa stain, confirming the rash to be LA (Fig 1). Attempts to control pruritus with topical fluocinolone acetonide 0.01% failed.

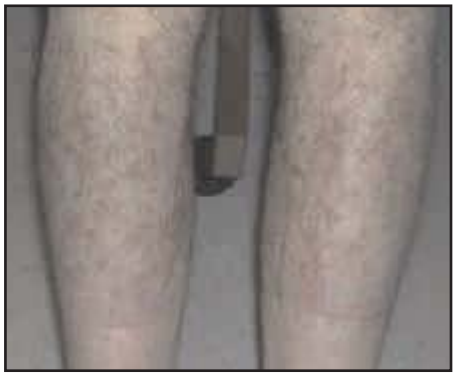
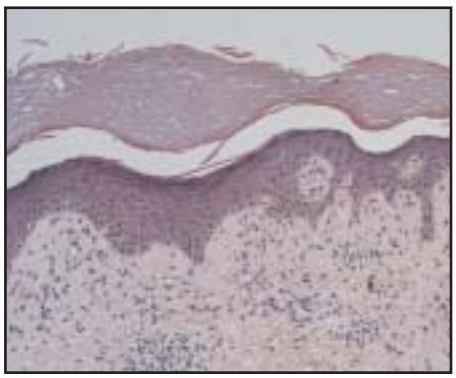


Figure 1. Patient's legs with multiple pretibial erythematous papules and corresponding histology, before treatment.



NBUVB was then instituted (18 treatments, 15.0 J/cm^2 cumulative dose, 4.45mW irradiance), followed by a reduction in itching and subsequent resolution of visible lesions. A repeat biopsy of previously-involved skin demonstrated no characteristics of LA and the acid-orcein-Giemsa stain was negative (Fig 2). The patient continued to be asymptomatic without further treatment for the following year.

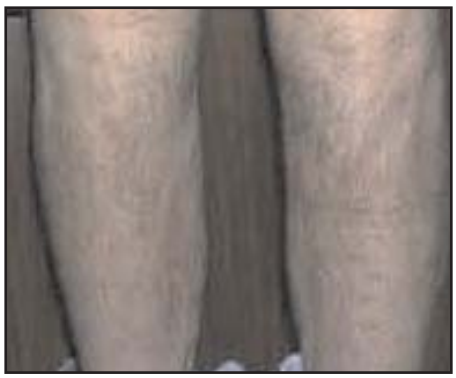
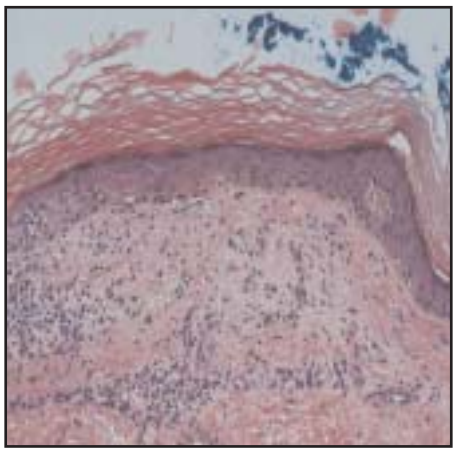


Figure 2. Same patient's legs and repeat biopsy's histology, after NBUVB treatment.



CASE 2

A 41-year-old otherwise healthy Asian female complained of a 2-year-old itchy rash on her legs and back. Examination of her legs revealed multiple erythematous papules in a pretibial distribution bilaterally. An erythematous hyperpigmented patch was found on the interscapular region of her back. Biopsy of a pretibial lesion showed pale eosinophilic deposits within the papillary dermis which stained light blue with acid-orcein-Giemsa, consistent with amyloid. The overlying epidermis showed focal hydropic degeneration of the basal layer, confirming a diagnosis of LA. A biopsy of the patch on her back also revealed eosinophilic deposits which stained pale blue with acid-orcein-Giemsa, consistent with a diagnosis of macular amyloidosis.

Treatment with NBUVB phototherapy (20 treatments, 28.5 J/cm^2 cumulative dose, 4.45mW irradiance) improved first her pruritus and then her lesions. Approximately one month later, however, the pruritus returned. Attempts to manage her itching with trials of triamcinolone acetonide cream 0.1%, doxepin hydrochloride cream 5%, tazarotene cream 0.1%, and halobetasol ointment 0.05% all failed. NBUVB phototherapy was again instituted (26 treatments, 24.8 J/cm^2 cumulative dose, 4.45mW irradiance) and again proved to be successful in controlling both her symptoms and preventing her lesions from returning. The patient's condition is being maintained with tazarotene cream 0.1% and NB-UVB as needed.

DISCUSSION

It is difficult to find an effective, lasting treatment for LA. We have presented two cases of resistant LA, which responded well to NBUVB phototherapy. In one patient, there was histologic clearance of the amyloid deposits after treatment, a result that has never been reported previously. This suggests that NBUVB phototherapy is a reasonable therapeutic option for patients with LA. Further trials

of NBUVB phototherapy for this condition are needed to establish its effectiveness and develop reproducible protocols. Given the resistance of this condition to most treatment options and the success NB-UVB had in these patients, phototherapy may also be used to elucidate the pathophysiology of the condition.

References

I Yashar S, Gielczyk R, Scherschun L, et al. Narrow-band ultraviolet B treatment for vitiligo, pruritus, and inflammatory dermatoses. Photodermatol Photoimmunol Photomed. 2003 Aug;19(4):164-8.

II Hudson LD. Macular amyloidosis: treatment with ultraviolet B. Cutis. 1986 Jul;38(1):61-2.

III Jin AG, Por A, Wee LK et al. Comparative study of phototherapy (UVB) vs. photochemotherapy (PUVA) vs. topical steroids in the treatment of primary cutaneous lichen amyloidosis. Photodermatol Photoimmunol Photomed. 2001 Feb;17(1):42-3.

IV Parsi K and Kossard S. Thermosensitive lichen amyloidosis. Int J Dermatol. 2004 Dec;43(12):925-8.

V Hughes A, Chan H, Aronson P, et al. Lichen amyloidosis treated with NB-UVB. Case presented at the 2003 Michigan Dermatological Society meeting at Wayne State University, Detroit, Michigan. Available at http://www.med.wayne.edu/dermatology/MichDerm03/case16.htm.

Epitheloid Angiosarcoma vs Atypical Epitheloid Hemangioma: A Diagnostic Dilemma

Theresa Ng, D.O.*, Schield Wikas, D.O.**
**1st year dermatology resident Tricounty Dermtology, Summa Health System: Cuyahoga Falls General Hospital, Cuyahoga Falls, OH*
***Program Director Tricounty Dermatology, Summa Health System: Cuyahoga Falls General Hospital, Cuyahoga Falls, OH*

ABSTRACT

Epitheloid angiosarcoma is a rare variant of high grade cutaneous angiosarcoma. It is clinically indistinguishable from the conventional cutaneous angiosarcomas. Histologically, epitheloid angiosarcomas can have similar features when compared to other epitheloid tumors and can have variable expression of cellular markers such as cytokeratin. Because of this, it often poses some diagnostic difficulties for both the clinician and dermatopathologist. We report a case of a 39 year old male who presented with nondescript papules on the penile shaft and subsequent biopsy yielded conflicting opinions. One expert favored the diagnosis of an epitheloid angiosarcoma while the other favored the diagnosis of an exuberant or atypical epitheloid hemangioma. We are reporting this case because of its unusual clinical presentation and its diagnostic dilemma it poses. We also reviewed the literature on epitheloid angiosarcoma and summarized the information in a concise table.

Case report:

39 year old male presents with complaint of a 2 month history of 2 asymptomatic nodules on the penis. Patient thought that this may have been due to injury. Patient relates that he was getting out of a "personal protective device" to release him from a parachute when he experienced an intense frictional event with the gear rubbing on his genital and groin region. Patient reports that there were no abrasions or cuts on the genitalia following this event. However, over the next few weeks, patient noticed the development of the penile lesions.

Physical examination reveals two mobile, well-circumscribed, purplish subdermal papules measuring approximately 2-2.5mm in diameter on the dorsal penile shaft, posterior to the corona. These penile lesions were biopsied.

Histopathology shows two intradermal nodular collections of large pleomorphic epitheloid endothelial cells arranged individually and in whorled aggregates. There were erythrocytes, lymphocytes, and scattered eosinophils. (Figure 1-3) Immunohistochemical studies reveal strong positivity for CD31 (Figure 4) and were negative for CD34, CEA, S100, and EMA. The histological features were suggestive of the diagnosis of an epitheloid angiosarcoma.

Because of the rarity of this tumor, extradepartmental consultations were obtained and yielded conflicting results. One of the experts confirms and favors the diagnosis of epitheloid angiosarcoma; whereas the other favors the diagnosis of an exuberant epitheloid hemangioma rather than an epitheloid angiosarcoma. Despite the conflicting opinions, both experts recommended that patient receive a definitive total surgical excision of the involved area.

Patient was subsequently referred to an urologist for definitive total surgical excision of involved area down to corpora. Final pathology revealed a micro focus of angiosarcoma with margins clear. This case was reviewed at a tumor board consisting of urologists and oncologists and the consensus was that radiation therapy be administered to the area. It was also agreed upon that no further extirpative surgery was necessary. A panel of blood work, consisting of complete blood count with differential, blood urea nitrogen, creatinine, electrolytes, glucose, and liver profile, and imaging studies, consisting of chest x-ray and CT scan of the abdomen and pelvis, were also obtained. All were unremarkable. At patient's 12 months follow up status post surgical excision and radiation therapy, patient has not had any recurrence of the tumor.

Discussion

A Epitheloid angiosarcoma is a rare variant of high grade cutaneous angiosarcoma.

Clinically, it is similar to conventional angiosarcomas. It often presents as a red or bluish patch, plaque, or nodule. These lesions tend to ulcerate. It most commonly occurs on the lower extremities and less frequently on the face and scalp. It commonly presents in the middle aged and elderly population, with male:female ratio being 2:1. (1,2,3) Underlying pathophysiology remains unclear. Proposed implicated causes include radiation exposure and foreign body reaction. (4,5)

Histologically, epitheloid angiosarcomas are composed of sheets of rounded epitheloid cells with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Irregular vascular channels lined by atypical endothelial cells may occasionally be seen dissecting through collagen bundles. A few intracytoplasmic vacuoles are seen. This is often an expression of

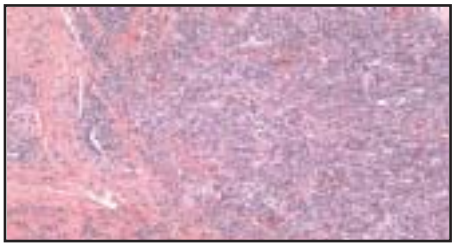


Figure 1
Low Magnification: Intradermal nodular collections of basophilic cells with extravasated RBCs

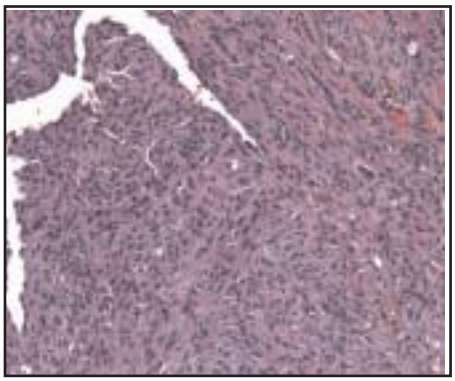


Figure 2
Higher Magnification: Irregular vascular channels are noted

primitive luminal differentiation. Immunohistochemical studies that can help demonstrate vascular differentiation include factor VIII-related antigen, which exhibit positivity in neoplastic cells in angiosarcomas; CD31, which is an antibody against adhesion molecule found in endothelial cells and is highly sensitive and specific marker for endothelial differentiation; CD34, which is the proposed discriminatory antibody to differentiate benign vs. malignant cutaneous vascular proliferation and is positive only in benign lesions; and Ulex europaeus I lectin, which is more sensitive but less

Table 1.

	Age/Sex	**Site**	**Treatments**	**Follow-up Data**
Perez-Atayde et al (16)	69/M	Scalp	Radiation therapy Surgical Excision	-Recurrent tumor and metastases to cerival lymph node and right humerus at 20 mos follow-up -Pt died 6 mos later secondary to meningitis due to direct extension of tumor to the meninges.
Marrogi et al (8)	41/M	Shoulder	Surgical excision Radiation therapy	-metastases noted axillary lymph nodes at 30 mos and cerival lymph nodes at 59 mos. -at 67 mos after treatment, pt is in good condition without further metastases or recurrence
	53/M	Nose	Surgical excision Radiation therapy	-tumor recurrence and metastases to lymph nodes and right posterior rib. -at 53 mos after initial excision, pt has remained healthy without clinical evidence of tumor
	72/F	Flank Groin	Chemotherapy	-10 months after presentation, pt is living with disseminated tumor

Fletcher et al (11)	62/M	Thigh	-	-at 3 weeks, tumor with rapid enlargement and metastases to inguinal lymph nodes and right lung -Pt died 2 mos after initial presentation
	63/M	Buttock	Surgical excision Radiation therapy	-after few weeks, metastases to right maxillary gingival -1 year later, metastases noted in femoral artery and abdominal aorta which was resected and grafted -2 ½ year after initial presentation, patient is alive and disease-free
	62/M	Deltoid Lung	Surgical excision Radiation therapy Right upper lobectomy of the lung and rib resection	-at 1 year follow-up after treatment, pt is alive and disease-free
	36/M	Perianal region	Tumor deemed inoperable at laparotomy Radiation therapy	-at 1 year follow-up, pt is terminally ill with extensive pelvic disease

Continue Table 1	**Age/Sex**	**Site**	**Treatments**	**Follow-up Data**
	68/F	Thigh	Palliative amputation	-at presentation, pt found to have multiple pulmonary and pleural metastases -pt died 4 mos after initial presentation
	32/M	Ankle	Surgical excision	-at 4 mos follow-up, there was local recurrence -pt lost ot follow-up
	62/M	Arm	Data unavailable	Data unavailable
	78/M	Thigh	Palliative radiation therapy	-at 2 mos follow-up, no evidence of mets noted
Prescott et al (12)	64/M	Scalp	Data unavailable	Data unavailable
	83/F	Forehead	Radiation therapy	-pt died 6 months later
	45/F	Breast	Radical surgical excision Radiation therapy	-pt died 5 years later after first recurrence secondary to lung metastases
	74/M	Forehead	Multiple surgical excisions Radiation therapy	-pt died 4 years later after metastases to lungs, adrenals, and kidneys as noted on autopsy
McCluggage et al (6)	61/M	Buttock	Surgical excision	-at 3 mos after initial excision, metastases noted on the right fibula which was removed. -no further follow-up data available
Hallel-Halevy et al (15)	64/F	Shin	Above knee amputation	-rare complication of elephantiasis -follow-up data unavailable

specific than factor VIII-related antigen in identifying angiosarcomas. (1) There have been a few reports of epitheloid angiosar-

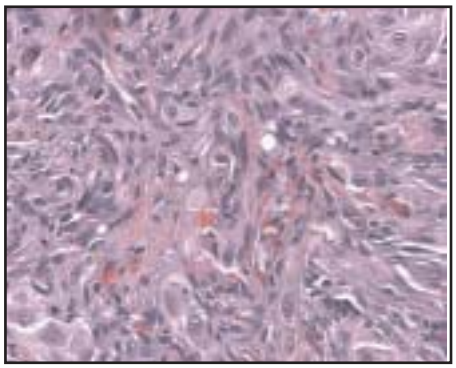


Figure 3
Higher Magnification: Large, pleomorphic endothelial cells arranged individually and in whorled aggregates with lymphocytic infiltrate containing a few scattered eosinophils and extravasated RBCs

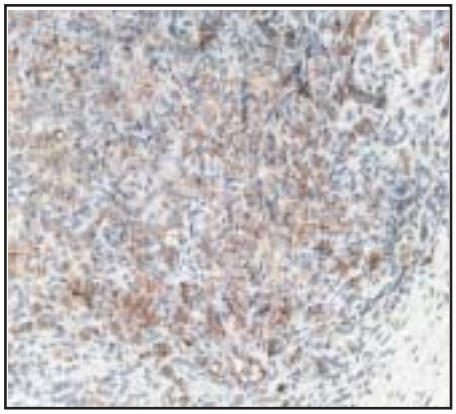


Figure 4
Immunohistochemical studies revealed strong CD31 positivity

comas expressing cytokeratin positivity. (6) Because of its variable expression of cytokeratin, it poses diagnostic difficulties in differentiating angiosarcoma vs. epitheloid melanoma and other carcinomas. (7) Ultrastructural studies often demonstrate abundant cytoplasmic intermediate filaments, numerous pinocytotic vesicles, intracytoplasmic vacuoles and scarce or no Weibel-Palade bodies in the neoplastic endothelial cells. (1,6,8)

Differential diagnoses of epitheloid angiosarcomas include epitheloid hemangioma, epitheloid hemangioendothelioma, epitheloid sarcoma, and epitheloid malignant melanoma. Epitheloid hemangioma is an uncommon benign vascular tumor. There have been typical and atypical or exuberant examples of epitheloid hemangiomas reported. The exuberant epitheloid hemangiomas can often be confused with epitheloid angiosarcomas. Histologically, they may be similar; however, epitheloid angiosarcomas exhibit a more pronounced destructive growth pattern, high mitotic rate with atypical mitoses, and significant nuclear variability. (9)

Epitheloid hemangioendothelioma is a low grade angiosarcoma that was first described by Weiss and Enzinger in 1982. Histologically, this tumor is characterized by a proliferation of cords and nests of plump, epitheloid eosinophilic cells embedded in a fibromyxoid or sclerotic stroma. Cytoplasmic vacuoles and slight pleomorphism and occasional mitotic figures are present. Large vascular channels are rarely seen except at the periphery. These features impart a histopathologic appearance intermediate between epitheloid hemangioma and epitheloid angiosarcoma. The latter differs from epitheloid hemangioendothelioma in that there is increase cellularity characterized by more solid sheets of neoplastic cells with marked atypia and pleomorphism and abundant mitotic figures. Furthermore, necrosis en masse is present where there is necrosis occurring in both individual cells and large areas of the neoplasm. (10)

Moreover, epitheloid angiosarcomas have been misinterpreted as carcinoma and epitheloid melanoma due to the fact that these tumors express cytokeratin. (6, 11, 12) Immunohistochemical studies, including S100, CD31, CD34, factor VIII-related antigen, Ulex europaeus I lectin, and EMA, are invaluable in delineating these differential diagnoses. (7, 13)

Epitheloid angiosarcomas often follow an aggressive behavior with high local recurrence and chance for metastatic disease in about one third of the cases. (14) However, there have been a few reported cases of epitheloid angiosarcomas with a slow, protracted course depicting a lower degree of malignancy. (8) Whether this tumor carries a better prognosis compared to the other variants of angiosarcomas remains unclear. Treatments for epitheloid angiosarcoma include surgical excision with wide margins with or without chemotherapy and radiation therapy.

Review of Literature

o Angiosarcoma was first systematically described by Caro and Stubenrauch in 1945. Its association with postmastectomy lymphedema was later described in 1948 by Stewart & Treves in 1948. Angiosarcomas occurring on the face and scalp of the elderly were described by Wilson-Jones in 1964. (14) Cutaneous epitheloid angiosarcomas have only been recently described. To the best of our knowledge, there have been a total 18 cases of cutaneous epitheloid angiosarcomas reported up to date in the English language. These cases are summarized and presented in Table 1. Of the 18 cases, 13 were men and 5 were females. The age of the patients ranged from 32 to 83. Sites of involvement in the order of decreasing frequency were: lower extremities (26%), upper extremities (16%), face (16%), Buttock (16%), scalp (11%), trunk (11%), and groin (1 case). Treatment regimens that these patients received ranged from varying degrees of surgical excisions, chemotherapy, and radiation therapy. One of the 18 patients succumbed to the disease 2 months after initial presentation before any treatment could be initiated. Treatment data was unavailable in 2 of the 18 cases; and follow-up data was unavailable in 3 of the 18 cases. Local recurrence was noted in 4 of the 15 cases (27%). Metastases were noted in 11 of the 15 cases (73%).

Conclusion:

In summary, cutaneous epitheloid angiosarcoma is a rare histiologic variant of cutaneous angiosarcoma which has a predilection for the lower extremities. However, there are some reports of this occurring on the scalp, face, upper extremities, and buttock regions. We report a case of cutaneous epitheloid angiosarcoma occurring on the dorsal penile shaft. Based on histological and morphological grounds, this tumor often poses diagnostic difficulties for both clinicians and pathologists. With regards to prognosis, there have been conflicting reports. Despite aggressive therapy, local recurrence and metastasis often occur because of its multifocality and its unapparent subclinical spread. (15)

References

11. Requena L, Sanqueza, OP. Cutaneous vascular proliferations. Part III: Malignant neoplasms, other cutaneous neoplasms with significant vascular component, and disorders erroneously considered as vascular neoplasms. J Am Acad Dermatol 1998; 38: 143-175.
2. Odom R, et al. Andrews' Diseases of the Skin. 9th ed. Philadelphia, PA: WB Saunders Co. 2000; pp 760-762.
3. Bolognia J, et al. Dermatology. 1st ed. New York: Elsevier ltd. 2003; pp 1833-1835.
4. Jennings TA, Peterson L, Axiotis CA, Freidlander GE, Cooke RA, Rosai J. Angiosarcoma associated wth foreign body material: A report of three cases. Cancer 1988;62:2436-2444.
5. Rao J, DeKoven JG, Beatty JD, Jones G. Cutaneous angiosarcoma as a delayed complication of radiation therapy for carcinoma of the breast. J Am Acad Dermatol 2003; 49: 532-538.
6. McCluggage WG, Clarke R, Toner PG. Cutaneous epitheloid angiosarcoma exhibiting cytokeratin positivity. Histopathology 1995; 27: 291-294.
7. Elder D, van den Oord (chair). Symposium 8: Pathology and pathophysiology of melanocytic disorder. Histopathology 2002; 41 (Suppl. 2): 120-146.
8. Marrogi AJ, Hunt SJ, Santa Cruz DJ. Cutaneous epitheloid angiosarcoma. Am J Dermatopath 1990; 12(4): 350-356.
9. Fetsch JF, Sesterhenn IA, Miettinen M, Davis CJ. Epitheloid Hemangioma of the Penis: A clinicopathologic and immunohistochemical analysis of 19 cases with special reference to exuberant examples often confused with epitheloid hemangioendothelioma and epitheloid angiosarcoma. Am J Surg Pathol 2004; 28: 523-533.
10. Forschner A, Harms D, Metzler G, Sonnichsen K, Ulmer A, Rassner G, Fierlneck G. Ulcerated epitheloid hemangioendothelioma of the foot in childhood. J Am Acad Dermatol 2003; 49: 113-116.
11. Fletcher CDM, Beham A, Bekir S, Clarke AMT, Marley NJE. Epitheloid angiosarcoma of deep soft tissue: A dis-

tinctive tumor readily mistaken for an epitheloid neoplasm. Am J Surg Pathol 1991; 15(10): 915-924.
12. Prescott RJ, Banerjee SS, Eyden BP, Haboubi NY. Cutaneous epitheloid angiosarcoma: A clinicopathological study of four cases. Histopathology 1994; 25: 421-429.
13. Breiteneder-Geleff S, Soleiman A, Kowalski H, Horvat R, Amann G, Kriehuber E, Diem K, Weninger W, Tschachler E, Alitalo K, Kerjaschki D. Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: Podoplanin as a specific marker for lymphatic endothelium. Am J Surg Pathol 1999; 154:385-394.
14. Perez-Atayde, AR, Achenbach J, Lack EE. High-grade epitheloid angiosarcoma of the scalp. Am J Dermatopath 1986; 8(5): 411-418.
15. Hallel-Halevy D, Yerushalmi J, Grunwald MH, Avinoach I, Halevy, S. Stewart-Treves Syndrome in a patient with elephantiasis. J Am Acad Dermatol 1999; 41: 349-350.

Erythromelalgia: Case Report and Review of Literature

Shannon M. Campbell, MSIV B.S.*, Dianne Kreptowski, D.O., Cynthia H. Halcin, M.D.*****
**4th year medical student at Ohio University College of Osteopathic Medicine.*
***Family physician in North Canton, Ohio.*
****Board certified dermatologist at the Dermatology Institute of Brevard in Rockledge, Florida.*

ABSTRACT

Erythromelalgia is a rare condition characterized by intense pain, erythema, and increased temperature of the skin, primarily affecting the hands and feet. Although the pathophysiology is not completely understood, it is hypothesized that erythromelalgia is the result of a combination of neuropathy and a disruption in vascular dynamics. Treatment of erythromelalgia is empirical with mixed outcomes. Recent clinical studies have suggested promising results with the use of calcium channel blockers and magnesium therapy. A case report and review of the literature is presented below.

Report of Case

A sixty-six year old Caucasian female was referred for dermatological evaluation after a year of an intensely painful, erythematous eruption that extended from the dorsal surfaces of the feet to the mid tibia region bilaterally in a circumferential pattern (Figure 1 and 2). There was thickening as well as a yellow discoloration of the nail plate in all ten toenails. The patient first noticed parasthesias in her left foot one year prior to presentation. Gradually, the left foot erythema and pain progressed in a cephalad fashion. A similar pattern followed in the right extremity a week later. Her past medical history was significant for ankle surgery on her left foot four years prior to presentation. Initially, she was diagnosed with cellulitis by her primary care physician and treated with cephalexin for 14 days. When her symptoms did not resolve, the patient was placed on vancomycin for a course of ten days. The vancomycin was discontinued when the patient's symptoms did not improve. In addition, toenail scrapings performed in the primary care office for fungal culture were negative.

On presentation to the dermatology clinic, gross examination of the lower extremities revealed extensive edema, scaling and erythema (Figure 3). The plantar surface of the feet were spared bilaterally. The skin of the foot and tibia was warm and blanched easily when light pressure was applied. All ten toenails demonstrated thickening as well as a yellow discoloration of the nail plate (Figure 3). Pedal pusles were present and normal bilaterally. KOH preparations of the toenails were repeated and found to be negative for fungal elements.

Laboratory evaluation was positive for antinuclear antibody (ANA) and an ESR level was positive at 95. Lupus panel, excluding ANA, was negative. CBC results, EKG, and chest x-ray were within normal limits. Repeated punch biopsies were normal and did not show any histological findings consistent with cellulitis, systemic lupus erythematosus, discoid lupus, sarcoidosis or scleroderma. Due to the patient's previous traumatic event of ankle surgery and her symptoms of abnormal heat, erythema and burning pain, reflex sympathetic dystrophy (RSD) was considered. However, it was excluded based on the patient's history. The patient's symptoms appeared spontaneously and were unrelenting. With RSD the symptoms can typically reverse and the involved limb can become cold and contracted, a feature not observed in this patient. Moreover, the progression of the patient's disease was bilateral. While RSD can present bilaterally, it typically follows a unilateral distribution. Based on the patient's history, description of symptoms, and laboratory findings, a diagnosis of erythromelalgia was made. Treatment was initiated with aspirin but was unsuccessful in relieving pain or other symptoms. Trials of calcium channel blockers, gabapentin, and the fentanyl patch were also tried but failed to offer the patient any relief. The patient still suffers from erythromelagia without significant pain relief and is currently experimenting with magnesium therapy.

Review of Literature

Erythromelalgia (EM) is a rare disorder consisting of erythema (erythros), burning pain (algia), and increased skin temperature typically affecting the lower extremity (melos). Erythromelalgia has also been referred to as erythermalgia, in order to recognize the increased skin temperature (thermos) so characteristic of the condition[1-3]. Currently, no definitive diagnostic studies exist to confirm the presence of the disease[2-5]. However, general criteria are utilized to make a diagnosis. In a study performed by Davis et al, three inclusion criteria were used: red, hot, and burning extremities[4]. Thompson et al set forth five criteria to establish a diagnosis of EM: 1) burning extremity pain, 2) pain aggravated by warming, 3) pain relieved by cooling, 4) erythema of the affected skin, and 5) increased temperature of the affected skin[2-

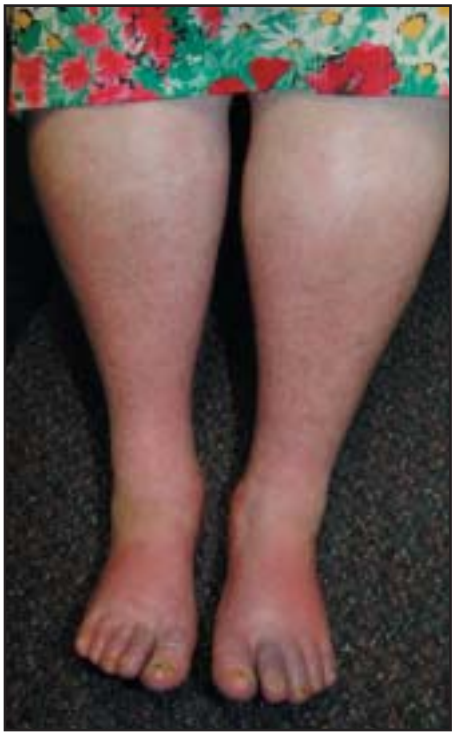


Figure 1
Anterior aspect patient's lower extremities. Note erythema and symmetrical involvement

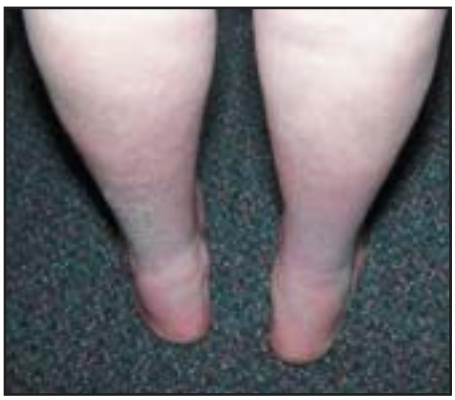


Figure 2
Posterior aspect of patient's lower extremities. Note cirumferential distribution

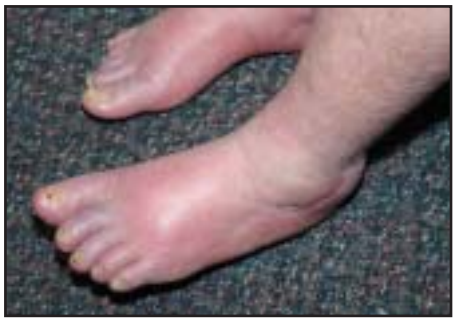


Figure 3
Patient's left foot. Note involvement of toenails, and edema and scaling of skin

[3]. While these inclusion criteria are helpful to establish a diagnosis of EM, the incidence and prevalence of erythromelalgia in the United States is not known5.

Researchers have classified erythromelalgia as primary or secondary[5,6]. Primary erythromelalgia arises spontaneously, affecting patients at any age, while secondary erythromelalgia is associated with a variety of disorders ranging from blood dyscrasias to autoimmune diseases. Further classification of EM by Mork divides erythromelalgia into two broad categories, "syndrome" and "phenomenon."[2] EM is a "syndrome" if there is a strong family history and symptoms are limited to the feet and legs and are diagnosed in childhood and adolescence, while "phenomenon" is reserved for all other cases. In this classification, "phenomenon" breaks down further into primary and secondary EM as described above.[2]

The exact pathophysiology of EM is unknown. The underlying pathophysiology appears to be an ambiguous interplay between a disruption in vascular dynamics and small fiber neuropathy[1,7]. The vascular component of EM's pathophysiology lies in a basic imbalance in blood perfusion[2,5,6]. Precapillary sphincters, responsible for delivering oxygen, become constricted. In response to this, the body increases blood flow to the affected area. Concurrently, arteriovenous anastomoses, responsible for heat and temperature regulation, are left open. The combination of these two events results in an increase in total blood perfusion with deficient nutritive perfusion. Consequently, there is "the coexistence of hypoxia and hyperemia in affected skin"[8] (page 191). Furthermore, Davis et al observed that most patients with EM have a small-fiber neuropathy[7]. Interestingly enough, there is speculation that the neuropathy affects vascular tone resulting in the pathological environment described previously. However, there is no conclusive evidence of how the two findings interact or which is the primary abnormality[7]. There is some speculation about the role of genetics in erythromelalgia. A study published in the American Journal of Human Genetics suggests that there is a primary erythromelalgia susceptibility gene located on chromosome 2q[31-329].

The natural history of erythromelalgia varies from patient to patient and has been compiled based on a study by Davis et al of 168 patients with EM4. The onset can be gradual, over a period of years, or sudden, spreading within a matter of weeks. Some cases remain mild and manifest only during acute exacerbations. Patients with mild erythromelalgia experience "flares" which typically strike late in the day. In between flares, patients are typically asymptomatic. Other sufferers of EM follow a constant course, of a mild or severe quality that may progressively worsen over time. Typically, erythromelalgia occurs in the feet and hands with a bilateral distribution. However, erythromelalgia may be unilateral and occur in areas where arteriovenous anastamoses are prevalent such as the nose and ears [3-5].

Patients with erythromelalgia are incredibly intolerant to heat, a reality which greatly affects their lifestyle. Heat serves as a trigger for flares and aggravates current episodes, increasing their severity and the patient's need for relief. Some patients are more sensitive to heat changes than others. To combat increases in environmental temperature, patients engage in water immersion, a practice that is frowned upon due to its increased risk of causing skin breakdown, irritant contact dermatitis, ulcers, and possible amputation[3,5]. Some victims of erythromelalgia find relief by elevating affected areas, avoiding constricting clothes or shoes, or carrying portable fanning devices wherever they may go. Other triggers for the disease include exercise, certain foods or drinks, such as alcohol, and psychological elements, such as stress or depression[5].

Not only can erythromelalgia be physically straining, it also has psychological and social costs to patients. The marked erythema, swelling, and nail changes are cosmetic concerns for many. The pain accompanying erythromelalgia impacts daily function, including activities of daily living and work performance. In addition, many patients avoid triggers such as heat, exercise or excessive movement, which includes walking to the store or traveling outside the home. Heat in particular has forced many EM patients to avoid warm weather, relocate their residence or avoid warm showers. As a result, many patients are confined to their homes, a risk factor for developing loneliness and depression1. Furthermore, suicide remains an often overlooked concern for both physicians and their patients. Patients, especially those with severe EM, become frustrated with their disease, its disabling nature, and the lack of consistently efficacious treatment options.

The treatment of erythromelalgia continues to be an unwieldy process of trial and error[5]. Lifestyle modification has proved quite helpful to many patients, ranging from simple adjustments like wearing open-toed shoes year round to more drastic measures such as relocating one's residence to cooler environments[1,5]. Initially, research demonstrated relief with capsaicin cream but later studies disputed this[4]. A vast array of medications have been used with mixed success. One of the most common options is aspirin, which has proved therapeutic for patients with secondary EM due to blood dyscrasias[5]. According to Cohen, calcium antagonists, especially diltiazem and amlodipine besylate (Norvasc™) are first line treatment for EM[11]. Similarly, magnesium, which also acts as a calcium antagonist, provides relief for EM patients[1,10,11]. Chelated or liquid magnesium typically yield the most beneficial results. Selective serotonin reuptake inhibitors, such as venlafaxine[12] (Effexor™), tricyclic antidepressants, and anticonvulsants such as gabapentin, have reduced pain associated with the disease. It is common to use gabapentin in combination with an SSRI or tricyclic antidepressant[5,11].

Other treatment options include parenteral approaches such as nitroprusside, which has been helpful in some children and adolescents and is considered to be the drug of choice for those age groups[5,11]. Lidocaine and prostaglandin infusions are also used with varying results. Invasive procedures available to EM patients include sympathetic blocks and epidurals, sympathectomies and the use of a dorsal column stimulator[5]. In addition, there has also been a documented case of a hyperbaric oxygen treatment[11]. For this patient, hyperbaric therapy did not improve symptoms but actually made them worse. Overall, treatment is a complicated process and should be approached in a stepwise fashion.

Erythromelalgia remains to be a rare condition that challenges both patients and clinicians. EM possesses a complicated profile, from its pathophysiology to its natural history and continues to have a profound effect on the physical, social, and psychological lives of patients.

References

1. Davis, M.D.P. Rooke, T. Erythromelalgia. Current Treatment Options in Cardiovascular Medicine 2002; 4(3):207-222.

2. Mork, C. Erythromelalgia: A Mysterious Condition? Archives of Dermatology 2000 Mar;136: 406-409.

3. Thompson G.H. Hahn, G. Rang M. Erythromelalgia. Clinical Orthopedics 1979;114:249-254.

4. Davis, M.D.P. O'Fallon W.M. R. Rogers, R.S. III, Rooke T.W. Natural History of Erythromelalgia: Presentation and Outcome in 168 Patients. Archives of Dermatology 2000;136:330-336.

5. Cohen J.S. Erythromelalgia: New Theories and New Therapies. Journal of the American Academy of

Dermatology 2000; 43(5 Pt 1):841-7.

6. Mork, C. Kvernebo, K. Asker, C.L. and Salerud, E.G. Reduced Skin Capillary Density During Attacks of Erythromelalgia Implies Arteriovenous Shunting as Pathogenic Mechanism. Journal of Investigative Dermatology 2002;119:949-953.

7. Davis, M.D.P. Sandroni, P. Rooke, T.W. Low, P.A. Erythromelalgia: Vasculopathy, Neuropathy, or Both? Archives of Dermatology 2003; 139:1337-1343.

8. Kalgaard O.M., Seem E., Kvernebo K. Erythromelalgia: A Clinical Study of 87 Cases. Journal of Internal Medicine 1997;242:191-197.

9. Drenth, J.P. Finely, W.H. Breedveld, G.J. Testers, L. Michiels, J.J. Guillet G. Taib, A. Kirby R.L. Heutink, P. The Primary Erythermalgia-Susceptiblity Gene is located on Chromosome 2q31-32. American Journal of Human Genetics 2001; May 68(5): 1277-82.

10. Cohen, J.S. High Dose Oral Magnesium Treatment of Chronic, Intractable Erythromelalgia. The Annals of Pharmacotherapy 2002; 36: 255-259.

11. Cohen, J.S. Current Information on Treating Erythromelalgia (handout). The Erythromelalgia Association. June 2002.

12. DiCaudo, D.J. Alleviation of Erythromelalgia with Venlafaxine. Archives of Dermatology 2004;140:621-623.

Gianotti-Crosti Syndrome: A case presentation

Dimitry Palceski, DO*, Schield Wikas, DO, F.A.O.C.D**
**3rd year dermatology resident*
***Program Director Cuyahoga Falls General Hospital Dermatology Residency, Ohio University College of Osteopathic Medicine*

Gianotti-Crosti (GSC) syndrome is a self-limited disorder with an acute onset and characterized by lymphadenopathy, monomorphic erythematous papules symmetrically distributed on the face, extremities and buttocks. We present a case and review of the literature.

A one-year-old Caucasian female, accompanied by her parents, presented with red papules on the arms, legs, and feet that had been evident for at least 5 days (figs. 1 & 2). This eruption was minimally pruritic and was non-progressive. Her parents noted that she had been irritable and somewhat lethargic for a few days prior to presentation, but did not have any fever, nausea, vomiting, or diarrhea. The child had been in good health with no history of recent illnesses. One week prior to presenting to the clinic, she had received a Haemophilus Influenzae type b and Hepatitis B vaccine. No other family members were affected and there was no significant travel history. The child was not taking any medications and did not have any known drug allergies. The past medical history was essentially unremarkable with an uncomplicated birth history. There was a positive family history of asthma.

At the time of examination, the child appeared well. Her development appeared appropriate for her age. There were discrete erythematous flat-topped papules and papulovesicles noted bilaterally on the arms, legs, and dorsal feet. The face, torso, palms, soles, and mucous membranes were spared. There was no lymphadenopathy or hepatosplenomegaly noted.

Blood cell counts demonstrated increased white blood cells (12.78 [3.5-10.0]), platelets (408 [133-364]), and lymphocytes (71 [16-41]). The hepatic function panel showed an elevated alkaline phosphatase of 1208 [50-136]. Serology was negative for HCV antibody (AB), HAV AB (IgM), HB surface antigen, and HB core AB (IgM).

The deratopathology evaluation of a skin biopsy demonstrated a dense superficial and mid dermal lymphohistiocytic infiltrate with reactive lymphoid atypia and focal lymphocytic exocytosis (figs. 3 & 4).

Based on the history, the physical findings and the dermatopathology a diagnosis of Gianotti-Crosti Syndrome (Papular Acrodermatitis of childhood) was established.

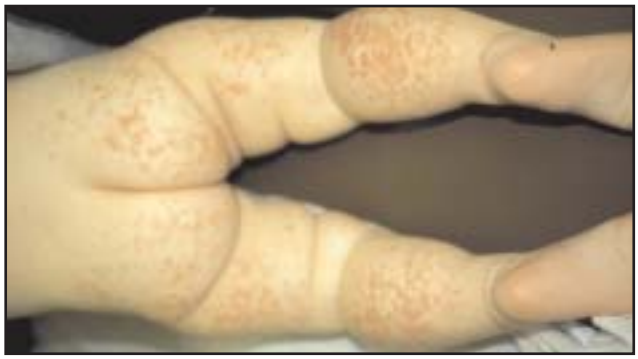


Figure 1

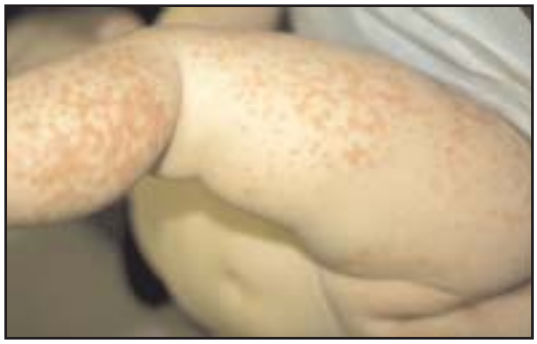


Figure 2

Papular acrodermatitis of childhood (PAC) was first described by Gianotti in 1955, and later by Crosti in 1956.[1,2] PAC is characterized by an acute onset (generally following infection) of generalized lymphadenopathy and monomorphic, nonconfluent, well circumscribed, symmetric, flat-topped, rose to red-brown, papules (2-5mm in diameter) localized to the face, extensor surface of limbs, and buttocks. These papules typically last 3-5 weeks, are nonpruritic, nonrelapsing, and may köbnerize. Mucous membranes are not affected.

Gianotti originally described three characteristics of the syndrome: nonrelapsing erythematopapular dermatitis localized to the face and limbs (lasting about 3 weeks); paracortical hyperplasia of lymph nodes; and acute anicteric hepatitis lasting at least 2 months (with the possibility of progressing to chronic liver disease).[3] When not associated with hepatitis, he named it papulovesicular acrolocated syndrome. [2]

Since that early description, studies have shown that GCS in Western countries is in fact more often associated with Epstein-Barr virus than HBV infection.[4] Other viral infections associated with GCS include cytomegalovirus, coxsackievirus, enteroviruses, human immunodeficiency virus, parainfluenza virus, human parvovirus B[19], varicella virus, human herpesvirus [6], and poxvirus.[5-9] GCS has also been reported following immunization with diphtheria-tetanus-acellular pertussis, oral polio, measles-mumps and rubella, hepatitis B and Japanese B Encephalitis vaccines.[10-16] An interesting case of GCS following milkers' nodules has also been reported by de la Torre.[17]

Since GCS is an enigmatic reaction to many different agents and that an etiologic diagnosis is reached in less than half of patients[18], Ricci et al, investigated the tendency of atopy in patients with this syndrome.[19] In this study of 29 patients, atopic dermatitis was observed in 24.1% of the children with GCS; a statistically significant percentage. Considering that atopic disease is not fully manifested at the age of the subjects studied in this investigation (mean 31 months), and that family history is a strong risk factor for the future development of atopy (73%), [20] it is suggested that the association between atopic individuals and GCS may be even higher.[19] This suggests an interesting correlation, that atopy may have an imparting a conditioning role for the development of GCS in children exposed to different microbiological agents.

There is history of disparity in the earlier descriptions regarding the entity of GCS. Diagnostic criteria have been set forth by Chuh (table 1). [21] All of the positive criteria have been shown to be 100% sensitive for diagnosis. The most specific and predic-

Table 1. Diagnostic Criteria for Gianotti-Crosti Syndrome

Diagnostic Criteria for Gianotti-Crosti Syndrome
Proposed Diagnostic Criteria
Patient exhibits all positive clinical features on at least one occasion or clinical encounter, and Patient does not exhibit any negative clinical feature on any occasion or clinical encounter related to rash, and
No differential diagnosis is considered more likely than diagnosis of GCS based on clinical judgment, and
If lesional biopsy is performed, findings are consistent with GCS
Positive Clinical Features
Monomorphous, flat-topped, pink-brown papules or papulovesicles 1-10 mm in diameter
Any 3 or all 4 sites involved: cheeks, buttocks, extensor surfaces of forearms, extensor surfaces of legs
Symmetry
Duration of 10 days or more
Negative Clinical Features
Extensive truncal lesions
Scaly lesions

tive criteria is a rash that has a duration of at least 10 days (61.3% and 47.8% respectively). Interestingly, symmetry was found to be least specific and predictive (19.4% and 30.6% respectively), Absence of extensive truncal lesions was reported 35.5% specific for GCS. It is important to note that the presence of truncal lesions does not exclude the diagnosis of GCS; truncal lesions may be present, but are usually considerably less pronounced and of less duration than acrally distributed lesions.[22]

The differential diagnosis requires that lichenoid eruptions be contrasted by onset, distribution, color, pruritus, and köbnerization. Eruptions to consider would include lichen planus, lichen nitidus, lichen striatus, pigmented purpura, and lichenoid drug eruption.[23] Other pathological conditions to entertain in the differential diagnosis would include acrodermatitis enteropathica, erythema infectiosum, hand-foot-and-mouth disease, Henoch-Schonlein purpura, Kawasaki disease, scabies, papular urticaria, viral exanthems, erythema multiforme, molluscum contagiosum, and asymmetric periflexural exanthem of childhood. Presence of another concomitant dermatologic condition does not rule out a diagnosis of GCS and conversely, failure to identify a pathogen (usually viral) does not exclude a case of GCS.[6]

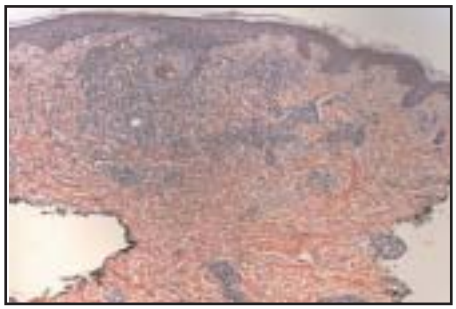


Figure 5

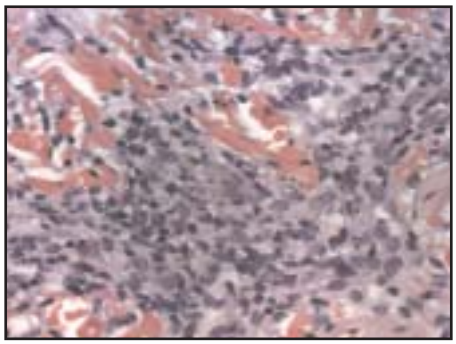


Figure 4

The histology of GCS is non specific. Dermatopathologic features typically include a perivascular and interstitial lymphohistiocytic infiltrate in the upper dermis, papillary dermal edema, a diffuse lichenoid infiltrate, mild basal vacuolar change, focal parakeratosis, psoriasiform epidermal hyperplasia, and occasionally red cell extravasation. Stefanato et. al. speculated that the various histopathologic patterns of GCS mirror the various etiologic agents that cause it.[24]

This syndrome generally resolves in 3-4 weeks with a good prognosis. Treatment should be symptomatically determined. Oral antihistamines are sometimes helpful while corticosteroids are usually ineffective.

References

1. Crosti A, Gianotti F. Dermatose eruptive acrosituee d origine probablement virosique. Acta Derm Venereol 1957;2:146-49.
2. Gianotti F. [Infantile papular acrodermatitis. Acrodermatitis papulosa and the infantile papulovesicular acrolocalized syndrome.] Hautarzt 1976;27:467-72.
3. Gianotti f. Papular acrodermatitis of childhood and other papulo-vesicular acro-located syndromes. Br J Dermatol 1979;100:49-59.
4. Chuh A, Lee A, Zawar V. The Diagnostic Criteria of Gianotti-Crosti Syndrome: Are they Applicable to Children in India? Pediatr Deramtol; 21:542-47.
5. Chuh A, Chan H, Seng S, et al. A Prospective Case Conrol Study of the Association of Gianotti-Crosti Syndrome with Human Herpesviurs 6 and Human Herpesvirus 7 Infections. Pediatr Dermatol 2002;19(6):492-97.
6. Carrascosa J, Just M, Ribera M, et al. Papular Acrodermatitis of Childhood Related to Poxvirus and Parvovirus B19 Infection. Cutis1998;61:265-7.
7. Yoshida M, Tsuda N, Morihata T. et al. Five patients with localized facial eruptions associated with Gianotti-Crosti syndrome caused by primary Epstein-Barr virus infection. J Pediatrics 2004;145(6):843-4.
8. Baldari U, Cattonar P, Nobile C et. al. Infantile acrodermatitis of Gianotti-Crosti and Lyme borreliosis. Acta derm Venereol 1996:76:242-3.
9. Metry D, Katta R. New and emerging pediatric infections. Dermatol Clin 2003;21(2):269-76.
10. Andiran N, Senturk G, Bukulmez G. Combined Vaccinatin by Measles and Hepatitis B Vaccines: A New Cause of Gianotti-Crosti Syndrome. Dermatol 2002;204:75-6.
11. Velangi SS, Tidman MJ. Gianotti-Crosti syndrome after measles-mumps and ruebella vaccination. Br J Dermatol 1998;139:1122-3.
12. Tay Y. Gianotti-crosti Syndrome following immunization. Pediatr Dermatol 2001;18(3):262.
13. Mruphy LA, Buckley C. Gianotti-Crosti syndrome in an infant following immunixation. Pediatr Dermatol 2000;17:225-6.
14. Erkek E. Gianotti-Crosti syndrome preceded by oral polio vaccine and followed by varicella infection. Pediatr Dermatol 2001;18(6):516-18.
15. Haug S. [Gianotti-Crosti syndrome following immunization]. Hautarzt 2002;53(10):683-5.
16. Kang NG, Oh CW. Gianotti-Crosti Syndrome Following Japanese Encephalitis Vaccination. J Korean Med Sci 2003;18:459-61.
17. de la Torre C. Gianotti-Crosti Syndrome Following Milkers Nodules. Cutis 2004;74:316-8.
18. Taieb A, Plantin P, Pasquier PD, Guillet G, Maleville J. Gianotti-Crosti syndrome: a study of 26 cases. Br J Dermatol 1985;115:49-59.
19. Ricci G, Patrizi A, Neri I et. al. Gianotti-Crosti Sydrome and Allergic Background. Acta Derm Venereol 2003;83:202-05.
20. Bolognia, Joseph Jorizzo, Fonald Rapini, eds. Dermatology. New York: Mosby, 2003.
21. Chuh A. Diagnostic Criteria for Gianotti-Crosti Syndrome: A Prospective Case-Control Study for Validity Assessment. Cutis 2001;68(3):207-13.
22. Chuh A, Truncal lesions do not exclude a diagnosis of Gianotti-Crosti syndrome. Aust J Dermatol 2003;44:215-16.
23. Tilly J, Drolet B, Esterly N. Lichenoid eruptions in children. J Am Acad Dermatol 2004;51(4):606-24.
24. Stefanato C, Goldberg L, Andersen W, Bhawan J. Gianotti-Crosti Syndrome Presenting as Lichenoid Dermatitis. Am J Dermatopathol 2000;22(2):162-5.

Unilateral Grover's Disease

Mary K. McGonagle, D.O.*, Stephen M. Purcell, D.O., Donald J. Adler, D.O.*****
**Lehigh Valley Hospital-Muhlenberg, Third Year Dermatology Resident, Allentown, PA*
***Chairman and Program Director of Lehigh Valley Hospital Dermatology Residency Program, Allentown, PA*
****Lehigh Valley Hospital Dermatology Residency Clinical Educator, Doylestown, PA*

ABSTRACT

Grover's disease is a transient acantholytic dermatosis that typically affects men over the age of forty.1 Lesions are found mostly on the trunk in a generalized pattern.2 Unilateral eruptions are rare.3 A case of Grover's disease that occurred in a unilateral fashion is reported. The clinical and histopathological features of Grover's disease in general are described. The etiology, associated medical conditions and treatment options are discussed.

Case Report:

Our patient is a 65 year-old white male who presented with a pruritic eruption on the abdomen and flank confined mostly to the right side. The eruption seemed to worsen during the winter months. Physical examination revealed erythematous, keratotic papules in a linear arrangement on the right abdomen extending onto the right flank. The eruption appeared to follow the lines of Blaschko (Figures 1A, B, C).

Histopathology of two punch biopsy specimens revealed acantholysis (Figure 2A) and focal dyskeratotic cells known as corps ronds and grains (Figures 2B, 2C).

Discussion

Transient acantholytic dermatosis was first described in 1970 by Ralph Grover, M.D.[4] It affects mostly men over the age of forty years.[1] Clinically, one sees numerous, discrete, small erythematous papules or papulovesicles. Lesions are distributed mostly on the trunk and commonly found around the clavicles, anterior chest, lower thoracic region, upper back and lumbar area.[2] The eruption may become disseminated, also affecting the deltoids, lateral neck and thighs.[5] There have been reports of localized cases, affecting only the face, lateral neck or lower extremities. The eruption typically spares the palms and soles.[6] The scalp is usually not involved and mucous membrane lesions are seen rarely in the larynx and nares.[5] When the oral cavity is affected, the lesions resemble aphthae. The presence of pruritus is variable. The condition is self-limited, but may persist for months to years.[2]

Histopathology

The most important histopathologic feature of Grover's disease is acantholysis. This typically follows four patterns:[5,7]

a. Darier-White disease pattern: there are sharply circumscribed areas of focal acantholysis with suprabasilar cleft formation. The presence of dyskeratotic cells in the form of corps ronds and corps grains are also characteristic.

Figure 1A

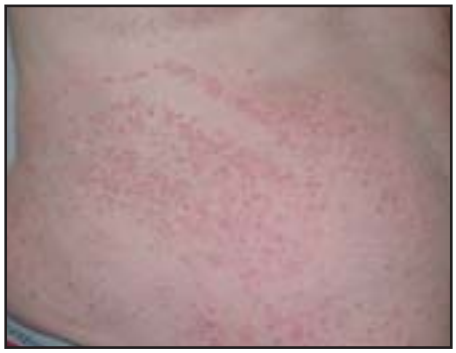


Figure 1B

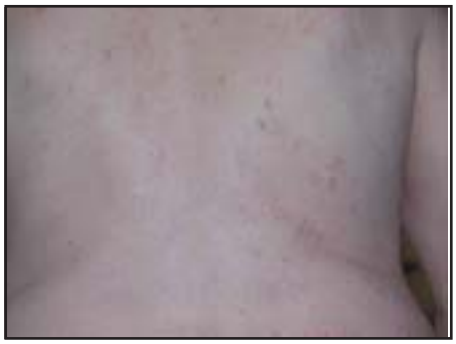


Figure 1C

Figures 1A, B, C: Erythematous papules distributed mostly unilaterally on the right abdomen, extending onto the right flank and right back distributed along the lines of Blaschko

b. Hailey-Hailey disease pattern: the classic dilapidated brick wall appearance of the epidermis is present with numerous acantholytic cells and scattered dyskeratotic cells. The epidermis is less hyperplastic and acantholysis is more localized than in classic Hailey-Hailey disease.

c. Pemphigus vulgaris variant: there are narrow, slit-like suprabasilar clefts with a few acantholytic cells. Typically dyskeratosis is not seen.

d. Spongiotic variant: tense well-circumscribed intraepidermal spongiotic vesicles with a few acantholytic cells are present. The presence of spongiosis and acantholysis disguishes this from spongiotic dermatitis.

A variable number of eosinophils may be present. The intensity of the eosinophilic infiltrate may correlate with the intensity of the pruritus.[2] Eosinophils may indicate a hypersensitivity reaction of some sort.[6] Generally, immunofluorescence testing has been negative.[3] When positive results were obtained, the findings were inconsistent.[2,8]

Etiology

The etiology of Grover's disease is largely unknown; however, several causes have been speculated. Grover's disease may be a reaction to excessive heat, as it frequently occurs on the backs of bedridden, febrile patients.[2,10,11] The eruption has also been reported in patients who are frequent users of steam baths, hot tubs or heating pads. Initial outbreaks coincident with recent extensive exposure to sunlight have also been seen.[2,6] There have been several reports of transient acantholytic dermatosis developing in cancer patients after radiation therapy.[2,11]

Only two medications have been associated with the development of Grover's disease. Sulfadoxine-pyrimethamine is an antimalarial thought to have caused Grover's disease by means of reducing the patient's erythema threshold for UVB radiation.[2,12] Recombinant IL-4 is thought to induce Grover's disease by activating the plasminogen/plasmin system. Plasminogen has been detected in the basal buds and acantholytic cells in Grover's disease.

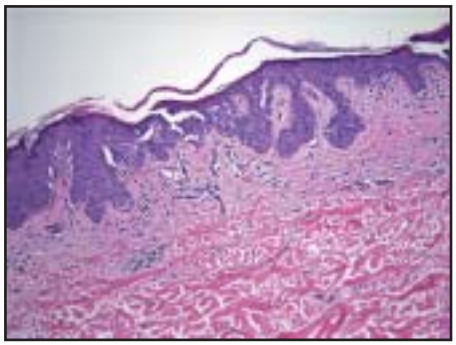


Figure 2A
[Right abdomen, specimen 1] There is suprabasilar clefting as well as early acantholysis.
Hematoxylin and Eosin stain, 10X

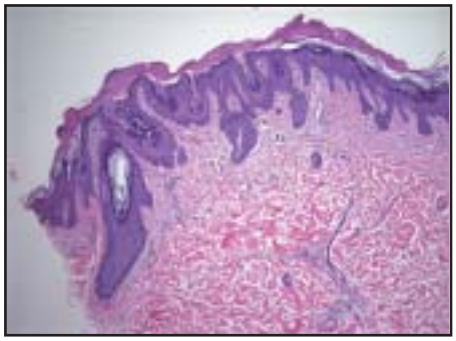


Figure2B
[Right abdomen, specimen 2] There is a parakeratotic stratum corneum, hypergranulosis and focal dyskeratosis in the granular layer as well as irregular acanthosis of the epidermis. A scant lymphocytic infiltrate is present in the upper dermis.
Hematoxylin and Eosin stain, 10X

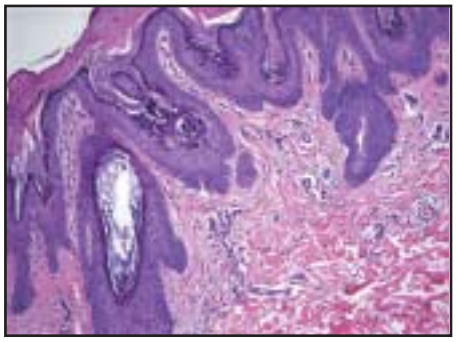


Figure 2C
On higher power, one can appreciate the focal collection of dyskeratotic cells in the stratum corneum. These dyskeratotic cells are more commonly known as corps ronds and corps grains.
Hematoxylin and Eosin stain, 40X

Plasminogen is known to break down desmosomes. [13]

Infection has been speculated to cause Grover's disease; however, there is no evidence to date to support a bacterial or viral cause.[2] Grover's disease may have been induced by the organism responsible for tinea versicolor, Malassezia furfur.[14] It has been speculated that perhaps the demodex mite may produce an enzyme-like substance that induces acantholytic changes in the epidermis.[15]

Nonspecific irritation or inflammation has been suggested to lead to the development of Grover's disease.[2,6] One large retrospective study did show a statistically significant association between transient acantholytic dermatosis and asteatotic eczema, atopic dermatitis and allergic contact dermatitis. Other dermatological conditions found loosely in association with Grover's disease include bullous pemphigoid, lichen planus and seborrheic dermatitis.[2,16]

Grover's disease has been associated with internal malignancies, particularly those of the genitourinary tract as well as some hematological malignancies such as acute myelogenous leukemia.[10,11] Many other malignancies have also been found in patients with Grover's disease. Some believe this to be a coincidence as Grover's disease typically affects the same age group when most malignancies occur. Still others believe there may be an association.

Other medical conditions found in association with Grover's disease include thymoma, benign monoclonal gammopathy, chronic gastritis, glomerulonephritis, rheumatoid arthritis, pregnancy, HIV and poliomyelitis viral infection. The significance of these associations has yet to be determined.[2]

Treatment

Treatment of Grover's disease is variably successful. Treatment is primarily aimed at reducing aggravating factors. Patients are advised to avoid strenuous exercise and excessive exposure to the sun in order to decrease heat-induced sweating.[1,9] Patients are also well advised to avoid drying soaps and detergents. Some effective topical remedies include oatmeal baths[16], mentholated and lactic acid lotions, urea-based topical products, high potency corticosteroids, topical retinoids, topical vitamin D analogues and zinc oxide ointment.[1,2]

Systemic therapies have included Vitamin A, isotretinoin, etretinate, systemic corticosteroids, methotrexate and antihistamines.[1,2,17] Ironically, PUVA has been shown to be effective in treating Grover's disease; however, one should expect a brief exacerbation of their condition.[2,18] The mechanism for PUVA's beneficial effects on Grover's disease is largely unknown.[18] Lastly, two or three treatments of grenz irradiation were shown to be effective in chronic cases of Grover's disease recalcitrant to other treatment modalities.[2]

Conclusion

Recognizing the various clinical presentations of Grover's disease and understanding the histopathology is essential in making the proper diagnosis in a timely fashion. Grover's disease was first described over thirty years ago, yet its etiology remains unknown. Although typical Grover's disease is well characterized, unusual presentations of Grover's disease may be overlooked. The cause of Grover's disease and the significance of its association with other diseases remain speculative. Therapy is generally empiric and results are variable. Further elucidation of the cause of this perplexing condition may lead to more effective targeted therapy.

References:

1. Heenan PJ, Quirk CJ. Transient acantholytic dematosis (Grover's disease). In: Freedberg IM, Eisen AZ, Wolff K, et al, editors. Fitzpatrick's Dermatology in General Medicine. New York: McGraw-Hill, 2003; 529-31.
2. Parsons JM. Transient acantholytic dermatosis (Grover's Disease): A global perspective. Journal of the American Academy of Dermatology. 1996; 35(5 Pt 1): 653-66.
3. Fantini F, Kovacs E, Scarabello A. Unilateral transient acantholytic dermatosis (Grover's disease) along Blaschko lines. Journal of the American Academy of Dermatology. 2002; 47(2):319-20.
4. Grover RW. Transient acantholytic dermatosis. Archives of Dermatology. 1970; 101(4):426-34.
5. Chalet M, Grover R, Ackerman AB. Transient acantholytic dermatosis: a reevaluation. Archives of Dermatology. 1977; 113(4):431-5.
6. Davis MD, Dinneen AM, Landa N, Gibson LE. Grover's disease: clinicopathologic review of 72 cases. Mayo Clinic Proceedings. 1999; 74(3):229-34.
7. Cohen LM, Skopicki DK, Harrist TJ, Clark WH. Noninfectious vesiculobullous and vesiculopustular diseases. In: Elder D, Elenitsas R, Jaworsky C, Johnson B, editors. Lever's Histopathology of the Skin. Philadelphia: Lippincott Williams & Wilkins, 1997; 244.
8. Bystryn JC. Immunofluorescence studies in transient acantholytic dermatosis (Grover's disease). American Journal of Dermatopathology. 1979;1(4):325-7.
9. Hu CH, Michel B, Farber EM. Transient acantholytic dermatosis (Grover's disease). A skin disorder related to heat and sweating. Archives of Dermatology. 1985;121(11):1439-41.
10. Manteaux AM. Rapini RP. Transient acantholytic dermatosis in patients with cancer. Cutis. 1990; 46(6):488-90.
11. Guana AL. Cohen PR. Transient acantholytic dermatosis in oncology patients. Journal of Clinical Oncology. 1994; 12(8):1703-9.
12. Ott A. Persistent acantholytic dermatosis in a patient with increased sensitivity to light. Z Hautkr. 1987; 62:369-78.
13. Mahler SJ, De Villez RL, Pulitzer DR. Transient acantholytic dermatosis induced by recombinant interleukin 4. Journal of the American Academy of Dermatology. 1993;29:206-9.
14. Segal R, Alteras I, Sandbank M. Rapid response of transient acantholytic dermatosis to selenium sulfide treatment for pityriasis versicolor. Dermatologica 1987;175:205-7.
15. Lindmaier A, Jurecka W, Lindemayr H. Demodicidosis mimicking granulomatous rosacea and transient acantholytic dermatosis (Grover's disease). Dermatologica 1987;175:200-4.
16. Grover RW. Rosenbaum R. The association of transient acantholytic dermatosis with other skin diseases. Journal of the American Academy of Dermatology. 1984; 11(2 Pt 1):253-6.
17. Helfman RJ. Grover's disease treated with isotretinoin. Report of four cases. Journal of the American Academy of Dermatology. 1985; 12(6): 981-4.
18. Paul BS, Amdt KA. Response of transient acantholytic dermatosis to photochemotherapy. Archives of Dermatology. 1984; 120:121-2.

A Cautionary Tale on Halo Nevi: Case Report & Literature Review

Andrew Racette, D.O.*, Joseph Machuzak, D.O., Stephen Kessler, D.O.***, Alissa Floman, B.S.****, Crystal Kunka, B.S.****

** 1st Year Resident, Western University Health Sciences, Mesa, AZ*

*** Research Fellow, Western University Health Sciences, Mesa, AZ*

**** Program Director, Western University Health Sciences, Mesa, AZ*

***** Research Assistants, Western University Health Sciences, Mesa, AZ*

ABSTRACT

The halo nevus is characterized by a central melanocytic nevus surrounded by a hypopigmented macular halo and has been thought of as a benign nevus. We report a case of a fifteen-year old boy who presented to our clinic with a typical halo nevus that was biopsied at the parent's insistence. The pathology report showed it to have severe cytologic atypia with features consistent of an early evolving melanoma. We report this case to revisit the topic of halo nevi and to remind clinicians that although most halo nevi are benign we must still remember the conditions when they should be regarded as suspicious lesions and the need for a biopsy.

Introduction

The halo nevus, a lesion characterized by a central melanocytic nevus surrounded by a hypo or depigmented macular halo, is generally considered a benign nevus. It most commonly occurs on the upper back of individuals under twenty years of age with no difference in incidence between males and females.

The halo of hypopigmentation develops over weeks to months with likely involution of the central nevus over the following months to years.1 The regression of the nevus is thought to be an example of immunosurveillance in humans since it is due to a combination of immunological factors, but is not known with exact certainty.2,3 It is thought to be due to either an immune response to antigenically altered dysplastic nevus cells or to a cell-mediated and or humoral reaction against non-specifically altered nevomelanocytes.1 For the first principle to be correct all halo nevi must be atypical. If the second principle is to be true there must be an insult, either physical or chemical, to alter the nevomelanocytes in a nonspecific way to cause an immunologic response. It is known that CLA+, CD4+, and CD8+ T cells infiltrate the halo nevus4, with an abundance of activated CD8+ T cells in the halo nevi.5,6 In addition, it has been shown that T cells from a patient with a halo nevus are able to lyse the melanocytes of a normal nevus7, with cytotoxic T-cells playing the predominant role in regression.8

Case Report:

A 13 year-old male was seen in our clinic because his parents were concerned about a changing mole on his right upper back. A total body exam was performed and multiple normal nevi were seen along with the lesion of concern on the upper back. Upon questioning the parents they informed us that this nevus had been present for an unknown amount of years, but was not present at birth. It had been changing in color and in the prior week it started to develop a rim of hypopigmentation and erythema. The lesion was asymptomatic to the patient and he had never received treatment for this lesion before. He denied any recent trauma or manipulation to the nevus. When his parents were questioned further they stated their was a family history of melanoma in a first degree relative. The lesion in question was a 7 mm macule consisting of a symmetric rim of hypopigmentation and slight erythema surrounding a nevus. The central nevus was symmetric, had regular borders, was uniformly brown in color, and measured 4 mm in diameter. It resembled a typical benign halo nevus and we felt the best course of action was to watch the lesion. However, at the parent's insistence the lesion was biopsied and sent to a dermatopathologist.

Histologically the lesion showed a compound dysplastic nevus with severe atypia. MART-1 stain showed no significant pagetoid growth, but did highlight several areas of early confluence along the dermal/epidermal junction. There was severe cytologic atypia of the melanocytes with extensive bridging of rete ridges worrisome for evolving melanoma (Fig. 1 & 2). The specimen was then sent for a second opinion with a similar diagnosis of compound dysplastic nevus with moderate to severe atypia and lymphohistiocytic infiltrate (consistent with halo phenomenon). Some cells had severe atypia and Spitzian features, thus it may be considered an overlap melanocytic nevus with features of a severely dysplastic nevus and a Spitz tumor. The lesion was then reexcised conservatively to ensure complete removal

Discussion

The typical halo nevus seen in children has long been thought of as a benign lesion that does not require treatment. One article from the Journal of Pediatrics in 2001 stated "we have never seen a case of a "malignant halo nevus."9 In this study seventy-eight pediatric dermatologists responded to questionnaires and stated that they had never seen a typical halo nevus come back as a malignant lesion. Even though these same dermatologists had never seen a malignant halo nevus 68% of them answered that they still biopsy halo nevi "if the central lesion looked unusual" with 4% answering that they biopsied all halo nevi "often."9 This information seemed to support the theory that the typical halo nevus does not undergo malignant transformation in children.9 This would then lead one to the conclusion that halo nevi would not be of great clinical concern with no need for biopsy.

More recently though there has been one case report of a possible malignant melanoma when the clinician believed the lesion was a typical halo nevus.10 In this report the practitioners were reluctant to biopsy the lesion, but did so at the patient's insistence. When the pathology report came back they were extremely surprised to see the result. This report is very similar to our case where we felt the lesion was a typical benign halo nevus but biopsied the lesion because of the family's heightened concern.

Upon talking with the dermatopathologist in our case she felt as if the lesion we biopsied was an early evolving melanoma and could have progressed to this entity given a few more years. The question then arises as to whether these lesions we call 'typical halo nevi' actually represent severely dysplastic nevi or early melanomas, which our immune system is able recognize, attack, and destroy. There has long been a theoretical link between circulating antibodies with halo nevi11 because of the ability of patients with halo nevi to produce antibodies against the cytoplasm of melanoma cells.12 However, these antibodies have never shown to correlate with the regres-

sion of the central nevus. Instead, the circulating antibodies seem to be a result of the destruction of the nevus cells with subsequent release of nevocellular antigen that is then processed and present by antigen presenting cells. This then leads to production of antibodies, but not until after the nevus cells have been lysed.12 Further evidence against this antibody model is provided through immunohistochemical studies, which have shown the infiltrating lymphocytes in the halo to be comprised of CD4+ T helper cells (25%)13 with the rest being CD8+ T cells.13,14 There is a lack of significant number of B-cells within the infiltrate suggesting that they do not play a major role in the regression process.13 Also, it is still not completely clear whether or not this lymphocytic infiltrate is directly responsible for the regression of the nevi or if there are other factors, which are still not yet understood.

It is clear that much work has been done to understand halo nevi at the cellular level. However, it is also clear that there are many parts of the process that we still do not understand. If we are able to elucidate the cellular interactions causing these lesions it may help us to answer some of the questions surrounding them clinically as well. Are we to rethink our stance on halo nevi as completely benign lesions or are these few reports of severely dysplastic halo nevi the exceptions?

References:

1. Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Mosby 2003.
2. Cui Z, Willingham MC. Halo naevus: a visible case of immunosurveillance in humans? Lancet Oncol. 2004 Jul;5(7):397-8.
3. Wayte DM, Helwig EB. Halo nevi. Cancer 1968 22:69.
4. Akusu R, From L, Kahn H. Characterization of the mononuclear infiltrate involved in regression of halo nevi. J Cutan Pathol 1994;21:302.
5. Fernandez-Herrera J, Fernandez-Ruis E, Lopez-Cabrera M, et. al. CD69 expression and tumor necrosis factor-alpha immunoreactivity in the inflammatory cell infiltrate of halo nevi. Br J Dermatol 1996;134:388.
6. Musette P, Bachelez H, Flageul B, Delarbre C, et al. Immune-mediated destruction of melanocytes in halo nevi is associated with the local expansion of a limited number of T cell clones. J. Immunol 1999;162:1789-1794.
7. Mitchell MS, Nordlund JJ, Lerner A. Comparison of cell-mediated immunity to melanoma cells in patients with vitiligo, halo nevi, or melanoma. J Invest Dermatol 1980;75:144.
8. Bayer-Garner IB, Ivan D, Schwartz M, Tschen J. The immunopathology of regression in benign lichenoid keratosis, keratoacanthoma, and halo nevus. Clin Med Res. 2004 May; 2(2): 89–97.
9. Lai CH, Lockhart S, Mallory SB. Typical halo nevi in childhood: Is a biopsy necessary? J Pediatr 2001;138:283-4.
10. Mandalia MR, Skillman JM, Cook MG, Powell BW. Halo naevus or malignant melanoma? A case report. Br J Plast Surg 2002;55:512-513.
11. Copeman PWM, Lewis MG, Phillips TM, Elliott PG. Immunological associations of the halo nevus with cutaneous malignant melanoma. Br J Dermatol. 1973;88:127-137.
12. Zeff RA, Freitag A, Grin CM, Grant-Keis JM. The immune response in halo nevi. J Am Acad Derm 1997;37:62-624.
13. Akasu R, From L, Kahn HJ. Characterization of the mononuclear infiltrate involved in regression of halo nevi. J Cutan Pathol 1994;21:302-311.
14. Bergman W, Willemze R, DeGraaff-Reitsma C, et al. Analysis of major histocompatibility antigens and the mononuclear cell infiltrate in halo nevi. J Invest Dermatol 1985;85:25-29.

Hyperimmunoglobulin E Syndrome

Rene Bermudez, D.O.*, Shield Wikas, D.O., Monte Fox, D.O.*****

**3rd year resident-Summa Health Systems-Cuyahoga Falls General Hospital, Cuyahoga Falls, Ohio*

*** Program Director- Summa Health Systems-Cuyahoga Falls General Hospital, Cuyahoga Falls, Ohio*

****Assistant Clinical Professor- Summa Health Systems-Cuyahoga Falls General Hospital, Cuyahoga Falls, Ohio*

Introduction

The hyperIgE syndrome, also named Job syndrome is a rare multisystem disorder that often presents in the first few months of life. It was first described as a primary immunodeficiency disorder characterized by staphylococcal skin abscesses, recurrent pneumonias with pneumatocele formation, eczema, peripheral eosinophilia, and elevated serum IgE levels.[1] Since the initial description by Davis et al in 1966, additional studies and case reports expanded on this initial description to include recurrent cutaneous infections of staphylococcal and streptococcal species, recurrent systemic infections particularly of the joints and lungs, chronic eczematous dermatitis often involving the flexural regions and the face, and elevated serum IgE levels.[2] Recurrent pneumonias with staphylococcus and streptococcus may lead to persistent pneumatocele formation, bronchopleural fistulas, cyst formation, and restrictive lung disease. Mucocutaneous candidiasis, characteristic facies and involvement of teeth, bone, and the immune system have all been reported. [3-4]

We report a case of a 6-year old boy who presented to our clinic with clinical manifestations, and a prior history suggestive of the hyperIgE syndrome. We have reviewed the literature in order to expand our knowledge of this rare disorder. As patients with the hyperIgE syndrome live longer, more phenotypic expressions of this syndrome will become apparent which will help clarify the etiology, pathogenesis and treatment options.

Case Report:

This 6 year old white male presented to our clinic with a history of recurrent skin infections, recurrent otitis media as an infant, chronic eczema, poor dentition with multiple dental caries, elevated serum IgE level, and peripheral eosinophilia. He was born at 29 weeks gestation with a birth weight of 720 grams. He was born to a 28 year old white gravida 3, para 1, stillborn 1, A negative female. The pregnancy was complicated by pregnancy induced hypertension, oligohydramnios, first trimester bleeding, and decreased fetal movement. After a 9 week stay at the Neonatal Intensive Care Unit, he was discharged in good health. Past medical history was unremarkable. Past surgical history included bilateral inguinal hernia repair shortly after birth. There is no family history of atopy or immunodeficiency disorders. Developmental milestones were achieved appropriately on time.

Physical examination revealed a single erythematous papule overlying his fourth metacarpal joint of his left hand on his initial visit. However, follow up visits revealed a few more erythematous excoriated papules located on his back, and lower extremities. See figure 1 and figure 2.

There was no evidence of secondary infections. Facial features revealed deep set eyes, prominent forehead, and wide spaced nasal ala. Oral examination revealed poor dentition. A history of bone fractures was denied, and on examination there was no evidence of hyperextensible joints or scoliosis. Although eczematous rashes had been described in his medical records, there was no evidence of any eczematous process on our initial examination except for mild xerosis. There were no hair, mucocutaneous, or nail changes noted on examination. Serum IgE levels fluctuated between 5,233 and 9,000 U/ml. Serum IgG and IgA were slightly decreased from normal. Serum IgM levels were within normal reference range. Serum complement levels were within normal range. Bone density scan was negative.

Histopathologic examination of the lesion on his left hand revealed nonspecific spongiotic dermatitis. In review of his medical records and past hospitalizations, the most commonly isolated pathogen in the previous skin abscesses and furuncles was Staphylococcus aureus. This patient has been on multiple courses of oral as well as intravenous antistaphylococcal antibiotics since the age of 2. His current prophylactic regimen consists of a first generation cephalosporin two times daily for the past 2 months. The application of mupirocin (Bactroban) cream to any new lesions twice daily was also recommended. He has not had any recurrent furuncles or abscess since being placed on prophylaxis.

Discussion

Background

The hyperIgE syndrome, also known as Job syndrome was first described by Davis et al in 1966. The term Job is derived from the Biblical character that was believed to be plagued with sore boils from the sole of his foot unto his crown. (Job2:7) This term refers to a subset of patients with the hyperIgE syndrome that are usually women of Italian descent, have red hair, hyperextensible joints, blue eyes, freckles, atrophic or dystrophic nails, and a tendency to develop huge chronic and recurrent cold staphylococcal abscesses that deform and distort the body contour. [2] As of the year 2001, approximately 200 cases have been reported since it was first described in 1966. [5] The hyperIgE syndrome affects men and women equally. A familial tendency has been observed. It can be seen in people of diverse ethnic backgrounds.

Clinical Manifestations

The clinical manifestations of the hyperIgE syndrome usually present within the first years of life. There may be any amalgamation of immunologic, cutaneous, dental, skeletal, and head and neck abnormalities seen in the hyperIgE syndrome. These patients suffer from recurrent infections of the skin including impetigo, cellulitis, furunculosis, paronychia, and cold abscess of the scalp, neck, axillae, and intertriginous region infected with S. aureus, C. albicans, or Group A Streptococcus. [6-7]

Dahl et al feel that patients with recurrent furunculosis in the absence of severe infections of the skin and other organs do not have this syndrome, even though patients with the syndrome often have furuncles. He also feels that patients invariably have severe and recurrent infections of other organs, especially of the lungs and upper respiratory tract. [8] Sinopulmonary infections come in the form of otitis media, otitis externa, sinusitis, recurrent bronchitis or pneumonia secondary to S. aureus, and H. influenza, lung abscesses, pneumatoceles with bacterial or fungal superinfections, and empyemas. [7] Grimbacher et al studied 30 patients with the hyperIgE syndrome and found that 77% of patients with pneumonia developed pneumatoceles. Acute pneumonias were caused most frequently by S. aureus or H. influenza; in contrast, superinfections of pneumatoceles were associated

with Pseudomonas aeruginosa and Aspergillus fumigatus. Fifteen patients required thoracotomy to drain the infected pneumatoceles. Other infections seen in their cohort were recurrent bacterial arthritis, staphylococcal osteomyelitis, chronic mucocutaneous candidiasis and candidal onychomycosis, median rhomboid glossitis, and Pneumocystic carinii pneumonia. [4]

Figure 1

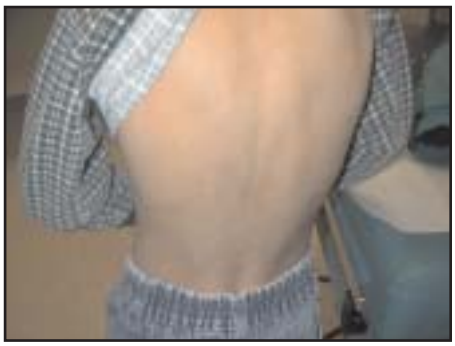


Figure 2

The cutaneous manifestations in the hyperIgE syndrome are often described as eczematous or atopic-like. The eczematous eruption can be seen in a flexural distribution, along the hair line, and posterior auricular region. It may even mimic the lichenification seen in atopic dermatitis.[7] However, Chamlin et al did a retrospective review of 8 patients diagnosed with the hyperIgE syndrome. They describe a distinctive papulopustular eruption as the initial manifestation of the disease, with an eczematous dermatitis developing later in the course of the disease. All 8 patients developed a papulopustular eruption in the first year of life, with the eruption developing in 6 patients within the first month of life. Crusting of these lesions was a prominent feature. [9] In contrast, Dahl feels the eruption can be categorized into three types. He describes the first type as mild inflammatory papules suggesting folliculitis but usually without many pustules. The second type is clinically indistinguishable from severe chronic eczema. The third type is similar to the eruption seen in incontinentia pigmenti.[8]

The dentition of patients with the hyperIgE syndrome can be affected. Grimbacher et al described the previously unrecognized feature of retained primary teeth. In their cohort 72% of patients who were older than eight years old reported retention of primary teeth. This observation was attributed to the lack of root resorption rather than faulty eruption in these patients.[4] Although our patient's history is consistent with multiple dental caries in his primary teeth, it remains to be seen if retained primary teeth will be observed in this patient. The dental caries occurred despite the patient's mother, whose occupation is a dental hygienist, meticulous dental care.

Skeletal abnormalities in the hyperIgE syndrome had been previously reported. Osteoporosis and the propensity to bone fractures was a recognized feature. This was known as osteogenesis imperfecta tarda. [10] However, the incidence of bone fractures was not known until Grimbacher et al reported that 57% of their patients had had at least 3 fractures. The fractures were often due to unrecognized or minor trauma. These fractures occurred on long bones, ribs, and pelvic bones. Other common skeletal findings among their patients were hyperextensible joints in 68%, and scoliosis in 76% of those 16 years or older. [4] Distinctive facial characteristics of patients with the hyperIgE syndrome have been described by Davis et al as well as Buckley et al. [11] In 1998 Borges et al evaluated the facial features of 9 patients from 7 kindreds with Job Syndrome. The most prominent findings in their patients were a prominent brow and supraorbital ridge with the impression of deep set eyes, increased width of the nose, a full lower lip, and thickening of the nose and ears. They feel a characteristic face can be seen in these patients. They report that these patients tend to look more like each other than other members of their family. [11] These findings were later supported by Grimbacher et al who found similar facial features to be universal by the age of 16 years. They had facial asymmetry with a suggestion of hemihypertrophy; a prominent forehead; deep seated eyes; a broad nasal bridge; a wide, fleshy nasal tip; and mild prognathism. Facial skin was rough, with prominent pores. The interalar distance was increased. Head circumference tended to be larger than normal. Craniosynostosis which had previously been reported was not found in their cohort. Anomalies in midline facial development were also observed. These anomalies consisted of high-arched palate in 71% of patients, a cleft lip and palate in one patient, and midline sagittal clefts in the middle third of the tongue in two sisters. [4] We feel our patient's facial features are characteristic of those described above, and will continue to look

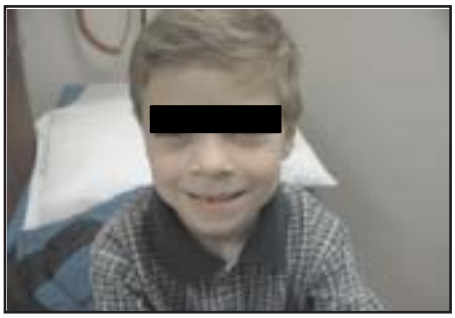


Figure 3

out for the development of any additional features as he ages. See figure 3.

Associated Disorders

In addition to the immunologic and non-immunologic findings already described, several diseases such as systemic mastocytosis, systemic lupus erythematosus, and 4 reports of malignancies have been reported. The malignancies reported were Hodgkin's lymphoma, histiocystic lymphoma of the brain, and 2 cases of Burkitt's lymphoma. [5] The finding of noninfectious vascular events of the central retinal artery, leaking berry aneurysm, bilateral aneurysms at the internal carotid artery bifurcation, cerebral embolus, and thrombotic strokes have also been described. [4]

Etiology and Pathogenesis

Although the primary cause remains unknown, most authors feel that the hyperIgE is an autosomal dominant disorder with variable expression. It has been located to a region on chromosome 4 in several families. [1,9] Most cases seem to be sporadic. Like the etiology, the pathogenesis is also unknown. Most authors feel the primary defect is caused by an intermittent chemotactic defect in neutrophils. [2] Others suggest an abnormality in T lymphocyte function, in particular an imbalance of the Th1 and Th2 cells, which secondarily affects neutrophil mobility. [12-13]

Despite all patients not showing a common immunologic defect, Grimbacher et al feel that the presence of peripheral eosinophilia, the presence of eosinophils in sputum and abscesses, defective granulocyte chemotaxis, T-cell abnormalities, defective antibody production, and the decreased production and or responsiveness of cytokines such as interleukin [4] and interferon gamma play a role.[4]

Histopatholgy

The histopathologic findings in the hyperIgE syndrome are non specific. In one study the most consistent finding on skin biopsy revealed eosinophilic spongiotic dermatitis. Other histopathologic findings were eosinophilic folliculitis, superficial and deep perivascular dermatitis with abundant eosinophils, and abundant eosinophils

extending into the subcutaneous fat. Demodex folliculitis was reported in one patient. [9]

Laboratory Findings

The laboratory findings in the hyperIgE syndrome consist of elevated serum IgE levels which can be anywhere from 10-100 times the normal value, elevated sputum and peripheral serum eosinophilia, elevated serum anti-S.aureus IgE, low or no serum and salivary anti-S.aureus IgA. [2-3] Although the name "hyper" IgE implies a chronically elevated serum IgE level, in approximately 20% of affected adults, the serum IgE levels may decline with time to reach normal levels. [3]

However, these patients have normal concentrations of IgG, IgA, IgM, and elevated levels of IgD.

Differential Diagnosis

The main disorder to differentiate from the hyperIg-E syndrome is atopic dermatitis. Unlike hyperIg-E syndrome, atopic dermatitis is a relatively common skin disorder. However their clinical similarity at times can not be denied. Other cutaneous disorders that mimic hyperIg-E syndrome are seborrheic dermatitis, Wiscott-Aldrich syndrome, DiGeorge syndrome, and Omenn's syndrome. In one study, the most common diagnosis prior to the diagnosis of hyperIg-E syndrome were infantile acne, acne rosacea, demodex folliculitis, bacterial folliculitis, candidal folliculitis, eosinophilic pustular folliculitis, scabies, impetigo, seborrheic dermatitis, and atopic dermatitis. [9]

Treatment

Treatment with long term anti-staphylococcal antibiotics, incision and drainage of appropriate abscesses, appropriate antibiotics and antifungals for specific infections, thoracotomy for superinfected pneumatoceles or those persisting for greater than six months, treatment of the eczematous component with topical steroids, and oral antihistamines for pruritus are the mainstays of therapy for the hyperIgE syndrome.[13] In cases refractory to the aforementioned treatment modalities, several studies suggest treatment with systemic therapy such as cimetidine, ascorbic acid, isotretinoin, cyclosporine A, IVIG, and methotrexate. According to Fitzpatrick et al, ascorbic acid and cimetidine have decreased the number of infections and the chemotactic defect in some patients. Isotretinoin has been reported to eliminate the recurrent staphylococcal abscess in an isolated patient without altering the immunologic status.[6] Etzioni et al reported the beneficial effects of Cyclosporin A in a 3 year old male with the hyperIgE syndrome in whom various therapeutic modalities were ineffective. This 3 year old boy was treated with Cyclosporin A at 3mg/kg/d for a total of 6 months. He did not experience any side effects. They believe the beneficial response seen in this patient was due to Cyclosporin A ability to shift the immune response from a predominance of Th2 to Th1. [14]

The results of various studies looking at the effectiveness of IVIG in the treatment of the hyperIgE syndrome are inconsistent. An open labeled study evaluating one patient with the hyperIgE syndrome and nine with atopic dermatitis failed to demonstrate clinical benefit in these patients. These patients received 10% solution of IVIG at a dose of 2 g/kg every 30 days for a total of seven infusions. It was well tolerated and minimal side effects occurred. The most common side effects were headache, fatigue, and myalgias as shown in other studies. The primary endpoints in this study were improvement in skin lesions, decreased in steroid medication, improvement in pulmonary function test or decrease in IgE production. Despite showing improvement in the primary endpoints, they failed to reach statistical significance. [15] However, Rutter and Luger cited improvement in the eczematous component in 2 patients with hyperIg-E syndrome and Kawasaki disease treated with IVIG monotherapy with one course of 0.4g/kg daily for 5 days. In addition a decrease in the serum IgE level was observed. [16] Finally, in a study from the Indian literature, 2 patients with the hyperIg-E syndrome were treated with methotrexate with a reported effectiveness in controlling the cutaneous symptoms. The long term effects were not reported since one patient died from complications of Burkitt's lymphoma and the other died of complications related to lobectomy for lung abscess. [5] Fortunately, our patient remains free of any lesions since being placed on prophylactic antibiotics.

References:

1. Grimbacher B, Holland SM, Shaffer AA, Gallin JI, Davis J, et al. Genetic Linkage of Hyper-IgE syndrome to chromosome 4. Am. J. Hum. Genet. 1999; 65: 735-744.
2. Hurwitz S. Eczematous Eruptions in Childhood. IN: Hurwitz S, Ed. Clinical Pediatric Dermatology. A Textbook of Skin Disorders of Childhood and Adolescence. Philadelphia, Pennsylvania, W.B. Saunders, Second Edition. 1993: 60-61.
3. Braunwald E, Fauci AS, Kasper DL, et al. Disorders of Granulocytes and Monocytes. IN: Braunwald E, Fauci AS, Kasper DL, et al, Eds. Harrison's Principles of Internal Medicine, San Francisco, California, McGraw-Hill, 15th edition. 2001: 371.
4. Grimbacher B, Holland SM, Gallin JI, Greenberg F, et al. Hyper-IgE Syndrome With Recurrent Infections-An Autosomal Dominant Multisystem Disorder. N. Engl. J. Med. 1999; 340: 692-702.
5. Pherwani AV, Madnani NA. Hyperimmunoglobulin E Syndrome. Indian Pediatrics. 2001; 38: 1029-1034
6. Fitzpatrick TB, Freedberg IM, Eisen AZ, Wolff K, et al. Genetic Immunodeficiency Diseases. IN: Fitzpatrick TB, Freedberg IM, Eisen AZ, Wolff K, et al, Eds. Fitzpatrick's Dermatology in General Medicine, San Francisco, California, McGraw-Hill, 5th Edition. 1999: 1404.
7. Spitz JL. Hyper IgE Syndrome. IN: Pine JW, Ed. Genodermatoses-A Full-Color Clinical Guide to Genetic Skin Disorders, Baltimore, Maryland, Lippincott Williams and Wilkins, 1st edition. 1996: 218-219.
8. Dahl MV. Hyper-IgE revisited. The International Society of Dermatology. 2002; 41: 612-621.
9. Chamlin SL, McCalmont TH, Cunningham BB, et al. Cutaneous manifestations of hyper-IgE syndrome in infants and children. Journal of Pediatrics. 2002; 141:572-5.
10. Brestel EP, Klingberg WG, Veltri RW, Dorn JS. Osteogenesis imperfecta tarda in a child with hyper IgE syndrome. Am. J. Dis. Child. 1982; 136: 774-776.
11. Borges WG, Hensley T, Carey JC, et al. The face of Job; Clinical and Laboratory Observations. Journal of Pediatrics. 1998; 133: 303-5.
12. Gorbach SL, Bartlett JG, Blacklow NR. Abnormalities of Neutrophil Granule Formation and Content. IN: Gorbach SL, Bartlett JG, Blacklow NR, Eds. Infectious Diseases, Philadelphia, Pennsylvania, W.B.Saunders, 2nd edition. 1998: 53.
13. Behrman RE, Kliegman RM, Arvin Ann M. Combined B and T cell Diseases. IN: Nelson WE, Ed. Nelson's Textbook of Pediatrics, Philadelphia, Pennsylvania, W.B.Saunders, 15th edition. 1996: 576-7.
14. Etzioni A, Shehadeh N, et al. Cyclosporin A in Hyperimmunoglobulin E syndrome. Ann. Allergy Asthma Immunol. 1997; 78: 413-4.
15. Wakim M, Alazard M, Yajima A, et al. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann. Allergy Asthma Immunol. 1998; 81: 153-8.

Rutter A, Luger TA. High dose intravenous immunoglobulins: An approach to treat severe immune-mediated and autoimmune diseases of the skin. J. Am. Acad. Dermatol. 2001: 44: 1010-24.

Poulos

Barnhill

Hanly

Dermatopathology

Nationwide

24 Hour Turn Around

GLOBAL PATHOLOGY

LABORATORY SERVICES

866 - 825 - 4422

Poulos

Barnhill

Hanly

Dermatopathology

Nationwide

24 Hour Turn Around

GLOBAL PATHOLOGY

LABORATORY SERVICES

866 - 825 - 4422

LASERS : BACK TO THE BASICS

Tony Nakhla, D.O.*, Navid Nami, D.O., Steven Shapiro, M.D.***, Layne Nisenbaum, D.O., FAOCD****

** Medical Intern, Saint Vincent's Midtown Hospital / New York*

*** 3rd Year Dermatology Chief Resident, Columbia Hospital West Palm Beach*

****Gardens Dermatology/Palm Beach Gardens, Voluntary Associate Professor-Department of Dermatology and Cutaneous Surgery University of Miami School of Medicine*

*****Program Director, Columbia Hospital /Nova Southeastern University / West Palm Beach, FL*

ABSTRACT

The continuous wave ruby laser was the first laser developed about 40 years ago and marks the birth of laser medicine. Considerable technological advances have been made in this field throughout the many disciplines of medicine. These advances have enabled the development of lasers with more efficacy and less adverse, unwanted effects. We will review the physics, mechanics, types and clinical indications of laser systems available today.

LASER BASICS

The term laser is an eponym for Light Amplification by Stimulated Emission of Radiation. Physics and the atom will help to better understand lasers. An electron circling an atom can be excited to a higher orbit by absorbing energy (stimulated absorptions) and conversely fall to a lower orbit by emitting energy (spontaneous emission). This energy is represented as a photon of light. Lasers deal with the concept of stimulated emission. Stimulated emission occurs when a photon is directed towards an atom containing a meta-stable electron in its orbit. This interaction results in the orbiting electron falling to a lower orbit and in turn emitting a new photon of light. Thus one original photon directed at this atom has brought about two resultant photons. The term light amplification refers to a chain reaction which occurs as these two emitted photons are directed towards other atoms creating even more photons. This light amplification process occurs in a device called an optical resonator. The optical resonator not only amplifies but also orients light. A cylindrical chamber filled with laser medium, an absorptive lining and mirrors on each end is responsible for creating collimated laser light. Photons are reflected between the mirrors. Any light not traveling in a parallel direction will get absorbed by the lining. At one end of this optical cavity with a partially reflecting mirror (which allows for 5% of energy to escape) is an instrument to release light periodically from the chamber.

How is laser light different from other sources of light? Laser light is monochromatic, coherent and collimated. Monochromatic light has a single wavelength or "color". Coherent light has wavelengths of light all in the same phase with the "same peaks and valleys". Collimated light is parallel and travels long distances without divergence allowing for precise destruction of the target. In contrast a flashlight produces white light that is incoherent and divergent[1].

Every laser system is unique based on its medium and the wavelength it emits. Laser mediums are composed of solids, gases or liquids. Examples of solid mediums include ruby crystals, alexandrite crystals, Nd:YAG crystals (Neodymium:Ytrium-Aluminm-Garnet) or Er:YAG crystals (Erbium:Ytrium-Aluinum Garnet). Examples of a gas medium include carbon dioxide, argon, krypton or copper vapor. Rhodamine is a fluorescent liquid dye used in some laser systems.

Laser-Skin Interactions

About 5-7% of laser light directed at the skin is reflected due to the large refractile index between the atmosphere and the skin. There is also some degree to reflection at the dermoepidermal junction. The rest of the light energy is either absorbed by the epidermis or scattered throughout the dermis. The final target of the photon is a specific chromophore. Chromophores are molecules in the skin that absorb the photon's energy if provided at an appropriate range of wavelengths. Optimally all the energy in the photon is extinguished and transferred to the chromophore. Examples of chromophores are water, oxy-hemoglobin, melanin and tattoo pigment. It is important to become familiar with the range of maximum wavelengths of light at which a given chromophore absorbs energy. This is demonstrated in the chromophore absorption curve. Water's absorption spectrum begins to increase at the mid to high infra-red wavelengths. Lasers that target the superficial layers of the skin where there is a high water content take advantage of this property. Examples are CO2 (10,600nm) or Er:YAG (2940nm) for ablative resurfacing procedures. Oxy-hemoglobin has a peak absorption spectrum at around 400-600nm where Pulse Dye Lasers (585nm/595nm) are most efficacious. Oxy-hemoglobin also has a second broad but smaller peak in absorption at about 1000nm where lasers such as Nd:YAG (1064nm) are utilized to treat deeper vascular lesions although with less efficacy than the previously mentioned PDL. Melanin has a wide absorption spectrum ranging from the infra-red region progressively increasing and peaking in the ultraviolet range. Due to this broad absorption spectrum and the presence of melanin in the basal layer of the epidermis, the potential for unintended absorption and unwanted dermal damage exists with almost any laser system[2]. This can lead to dyspigmentation and has increased risk in patients with darker skin. The competitive absorption of light energy by epidermal melanin can also lessen the energy transferred to the target chromophore and in turn decrease the desired clinical effect. Using a longer wavelength laser, for example Nd:YAG (1064nm), allows deeper penetration beyond the basal layer with less melanin absorption.

Parameters

Important parameters of light and lasers are wavelength, energy, power, fluence, pulse width and spot size. The electromagnetic spectrum is represented in wavelengths measured in nanometers. From the lowest wavelengths of gamma rays to the highest wavelengths of microwaves. In between these extremes are ultraviolet (200-400nm), visible (400-760nm) and infrared (760-10,000nm) lights. As a general rule, longer wavelengths of light are able to penetrate the skin to a deeper level due to the fact that these are scattered less by dermal collagen. Mid-high infra-red wavelengths are an exception because water becomes the principal chromophore. As a result light will only penetrate the skin superficially because of its high water content. Ablative resurfacing lasers take advantage of this phenomenon.

Energy which is inversely proportional to wavelength, is measured in Joules. Power is the rate of energy delivered is measured

in Joules/second. Fluence is the amount of energy delivered per area and is measured in Joules/cm^2. This amount of energy must be enough to heat the target above its damage threshold. Fluence is increased to deliver more energy to deeper lesions and should be used at more conservative levels in darker skin photo-types to lower the risk of dyspigmentation. Wave mode is as important as fluence. Lasers can either be continuous or pulsed. Because continuous laser light has no interruptions in energy delivered, non-selective tissue injury and greater risk of damage and scarring can occur. On the other hand in pulsed lasers, the energy is generated in surges allowing the target chromophore enough time to dissipate energy prior to receiving a subsequent pulse and to limit any unwanted energy transfer to surrounding tissue. This ability to provide enough energy to only affect the target tissue and spare surrounding tissue is defined by the term "Selective Photothermolysis". Lasers can have longed pulse widths measured in milliseconds or short pulse widths measured in microseconds. Pulses must be sufficiently short in duration to deliver enough energy to the target before it cools. This results in appropriate and localized heating. Exposure duration or pulse duration/width must be shorter than the specific chromophore's Thermal Relaxation Time (TRT)[3]. TRT is the time required for 50% of peak heat to diffuse out of a chromophore. If the TRT is exceeded, heat will diffuse into the surrounding tissue and yield collateral damage and unwanted results. Chromophores such as melanin and tattoo pigment have TRT in the micro and nanosecond ranges respectively. To stay within the limits of this very short pulse width, lasers can be Q-Switched. In such systems, electro-optical shutters are used to release stored energy and obtain ultra-short powerful pulses. The TRT for hair follicles and vessel are 100ms and 1-10ms respectively.

Cooling

Most laser systems must be used with adjunctive cooling. Benefits of cooling are less epidermal damage, allowing higher fluences and anesthetic effect for the patient. Cooling can be accomplished by contact, dynamic spray or air blowers. Contact and dynamic spray cooling are usually contained and as part of the laser device. Contact cooling uses a chilled probe tip in direct contact with the epidermis. Dynamic cooling produces a cryogen spray prior each laser pulse. Chilled air blowers can also be used. In addition cold gels or ice cubes can be applied on skin prior to therapy.

TYPE OF LASERS

The following section will discuss ablative resurfacing lasers (CO2 and Er:YAG), vascular lasers (pulsed-dye) and systems used in removal of hair and pigmented lesions (Nd:YAG and alexandrite).

Resurfacing

The CO2 (10,600nm) and the Er:YAG (2940nm) with their longer wavelengths take advantage of targeting water molecules in the superficial layers of the skin to cause tissue vaporization and collagen contraction[4]. This will result in re-epithelialization and new skin formation. Because of its longer wavelength the CO2 laser is more destructive than its Er:YAG counterpart. CO2 laser light can be focused or defocused. Focused laser light is utilized in precise surgical cutting otherwise referred to as "the light scalpel" and is currently being used by Gynecologists (Colposcopy), General Surgeons (Laparoscopy) and Neurosurgeons[5]. Defocused CO2 lasers are used in ablative resurfacing and treatment of certain lesions such as verruca vulgaris, trichoepithelioma, xanthelasma and rhinophyma. Depending on the number of passes, the depth of penetration can be controlled. More passes can not only cause epidermal ablation but also result in dermal remodeling via collagen shrinkage. Disadvantages and adverse effects of ablative resurfacing are post-treatment erythema and the risk of dyspigmentation, scarring and infection[6]. Post-treatment erythema which can last about 2-4 weeks with Erbium:YAG and 1-3 months with CO2 Laser is due to skin re-epithelialization and is bothersome to patients. Longer post-treatment erythema and pruritis may be caused by overgrowth of yeast or fungus[7]. This post operative period is sometime referred to as "down time". The Er:YAG laser has less ability to penetrate the dermis and cause collagen contraction and eventual remodeling. However it can be used more readily in darker skin types who are at risk for dyspigmentation and scarring, and also results in a shorter "down time". The Er:YAG can be used with longer pulse widths to increase tissue damage and reach the same levels as CO2 lasers. These two are the best systems available today for ablative resurfacing on the surface of the skin, and can regenerate collagen and elastin from within. It is recommended for patients to be off of Accutane fro 6-12 months prior to these interventions. Other lasers such as PDL, Nd:YAG, KTP, and alexandrite in addition to non laser sources such as Pulsed Light and Light Emitting Diode (LED) can be used as non-ablative rejuvenation for photo-aged skin by causing collagen/elastin growth and remodeling with preservation of epidermal integrity. These systems also target and improve pigmentation and vascular changes. For non-ablative therapy, these lasers use a low energy. Other long wavelength non-ablative systems used to treat photo-aging, acne and scarring include Nd:YAG (1320nm), diode (1450nm), Erbium:Glass (1540nm) and various pulsed lights.

Pulse Dye Lasers

Oxy-hemoglobin has a multi-peak absorption spectrum at wavelengths of 410nm-429nm, 541nm and 577nm. Argon (410nm-420nm/540nm/580nm) laser was the first system to target this chromophore. Due to its higher incidence of dyspigmentation and scarring in children, argon lasers have fallen out of favor. Pulse-Dye Lasers (585nm/595nm) are now being implemented to target vascular lesion such as rosacea, port-wine stains and angiomas. They are also used to destroy vessels that feed lesions such as verruca vulgaris, erythematous striae and hypertrophic scars. The PDL uses a flash-lamp for energy and contains a fluorescent dye (Rhodamine) as its medium. One major disadvantage in using PDL is 7-10 days of post operative purpura due to superficial vessel rupture[8]. This can be minimized by lowering fluences or increasing the pulse width. This maneuver will however decrease efficacy. Lower fluences should also be used on more delicate skin such as in children. PDLs are best for the treatment of more superficial vascular lesions. By increasing the spot size on the laser probe the light is better able to penetrate the skin and target deeper vessels at the expense of losing out on the total energy delivered. Nd:YAG laser (1064nm), because of its higher wavelength, is also a good option for treatment of deeper vessels. It takes advantage of a second yet smaller oxy-hemoglobin peak at the near infra-red region. Nd:YAG for vascular lesions is less effective than PDL but does not cause post operative purpura and as much pigmentary alteration in patients of darker skin types. The double frequency Nd:YAG (532nm) and KTP(532nm) can also be used to treat very superficial telangectasias without post-op purpura. A second type of PDL (510nm) is also worth mentioning because it can target superficial pigmented lesions and orange/red tattoos but has fallen out of favor due to pigmentary and scarring side effects[9].

Alexandrite Lasers

The alexandrite (755nm) is the most widely used hair removal laser. It also treats pigmented lesions and vascular lesions like leg veins. This laser can also be Q-switched to treat lesions with melanin

Laser Types and Application

Laser	Wavelength (nm)	Common Applications
Argon	488, 514	Vascular
Ruby	694	Pigment / Hair Removal
Nd:YAG	1064	Hair Removal / Pigment Deep Vascular
KTP	532	Superficial Vascular & Pigment
Alexandrite	755	Hair Removal / Pigment Deep Vascular
Diode	810	Hair Removal / Pigment Deep Vascular
Pulsed Dye	585, 595	Vascular
Q-Switched		Tattoo
COs / Erbium:YAG	10,600 / 2940	Ablative Resurfacing

Thermal Relaxation Time (TRT) & Pulsewidths for Specific Chromophores

Chromophore	Diameter	TRT	Laser Pulsewidth
Tattoo Ink Particle	0.1 microns	10 ns	10 ns
Melanosome	0.5 microns	250 ns	10 ns
PWS Vessel	30-100 microns	1-10 ms	0.4-20 ms
Hair Follicle	300 microns	100 ms	3-100 ms
Leg Vein	1 mm	1 sec	0.1 sec

as well as tattoo pigment. It is the most effective laser used for photoepilation because its wavelength is able to target deeper melanin pigment contained by the hair shaft and matrix. Its major draw back is dyspigmentation if used on darker skin photo-types[10]. As stated earlier, this is due to unwanted absorption by melanin in the basal layer of the epidermis.

Nd:YAG Lasers

The Nd:YAG (1064nm) laser is probably the most versatile laser system available. It can be applied for hair removal, vascular lesions, and non-ablative remodeling. This laser can also be Q-Switched to treat melanin containing pigmented lesions and tattoos. It is less effective than PDL for vascular lesions and less effective than the alexandrite for hair removal but should be used in a subgroup of patients with darker skin types who are more prone to post treatment pigmentary alterations. Its longer wavelength enables it to penetrate more deeply with less disruption of basal cell layer pigment. Nd:YAG (1320nm) with its even longer wavelength best targets water in the superficial layers of skin and is now being used for treating acne, scarring and non-ablative remodeling. Using a potassium titanyl phosphate crystal (KTP), the frequency of the Nd:YAG 1064nm can be doubled to 532nm (halving of wavelength) enabling it to better target superficial vessels, melanin and tattoo pigment at a lower wavelength.

INDICATIONS

Vascular Lesions

The best option for laser treatment of vascular lesions is the PDL. Because of its lower wavelength, this laser is most efficacious in treating more superficial vessels. The goal is to cause vessel coagulation and collapse. PDL is used to treat port-wine stains, hemangiomas, telangectasias, psoriasis, poikiloderma and superficial leg veins. KTP (532nm) is also very effective for treating superficial vessels. Because of their deeper penetration, the Nd:YAG (1064nm) and the diode (810nm) laser can be used to treat deeper and thicker veins of the leg[11]. As mentioned above, the Nd:YAG laser spares the patient of post operative purpura and dyspigmentation. It is best for darker skin types.

Hair Removal

Laser Hair Removal is probably the most widely utilized application of lasers today. Also known as Photoepilation, it is used for cosmetic indications as well as conditions like Hirsutism[12] and Pseudofolliculitis barbae[13]. The patient must avoid waxing, plucking or electrolysis for about one month prior for best results. Photoepilation is best performed using a laser with a longer wavelength because the target chromophore is deeper. The target for photoepilation is follicular melanin in the anagen hair bulb[14]. The alexandrite (755nm) is the best modality for this indication followed by the Nd:YAG which has lower efficacy in hair follicle destruction. The advantage of Nd:YAG is less epidermal melanin interaction and unwanted post operative pigmentary changes seen in darker skin types. Lasers used in hair removal are also long pulsed. This is done because follicular melanin has a greater TRT than epidermal melanin. This difference in TRT is because follicular melanin has a larger volume to surface ratio and is less capable of radiating the absorbed energy through its relatively small surface. The longer pulse duration also allows us to exceed the TRT for the melanin pigment allowing energy to dissipate and destroy surrounding non-pigmented hair follicles and hair bulge where stem cells are located. Other options for hair removal include Diode (810nm) and Ruby (694nm) lasers. Expected post therapy response include erythema and perifollicular edema in the first few days and expelled follicles in about two weeks[15]. Gray hair with no pigment and red/blond hair with pheomelanin are more resistant to these treatments and may require shorter pulse widths. This is due to the lack of eumelanin which is the best target for photoepilation. Currently several other modalities are being studied for removal of lighter hair. These include using synergy with electrical radiofrequency, photodynamic therapy and prior hair coating with squid melanin or carbon solution. Photoepilation can also be enhanced with adjunctive topical medication Eflornithine (Vaniqa) which inhibits orthinine decarboxylase.

Pigmented Lesions

Because of its wide absorption spectrum, melanin can be targeted with many laser systems. As mentioned above some of this targeting is unwanted. Ruby (694nm) lasers, one of the first lasers developed for pigment with a high affinity for melanin, currently have limited use due to the amount of epidermal damage. After the ruby, the next best laser for melanin is the alexandrite (755nm), followed by the diode (810nm) and the Nd:YAG (1064nm).

Due to the very short TRT of melanin pigment, most of these lasers must be Q-Switched for optimal results. The lower wavelength lasers are better able to target melanin because the absorption spectrum of melanin will increase towards the ultraviolet range. Shorter wavelength lasers will not be able to penetrate the skin as well as higher wavelength systems and are only best for superficial pigmented lesions16. Superficial pigmented lesions such as lentigines, ephelids, café au-lait spots are best targeted with Q-Nd:YAG (532nm). Q-Nd:YAG (1064nm) and Q-alexandrite (755nm) are also very effective for these superficial lesions but can be used to treat deeper lesions like Blue nevi, Nevi of Ito or Ota, Becker's nevi and post inflammatory pigmentary changes. Many pigmented lesions are difficult to treat with unpredictable results. Post inflammatory pigmentary alterations and melasma have the most variable response to therapy. In addition, lesions that are clinically suspicious must be biopsied to rule out malignancy prior to laser therapy. IPL devices, although not lasers, are also effective in treating superficial pigmentation.

Tattoos

Lasers used to treat tattoo pigment also need to be Q-Switched[17]. As light energy is delivered to this exogenous chromophore, the pigment is dispersed into small clusters and subsequently removed by macrophages. This process is least effective on lower extremities due to decreased lymphatic flow. Fracturing of pigment is not only due to particle expansion from heat, but also do to a mechanical "shock wave" effect termed photoacoustic effect. There are five types of tattoos : amateur, medicinal, traumatic, cosmetic and professional. Professional and cosmetic tattoos are more resistant due to their deeper location and heavy concentration of pigment. Traumatic tattoos, for example from gun powder or asphalt can be treated with more ease and less treatments. Lower fluences should be used for darker or retouched tattoos to avoid hyperpigmentation and scarring. Options for tattoo removal are Q- ruby (694nm), Q-Nd:YAG (1064nm), the double frequency Nd:YAG (532nm) and the Q-alexandrite (755nm) lasers[18]. All are most effective at targeting black pigment and not as effective in targeting yellow or white pigment. In fact, treatment of white pigment (titanium dioxide) can result in an immediate paradoxical blackening response through an oxidation reaction. If this occurs a re-treatment is necessary to target the newly formed black pigment. Some tattoo artists may also use white pigment to create a pink, gray or light green/blue color.

Q-alexandrite and Q-ruby (694nm) have greater affinity for blue and green pigments while the Q-Nd:YAG (532nm) is better for removal of red and orange pigments. Since many wavelengths are needed to treat multicolored tattoos, more than one system must be utilized for optimal results.

Conclusion

Laser technology is a useful tool and has greatly contributed to improvement in both medical care and cosmetic outcome for many years. As this technology is refined, newer lasers and applications can be anticipated with even more impressive results and reduced side effect profiles. Lasers will continue to be an integral part of Dermatology as well as other areas of medicine.

References:

1. Elizabeth L Tanzi, et al. Lasers in dermatology: Four decades of progress. JAAD 2003;49(1):1-31
2. Jackson BA.. Lasers in ethnic skin: A review. JAAD 2003;48(6):13-138
3. Altshuler GB et al. Extended theory of selective photothermolysis. Lasers Surg Med. 2001;29(5):416-32
4. Fitzpatrick RE et al. Collagen tightening induced by carbon dioxide laser versus erbium:Yag laser. Lasers Surg Med 2000;27(5):395-403
5. Absten GT.Physics of light and lasers. Obstet Gynecol Clin North Am 1991;18(3):407-27
6. Ratner D et al. Cutaneous laser resurfacing. JAAD September 1999;41(3):365-92
7. Alam M et al. A prospective trial of fungal colonization after laser resurfacing of the face: correlation between culture positivity and symptoms of pruritis. Dermatol Surg 2003;29(3): 255-60
8. Cantatore J et al. Laser surgery : An approach to the pediatric patient. JAAD2004;50(2):165-84
9. Dover J et al. Guideline of care for laser surgery. JAAD 1999;41(3):484-95
10. Weisberg NK et al. Pigmentary changes after alexandrite laser hair removal. Dermatol Surg 2003;29(4):415-9
11. Nayomi E et al. Treatment of reticular leg veins with a 1064nm long-pulsed Nd:YAG laser. JAAD 2003;48(1):76-81
12. Wendelin DS et al. Hypertrichosis. JAAD 2003;48(2):161-79
13. Ross EV et al. Treatment of pseudofilliculitis barbae in skin types IV, V, and VI with a long-pulsed neodymium:yttrium aluminum garnet laser. JAAD 2002;47(2):263-70
14. Oslen EA. Methods of hair removal. JAAD 1999;40(2):143-58
15. Nanni CA et al. Laser-assisted hair removal: Side effects of Q-switched Nd:YAG, long-pulsed, and alexandrite lasers. JAAD 1999;41(2):165-71
16. Hamilton MM. Laser treatment of pigmented and vascular lesions in the office. Facial Plast Surg 2004 Feb;20(1):63-9
17. Kuperman-Beade M et al. Laser removal of tattoos. Am J Clin Dermatol 2001;2(1):21-5
18. Prinz BM et al. Efficacy of laser treatment of tattoos using lasers emitting wavelengths of 532nm, 755nm and 1064nm. Dr J Dermatol 2004;150(2):245-51

Hypertriglyceridemia in Eruptive Xanthoma, A Case Report and Review of the Literature

David M. Bracciano, D.O.*, Kimball Silverton, D.O.**

**2nd Year Resident, Michigan State University Genesys Regional Medical Center, Grand Blanc, Michigan*

***Program Director, Dermatology Residency, Genesys Regional Medical Center, Grand Blanc, Michigan*

ABSTRACT

Lipid disorders have become increasingly common in the United States. Often dyslipidemias may present with easily recognized dermatologic manifestations. It behooves all clinicians to become familiar with these presentations in order to institute appropriate treatment for patients. While the majority of Xanthomas represent benign conditions, certain lesions can be associated with significant clinical disorders.

We present a case of Eruptive Xanthoma associated with massive hypertriglyceridemia and hypercholesterolemia with serum lipid levels elevated above those found in a search of the relevant literature.

Lipid disorders have become increasingly common in the United States. Often dyslipidemias may present with easily recognized dermatologic manifestations. It behooves all clinicians to become familiar with these presentations in order to institute appropriate treatment for patients. While the majority of Xanthomas represent benign conditions, certain lesions can be associated with significant clinical disorders.

We present a case of Eruptive Xanthoma associated with massive hypertriglyceridemia and hypercholesterolemia with serum lipid levels elevated above those found in a search of the relevant literature.

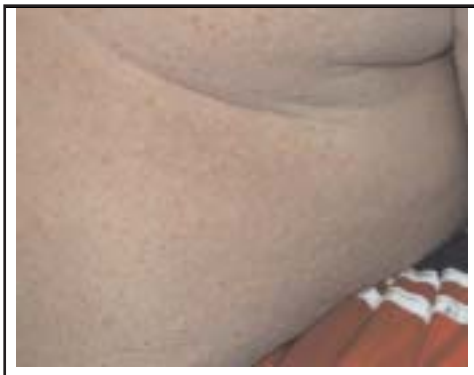
Report of a Case

TA 33-year-old white male presented to the Department of Dermatology with a chief complaint of a "rash". He described a history of a pruritic eruption that began on his extensor surface of the arms and progressed to his back, chest, abdomen, and lower extremities during the month prior to presenting at our clinic. He denied any history of similar lesions. He denied any systemic complaints. Past medical history included hypertension, depression and sleep apnea. Medications include Atenolol and Zyprexa (Olanzapine). The pruritic eruption however began before the institution of Olanzapine therapy. Past surgical history included splenectomy. He was a non-smoker with no known allergies. He admits to drinking two cans of beer per day, and eating fast food hamburgers and fried chicken on a regular basis.

Physical exam revealed a moderately obese male in no acute distress. He exhibited multiple 2-3mm yellow papules with mild surrounding erythema across his chest, back, upper and lower extremities. There were a few scattered lesions on the face; the palms and soles were spared. Punch biopsy of a lesion was performed. Histology was consistent with Eruptive Xanthoma. This showed nodular aggregates of foam cells in the upper and mid dermis. Nuclei were centrally placed in a foamy cytoplasm. There was no atypia. There was a background of lymphocytic infiltration of the perivascular zones.

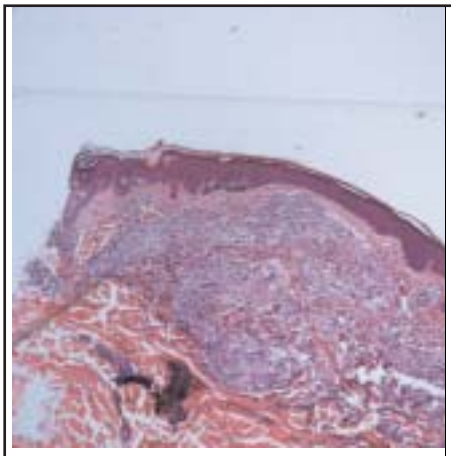
Screening laboratories were remarkable for a Triglyceride level of 15,125 mg/dl with a lab normal being less than 150 mg/dl. Total serum cholesterol was 1,331 mg/dl with a lab normal of less than 200 mg/dl.

Nodular aggregates of foam cells are seen in low power to involve the upper and

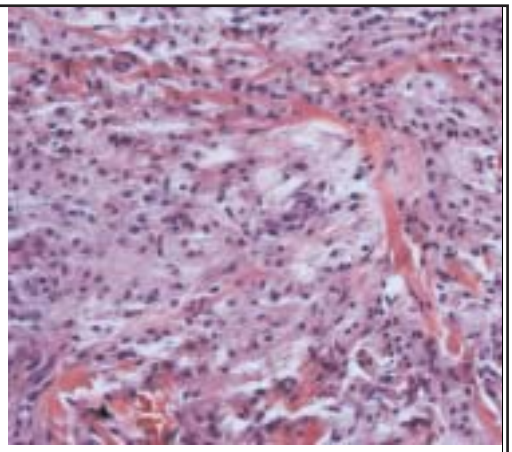


Multiple 2-3mm yellow papules.

Papules with inflammatory halo.



Nodular aggregates of foam cells are seen in low power to involve the upper and mid dermis. There is background perivascular inflammation.



Medium power shows foam cells with a centrally placed nucleus and characteristic foamy cytoplasm.

mid dermis. There is background perivascular inflammation.

Medium power shows foam cells with a centrally placed nucleus and characteristic foamy cytoplasm.

The patient was informed of the diagnosis of Eruptive Xanthoma with underlying hypercholesterolemia and hypertriglyceridemia. The Olanzapine was discontinued and dietary changes were discussed. The patient was begun on Simvastatin (Zocor) and Fenofibrate (Tricor). After approximately two months of therapy the patients' lesions had completely resolved.

His lipid levels remain normal seven months later with only Simvastatin therapy.

Discussion

Xanthomas are due to lipid infiltration in the dermis and tendons. The major types include eruptive xanthomas, tuberous xanthomas, tendinous xanthoma, and plane xanthomas. In the U.S. it is estimated that over 100 million people have a serum cholesterol greater than 200mg/dl.[11] Eruptive Xanthomas are usually associated with elevated triglyceride levels.[1] They most often present as small 1-4 mm yellow to orange papules in clusters.[2] The buttocks, extremities and torso are most common locations. A generalized form can be seen in severe cases. The lesions are tender and may be pruritic with a surrounding inflammatory halo.

In eruptive xanthoma the hypertriglyceridemia may be the result of a primary genetic defect in lipid metabolism (primary hyperlipoproteinemia), or due to a secondary cause.[3] Abnormal transport of lipoproteins may be due to increased endogenous production, defective removal, or a decrease in catabolism. Secondary causes of hyperlipoproteinemias include; diabetes mellitus, obesity, pancreatitis, chronic renal insufficiency, hypothyroidism, cholestatic liver disease, paraproteinemias, and drugs.

Drugs known to induce or exacerbate hyperlipoproteinemias include estrogens, corticosteroids and retinoids.[4,5] Retinoid therapy can induce hypertriglyceridemia via induction of hepatic VLDL secretion.[11]

Recently eruptive xanthomas have been reported in association with Olanzapine (Zyprexa) use.[6] These cases all showed evidence of hypertriglyceridemia, however even the most severe cases had levels significantly lower than our patient.[5] In our patient the Olanzapine therapy had been instituted two weeks prior to his initial Dermatology Clinic visit by his primary care physician due to perceived "depression" due to his "rash". It is quite possible that the Olanzapine contributed to the already existing hypertriglyceridemia of the patient to cause these heretofore unseen rises in serum lipids. Review of the literature reveals no cases of eruptive xanthoma with higher elevation of cholesterol or triglyceride levels than our patient.[3,7,6,8,9,10,11]

Summary

In this article we present a case of eruptive xanthoma with serum triglyceride and cholesterol levels at previously unreported levels. This patient illustrates a possible additive effect of drug-induced lipoproteinemia in combination with underlying hyperlipidemias to cause massive dyslipidemia. Dermatologists must be vigilant in searching for drug associations when patients present with eruptive xanthoma. Left untreated this patient most certainly would be at a higher risk for atheromatous disease including myocardial infarction and stroke.[11]

References:

1. Love JR. Dubin HV, Xanthomas and lipoproteins., Cutis. 1978 Jun:21(6):801-5.
2. Gotto AM Jr., Clinical diagnosis of hyperlipoproteinemia. Am J Med. 1983 May 23;74(5A):5-9.
3. Bickley L., Yellow papules on a middle-aged woman, Eruptive Xanthoma, Arch Dermatol. 1989 Feb:125(2):288-9, 291.
4. Parker F, Xanthomas and hyperlipidemias, J Am Acad Dermatol, 1985 July Vol 13 (1): 1-34.
5. Dicken CH, Connolly SM, Eruptive xanthomas associated with isotretinoin., Arch Dermatol. 1980 Aug:115(8):951-2.
6. Chang HY, Eruptive Xanthomas associated with Olanzapine use. Arch Dermatol. 2003:139:1045-1048.
7. Sanchez RL, Papular xanthoma. A clinical, histologic, and ultrastructural study., Arch Dermatol. 1985 May :121(5):626-31.
8. Barker DJ, The Koebner phenomenon in eruptive xanthoma. Arch Dermatol. 1979 Jan:115(1):112.
9. Miwa N, The Koebner phenomenon in eruptive xanthoma. J of Dermatol. Vol.19:48-50,1992.
10. Miller DM, Brodell RT, Eruptive xanthomatosis with linear koebnerization. J Am Acad Dermatol. 1995 Nov:33(5 Pt 1):834-5.
11. Massengale WT, Xanthomas in Bolognia J, Jorizzo JL, Rapini RP, Dermatology, Mosby, 2003, 1447-1454.

Leukemia Cutis- Case Reports and Discussion

Suzanne Sirota Rozenberg, DO*, David Kessler, DO, Marvin Watsky, DO*****
**3rd year resident St. Johns Hospital Far Rockaway, New York*
***Assistant clinical professor of dermatology at Touro College of Osteopathic Medicine*
****Program Director of Dermatology, St. Johns Hospital Far Rockaway, New York*

ABSTRACT

Leukemia cutis is an uncommon disease process by which neoplastic leukocytes infiltrate the skin locally or diffusely. It is generally a sign of disseminated systemic disease or a relapse of an existing leukemia. Generally, patients are older than 50, however, it can be seen in younger patients depending on the type of leukemia. 25- 30% of infants with congenital leukemia, especially of the myelogenous type, will have leukemia cutis. Leukemia cutis is most commonly seen in patients with acute monocytic leukemia M5 and acute myelomonocytic leukemia M4. Very often, Leukemia cutis is the presenting disease prior to bone marrow infiltration and systemic symptoms. Besides skin biopsy, these patients need hematologic studies with complete analysis of bone marrow aspirate and peripheral blood smear. Cutaneous histopathology- and immunophenotyping are essential. Treatment and prognosis of Leukemia cutis is directly related to the underlying disease. Cojoint management of these patients with the hematologist, oncologist and radiation oncologist is key.

Leukemia cutis

Case #1

61 year old white male presented to the office with a rash on his face and body for a duration of 4 weeks. The patient states he had been on Esomeprazole for acid reflux for 4 weeks. The rash started at that time, so he was switched to Lansoprazole by his family doctor. The patient was started the previous day to presentation on Prednisone by his doctor. He also stated that he had felt weak and had muscle aches since on started on the medications.

On further questioning, the patient stated that the rash had started on the abdomen and spread to the face and extremities. His review of systems was positive for a 6 pound weight loss in the prior month and fatigue. He denied fever, chills, and night sweats. He had no shortness of breath or chest pain. A prior work-up for chest pain was negative.

His past medical history was significant for GERD, and his past surgical history was positive for a hemorrhoidectomy. He had no known allergies. His recent medications were Rabeprazole, Aprazolam, Loratidine, and Acetaminophen.. His father had diabetes and two siblings have diabetes and coronary artery disease. His social history was negative for tobacco, alcohol, and drugs. He was a school teacher.

Figure 1

Figure 2

Figure 3

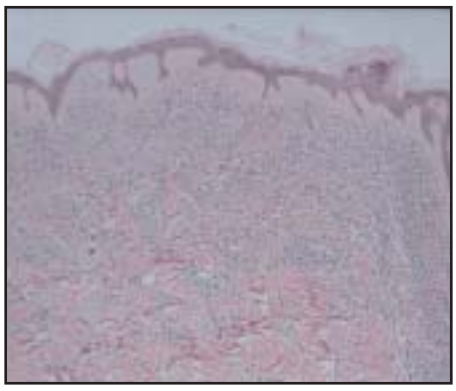


Figure 4
h and e, low magnification

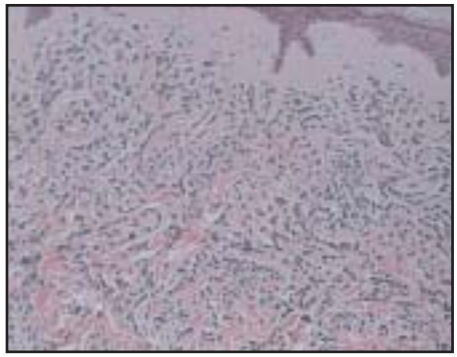


Figure 5
higher power

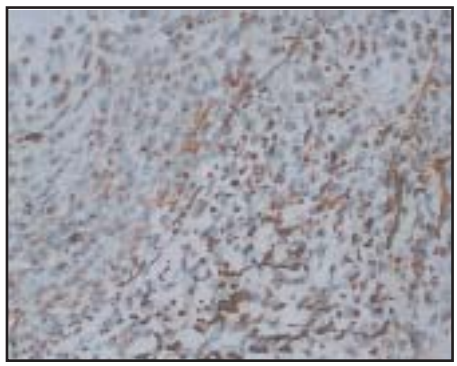


Figure 6
lysozyme stain

On physical exam, multiple indurated, erythematous to violaceous nodules of the face, chest and back were noted. The rest of the physical was essentially negative. Especially important to note no lymphadenopathy was present. (see figures 1-4)

His laboratory results of the CBC were 3.1, 10.9/ 31.8 , 241

RDW-16.9%.

The skin biopsy revealed mononuclear cells infiltrating between collagen bundles

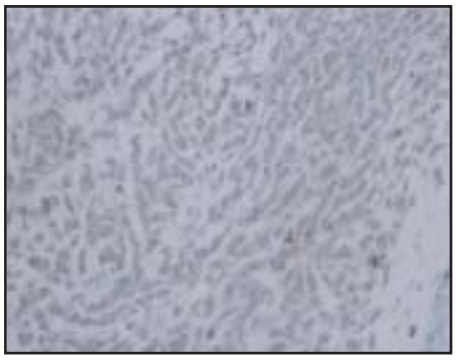


Figure 7
CD45 Ro

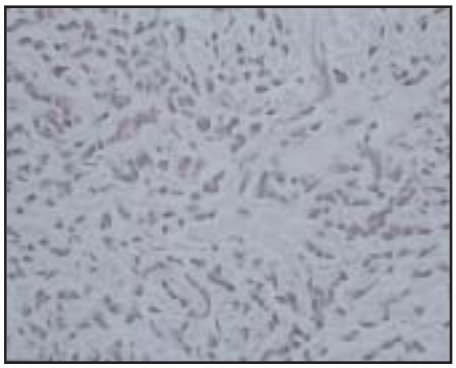


Figure 8
leder stain

in the superficial and mid dermis. The mononuclear cells have high nuclear to cytoplasmic ratios, irregular nuclear borders, prominent nucleoli and scant basophilic cytoplasm. The epidermis appears unremarkable . Cells are positive on Leder stain and are highlighted on immunohistochemical stains for lipozyme and CD45. Myeloperoxidase, CD-3, CD-20, and CD34 immunohistochemical stains are negative. (see figures 5-8)

Final Diagnoses- Leukemia Cutis

Case 2

79 year old white male complained of a rash for the past one and one-half months

on both arms, scalp, and face. The patient stated that he had no symptoms or pain. 6 months earlier, the patient had multiple skin nodules that resolved on their own. He sought no prior medical treatment. Review of symptoms was positive for bilateral testicular masses not related to the present condition. He denied nausea, vomitting, diarrhea, constipation, fever, chills, bleeding, or weight loss. He had no prior medical or surgical history. He also denied any allergies.

On physical exam, multiple 1-3 cm erythematous nodules and papules of the face, arms, back, chest, and legs were noted. Besides the right testicular mass of 10 cm, and the left one of 7 cm, the

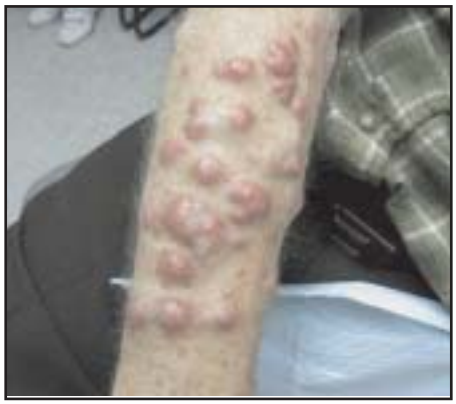


Figure 9

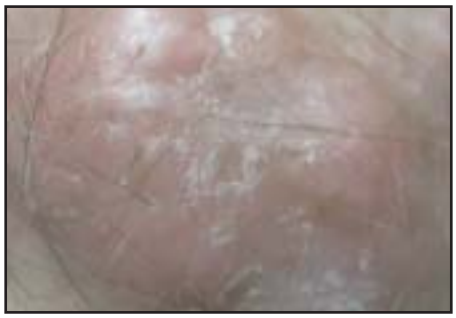


Figure 10

Figure 11

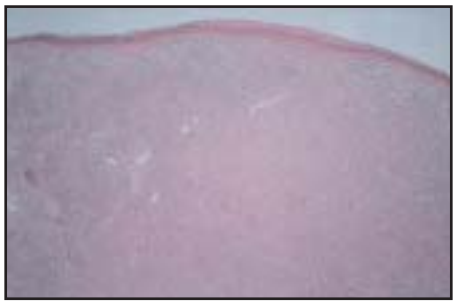


Figure 12
h and e, low power

remainder of the physical was negative, except for +1 edema of the lower extremities. No lymphadenopathy was present. (see figures 9-11)

Skin Biopsy revealed Leukemia cutis with dense and diffuse infiltrate of atypical mononuclear cells characterized by vesicular and irregularly shaped nuclei and relatively abundant pale-staining cytoplasm.

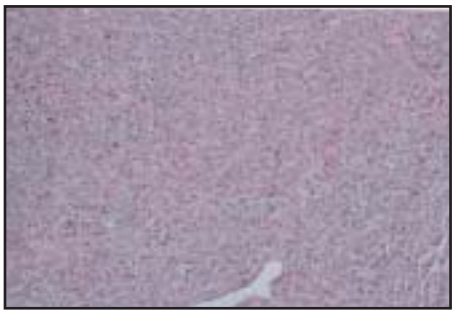


Figure 13
higher magnification

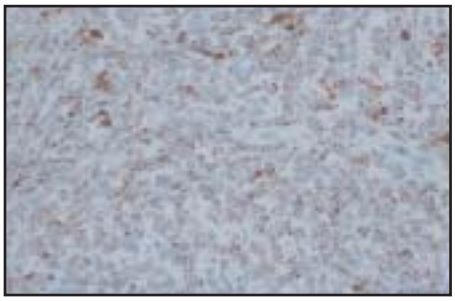


Figure 14
CD68

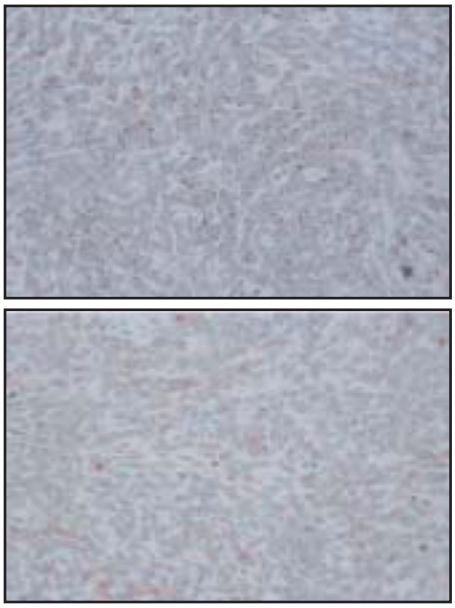


Figure 15
CD43, Lysozyme

Numerous mitotic figures are present. CD68, CD43, and lysozyme are positive, Myeloperoxidase, CD3, CD20, CD30, CD79A are all negative. (see figures 12-15)

His laboratory results were CBC- 5.1/ 9.5/ 27.6/ 165 RDW- 19.6 RBC- 3.22 Peripheral Blood Smear showed a normocytic anemia, mild neutropenia. Bone Marrow Biopsy and Aspirate revealed a hypercellular marrow, trilineage hematopoiesis with myeloid and megakaryocytic hyperplasia, patchy, mild to moder-

ate reticular fibrosis, and increased storage iron.

Assessment and Plan- Leukemia Cutis-diagnosis based on biopsy, Patient was sent for hematological and oncological evaluation and to begin treatment for acute leukemia. Unfortunately, this patient expired within the year from the time of diagnosis.

Leukemia Cutis

Leukemia cutis is a disease process seen in the skin either as a sign of dissemination of systemic disease or relapse of an existing leukemia. The skin is infiltrated with leukemic cells locally or in a diffuse manner. The leukemic cells are neoplastic leukocytes. Leukemia cutis is most commonly seen in patients with acute monocytic leukemia M5 and acute myelomonocytic leukemia M4. These patients tend to be older than 50 years but can be at any age, depending on the type of leukemia. The incidence of Leukemia cutis is high, 25- 30% in infants with congenital leukemia. Most of these cases are of the myelogenous type. (1,5,7)

Leukemia cutis is seen with or without a diagnoses of hematologic malignancy. It can be seen before the systemic leukemia presents itself.. It is generally uncommon and varies in incidence from <5 to 50%. In as many as 7% of patients with leukemia cutis, local disease occurs prior to bone marrow infiltration and systemic symptoms. Leukemia cutis is seen in both men and women, with a slightly higher prevalence in men.(6,1)

The primary skin lesions seen in Leukemia cutis are small papules, 2-5 mm, nodules, or plaques. The color tends to be pink, violaceous or darker than normal skin. The lesions are palpable, indurated, and firm. Patients may present with single or multiple nodules. They appear as guttate psoriasiform or lymphomatoid papulosis-like. Leukemia cutis tends to be nontender, localized or disseminated. Lesions can be found on the trunk, extremities, and face. There is considerable overlap with other inflammatory eruptions. Secondary lesions may be seen in Leukemia cutis. When thrombocytopenia is present, hemorrhage is possible. Ulceration may be present, as well as generalized erythroderma. With acute monocytic leukemia, leukemic gingival infiltration may occur. (1)

Inflammatory disorders in leukemic patients occur with unusual presentations due to the participation of leukemic cells in the infiltrates. Associated reaction patterns that can be seen are Sweets Syndrome, bullous pyoderma gangrenosum lesions, urticaria and palpable purpura.(1,6)

All types of leukemias result from the abnormal development of leukocytes in the bone marrow. Maturational arrest occurs and a proliferative clonal population of cells result. Leukemia cutis results possibly from the local proliferation of leukemic cells within the skin. But how does this occur? Why do leukemic cells migrate to the skin? The answer is unclear. Several theories are ongoing. One theory is that in HTLV-1 induced leukemia, there is an abundant expression of the cc chemokine receptor 4 (CCR4) on the cell surface of the leukemic cells. In adult T-cell leukemia involving the skin, the ligands thymus and activation regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL22) are seen in the skin. Another theory is that the presence of T-cell related antigens on the cell surface of leukemic cells in acute monocytic leukemia (AML-M5) in patients with leukemia cutis may promote selective homing to the skin.(1)

Leukemia cutis is relatively rare. The highest incidence is seen in adult T-cell leukemia/lymphoma (ATLL) with acute myelogenous leukemia(AML) following behind subtypes M4 and M5. Leukemia cutis is also seen in children, especially those infants with congenital leukemia.(7,1)

In evaluating the patient with Leukemia cutis, history is very important. Signs and symptoms to consider are extramedullary involvement, meningeal signs, anemia , secondary neutropenia, and other constitutional signs and symptoms. Bacterial, viral, or fungal infections can be present. CNS involvement can be seen as well as bone and joint pain due to leukemic infiltration.(1,9)

On physical, pallor, organomegaly, purpura, petechia, drug reactions, LCV, infections, thrush, and disseminated zoster may be present. Inflammatory cutaneous reactions may occur due to medications, infections, and the leukemia itself. Examples of this are graft vs. host disease, acute febrile neutrophilic dermatosis, and persistent arthropod bite-like reaction. More unusual lesions vary depending on the underlying leukemia.

AML-M4 and AML-M5 have characteristic gingival hypertrophy due to leukemic infiltration. One might see erythema nodosum, erythema annulare centrifugum, pyoderma gangrenosum, urticaria, urticaria pigmentosum, guttate psoriasis, leonine facies, and macular erythema. Leukemia cutis may occur within established scars and within recent areas of trauma.(1)

The differential diagnoses of Leukemia cutis is wide and varied. Disseminated infections occurring in the immunocompromised neutropenic host must be thought of. The inflammatory differential includes as previously mentioned; Sweets Syndrome, adverse drug reactions, transfusion reactions, GVHD, vasculitis and erythema multiforme. Metastatic carcinoma of the skin, CD30+ large cell anaplastic lymphoma, and non-Hodgkins lymphomas are malignant disease to consider in the differential.(3,1,10)

Laboratory studies should be done when a patient presents with leukemia cutis. A complete blood count helps to assess anemia, thrombocytopenia, neutropenia, or leukocytosis. Peripheral blood smear will tell of circulating leukemic cells. Chemistry profiles will assess BUN and Creatinine levels, especially important for chemotherapy. LDH and uric acid tends to be elevated in leukemic patients. If a patient has fever or signs of infection, cultures should be done. Imaging studies should be done appropriate to the cancer/ leukemia suspected and to assess extent of the disease.(1,8)

Skin biopsy is essential. An adequate punch or excisional biopsy should be done. Immunohistochemical staining is key to the diagnoses. The help to determine the cell lineage. CD45(LCA) and CD45RO are positive for T-cell lineage. CD20 is usually positive for B cells and CD43 is negative. Lysozyme and chloroacetate esterase is positive in granulocytes, while CD68 is negative. Lysozyme and CD68 are positive for monocytes, while chloroacetate esterase is negative.(4,1)

Bone marrow aspiration and biopsy are definitive for diagnosis of systemic leukemia. Special stains should be done to determine cell lineage and degree of maturation.

Histologic findings vary with the subtype of leukemia. In the dermis, a leukemic infiltrate is present. It is perivascular and periadnexal. Collagen bundles are sepatated by leukemic cells. Leukemic cells may infiltrate the lumina of blood vessels, their walls and down the fibrous septae of subcutaneous fat. The epidermis remains relatively normal and a Grenz zone is present.(1)

In AML, cells are large with an oval, vesicular nucleus and basophilic cytoplasm. In CML, all different degrees of maturation are seen as well as eosinophils. ALL has medium to large blasts, with a high nuclear-cytoplasmic ratio. CLL is more uniform, mature lymphocytes. Monocytic leukemia resembles large cell lymphoma but involves the entire dermis and superficial panniculus. ATLL cells have indented to lobulated nuclei. Epidermotropism is present. Hairy cell leukemia has monomorphous mononuclear cell. (1)

Prognosis of patients with leukemia cutis is directly related to the underlying disease. Most patients die within months of the diagnoses. Patients should be treated systemically form the time of diagnosis since the prognosis is so poor. Treatment is aimed at the type of leukemia found. Combination therapy is best; systemic chemother-

apy and local radiation. PUVA can also be considered. Treatment should be in conjunction with the hematologist and oncologist.(1,8)

References:

1. Rencic, Adrienne, et al. Leukemia Cutis emedicine.com/derm/topic 924.h+m 2004
2. McCollum, Amy BS; Bigelow, Carolyn L. MD et al. Unusual Skin Lesions in Chronic Myelomonocytic Leukemia, Southern Medical Journal 2003; 96:681-684
3. Wong, Raymond; Couriel, Daniel et al. The graft-vs.-leukemia effect in leukemia cutis Transplantation 2003; 76: 619-620
4. Miller, Michael K. MD et al. Concurrent Chronic Lymphocytic Leukemia Cutis and Acute Myelogenous Leukemia Cutis in a patient with Untreated CLL American Journal of Dermatopathology 2001: 23(4) 334-340
5. Chang, Howard Y. MD et al. Myelogenous Leukemia Cutis resembling stasis dermatitis JAAD 2003; 49:128-129
6. Sakalosky, Pamela E. MD et al. A Case of Acantholytic Dermatosis and Leukemia Cutis: Cause or Effect? The American Journal of Dermatopathology 2002; 24(3) 257-259
7. Isaacs, Hart Jr. MD. Fetal and Neonatal Leukemia. Journal of Pediatric Hematology/Oncology 2003; 25(5) 348-361
8. Zweegman, Sonja et al. Leukaemia cutis: clinical features and treatment strategies. Haematologica 2002; 87(04) ECR13
9. Bolognia, Jean MD, et al. Dermatology, Philadelphia, Pennsylvania, Leukemia Cutis; 2003 p.1946-1950
10. Odom, Richard B, et al. Andrew's Diseases of the Skin, Philadelphia, Pennsylvania Leukemia Cutis; 2000. p. 937-940

In Office Clinical Study
Sub Antimicrobial Dose Doxycycline in the Treatment of Acne Vulgaris

Jason A. Barr, D.O.*, Don A. Anderson, D.O.**
**3rd year resident, AZ Desert Dermatology/Midwestern University/Kingman Regional Medical Center*
***Program Director; AZ Desert Dermatology/Midwestern University/Kingman Regional Medical Center*

ABSTRACT

In the treatment of acne, sub antimicrobial dose doxycycline offers the proven benefit of decreasing inflammation without the side effects associated with traditional dosing. Patients receiving 25mg twice daily achieved a modest reduction of lesion counts without any side effects. Sub antimicrobial dose doxycycline should be considered as an adjunctive or maintenance therapy in the treatment of acne.

Introduction

Acne vulgaris is a common disease which carries significant psychosocial morbidity in its potential to scar. In the United States, acne affects most people between the ages of 11 and 30. (1) The goals of therapy include inhibition of microcomedone formation and reduction of inflammation. For the latter, tetracyclines have traditionally been used in antimicrobial (standard) doses. Excellent clinical results appear to correlate with reduced Propionibacteria acnes (P. acne) counts. (2)

Additionally, the tetracyclines have benefit independent of their antimicrobial properties. Using adult periodontitis as a model, investigators have demonstrated cytokine inhibition, decreased matrix metalloproteinase (MMP) activity and subsequent collagenolysis. (3, 4) Acne, like chronic periodontitis involves an exaggerated host response to overgrowth of resident bacteria.

Doxycycline is a member of the tetracycline class of antibiotics which binds and inhibits the 30S ribosome thereby inhibiting protein production. Doxycycline has a more favorable side effect profile than minocycline or tetracycline and appears to be a more potent MMP inhibitor. (5) Side effects of antimicrobial dose doxycycline include photosensitivity, gastrointestinal irritation, vaginitis and gram negative folliculitis.(6) Because of the common and long term use of the tetracyclines, increasing P. acnes resistance has been reported and must be considered when using doxycycline. (7)

Recently, sub antimicrobial dose doxycycline (Periostat, 20 mg) has proven to be effective and well tolerated in the treatment of acne without inducing bacterial resistance.(8) Our objective was to investigate the effectiveness and tolerability of sub antimicrobial dose doxycycline in a rural dermatology practice.

Methods:

Six patients with moderate acne vulgaris were treated with doxycycline hyclate 100mg, _ tablet by mouth twice a day. This formulation was chosen due to the lower cost compared to doxycycline hyclate 20mg. tablets. No other systemic or topical medications were allowed, including oral contraceptives were allowed. None of the patients had ever used isotretinoin. Lesion counts included open comedones, closed comedones, and cysts. Patients were asked if they experienced any side effects, including gastrointestinal irritation, photosensitivity or vaginitis. Initial lesion counts were compared to six week and three month lesion counts.

Results:

All patients tolerated the therapy well. No side effects were reported. All patients reported excellent compliance. All lesion counts were reduced. Open comedone counts were reduced 3% to 44%. Closed comedone counts were reduced 25% to 78%. Cysts were reduced 100%.

Patient-lesion count (open/closed/cysts)	6 weeks	3 months	% change
1 (50/31/2)	(36/25/0)	(28/18/0)	(-44%/-42%/-100%)
2 (42/25/0)	(32/12/0)	(33/13/0)	(-23%/-48%/0%)
3 (53/32/3)	(38/17/1)	(41/15/0)	(-23%/-54%/-100%)
4 (38/20/3)	(40/18/2)	(37/15/0)	(-3%/-25%/-100%)
5 (27/15/0)	(25/8/0)	(22/5/0)	(-19%/-78%/0%)
6 (48/29/2)	(32/21/1)	(30/12/0)	(-38%/-59%/-100%)

Discussion

The multi factorial effect of doxycycline makes it an excellent choice in the therapy of acne vulgaris. At traditional doses it works favorably but has the potential for causing GI irritation, vaginitis, photosensitivity, gram negative folliculitis and P. acnes resistance. The anti inflammatory effects of doxycycline include decreased polymorphonuclear leukocyte (PMN) chemotaxis and MMP activity, inhibition of cytokines, and decreased collagenolysis. These effects are independent of the anti microbial effect of doxycycline.

In our small series of patients we observed a modest reduction in the number of total and inflammatory lesions without any unwanted side effects. We believe sub antimicrobial dose doxycycline is an excellent choice for adjunctive therapy in combination with topical retinoids. This regimen may also be useful as a maintenance therapy once clinical improvement has been made with standard dose doxycycline alone or in combination with other therapy.

References:

1) Leyden JJ. Therapy for acne vulgaris. N Engl J Med. 1997; 336:1156-1162.

2) Bikowski JB. Subantimicrobial dose doxycycline for acne and rosacea. Skinmed. 2003:2(4):234-45.

3) Golub LM, Lee HM, Ryan ME, Giannobile WV, Payne J, Sorsa T. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res;12(2):12-26.

4) Choi DH, Moon IS, Choi BK, Paik JW, Kim YS, Choi SH, Kim CK. Effects of sub-antimicrobial dose doxycycline therapy on crevicular fluid MMP-8, and gingival tissue MMP-9, TIMP-1 and IL-6 levels in chronic periodontitis. J Periodontal Res. 2004;39(1):20-6.

5) Burns FR, Stack S, Gray RD. Inhibition of purified collagenases from alkali-burned rabbit corneas. Invest Ophthlmol Vis Sciences. 1989;30:1569-1575.

6) Vibramycin [package insert] New York, NY: Pfizer Inc; 1993.

7) Del Rosso JQ A status report on the use of sub antimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. Cutis. 2004;74(2):118-22.

8) Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J, Powala C, Ashley R. Effects of sub antimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol. 2003;139(4):459-64.

Dermatological Applications of Negative Pressure Wound Therapy (NPWT): Review of Technique and Mechanisms

Daniel J. Hansen, D.O., M.B.A.*, Steven K. Grekin, D.O., F.A.O.C.D.**
*** Intern, Oakwood Southshore Medical Center, Trenton, Michigan**
**** Dermatology Residency Program Director, Oakwood Southshore Medical , Center, Trenton, Michigan**

ABSTRACT

Over the past several years the use of negative pressure wound therapy has continued to increase. Its efficacy continues to be demonstrated in the hospital setting. Most dermatologists have yet to incorporate this modality into the treatment of wounds encountered in the ambulatory setting. The technique is described and the mechanisms are discussed. Benefits and costs of negative pressure wound therapy are explained.

Introduction

The negative pressure dressing is a relatively new concept in the management of both acute and chronic wounds. Wounds that were once treated in an open environment can now be treated in a closed, negative pressure environment that sets up conditions ideal for healing. The use of the negative pressure dressing has become more common since Morykwas et al demonstrated its effectiveness on swine models in 1997.[1] In the original study four parameters were measured: the amount of granulation tissue, bacterial clearance, Doppler measured flows in the surrounding tissue, and the amount of nutrient flow measured by random pattern flap survival. Each of these parameters showed improvement with the use of a negative pressure dressing.[1]

Over the last several years the use of negative pressure wound therapy has become more widespread, especially in hospitals and extended care facilities, but it has yet to make a large foothold in the ambulatory care setting.

Names by which the negative pressure dressing has been known are topical negative pressure therapy or TNP, vacuum ceiling technique or VST, sub-atmospheric pressure device or SPD, sealed surface with suction SSS, and the commonly used and proprietary term vacuum-assisted closure or VAC.

NPWT Technique

TThe Vacuum Assisted Closure (VAC) device is supplied by Kinetic Concepts Incorporated (KCI, San Antonio, Texas) who has been the exclusive manufacturer in the United States. This device uses medical grade, open cell polyurethane foam approved by the FDA as a wound dressing to fill the cavity of the wound. The foam is cut to fit the wound, filling the base, walls and undermined portions of the wound. The evacuation tube with side ports is then embedded into the foam and an adhesive plastic drape is applied over the area with a 3 to 5 cm border of intact skin. The opposite end of the tube is then attached to the vacuum with a canister for collection of wound effluent. The vacuum can be set for continuous negative pressure or intermittent cycles. There is a range of negative pressures to which the machine can be set depending on the wound and physician preferences.

The original study performed by Morykwas et al demonstrated that peak blood flows, measured by Doppler ultrasonography, were recorded with the vacuum setting of 125 mmHg. At more negative pressures blood flows began to decrease. It was also discovered that blood flows declined after five to seven minutes of negative pressure, eventually returning to baseline. After removing the negative pressure for a short period of time, increased flows and again be established.[1] Using this information, many clinicians have adopted a five minutes on, two minutes off regimen.

Many of the recommendations are based on anecdotal experience rather than scientifically proven protocols for every type of situation. It is felt that lower pressures are better suited for chronic ulcers, skin grafts, and certain painful wounds. Higher pressures are recommended for larger cavities and for acute traumatic wounds.[2] Banwell et al[3] recommends that the negative pressure dressing be changed every four to five days. However, if the wound is infected the suggested time interval for negative pressure dressing changes is every 48 hours. Still, these recommendations are based on anecdotal evidence.

Mechanisms of Action

For a wound to heal, keratinocytes must migrate from one side to the other and re-epithelialise the defect in the skin. Before this happens debris must be removed, infection controlled, inflammatory processes toned down, and granulation tissue must form. Proliferation, angiogenesis, chemotaxis, cell migration, gene expression, and protein production are all vital steps in wound healing. Any disruption in these processes can lead to the formation of a chronic wound.

Research is still being done to determine the exact mechanisms through which the negative pressure dressing speeds wound healing. Since the first publication by Morykwas et al in 1997, the number of studies on the effects of negative pressure wound therapy has greatly increased. The studies are based around the proposed mechanisms of reducing edema, increasing blood flow, increasing granulation formation, direct mechanical stress, and decreasing bacterial colonization.

Edema Reduction: It is postulated that by applying negative pressure to the wound excess edema can be removed. This edema can compress blood vessels and lymphatics, limiting their flow. The fluid removed by TNP has been analyzed and has been found to contain high amounts of proteolytic enzymes.[3] When left in the wound these enzymes slow collagen matrix formation. Removal of wound effluent encourages the diffusion of nutrients through the tissues.

Increased Blood Flow: The negative pressure encourages blood flow to the area. Using needle probe laser Doppler flowometry, Morykwas et al[1] demonstrated a fourfold increase in blood flow at a subatmospheric pressure of -125 mmHg on pigs models. Chen et al[4] recently used a rabbit model to show that the increase in blood flow is related to the increase in capillary caliber, density, and with angiogenesis. NPWT placed on human burns has also shown a similar increase in blood flow.[3] These direct effects on the vasculature are thought to increase vasomotor tone and cause the release of vasoactive mediators.

Mechanical Stress: It has been demonstrated that mechanical stress on the intracellular cytoskeleton, which is normally balanced by the extra cellular matrix, causes increased transcription for protein that leads to matrix molecule synthesis[5], angiogenesis[6], and re-epithelialization[7]. This process is then progressively up regulated by using the intermittent vacuum set-

ting, accounting for the faster healing times seen by Morykwas.[1]

Granulation tissue: Morykwas et al[1] demonstrated increased granulation tissue formation in swine models by making daily alginate molds of wounds treated with NPWT. These casts showed an increase in granulation tissue formation over the control of 63% on continuous suction and 103.4% with intermittent suction. The observation of increased granulation tissue production has been repeated by Fabian et al and Joseph et al using rabbit ear models.[8,9]

Bacterial Colonization: The use of negative pressure wound therapy correlates with a decrease in wound infection rates.[1,10,11] This improvement is thought to be due to the closed nature of the dressing, removal of edema, and fewer dressing changes.

Edema slows wound healing by impeding capillary blood flow to the wound bed and serving as a reservoir for infection. The negative pressure removes excess edema allowing an increase in blood flow to the area, which in turn and brings neutrophils and macrophages along with an increased supply of oxygen for the oxidative burst killing of bacteria.

In addition, polyurethane foam placed in the wound bed has been found to be an attractant for immune cells, possibly due to a foreign body type reaction.[12]

Indications/Contraindications

The use of negative pressure wound therapy is indicated for chronic open wounds, diabetic ulcers, dehisced wounds, partial thickness burns, pressure ulcers, flaps and grafts, acute and traumatic wounds. Contraindications include malignancy in the wound, untreated osteomyelitis, presence of necrotic tissue, and frank pus. The physician must also use good judgment when treating a wound with active bleeding and when treating a patient on anticoagulants.

Dermatological Applications

To date, the majority of clinical negative pressure wound therapy studies have been performed by surgeons and those in surgical subspecialties with patients who reside in either a hospital or a nursing home. This has largely been due to the static nature of the Vacuum Assisted Closure (V.A.C.TM) device supplied by Kinetic Concepts Incorporated (KCI, San Antonio, Texas) who has been the exclusive manufacturer in the United States. However, KCI has recently introduced a more compact, portable model that is better suited for the ambulatory patient more frequently encountered by dermatologists.

Chronic ulcers: Dermatologists frequently encountered patients with chronic leg ulcers that require meticulous care and repeated wound dressings as the healing process slowly takes place. The negative pressure wound dressing increases the rate of granulation tissue formation by increasing blood flow, removing metalloproteinase laden edema and decreasing bacterial colonization allowing the chronic ulcer to heal.

A group in France has studied the negative pressure wound therapy technique for chronic leg ulcers. Fifteen patients who had been unsuccessfully treated by other methods used negative pressure therapy. After six days four patients had greater than 50% reduction in wound size and six patients had greater than 25% reduction.[13]

Flaps and grafts: Negative pressure wound therapy is indicated for use on flaps and grafts. It aids in preparing a suitable wound bed of granulation tissue for placement of the graft. Once the graft or flap is in place, the dressing acts as a bolster, providing a firm fixation and preventing shearing forces.[14] The vacuum dressing is useful because it adapts easily to both convex and concave surfaces. The negative pressure aids in the evacuation of seromas and hematomas that could threaten the viability of the tissue transplant.[15] As previously mentioned, there is also an increase in oxygen tension and angiogenesis and a decrease of infection rates when using negative pressure dressings.

Cost

One of the earliest objections to the use of negative pressure wound therapy was unnecessary expense. There are costs associated with the purchase or hire of a VAC unit and the specialized dressing materials: foam, adhesive covering, and tubing. Reported analysis show that these high costs are offset by the shorter length of treatment when compared to a more traditional bandaging regimen.[16]

Once medical necessity is determined, the equipment is obtained from KCI who is currently the only supplier of negative pressure wound therapy equipment in the United States. Medicare or other third party reimbursement is sent directly to KCI. Reimbursement criteria for the use of NPWT vary state to state and should be reviewed before prescribing its use.

Conclusion

Negative pressure wound therapy is a relatively new concept in wound management. It has been shown to be a useful and effective modality for wound treatment. So far, the focus of its use has been on the non-ambulatory patient. Because wounds are as varied as are patients, negative pressure wound therapy is not indicated in all situations. As knowledge of its effectiveness grows more suppliers of the equipment will enter the marketplace, bringing its cost down. It may soon find its way into the dermatologist's armamentarium to treat chronic, non-healing ulcers and as an adjunct therapy in the treatment of surgical wounds.

References:

1. Morykwas MJ, Argenta LC, Shelton-Brown EI, et al. Vacuum assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 1997;38:553–562.
2. Morykwas MJ, Argenta LC. Vacuum assisted closure: a new method for wound control and treatment: clinical experience. Ann Plast Surg 1997;38:563–576.
3. Banwell PE, Teot L, Topical negative pressure (TNP): the evolution of a novel wound therapy. J Wound Care 2003;12:28–30.
4. Chen SZ, Li J, Li XY, et al. Effects of Vacuum-assisted closure on wound microcirculation: an experimental study. Asian Jour of Surg 2005;28:211-7
5. Ilizarov GA, The tension stress effect on the genesis and growth of tissues. Part I. The influence of stability of fixation and soft tissue preservation. Clin Orthop Relat Res 1989;238:249–281.
6. Ichioka S, Shibata M, Kosaki K, et al. Effects of shear stress on wound-healing angiogenesis in the rabbit ear chamber. J Surg Res 1997;72:29-35
7. Brunette DM, Mechanical stretching increases the number of epithelial cells synthesizing DNA in culture. J Cell Sci 1984;69:35-45
8. Fabian TS, Kaufman HJ, Lett ED, et al. The evaluation of subatmospheric pressure and hyperbaric oxygen in ischemic full-thickness wound healing. Am Surg 2000;66:1136-43
9. Joseph E, Hamori CA, Bergman S, et al. A prospective randomized trial of Vaccurm-assisted closure versus standard therapy of chronic nonhealing wounds. Wounds 2000;3:60-7
10. Gustaffson R, Johnsson P, Algotsson L, et al. Vacuum assisted closure therapy guided by C reactive protein level in the treatment of deep sternal wound infection. J Thorac Cardiovasc Surg 2002;123:895–900.
11. Buttenschoen K, Fleischmann W, Haupt U, et al., The influence of vacuum assisted closure on inflammatory tissue reactions in the post operative course of ankle fractures, Foot Ankle Surg 2001;7:165–173.
12. Gouttefangeas C, Eberle M, Ruck P, et al. Functional T lymphoctyes infiltrate implanted polyvinyl alcohol foams during surgical wound closure therapy, Clin Exp Immunol 2001;24:398–405.
13. Loree S, Dompmartin A, Penven K, et al., Is vacuum assisted closure a valid technique for debriding chronic leg ulcers? J Wound Care 2004;13:249–252
14. Blackburn JH 2nd, Boemi L, Hall WW, et al. Negative-pressure dressings as a bolster for skin grafts. Ann Plast Surg. 1998;40:453-7
15. Schneider AM, Morykwas MJ, Argenta LC. A new and reliable method of securing skin grafts to the difficult recipient bed. Plast Reconstr Surg 1998;102:1195-8
16. Philbeck TE Jr, Whittington KT, Millsap MH, et al., The clinical and cost effectiveness of externally applied negative pressure wound therapy in the treatment of wounds in home healthcare medicare patients. Ostomy Wound Manage 1999;45:41-50

Imiquimod in the Treatment of Extramammary Paget's Disease

David M. Bracciano, D.O.*, Kimball Silverton, D.O.**
***3rd Year Resident, Michigan State University, Genesys Regional Medical Center, Grand Blanc, Michigan**
****Program Director, Dermatology Residency, Genesys Regional Medical Center, Grand Blanc, Michigan**

ABSTRACT

The diagnosis and treatment of Extramammary Paget's Disease can be challenging for even the most accomplished dermatologist. Surgery remains the "gold standard' of treatment, however the morbidity associated with excision in elderly patients is high. In this paper we present a novel approach to treatment of Extramammary Paget's disease with immiquimod applied topically. The history of Extramammary Paget's disease and other treatment options will also be discussed.

Introduction

Extramammary Paget's (EMPD) disease is relatively rare intraepithelial neoplasm that often proves difficult to treat. Multiple treatment modalities have been attempted in the past with mixed results. These include wide local surgical excision, radiation therapy, chemotherapy, photodynamic therapy, and MOHS micrographic surgery.4,5,6,7 Despite these efforts high local reoccurrence rates continue to frustrate patients and their physicians. The introduction of biologic response modifiers offers many theoretical benefits when applied to the treatment of cutaneous viral and neoplastic disease. In this paper a case of Primary Cutaneous Extramammary Paget's disease of the scrotum is treated with imiquimod as monotherapy. We will also review the current literature in order to provide a rational framework for clinicians when treating this perplexing entity.

Case Report

A 93 year old white male was referred to the Department of Dermatology due to a left inguinal area "rash". The patient stated that he first noticed itching and redness at the left inguinal area and scrotum approximately six months prior to his visit. He self-treated this area with topical antibiotics without improvement. His primary care physician prescribed topical antifungal medications, and there was no improvement. He denied any pain or discomfort in the area. He denied any change in urinary or bowel habits. On exam there was diffuse erythema with some excoriation at the left inguinal and scrotal areas. The penis, rectum, and right scrotal and right inguinal areas showed no abnormalities. KOH prep and fungal cultures of the site were negative.

Punch biopsy of the left inguinal area revealed large polygonal cells with focally vacuolated pale cytoplasm, large nuclei, and prominent nucleoli (Fig.1). Similar tumor cells extended along the apocrine duct epithelium. These cells are mucicarmine (Fig.2) and alcian blue/PAS (+), pancytokeratin (AE1/3) (+), EMA (+), HMB45 (-), and S100 protein (-).

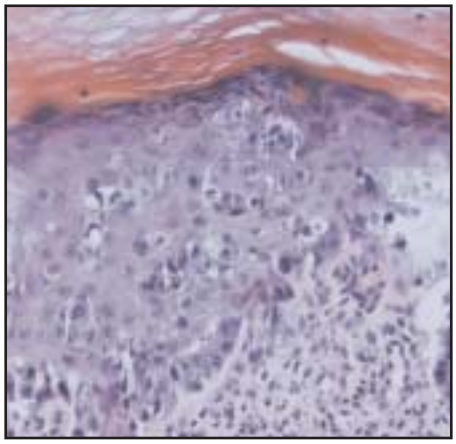


Figure 1
H & E Stain

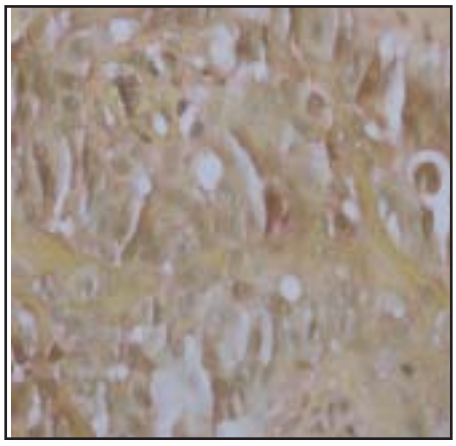


Figure 2
Mucicarmine stain

The patient underwent CT scanning of the abdomen which revealed no masses or adenopathy. Urology and Gastroenterology evaluations including cystoscopy and colonoscopy were unremarkable.

The patient and his family were apprised of the diagnosis of Primary Extramammary Paget's Disease, and treatment options were discussed in detail. The extent of skin involved at the left scrotum and inguinal area (11cm x 9.5cm) meant that surgical treatment would require significant flaps or grafts to close the defect (Fig 3). The patient and his family were concerned about the patient's ability to tolerate such an exten-

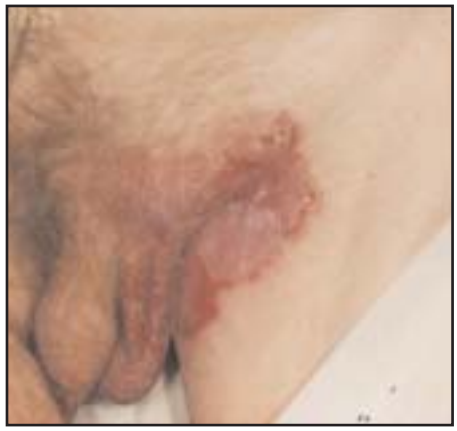


Figure 4
Pretreatment

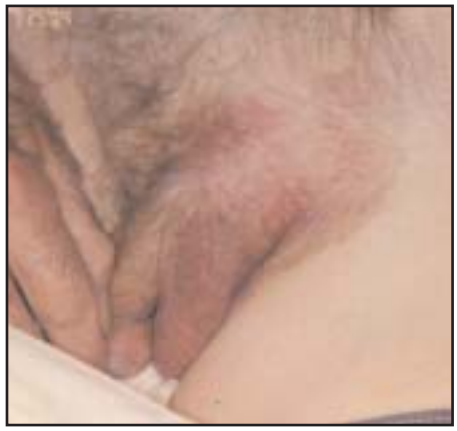


Figure 5
Post Imiquimod treatment

sive procedure at his advanced age. At the time of the patients' diagnosis a literature search uncovered a few initial case reports showing promising results in the treatment of EMPD with imiquimod.13,12 It was explained to the patient that a trial of the therapy with imiquimod could be attempted, with surgical salvage reserved for treatment failure.

Treatment was begun with imiquimod applied to all areas of erythema once a day for five days a week, for a total of six weeks. The patient was instructed to apply the cream to the entire area involved, and to include a 2cm area of normal appearing surrounding skin. Initially the patient developed mild burning at the application site, this resolved after a five day pause in the treatment. After three weeks of treatment there was mild weeping at the center of the treatment area. Upon completion of the six week course of imiquimod there was noted to be central clearing of the erythema and the patient denied pruritis or discomfort. After one month another six week course of imiquimod was instituted. After four weeks a third six week course was completed. The second and third courses of treatment were well tolerated. Clinically the lesion had markedly improved (Fig 4). Repeat biopsy, however, showed a small (2.4cm) area of residual disease. Again surgery versus further imiquimod was discussed, and the patient is currently undergoing his fourth course of topical imiquimod therapy.

Discussion

Sir James Paget first described a lesion involving the nipple in 18741. This case was associated with underlying breast carcinoma. In the same paper he also described a similar lesion with a "rawness" of the glans penis. The "raw" erosive lesions which he described became known as "Paget's Disease". In 1889 Crocker reported the first case of scrotal EMPD2. As of 2001 less than 100 cases of scrotal EMPD had been described in the literature3. The exact etiology of Extramammary Paget's Disease (EMPD) remains controversial. Most authors believe that it originates from malignant degeneration and aberrant proliferation of epithelial stem cells, often of apocrine origin, presenting as a solitary primary epithelial neoplasm referred to as Primary Cutaneous Extramammary Paget 's disease. There has long been known to be a subtype of EMPD associated with adenexal and visceral malignancies. Study estimates vary widely as to the incidence of this association with underlying malignancy. A recent study suggests a range of 10% to 40% of patients with EMPD have a concurrent and related cancer.8 The most frequent sites of associated cancers are rectal, genitourinary, uterine, breast, hepatic, pancreatic, and adenexal (porocarcinoma).

The apocrine derivation of EMPD is supported by its histologic picture and immunohistochemical studies. Paget's cells are large round cells with abundant pale staining cytoplasm, and a large central reticulated nucleus. Paget's cell may be seen singly, or in clusters, scattered throughout the epidermis. There is epidermal acanthosis or hyperkeratosis. Definitive diagnosis of EMPD requires immunohistochemical staining.10 Due to its' epithelial origin cytokeratin is found in Pagetoid cells. Therefore staining with Cytokeratin 7 (CK7) and Cytokeratin 8 (CK8) will be positive. The apocrine association of the tumors is reflected by the presence of mucin in the Paget's cells. Subsequently, staining for mucin with musicarmen, alcian blue, aldehyde fuschsin, and colloidal iron will be positive.6 Slides are PAS-positive, and diastase-resistant. Other immunohistochemical studies with antibodies directed against low-molecular weight keratins will yield positive results (GCDF-15, EMA, Cam 5.2,). CEA levels may also be elevated in cases associated with underlying malignancy.

EMPD is more prevalent in women than men, with an incidence ratio of 1.4/1.0 and an average age of onset greater than 50 years. In most cases EMPD eludes diagnosis for a period of years. Lesions present on the vulva in 60%, perianal area in 33%, with the remainder occurring at other sites; axillae, eyelids, umbilicus, external auditory canals, mucocutaneous junctions, and most recently the face.14 The presenting symptom is often pruritis at the site. The skin examination reveals a non-descript area of erythema. There may be weeping and oozing with excoriations. Chronic findings include a localized area of eczematous skin with plaque formation averaging 6 to 12 cm in diameter. Crusts, scales and ulcerations may eventually signal the malignant nature of the disease. The non-specific clinical presentation often leads to misdiagnosis. Usually patients are treated for such entities as tina cruris, pruritis vulva, lichen sclerosis et atrophicus, or candidiasis for an average of two years before a biopsy confirms the true diagnosis of EMPD.

Recent treatment protocols for EMPD have emphasized the need for a vigorous search for underlying malignancy once the cutaneous disease has been identified. If an underlying malignancy is found, up to 50% of patients will already have metastatic disease and a poor prognosis with average survival of less than three years. Treatment options include: wide local excision with 2 cm margins, Mohs surgery, radiation therapy, chemotherapy, photodynamic therapy and most recently topical therapy with imiquimod.7,11 Surgical therapy presently is the "gold standard" for treatment of EMPD. Mohs surgery in particular has shown improvement in the high rate of reoccurrences. The multicentric nature of EMPD is a leading cause of treatment failure. Mohs surgery with intraoperative immunostaining with cytokeratin 7 can help to map out the peripheral margins of the tumor.9

Conclusion

Due to the location, a surgical approach to primary EMPD of the scrotum is fraught with difficulty. Often these patients are elderly, and wide excision with flaps and/or grafts for closure of the defect can expose these patients to significant perioperative morbidity and mortality rates. Thus the promise of imiquimod as topical monotherapy is quite attractive. Imiquimod is a biologic response modifier that stimulates both innate and acquired immunity. Stimulation of cytokine production by macrophages and dendritic cells activates the innate immune response via increased natural killer cell activity. The acquired arm of immunity is indirectly stimulated by increased cytokine production. Interleukin 2 production is increased and causes interferon gamma production from T lymphocytes. Bcell activation has also been shown to stimulate higher immunoglobulin production. Imiquimod also increases Langerhan cell migration from skin to lymph nodes, therefore increasing antigen presentation.

Phase 1 clinical trial of oral imiquimod reveals possible systemic effects similar to injectable interferon. In-vitro studies have shown imiquimod to inhibit tumor-associated angiogenesis. In patients with melanoma, renal cell carcinoma, and hairy cell leukemia this promises to provide the benefits of interferon therapy without the associated immunogenicity and tolerance seen with injectable interferon treatments today. Topical imiquimod has little (less than 1%) systemic absorption. However side effects include local irritation, fever, malaise, fatigue, nausea, arthralgias and diarrhea.12 Local irritation occurs more often when treating skin cancers and may be exacerbated by increased absorption through the actinically damaged skin. Case reports of imiquimod in the treatment of verruca, basal cells, squamous cells, melanoma, colon cancer, sarcoma bladder cancer, and EMPD will lead to further investigation in both topical and oral therapy in the future.

In summary, Extramammary Paget's Disease of the scrotum is a somewhat rare and difficult to treat entity. Often EMPD presents in elderly patients in whom traditional surgical or radiation treatment is precluded due to patient comorbidity factors. With further studies treatment protocols with topical imiquimod may have a significant role in the dermatologist's armamentarium.

References:

1. Paget J: on disease of the mammary areola preceding cancer of the mammary gland. St. Bartholomew's Hosp Rep 10:87-89,1874.
2. Crocker HR: Paget's disease affecting the scrotum and penis. Transcr Pathol Soc Lond 40: 187-191, 1889.
3. Ng LG: Extramammary Paget's Disease of the Scrotum. Urology 58(1), 105ix-105xi, 2001.
4. Guerrieri M: Extramammary Paget's Disease: Role of radiation therapy. Australasian Radiology 46, 204-208, 2002.
5. Hendi, A, Zittelli, JA,: Extramammary Paget's Disease: Surgical treatment with Mohs micrographic surgery. J Am Acad Dermatol Vol 51:5 Nov 2004:767-773.
6. O'Connor, WJ: Comparison of Mohs Micrographic Surgey and Wide Excision for Extramammary Paget's Disease. Dermatol Surg 29:7 July 2003, 723-727.
7. Berman, B: Novel Dermatologic Uses of the the Immune Response Modifier Imiquimod 5% Cream, Skin Therapy Letter, Vol7:9 Nov 2002, 1-6.
8. Braverman, IM: Skin Manifestations of Internal Malignancy. Clinics in Geriatric Medicine, Vol 18:1, February 2002, 1-19.
9. Naohito H: Sentinel Lymph Node Biopsy in Patients with Extramammary Paget's Disease. Dermatol Surg 30:10: October 20041329-1334
10. Yang, C-C: Depigmented Extramammary Paget's Disease. British Journal of Dermatology 2004, 151:1049-1053.
11. Shieh S: Photodynamic therapy of the treatment of Extramammary Paget's Disease. British Journal of Dermatology 2002; 146: 100-1005.
12. Wang LC: Successful treatment of recurrent Extramammary Paget's Disease of the vulva with topical imiquimod 5% cream. J Am Acad Dermatol, Volume 49, Number 4, October 2003, 769-770.
13. Zampogna JC: Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy: Two case reports. J Am Acad Dermatol, Volume 47, Number 4, October 2002, S229-S235.
14. Cohen MA: Extramammary Paget's Disease Presenting on the Face. Dermatol Surg, 30:10:October 2004, 1361-1363.

NOW APPROVED

FOR ACTINIC KERATOSIS AND SUPERFICIAL BASAL CELL CARCINOMA

3M Pharmaceuticals

3M

Members of the AOCD may advertise "position available."

This is a free service for all active members of the AOCD. A 3" column black and white ad will be provided in the journal as a free service. If members wish to use a larger space, they may do so. The cost for this advertising is:
Black and White - 1/4 page-$125, 1/2 page-$200, full page-$350
Full 4 color ad - 1/4 page-$275, 1/2 page-$350, full page-$500
Resident members may run a 3" column black and white ad stating their desired professional position.
These ads must be submitted as an e-mail attachment and sent to jaocd@aol.com.
Any photos to be included in an active member's ad, must be in a .pdf format.

Position Available Soon!!

MIRAMAR, FLORIDA. Brand new practice. Great demographics! On the prestigious Memorial Miramar Hospital campus, 6 exam rooms (including two surgical rooms), in office frozen section for surgery, esthetic room, full time esthetician, full time PA, paperless electronic health records (no charts, no Rx pads and no note pads), unique skin care product line, state of the art web site allowing for patient registration and skin care product sales, Lumenis IPL, LightSheer hair removal laser, Iridex Diolite laser, in office marketing and patient education with flat screen monitors in every exam room, reception area and in the in-office surgical waiting area. XFM music throughout office, employee biometric time clock. Looking for dermatologist wanting to build a great practice in a great location. May be part time. Willing to talk to dermatology residents graduating in the next 18 months. Physician inquiries only, No employment services

Please Inquire:
Jay S. Gottlieb, DO, FAOCD
www.miramarDermatology.com
E-mail: jay1953@aol.com
Phone: 954-963-5875

Palisaded Neutrophilic Granulomatous Dermatitis A Disease Spectrum: A Case Report And Review Of The Literature

Carissa Summa, D.O.*, Risa Gorin, D.O., Cindy Hoffman, D.O.***, Damian DiCostanzo, M.D. ******

**3rd Year Resident, Lutheran Medical Center, Brooklyn, New York*

***Attending Dermatology Physician, New Jersey*

****Program Director, Lutheran Medical Center, Brooklyn, New York*

*****Dermatopathologist, Ameripath Inc., Port Chester, New York*

ABSTRACT

Palisaded neutrophilic granulomatous dermatitis (PNGD) is an entity that has not been clearly defined either clinically or histopathologically. It typically presents in patients with rheumatoid arthritis and other connective tissue diseases. The various clinical and histologic presentations of PNGD have given rise to several different names. A case of a 61 year-old female with rheumatoid arthritis developing PNGD is presented. In addition, clinical and histologic features of PNGD are reviewed. It is proposed that PNGD should be viewed as a disease spectrum with many clinical and histologic presentations, which coincide with the disease progression.

Case Report

A 61 year-old Hispanic female presented to Dermatology clinic for evaluation of several lesions. The lesions began on the elbows several years prior and subsequently developed on the hips and distal fingers. Topical antibiotics and oral steroids were used twice daily without relief.

The patient had a known history of diabetes mellitus, hypertension, congestive heart failure, peripheral vascular disease, and rheumatoid arthritis. Past surgical history was significant for bilateral below the knee amputations, which left her wheel chair bound. She denied any allergies to medications. She was taking Azathioprine, Etanercept, Furosemide, Nitroglycerin, Colchicine, calcium, and oral steroids.

A comprehensive cutaneous examination revealed well defined annular erythematous to violaceous plaques on bilateral elbows (Figure 1). Multiple grouped tense vesicles on the left hip and crusted erosions on the right hip were noted a few weeks prior to presentation (Figure 2). Violaceous nonblanchable macules on the right first and fourth and left fourth and fifth digits were noted a few days earlier (Figure 3). Mucous membranes were spared. Positive laboratory studies included a rheumatoid factor of one to sixteen and antinuclear antibody of one to forty in a speckled pattern.

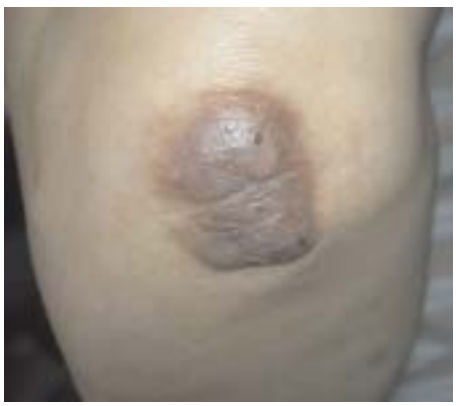


Figure 1
Erythematous and violaceous plaque on right elbow

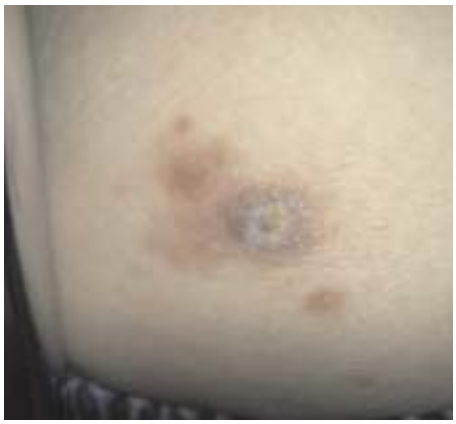


Figure 2
Crusted erosions on left hip

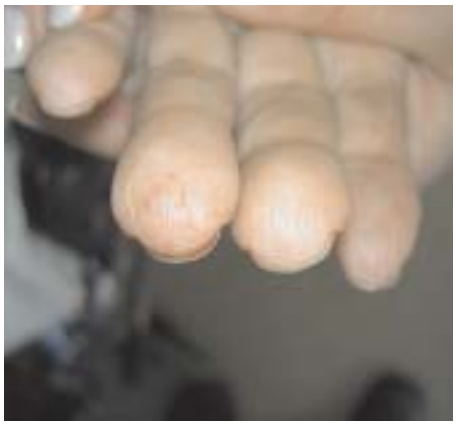


Figure 3
Erythematous macules on right digits

The clinical differential diagnosis of the elbow lesions included psoriasis, erythema elevatum diutinum, urticarial vasculitis, Sweet's syndrome, rheumatoid neutrophilic dermatitis, palisaded neutrophilic granulomatous dermatitis, bowel-associated dermatosis-arthritis syndrome, pyoderma gangrenosum, and Behcet's disease. The hip and digit lesions were believed to be a separate disease process at this time. The differential diagnosis of the hip included Herpes simplex virus, pressure or friction blisters secondary to the wheel chair, and autoimmune bullous disease. Vasculitis, trauma and infection were considered for the digit lesions.

Two 3 mm punch biopsies were taken from the right elbow and left hip. The patient refused a digit biopsy. Histologically, the elbow biopsy revealed palisaded granulomas with suppuration and neutrophilic dust. A dense perivascular and interstitial neutrophilic infiltrate, collars of fibrin in blood vessel walls and diffuse fibrosis was noted (Figures 4 and 5). These findings were consistent with a diagnosis of PNGD. Subepidermal bullae with neutrophils and focal necrosis were found on the hip biopsy. These findings are representative of the spectrum of histologic findings associated with PNGD.

Therapy with Fluocinonide ointment 0.5% and mupirocin cream was initiated twice daily. The patient was also continued on the biologics and immunosuppressives by the rheumatologist. Lesions improved over the course of several weeks. The patient has since been lost to follow up.

Comment

Palisaded neutrophilic granulomatous dermatitis (PNGD) is still considered an unusual entity that has not been completely defined, either clinically or histologically.1 This process has been given a variety of names throughout its evolution.

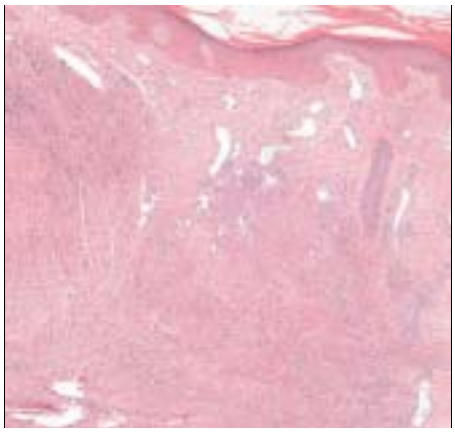


Figure 4
H & E stain of 3 mm punch biopsy of right elbow at 100X showing palisaded neutrophilic and granulomatous dermatitis with suppuration and neutrophilic dust. There is a dense perivascular and interstitial neutrophilic infiltrate, collars of fibrin in blood vessel walls and diffuse fibrosis.

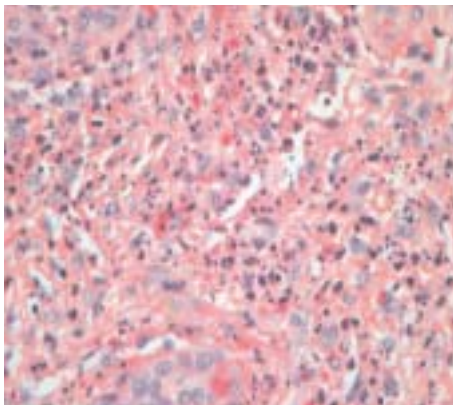


Figure 5
H & E stain of elbow biopsy at 400X with diffuse and dense neutrophilic dust.

These include Churg-Strauss granuloma, cutaneous extravascular necrotizing granuloma, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis, linear subcutaneous bands, and interstitial granulomatous dermatitis with cutaneous cords and arthritis.[2,3,4,5] This process has been associated with rheumatoid arthritis, systemic lupus erythematosis, other connective tissue diseases, inflammatory bowel disease, and systemic vasculitis.[1]

The numerous terms are a reflection of the spectrum of clinical presentations associated with PNGD. In 1965, Dykman et al were the first to report on patients with PNGD and severe rheumatoid arthritis.[4] These patients presented with linear subcutaneous bands on the lateral trunk which histologically resembled rheumatoid nodules. In 1995, Gottlieb and Ackerman reported ten patients with similar linear band lesions with rheumatoid nodule features.[1] In 1989, Smith et al described papular lesions in patients with rheumatoid arthritis with features of leukocytoclastic vasculitis and palisading granulomas.[6] In 1990, Sanchez and Cruz described three patients with rheumatoid arthritis with nodules and papules over the extremities. Histologic exam revealed a dense neutrophilic infiltrate resembling Sweet's syndrome.[7]

Of note is a review of PNGD and rheumatoid arthritis by Sangueza et al in 2002.[1] Clinically patients presented with erythematous to violaceous plaques, papules, and nodules, and subcutaneous linear bands. Lesions varied from painful to asymptomatic and occurred on different body areas including fingers, buttocks, shoulders, wrists, thighs, chest, and sacrum. The majority of these patients had rheumatoid arthritis or another associated connective tissue disease.

The above references demonstrate the spectrum of clinical presentations of PNGD. There are several differential diagnoses to be entertained when a patient presents with cutaneous lesions and a history of rheumatoid arthritis or another connective tissue disease. These diagnostic possibilities should be grouped as neutrophilic dermatoses associated with connective tissue diseases. The most notable are PNGD, rheumatoid neutrophilic dermatitis, erythema elevatum diutinum, and Sweet's syndrome.

Ackerman originally described rheumatoid neutrophilic dermatitis in 1978.[1] These lesions typically present on the trunk, shoulders, neck and extremities and occur most in association with high rheumatoid factors in middle-aged women. Erythema elevatum diutinum presents most often as symmetric papules or plaques on the extensors that wax and wane for several years. Sweet's presents as erythematous plaques with a "mountain range" appearance on various body sites. Lesions may be painful at times. All of these diseases have similar clinical presentations and may occur with connective tissue diseases. Histologically, they all have a prominent neutrophilic infiltration.

In addition to the clinical spectrum of PNGD, a histologic spectrum has been described which corresponds to the progression of the disease. In 1994, Chu et al evaluated several patients with diagnosed PNGD and reviewed the histopathologic trend.[8] Multiple biopsies showed early lesions typically demonstrate a small vessel vasculitis. Leukocytoclastic vasculitis was evident throughout the entire dermis. A pandermal neutrophilic infiltrate and collagen degeneration were noted. Vasculitic foci had a palisaded appearance where broad collars of fibrin separated vessels. In fully developed lesions, neutrophils were diminished in number. Palisaded granulomas surrounded fibrin and thick collagen bundles. In old lesions, palisaded granulomas contained degenerated collagen and only scattered neutrophils. No fibrin was found in vessel walls, but the dermis was fibrotic.[8]

The exact cause of this disease progression is only speculative at best. These lesions appear to begin as a vasculitis most likely from immune complex deposition secondary to the associated connective tissue diseases. The vasculitic injury causes ischemia, altering collagen and inducing a granulomatous reaction. These immune complexes may also trigger a granulomatous reaction.

A histologic differential diagnosis must also be examined for completeness. Since early lesions of PNGD are a distinctive small vessel vasculitis, it has to be differentiated from conventional leukocytoclastic vasculitis. LCV has abundant extravasation of red blood cells and PNGD has collagen degeneration occurring with the vasculitis. Rheumatoid neutrophilic dermatitis (RND) should be considered in early lesions as well. RND has a dense neutrophilic infiltrate without LCV. RND does not develop a granulomatous reaction. Features of PNGD may overlap with rheumatoid nodules, but PNGD is mostly dermal and rheumatoid nodules extend into the subcutis. Fully developed lesions may resemble granuloma annulare, but only PNGD has thick altered collagen bundles. Erythema elevatum diutinum is a form of localized vasculitis that resolves with fibrosis, but no development of palisaded granulomas.[8]

PNGD should be regarded as a clinical and histologic spectrum of a disease process. PNGD has various clinical and histologic presentations that coincide with the disease evolution. Early lesions appear both clinically and histologically as a vasculitis. With progression, lesions appear both clinically and histologically as a granulomatous, dermal process and may vesiculate. It should be stressed that PNGD is a neutrophilic dermatosis and occurs in the setting of a connective tissue disease, most notably rheumatoid arthritis. The pathophysiologic role of immune complexes requires further investigation.

This patient appeared to show lesions in various stages of PNGD. The digits appeared as early vasculitis clinically. The hip lesions resembled the progression to granuloma formation and the elbows are the old lesions with fibrosis and collagen degeneration. In addition, she had severe rheumatoid arthritis with a positive rheumatoid factor. In conclusion, PNGD and other neutrophilic dermatoses should

be considered in any patient with rheumatoid arthritis or another connective tissue disease and cutaneous findings. Treatment is symptomatic and if no resolution, immunosuppressives and/or Dapsone may be implemented. Let us not forget that cutaneous manifestations of internal disease are often the first presentation. It is imperative that as Dermatologists we work in conjunction with the primary care providers and/or rheumatologists in treating these patients.

References:

1. Sangueza OP, Caudell MD, Mengesha YM. Palisaded neutrophilic granulomatous dermatitis in rheumatoid arthritis. J Am Acad Dermatol 2002;251-7.
2. Finan MC, Winkelmann RK. The cutaneous extravascular necrotizing granuloma, and systemic disease:a review of 27 cases.Medicine 1983;62:142-58.
3. Magro CM, Crowson AN, Schapiro BL. The interstitial granulomatous drug reaction:a distinctive clinical and pathologic entity. J Cutan Pathol 1998;25:72-8.
4. Dykman CJ, Galens GJ, Good AE. Linear subcutaneous bands in rheumatoid arthritis:an unusual form of rheumatoid granuloma. Ann Intern Med 1965;63:134-40.
5. Gottlieb GJ, Duve RS, Ackerman AB. Interstitial granulomatous dermatitis with cutaneous cords and arthritis: linear subcutaneous bands in rheumatoid arthritis revisited. Dermatopathology: Practical and Conceptual 1995;1:3-6.
6. Smith ML, Jorizzo JL, Semble E, Arrington JH, White WL. Rheumatoid papules: lesions showing features of vasculitis and palisaded granulomas. J Am Acad Dermatol 1989;20:348-52.
7. Sanchez JL, Cruz A. Rheumatoid neutrophilic dermatitis. J Am Acad Dermatol 1990;22:922-5.
8. Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neutrophilic granulomatous dermatitis in patients with collagen vascular disease. Arch Dermatol 1994;130:1278-83.

A Case of Pemphigus Foliaceus Transforming into Pemphigus Vulgaris

Michael R. Hohnadel D.O.*, Bill V. Way, D.O., F.A.O.C.D., Robert J. Lin, B.S.*****
**3rd Year Resident, K.C.O.M. Dept of Dermatology, TX Division. Duncanville, TX.*
***Chairman, Dept. of Dermatology KCOM, TX Division, Duncanville, TX.*
**** Graduate-College of Electrical Engineering, University of California, San Diego*

ABSTRACT

A male patient initially presented with biopsy proven pemphigus foliaceus. After six months, he developed the clinical and histopathologic findings of pemphigus vulgaris. Methotrexate therapy, which had originally controlled the patient's symptoms, became ineffective and ultimately high dose oral prednisone and mycophenolate mofetil were required. A literature review discussing similar cases and the immunologic basis for the change is presented.

Initial Presentation

A 31-year-old Hispanic male initially presented with a one-month history of a non-healing, erythematous, weeping erosive papules distributed bilaterally on the malar facial area, central chest, back, scalp and on the thighs. Lesions exhibited a collarette of scale as well as a peri-lesional Nikolsky's sign (Figures 1 and 2). No oral lesions or nails changes were noted.

Two punch biopsies from the upper arm were obtained at the time of presentation for H&E and immunofluorescence studies. The H & E biopsy revealed superficial acantholysis with suppuration between the stratum corneum and the superficial granular layer as well as a mixed inflammatory cell infiltrate in the dermis consistent with a superficial blistering disorder (Figure 3). Direct immunofluorescence (DIF) studies of peri-lesional skin revealed IgG and complement deposition in the epidermis. Indirect immunofluorescence (IIF) was positive with a 1:80 titer for intracellular substance antibodies (Ab) and negative for the basement membrane zone antibodies.

Based on the clinical presentation and laboratory findings, a diagnosis of pemphigus foliaceus (PF) was entertained. Topical and oral steroids were used initially. Methotrexate (MTX), 15 mg/week was then instituted over several months. The patient's symptoms remained well controlled for six months, with the development of some new lesions, which were localized to the skin. There were no oral lesions.

New Presentation

Six months after his initial presentation, the patient developed new painful oral erosions. Examination revealed aphthous like ulcers scattered primarily over the gingival mucosa (Figure 4). The cutaneous lesions had flared significantly, with an increase in both size and number. The distribution of the new lesions was similar to his initial presentation. The patient developed erythematous to violaceous subungual hemorrhages and discoloration along the proximal nail folds and lunulas of all fingernails and most toenails (Figure 4). Because of his oral discomfort, the patient found it difficult to eat and was losing weight.

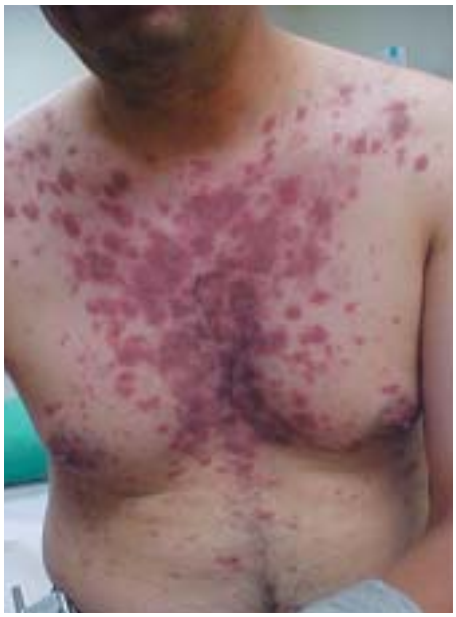


Figure 1

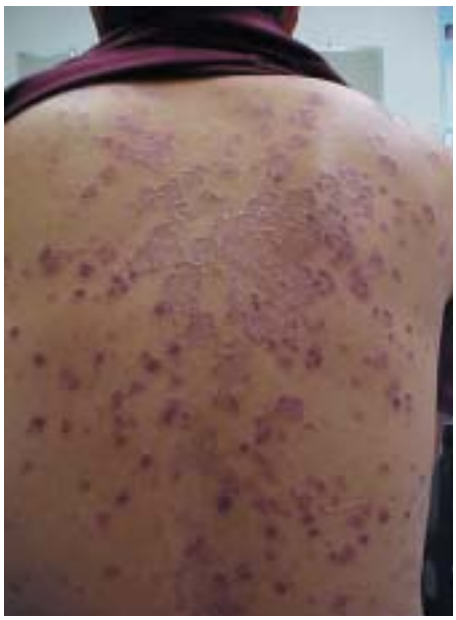


Figure 2

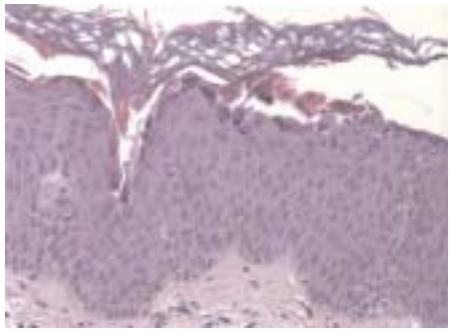


Figure 3

Several etiologies for the patient's new presentation were considered. The oral lesions and nail changes suggested a diagnosis of pemphigus vulgaris. Paraneoplastic pemphigus, idiopathic aphthous ulcer formation, MTX adverse drug reaction, infection were also in the differential diagnosis. Repeat biopsy with H&E and immunofluorescence studies were performed.

The H& E stain revealed a poorly inflammatory, suprabasilar acantholytic blister characteristic of PV (Figure 5) . Direct immunofluorescence studies revealed IgG deposition on the keratinocyte cell surfaces homogeneously distributed throughout the

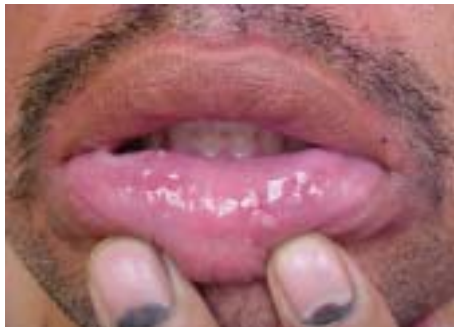


Figure 4

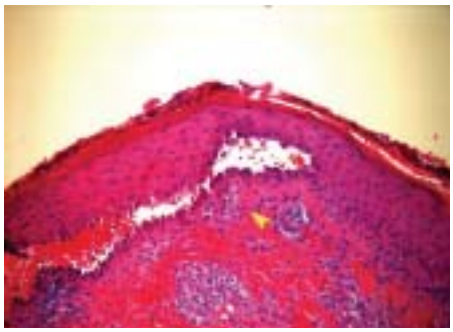


Figure 5

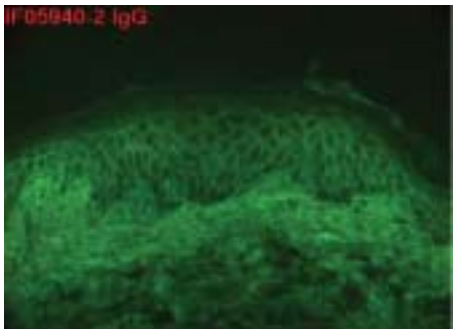


Figure 6

epidermis (Figure 6). No IgG was seen along the basement membrane. Indirect immunofluorescence studies showed circulating IgG antiepithelial cell surface antibodies with a titer of 1:1280. No evidence of IgA antibodies or antiepithelial antibodies directed to mouse bladder was detected. This negated paraneoplastic pemphigus.

The patient was diagnosed with pemphigus vulgaris. Prednisone 100 mg/day was instituted. MTX was discontinued and mycophenolate mofetil (MMF) was initiated at 3,000 mg/day and the prednisone was tapered slowly. The patient responded well and the oral and cutaneous lesions began resolving. He tolerated this therapy without difficulty. The patient has been referred to an outside institutution and continues to do well on MMF.

Discussion

The etiology for the epidermal blisters in PF and PV, is explained by the desmoglein compensation theory. This suggests that the deposition of IgG antibodies directed at desmoglein-1 (DSG-1) and desmoglein-3 (DSG-3) results in these blistering dermatoses. Desmogleins are critical for proper cell to cell adhesion through desmosomal structures. In the epidermis, DSG-1 is expressed more prominently in the superficial regions near the granular layer and its dissolution explains the superficial blister formation of PF. This is in contrast to PV, where the IgG antibodies may be directed at only DSG-3 or to both DSG-1 and DSG-3. Antibodies directed at only DSG-3 disrupts oral mucosa primarily, as this is the predominant adhesion molecule present in this mucosa. This results in the well-known oral erosions that herald PV. Antibodies directed against both desmoglein types 1 and 3 results in full thickness epidermal dissolution as well as the mucosal lesions seen in PV. [1, 2]

The evolution of PF into PV is rare event. Although the acquisition of DSG –1 antibodies is frequently seen in PV, the development of DSG-3 antibodies has seldom been reported in PF. Komai et al reported on several cases of PF to PV transformations. Through the use of enzyme-linked immunosorbent assay (ELISA), Komai was able to show that initially only anti DSG-1 antibodies were present in the PF patients and that anti DSG-3 antibodies developed in these patients over time. The increase in anti-DSG-3 antibodies correlated with the clinical onset of PV. [3]

Another possible explanation for our patient's transformation, was that this patient had a rare 'cutaneous only' type of PV. Yoshida et al described four cases where patients were first diagnosed with entities such as PF or dermatitis herpetiformis, and only later proved to have PV. In these cases, it was found that DSG-1 antibodies were co-expressed with DSG-3 antibodies, however, the DSG-3 antibodies were expressed in lower numbers than those of DSG-1 antibodies. In addition, the DSG-3 antibodies were theorized to possess less pathogenic potential than those normally found in PV. The authors speculated that the DSG-1 antibodies in combination with the less potent DSG-3 antibodies could induce cutaneous blisters typical of PV but could not induce oral erosions.[4]

None of the 'cutaneous only' PV patients in Yoshida's article transitioned with oral lesions over time. In addition, these patients showed evidence of PV-like histopathology. Since our patient's initial presentation demonstrated a clear PF picture, this discounted a 'cutaneous only' form of PV as possible etiology.

The transformation from PF to PV has several implications. PV is generally a more severe entity than PF, especially the mucocutaneous form. The lesions are usually more painful and prevent proper dietary intake. The morbidity and the mortality in these patients is also higher.[5, 6]

PV requires significantly more aggressive therapy than PF. Interruption of antibodies binding to the epidermis is necessary to stop the chain of events leading to loss of cell to cell adhesion in PV and presumably in PF. Immunosuppressive therapy is the cornerstone of treatment. A greater level of suppression may be required for PV as compared with PF.[7]

In our case presentation MTX became ineffective when the PV symptoms developed. MTX is a competitive inhibitor of dihydrofolate reductase (DHFR), inhibiting cell division and acting as a broad immunosuppressant. In addition it has strong anti-inflammatory properties in the epidermis. Unfortunately, high doses of MTX may be required for the level of B-cell suppression required to impact severe blistering disorders such as PV, which could result in other dangerous side effects such as pancytopenia.[6, 8] For this reason MMF was started.

MMF inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH) blocking de novo synthesis of guanine nucleotides and there subsequent incorporation in DNA. MMF preferentially inhibits synthesis of DNA in B and T lymphocytes because these cells lack the purine salvage pathway and are dependent on de novo purine synthesis. Therefore, MMF is a potent inhibitor of B cell activity limiting pathogenic antibody production. The major side effects of MMF include nausea, vomiting and abdominal cramping. Other less rare but potentially serious side effects including pancytopenia and hepatic toxicity have been reported. Ultimately a limiting factor for MMF may be expense. [6,8,9]

Conclusion

This case represents an interesting study of immunobullous disorders and their manifestations. Our experience demonstrates that autoimmune bullous disease is not always a static condition and that evolution to different autoimmune conditions can have great impact on patient care and prognosis.

References:

1.) Amagi M. Desmoglein as a Target in Autoimmunity and Infection. JAAD 2003; 48-2: 244-52.
2.) Anhalt G, Diaz, L. Pemphigus vulgaris-A model for cutaneous autoimmunity. JAAD 2004; 51: S20-1.
3.) Komai A. The Clinical Transition between pemphigus foliaceus and pemphigus vulgaris correlates well with the changes in autoantibody profile assessed by ELISA. Br J Dermatol 01/2001. 144(6): 1177-82.
4.) Yoshida K. et al. Cutaneous type pemphigus vulgaris: A rare clinical phenotype of pemphigus. JAAD 52:839-845.
5.) Sami N, Yeh SW, Ahmed AR. Blistering diseases in the elderly: diagnosis and treatment. Dermatology clinics 2004; 22(1): 73-86
6.) Bolognia J. Dermatology. Mosby 2003.
7.) Nousari HC Pemphigus and pemphigoid. Lancet 1999; 354(9179): 667-72
8.) Wolverton S. Comprehensive Dermatologic Drug Therapy. Saunders 2001.
9.) Korman N. New immunomodulating drugs in autoimmune blistering diseases. Derm clinincs 2001; 19(4): 637-48.

Pustular Vasculitis: A Case Presentation and Review of the Literature

Chava Frankl Lustig D.O.*, Stanley Skopit D.O., FAOCD**
***3rd year resident Nova Southeastern University/BGMC**
****** Program Director Nova Southeastern University/BGMC**

ABSTRACT

Pustular vasculitis is a rare reported condition that occurs on the dorsal hands and clinically resembles atypical Sweet's syndrome and pyoderma gangrenosum. These three conditions all represent different spectrums in the classification of neutrophilic dermatosis. We report one case of pustular vasculitis in a woman that occurred shortly after receiving a glycolic peel to her dorsal hands for lentigines. After appropriate work up to rule out any underlying malignancy or inflammatory disorder, we feel that these lesions developed as a result of the glycolic peel either due to pathergy or a hypersensitivity reaction. The patient had clearing with a tapering dose of prednisone over the course of 3 months.

Case Presentation

The patient is a 50 year old white female with a 2 week history of painful slowly enlarging sores on hands after receiving a glycolic peel on her dorsal hands at a local salon. There was no change in her symptoms after her family physician placed her on Keflex and Tequin

She denies trauma to the area and complains of minimal pain. Her past medical history is significant for arthritis and fibromyalgia. Family history is negative for any connective tissue disease or malignancy. Her medications include paxil, xanax, darvocet. Review of systems reveals generalized aches which are unchanged for several years. She denies hematochezia, SOB, or weight loss.

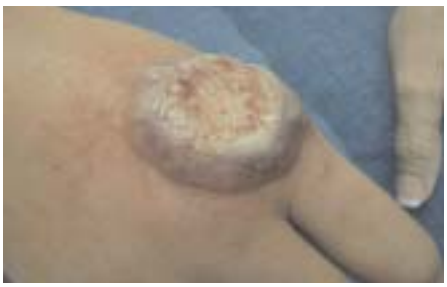


Figure 1 Right Hand

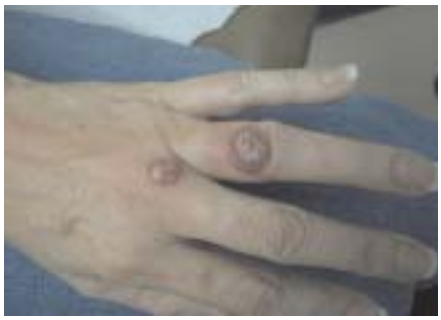


Figure 2 Left Hand

On physical exam she appears well nourished and slightly anxious. There is a 4 cm necrotic ulcer with an erythematous and edematous border. Yellow adherent exudate is appreciated in the center of the lesion on the right hand, and two ulcerating nodules on the left hand measuring 1.3 and 0.9 cm in size (figures 1 and 2). There is also minimal erythematous lymphatic spread on the right arm. No lymphadenopathy is appreciated in the trochlear and axillary lymph nodes.

Labs and Histopathology

CBC, sedimentation rate, and peripheral smear were normal. Hepatitis panel and HIV were negative. Bacterial wound culture, PAS and AFB were negative for microorganisms.

Dermatopathology examination of a representative biopsy of the ulcer reveals a heavy neutrophilic infiltrate with leukocytoclastic vasculitis and edema (figures 3 and 4). These findings are suggestive of pustular vasculitis.

Discussion

Pustular vasculitis is an uncommon presentation of a neutrophilic dermatosis that is clinically indistinguishable from hand involvment in atypical Sweet's syndrome and bullous pyoderma gangrenosum. It has also been shown that there is considerable overlap in the histological picture and response to treatment between these three dermatological conditions (1).Galaria el al. described three patients as having clinical lesions similar to pustular vasculitis and histological changes of Sweet's syndrome. For this reason he referred to this group as neutrophilic dermatosis of the hands (2). For purposes of this paper, these diseases will be discussed separately.

Sweet's Syndrome is described as an acute febrile neutrophilic dermatosis occurring mostly in females in a 4:1 ratio. These lesions usually involve the head, upper trunk, and proximal extremities. The atypical designation refers to lesions that occur in uncommon locations. The patients often times initially present with URI symptoms

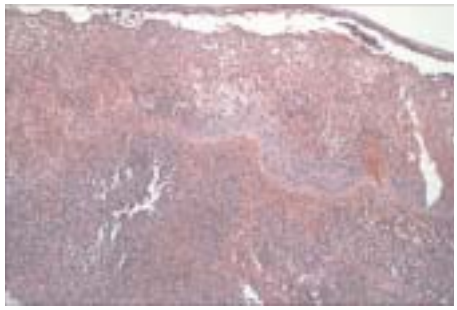


Figure 3: Heavy neutrophilic infiltrate

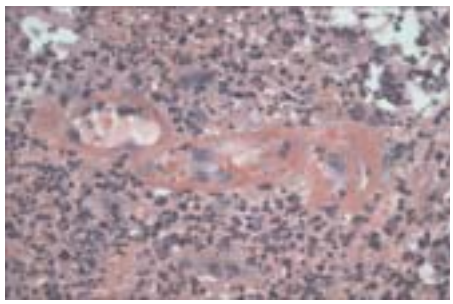


Figure 4: Leukocytoclastic vasculitis and fibrinoid change

and subsequently develop sharply marginated tender erythematous painful elevated plaques. One-third of patients have associated systemic symptoms such as fever, arthralgia, & myalgia (3). Five subtypes of Sweet's syndrome have been described. These include classic, associated with malignancy (10-20%), associated with inflammatory and autoimmune processes, associated with pregnancy, and drug induced (such as granulocyte colony-stimulating factor and oral contraceptives). Biopsy of these lesions reveals a heavy dermal infiltrate consisting of many neutrophils and papillary dermal edema. Fibrin deposition and leukocytoclastic vasculitis is not a feature of Sweet's syndrome (4).

There have been reports of an association of preleukemia and leukemia with atypical Sweet's syndrome and bullous pyoderma gangrenosum, a superficial variant of pyoderma gangrenosum (5-10).

Figure 5: Right hand after 3 months of treatment

Chan et al reported that in his review of patients with sweet's syndrome, 40% were associated with a hematological malignancy and 7% associated with solid tumors. Other reports show varying percentages of association between Sweet's syndrome and malignancy, however these differences may be due to bias from the associated medical center referral base (1, 11, 12). Reports by DiCaudo involving seven female patients showed no association with malignancy, arthritis, or inflammatory bowel disease (13).

The condition of pustular vasculitis as reported in the literature is consistent with lesions that clinically resemble Sweet's syndrome, however display leukocyclastic vasculitis on the biopsy. Frequently, these patients are initially misdiagnosed as having bacterial, mycobacterial infection, Sweet's syndrome, pustular drug reaction, erythema elevatum diutinum, and pyoderma gangrenosum (14). These lesions, as in Sweet's and pyoderma gangrenosum,

Figure 6: Left hand after 3 months of treatment

are not responsive to oral antibiotics and rapidly respond to oral prednisone. In a previous report, a patient that was exposed to a chemical fertilizer containing ammonium nitrate and calcium salts developed lesions described as pustular vasculitis. They concluded in this case report that the exposure to this chemical compound might have caused the lesions described as pustular vasculitis (14).

In our patient, the exposure to glycolic acid on her hands might have been the etiological factor either through pathergy or a hypersensitivity reaction. Following her negative work up, the patient had rapid clearance of her lesions with a tapering dose of oral prednisone supplemented with calcium, vitamin D, and fosamax. Local wound care was performed to the lesions and complete resolution occurred in 12 weeks (figures 5 and 6).

In conclusion, there is an inconsistency in the literature regarding the terminology of atypical Sweet's syndrome, pyoderma gangrenosum, neutrophilic dermatosis, and pustular vasculitis when the hands are involved. Also, there have been some suggestions that these lesions represent different spectrums of the same condition. Regardless of the terminology, it is important to rule out any underlying malignancies or inflammatory conditions when these lesions develop.

References:

11. Weenig RH, Bruce AJ, McEvoy MT, Gibson LE, Davis MDP. Neutrophilic dermatosis of the hands: four new cases and review of the literature. Int Journal of Derm 2004; 43: 95-102.
2. Galaria NA, Junkins-Hopkins JM, Kligman D, James WD. Neurtophilic dermatosis of the dorsal hands: pustular vasculitis revisited. J Am Acad Dermatol 2000; 43: 870-874.
3. Bolognia JL et al. Dermatology. Mosby. 2003 page 412
4. Barnhill RL.Textbook of Dermatopathology. McGraw-Hill Companies, Inc. 1998. pages 108-110
5. Vance E, Granter S, Skarin A. Sweet's syndrome. J Clin Oncol 1997; 15: 860-861.
6. Cramers M. Bullous pyoderma gangresonsum in association with myeloid leukaemia. Acta Derm Venereol 1976; 56: 311-312
7. Sheps M, Sharpero H, Ransay C. Bullous pyoderma gangrenosum and acute leukemia. Arch Dermatol 1978; 114: 1842-1843.
8. Hay CR, Messenger AG, Cotton DW, et al. Atypical bullous pyoderma gangresnosum associated with myeloid malignancies. J Clin Pathol 1987; 40: 387-392.
9. Dompmartin A, Trussard X, Lorier E, et al. Sweet syndrome associate with acute myelogenous leukemia. Atypical form simulating facial erysipelas. Int J Dermatol 1991; 30: 644-647.
10. Koester G, Toarnower A, Levisohn D, Burgdorf W. Bullous pyoderma gangrenosum. J Am Acad Dermatol 1993; 29: 875-878.
11. Fett DL, Gibson LE, Su WP. Sweet's syndrome: systemic signs and symptoms and associated disorders. Mayo Clin Proc 1995; 70: 234-240.
12. von den Driesch P. Sweet's syndrome (acute febrile neutophilic dermatosis). J Am Acad Dermatol 1994; 31: 535-556.
13. Dicaudo DJ, Connolly SM. Neutophilic Dermatosis (Pustular Vasculitis) of the Dorsal Hands: A Report of 7 Cases and Review of the Literature. Arch Dermatol 2002; 138: 361-365.
14. Aydin F, Senturk N, Yildis L, Canturk MT, Turanli AY. Neutophilic dermatosis of the dorsal hands in a farmer. European Acad Derm and Venereology 2004; 18: 716-717.

Pyoderma Gangrenosum: A Case Study and Review of Treatment Options

Evangeline Perez, D.O. *, Marvin S. Watsky, D.O. **
*** 2nd year Resident, St. John's Episcopal Hospital, Far Rockaway, New York**
**** Program Director, St. John's Episcopal Hospital, Far Rockaway, New York**

ABSTRACT

Pyoderma gangrenosum (PG) is a rare, destructive neutrophilic skin disease whose etiology continues to remain obscure. It is because of this that success in particular treatment options is so varied. We report a case of PG associated with ulcerative colitis (UC) that was treated successfully with systemic corticosteroids. In addition, we review the anecdotal literature of treatment options one can consider when systemic steroids fail or when adverse effects of therapy become intolerable.

Pyoderma gangrenosum

Pyoderma gangrenosum was first described by Brunsting, Goekerman, and O'Leary in 1930,1 and is a rare, destructive inflammatory dermatoses that has most commonly been associated with inflammatory bowel disease.2 When associated with ulcerative colitis (UC), the disease activity does not always parallel the bowel disease.3

The lesion of PG often begins as a painful papule or pustule that breaks down to form a rapidly enlarging ulcer. The ulcers may demonstrate pathergy, which is an exaggerated response to trivial trauma that can result in extension of the ulcer.

Several possible mechanisms have been suggested for the etiology of PG including abnormalities in neutrophil function and disturbances in immunoregulation and immunologic effector functions, but none of these have consistently proved to be the main etiology.3

Histological findings are nonspecific and mainly serve to rule out other possible entities such as infection and malignancy. The diagnosis is based on clinical findings and is mainly one of exclusion. It is necessary to rule out other possible infections, collagen vascular diseases, and various vasculitides 4 prior to making a definitive diagnosis.

Systemic corticosteroids continue to be the mainstay of therapy and are still the most effective therapeutic option for PG.3

Case study

A 52-year-old African-American female with a history of UC was admitted to the hospital with a painful recurrent eruption involving the abdomen, groin, and upper thighs for two weeks. The eruption began as a papulovesicle which broke down to form an extending area of ulceration. She was previously admitted twice in the last two years for similar episodes that were diagnosed and treated as infectious processes.

Figure 1 Confluent and well demarcated ulceration

On physical examination, there was an exquisitely tender, well demarcated and symmetric area of confluent ulceration involving the umbilicus, groin, and upper inner thighs that was exquisitely tender to palpation (Fig. 1). The borders were violaceous and undermined, and the base was covered with necrotic material (Fig. 2).

Histological examination revealed dermal edema, massive neutrophilic inflammation, vascular engorgement and thrombosis(Fig. 3). Bacterial studies and fungal stains were negative.

The diagnosis of PG was made given the history of UC, the recurrent nature and history of the eruption, and the histological findings which failed to reveal an infectious or malignant process. The patient was treated with oral prednisone (40mg/day) for one month. This resulted in a dramatic and rapid improvement of the patient's eruption. The patient was maintained on oral prednisone (20mg/d) which was eventually tapered off. She continued to experience remission of her disease (Fig. 4). At her nine months follow up, she had experienced two recurrences which were successfully treated with short term courses of oral prednisone.

Figure 2 Undermined violaceous borders

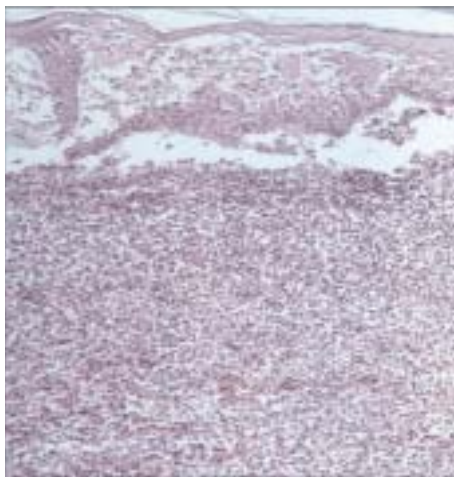


Figure 3 Massive neutrophilic inflammation, edema, and necrosis

Treatment options

Systemic corticosteroids

Systemic corticosteroids are the mainstay of therapy as they dramatically halt progression and prevent the development of new lesions.5 Pulse dosing with suprapharmacologic doses of methylprednisolone (1g/d x 5d) can be used for severe cases6 and is the first line of treatment at many institutions.3 Unfortunately, the chronic administration of systemic steroids is fraught with many potential adverse effects which makes the exploration of other drug classes necessary.

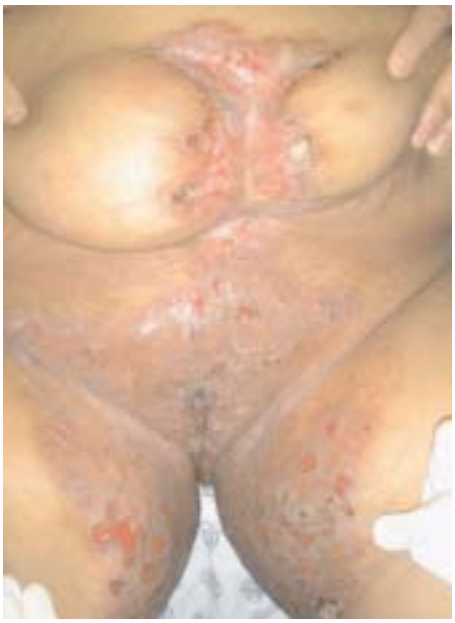


Figure 3 Massive neutrophilic inflammation, edema, and necrosis

Mycophenolate mofetil

Mycophenolate mofetil is an immunomodulatory drug that suppresses lymphocyte proliferation by inhibiting de novo purine synthesis which results in decreased antibody production.12 Its major drawbacks include the possible increased risk of carcinogenicity9 and infection.9,12 Several reports of refractory PG that had been treated unsuccessfully with prednisone, dapsone, some of the other commonly used cytotoxic agents, and the biological immunomodulator, infliximab, showed dramatic improvement and long term remission when treated with mycophenolate mofetil.13,14

Cyclosporine

Cyclosporine is an immunosuppressant that significantly inhibits cellular immunity by inhibiting interleukin-2 production leading to a decline in activated CD4 and CD8 cells in the epidermis.15 It also reduces the chemotactic ability of neutrophils.16 Its major drawbacks include nephrotoxicity, hypertension, and the potential for many drug interactions. Although it is generally regarded as an alternate form of therapy, one report suggests that it be seriously considered as a primary form of therapy for PG.17

Tacrolimus

Tacrolimus (FK 506) has a similar mechanism of action, similar side effects and greater bioavailability than cyclosporine. The specific mechanism of action by which it acts to ameliorate PG is unclear but it is thought to inhibit the accumulation and activation of neutrophils by inhibiting granulocyte-macrophage-colony- factor (GM-CSF).2 Several studies have shown complete and rapid clearing of refractory PG with systemic tacrolimus.2,18 An anecdotal report claims clearing of a prednisone resistant PG lesion with topical tacrolimus.19 The proposed mechanism of action was the decreased expression of interleukin-8 which leads to impaired neutrophil chemotaxis.19

Thalidomide

Thalidomide is an immunomodulatory and anti-inflammatory agent that inhibits tumor necrosis factor alpha (TNF-a), suppresses interleukin-2 production, and decreases neutrophil chemotaxis and phagocytosis. Its major drawbacks include teratogenicity, peripheral neuropathy, and sedation. It was shown to improve long standing refractory PG and prevent recurrence in a patient with extensive disease.20

Nicotine

Ulcerative colitis is largely a disease of nonsmokers. It has been observed that patients who smoke intermittently often experience improvement of their symptoms during periods of smoking.21 Pyoderma gangrenosum, which is commonly associated with UC, seems to respond to similar treatment modalities. Based on this premise, topical nicotine was applied to refractory PG lesions in several studies. This resulted in an improvement and clearance of lesions.21,22

Colchicine

Colchicine is an anti-inflammatory and anti-mitotic immunomodulatory that concentrates well in leukocytes.23 It also decreases polymorphonuclear motility, adhesiveness, and chemotaxis making it very successful in the treatment of neutrophilic dermatoses.24 A recent report showed clearance of refractory PG lesions in two patients when treated with low dose colchicine.23

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) has been shown to be successful in refractory PG and to induce complete healing within a few months.25 Although the mechanism of action is unknown, it is believed that it alters cytokine and cytokine antagonist levels.25

Leukocytapheresis

Leukocytapheresis, which is the extracorporeal removal of leukocytes, was successful in a patient with ulcerative colitis and refractory PG.26 Rapid clearing was achieved without recurrence or major complications.

Infliximab

Infliximab was shown to be successful in several patients in three separate studies.27,28,29 These patients had refractory PG which failed to improve with conventional therapies and demonstrated rapid clearing with infliximab. Infliximab, which is a chimeric anti-TNF alpha monoclonal antibody that binds specifically to and decreases TNF-alpha levels, infiltration of inflammatory cells, interleukin-6 levels, and C-reactive protein concentrations. Its major drawbacks include the potential for immediate hypersensitivity reactions and the possible increased long term risk of developing lymphoma.

Etanercept

Etanercept is a divalent recombinant fusion protein that targets and neutralizes TNF-alpha. A study based on the successful use of infliximab showed rapid and complete healing with the use of etanercept as a steroid-sparing agent in recalcitrant disease and suggested the possible role of TNF-alpha in the pathogenesis of PG.30

Conclusion

Pyoderma gangrenosum remains to be a disease of unknown etiology with an unpredictable course and a highly variable response to multiple therapies. Systemic corticosteroids continue to be the most effective treatment and should still be considered as first line therapy. For severe and refractory cases, or cases where the side effects of systemic corticosteroids may be intolerable, there are, however, many other options available that have shown some degree of success.

References:

1. Brunsting LA, Goekerman WH, O'Leary PA. Pyoderma gangrenosum: clinical and experimental observations in five cases occurring in adults. Arch Dermatol 1930; 22:655-80.
2. Weichert G, Sauder DN. Efficacy of tacrolimus (FK506) in idiopathic treatment-resistant pyoderma gangrenosum. J Am Acad Dermatol 1998; 39:648-50.
3. Wolff K, Stingl G. Pyoderma gangrenosum. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. Fitzpatrick's Dermatol-

ogy in General Medicine. 6th ed. New York, NY: McGraw-Hill; 2003: 969-76.
4. Trent JT, Kirsner RS. Diagnosing pyoderma gangrenosum. Adv Skin Wound Care 2001; 14:1.
5. Hickman JG, Lazarus GS. Pyoderma gangrenosum: New concepts in etiology and treatment, in Dermatology Update: Review for Physicians, edited by SL Moschella. New York, Elsevier, 1979; 325.
6. Chow RK, Ho VC. Treatment of pyoderma gangrenosum. J Am Acad Dermatol 1996; 34:1047.
7. Hall RP. Dapsone. In: Wolverton SE, ed. Comprehensive Dermatologic Drug Therapy. Philadelphia, PA: W.B Saunders Company; 2001:230-250.
8. Arbeiser JL, Moschella SL. Clofazimine: A review of its medical uses and mechanisms of action. J Am Acad Dermatol 1995; 32:241.
9. Pan TD, McDonald CJ. Cytotoxic agents. In: Wolverton SE, ed. Comprehensive Dermatologic Drug Therapy. Philadelphia, PA: W.B Saunders Company; 2001:180-204.
10. Badalamenti S, Kerdel FA. Azathioprine. In: Wolverton SE, ed. Comprehensive Dermatologic Drug Therapy. Philadelphia, PA: W.B Saunders Company; 2001:165-179.
11. Callen JP, Kulp-Shorten CL, Wolverton SE. Methotrexate. In: Wolverton SE, ed. Comprehensive Dermatologic Drug Therapy. Philadelphia, PA: W.B Saunders Company; 2001:147-164.
12. Mutasim DE. Management of autoimmune bullous diseases: Pharmacology and therapeutics. J Am Acad Dermatol. 2004; 51:859-877.
13. Nousari HC, Lynch W, Anhalt GJ. The effectiveness of mycophenolate mofetil in refractory pyoderma gangrenosum. Arch Dermatol. 1998; 134:1509-11.
14. Daniels NH, Callen JP. Mycophenolate mofetil is an effective treatment for peristomal pyoderma gangrenosum. Arch Dermatol. 2004;140:1427-9.
15. Baker BS, Griffiths CEM, Lambert S, et al. The effects of cyclosporine A on T lymphocyte and dendritic cell subpopulations in psoriasis. Br J Dermatol 1987; 116:503-10.
16. Demidem A, Taylor JR, Grammer SF, et al. T-lymphocyte-activating properties of epidermal antigen-presenting cells from normal and psoriatic skin: evidence that psoriatic epidermal antigen-presenting cells resemble cultured normal Langerhans cells. J Invest Dermatol 1991; 97:454-60.
17. Matis WL, Ellis CN, Griffiths CE, et al. Treatment of pyoderma gangrenosum with cyclosporine. Arch Dermatol. 1992; 128:1060-4.
18. Baumgart DC, Wiedenmann B, Dignass AU. Successful therapy of refractory pyoderma gangrenosum and periorbital phlegmona with tacrolimus (FK506) in ulcerative colitis. Inflamm Bowel Dis. 2004; 10:421-4.
19. Richter-Hintz D, Schuppe HC, Homey B, et al. Topical tacrolimus (FK506) is effective in the treatment of pyoderma gangrenosum. J Am Acad Dermatol. 2000; 42:304.
20. Hecker MS, Lebwohl MG. Recalcitrant pyoderma gangrenosum: treatment with thalidomide. J Am Acad Dermatol. 1998; 38:490-1.
21. Wolf R, Ruocco V. Nicotine for pyoderma gangrenosum. Arch Dermatol. 1998; 134:1071-2.
22. Patel GK, Rhodes JR, Evans B, et al. Successful treatment of pyoderma gangrenosum with topical 0.5% nicotine cream. J Dermatolog Treat. 2004; 15:122-5.
23. Kontochristopoulos GJ, Stavropoulos PG, Gregoriou S, et al. Treatment of Pyoderma gangrenosum with low-dose colchicine. Dermatology. 2004; 209:233-6.
24. Davis LS. Newer uses of older drugs-an update. In:Wolverton SE, ed. Comprehensive Dermatologic Drug Therapy. Philadelphia, PA: W.B Saunders Company; 2001:426-444.
25. Dirschka T, Kastner U, Behrens S, et al. Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. J Am Acad Dermatol. 1998; 39:789-90.
26. Fujimoto E, Fujimoto N, Kuroda K, et al. Leukocytapheresis treatment for pyoderma gangrenosum. Br J Dermatol. 2004; 15:1090-2.
27. Tan MH, Gordon M, Lebwohl O, et al. Improvement of pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumor necrosis factor alpha monoclonal antibody. Arch Dermatol. 2001; 137:930-3.
28. Andersen TH, Moerk NJ. Infliximab therapy in patients with severe active refractory pyoderma gangrenosum. J Am Acad Dermatol. 2004; 50.
29. Lopez AS, Bermejo F, Aldanondo I, et al. Pyoderma gangrenosum associated with ulcerative colitis: response to infliximab. Rev Esp Enferm Dig. 2004; 96:420-4.
30. McGowan JW, Johnson CA, Lynn A. Treatment of pyoderma gangrenosum with etanercept. J Drugs Dermatol. 2004; 3:441-4.

For anywhere there's acne, there's EVOCLIN.

Finally, an acne formulation that's easy to apply over multiple body areas.[1] EVOCLIN comes in a patient-preferred foam vehicle, with minimal residue.[1,2] It's effective in reducing inflammatory and noninflammatory lesions. Plus it's safe and well tolerated.[3] Looking for a treatment that works anywhere there's acne? EVOCLIN is here.

EVOCLIN is a once-a-day topical clindamycin foam for the treatment of acne vulgaris. The most common adverse events were headache (3%) and application-site reactions including burning (6%), itching (1%), and dryness (1%). EVOCLIN is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, or a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and pseudomembranous colitis have been reported with systemic and rarely with topical clindamycin. Discontinuation is recommended if diarrhea develops.

Please see following page for full prescribing information. For further details, visit www.evoclin.com.

evoclin™
(clindamycin phosphate) Foam, 1%
For acne anywhere.

evoclin™
(clindamycin phosphate) Foam, 1%
FOR ACNE ANYWHERE.

References: 1. Feldman SR, Sangha N, Setaluri V. Topical corticosteroid in foam vehicle offers comparable coverage compared with traditional vehicles. *J Am Acad Dermatol.* 2000;42:1017-1020. **2.** Data on file [001], Connetics Corporation. **3.** EVOCLIN™ prescribing information.

PRM-CLF-030
2/05
Printed in USA

evoclin™

(clindamycin phosphate) Foam, 1%

Rx Only

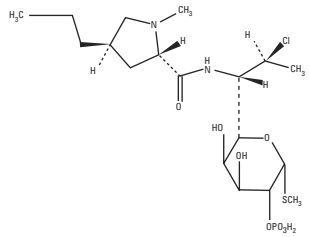
FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Evoclin (clindamycin phosphate) Foam, 1%, a topical antibiotic in a foam vehicle, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a vehicle consisting of cetyl alcohol, dehydrated alcohol (ethanol 58%), polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol, pressurized with a hydrocarbon (propane/butane) propellant.

Chemically, clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7 (S)-chloro-substitution of the 7 (R)-hydroxyl group of the parent antibiotic, lincomycin, and has the structural formula represented below:

Figure 1: Structural Formula



The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

CLINICAL PHARMACOLOGY

Pharmacokinetics: In an open label, parallel group study in 24 patients with acne vulgaris, 12 patients (3 male and 9 female) applied 4 grams of Evoclin Foam once-daily for five days, and 12 patients (7 male and 5 female) applied 4 grams of Clindagel® (clindamycin phosphate) Topical Gel, 1%, once daily for five days. On Day 5, the mean C_{max} and AUC(0-12) were 23% and 9% lower, respectively, for Evoclin Foam than for Clindagel®.

Following multiple applications of Evoclin Foam less than 0.024% of the total dose was excreted unchanged in the urine over 12 hours on Day 5.

Microbiology: The clindamycin component has been shown to have in vitro activity against *Propionibacterium acnes*, an organism which is associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product. Cross-resistance between clindamycin and erythromycin has been demonstrated.

CLINICAL STUDIES

In one multicenter, randomized, double-blind, vehicle-controlled clinical trial patients with mild to moderate acne vulgaris used Evoclin (clindamycin phosphate) Foam, 1% or the vehicle foam once daily for twelve weeks. Treatment response, defined as the proportion of patients clear or almost clear, based on the Investigator Static Global Assessment (ISGA), and the mean percent reductions in lesion counts at the end of treatment in this study are shown in the following table:

Efficacy Parameters	Evoclin Foam N=386	Vehicle Foam N=127
Treatment response (ISGA)	31%	18%*
Percent reduction in lesion counts		
Inflammatory Lesions	49%	35%*
Noninflammatory Lesions	38%	27%*
Total Lesions	43%	31%*

*P< 0.05

INDICATIONS AND USAGE

Evoclin is indicated for topical application in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS.)

CONTRAINDICATIONS

Evoclin is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea. Antiperistaltic agents, such as opiates and diphenoxylate with atropine, may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Avoid contact of Evoclin with eyes. If contact occurs, rinse eyes thoroughly with water.

PRECAUTIONS

General: Evoclin should be prescribed with caution in atopic individuals.

Drug Interactions: Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of a 1% clindamycin phosphate gel similar to Evoclin was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 3 and 15 times higher than the human dose of clindamycin phosphate from 5 milliliters of Evoclin, assuming complete absorption and based on a body surface area comparison. No significant increase in tumors was noted in the treated animals.

A 1% clindamycin phosphate gel similar to Evoclin caused a statistically significant shortening of the median time to tumor onset in a study in hairless mice in which tumors were induced by exposure to simulated sunlight.

Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Reproduction studies in rats using oral doses of clindamycin hydrochloride and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

Pregnancy: Teratogenic effects - Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride and clindamycin palmitate hydrochloride. These studies revealed no evidence of fetal harm. The highest dose used in the rat and mouse teratogenicity studies was equivalent to a clindamycin phosphate dose of 432 mg/kg. For a rat, this dose is 84 fold higher, and for a mouse 42 fold higher, than the anticipated human dose of clindamycin phosphate from Evoclin based on a mg/m² comparison. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether clindamycin is excreted in human milk following use of Evoclin. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Evoclin in children under the age of 12 have not been studied.

Geriatric Use: The clinical study with Evoclin did not include sufficient numbers of patients aged 65 and over to determine if they respond differently than younger patients.

ADVERSE REACTIONS

The incidence of adverse events occurring in ≥1% of the patients in clinical studies comparing Evoclin and its vehicle is presented below:

Selected Adverse Events Occurring in ≥1% of Subjects

Adverse Event	Number (%) of Subjects	
	Evoclin Foam N = 439	Vehicle Foam N = 154
Headache	12 (3%)	1 (1%)
Application site burning	27 (6%)	14 (9%)
Application site pruritus	5 (1%)	5 (3%)
Application site dryness	4 (1%)	5 (3%)
Application site reaction, not otherwise specified	3 (1%)	4 (3%)

In a contact sensitization study, none of the 203 subjects developed evidence of allergic contact sensitization to Evoclin.

Orally and parenterally administered clindamycin has been associated with severe colitis, which may end fatally.

Cases of diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS). Abdominal pain and gastrointestinal disturbances, as well as gram-negative folliculitis, have also been reported in association with the use of topical formulations of clindamycin.

OVERDOSAGE

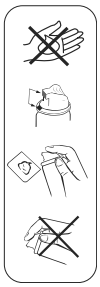
Topically applied Evoclin may be absorbed in sufficient amounts to produce systemic effects (see WARNINGS).

DOSAGE AND ADMINISTRATION

Apply Evoclin once daily to affected areas after the skin is washed with mild soap and allowed to fully dry. Use enough to cover the entire affected area.

To Use Evoclin:

1. Do not dispense Evoclin directly onto your hands or face, because the foam will begin to melt on contact with warm skin.
2. Remove the clear cap. Align the black mark with the nozzle of the actuator.
3. Hold the can at an upright angle and then press firmly to dispense. Dispense an amount directly into the cap or onto a cool surface. Dispense an amount of Evoclin that will cover the affected area(s). If the can seems warm or the foam seems runny, run the can under cold water.
4. Pick up small amounts of Evoclin with your fingertips and gently massage into the affected areas until the foam disappears.



Throw away any of the unused medicine that you dispensed out of the can.
Avoid contact of Evoclin with eyes. If contact occurs, rinse eyes thoroughly with water.

HOW SUPPLIED

Evoclin containing clindamycin phosphate equivalent to 10 mg clindamycin per gram, is available in the following sizes: 100 gram can - NDC 63032-061-00 and 50 gram can - NDC 63032-061-50

STORAGE AND HANDLING

Store at controlled room temperature 20°- 25°C (68°- 77°F).

FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.

Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperature above 120°F (49°C).

Keep out of reach of children.

Manufactured for
Connetics Corporation
Palo Alto, CA 94304
USA

Printed in USA
October 2004

For additional information:
1-888-500-DERM or visit
www.evoclin.com

AW No: AW-0317-r3

U.S. Patent Pending

connetics®

DELIVERED IN
VersaFoam®

Scleromyxedema: A Case Report

Jennifer Bucci, DO*, Schield Wikas, DO, FAOCD**
***2nd year resident, SUMMA Cuyahoga Falls General Hospital**
****Program Director, Dermatology Residency, Clinical Professor Ohio University College of Osteopathic Medicine, Athens, Ohio**

ABSTRACT

Scleromyxedema is a chronic, disabling condition with little tendency for spontaneous remission. Systemic involvement can prove fatal. Cutaneous and extracutaneous manifestations can be associated with considerable disability. Due to the rarity of this condition, no studies have been preformed regarding therapeutic options for these patients. Only case reports exist describing success or failure of patients undergoing therapy.

A 39 year-old Caucasian female met specific criteria for the diagnosis of scleromyxedema including a generalized papular and sclerodermoid eruption of the skin, histologic evidence of mucin deposition, fibroblast proliferation, fibrosis and a monoclonal gammopathy. 1.

Case Report:

This is a case of a 39 year-old Caucasian female who presented with a skin rash of several months duration on the bilateral upper extremities and face. She later developed many extracutaneous manifestations including xerostomia, dysphagia, fatigue, anorexia with subsequent weight loss, and paresthesias of the bilateral lower extremities. Most disconcerting to her, however, was an accelerating loss of motor function; she had difficulty getting out of a chair and walking up stairs.

Her past medical history was significant for an episode of expressive aphasia and visual disturbance which was diagnosed as a possible transient ischemic attack after a negative work-up was completed.

The patient was a Caucasian female, approximately 67 inches tall and weighed 160 pounds. The dorsal hands and wrists demonstrated 2-3 millimeter firm, waxy papules symmetrically present in no particular arrangement. (See figures 1 and 2). The range of motion in the joints of the hands or wrists was not limited and there was no associated induration. Similar firm, waxy papules were present symmetrically in the pre-auricular area of the face and along the nasal sidewall. There was mottled pigmentary change of the skin, noted especially over the bilateral lower extremities, consistent with livedo reticularis. Pulses were easily palpable over distal arteries in the lower extremities. Neurologic examination was unremarkable except slightly diminished reflexes at the ankle.

Over the next several months the patient developed a generalized induration of the skin over the anterior and posterior shoulders. The patient exhibited sclerodactyly with decreased movement of the bilateral metacarpal phalangeal, proximal, and distal interphalangeal joints. Microstomia however was not appreciable on physical

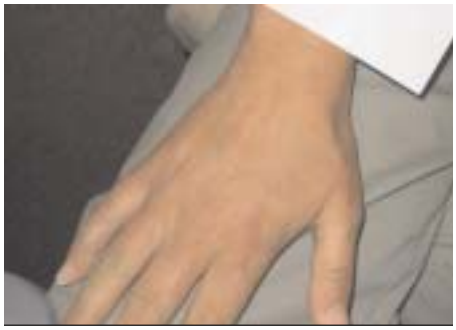


Figure 1:
Right hand and wrist demonstrating firm 2-3 millimeter firm, waxy papules

Figure 2:
Left hand demonstrating similar firm 2-3 millimeter firm, waxy papules

examination. The left parietal scalp had diffuse hair thinning without evidence of cicatricial alopecia. The hairs did not have increased fragility. She had progressive weight loss recorded on evaluations prior to onset of therapy.

A skin biopsy taken from the right hand prior to onset of therapy was a punch specimen. The changes were compatible with lichen myxedematosus. The epidermis was intact with a dermal proliferation of fibroblasts and increased interstitial mucin confirmed with a colloidal iron stain. (See figures 3 and 4).

Antibody screening was negative for antinuclear antibody (ANA), anti-doublestranded DNA (anti ds-DNA), rheumatoid factor (RF), SSA and SSB antibodies, and scl-70. Serum protein electrophoresis (SPEP) confirmed an IgG kappa monoclonal gammopathy. Quantitative immunoglobulins were within normal limits. Thyroid studies revealed hypothyroidism. Thyroid stimulating hormone (TSH) was elevated at 10.956 and triiodothyronine (T3) was decreased at 248. The muscle enzymes were elevated. The creatinine phosphokinase (CPK) was 585, lactate dehydrogenase (LDH) was 230, and the aldolase was17.2. The erythrocyte sedimentation rate (ESR) at 57.

Barium esophogram revealed incomplete relaxation of the cricopharyngeus muscle. Electromyography revealed an acute generalized myositis that was moderate to severe in nature involving both proximal and distal musculature. Computerized tomography (CT) scan of the abdomen and pelvis showed no acute pathology. Bone marrow aspiration and biopsy were essentially non-diagnostic. Plasma cells accounted for less than five percent of marrow cellularity. Thyroid scan revealed mild elevation in uptake. Thyroid ultrasound revealed a non-enlarged gland with multiple tiny colloid cysts and foci of calcification.

A diagnosis of scleromyxedema was made. This patient was referred to several sub-specialties including a neurology, hematology/ oncology, rheumatology, as well as physical therapy. After collaboration among the sub-specialists combination therapy including an alkylating agent, melphalan, (L-Phenylalanine Mustard) and intravenous immune globulin (IVIG) was initiated. Acknowledging the potential side effects of this medication regimen, the patient's worsening physical condition justified there introduction.

Melphalan was dosed at 2 milligrams (mg) every other day for one month until

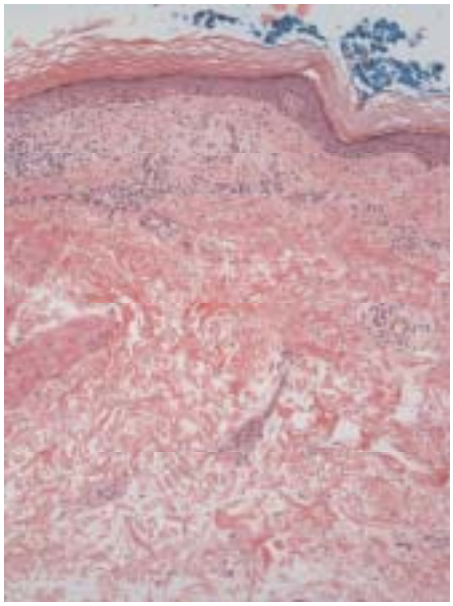


Figure 3

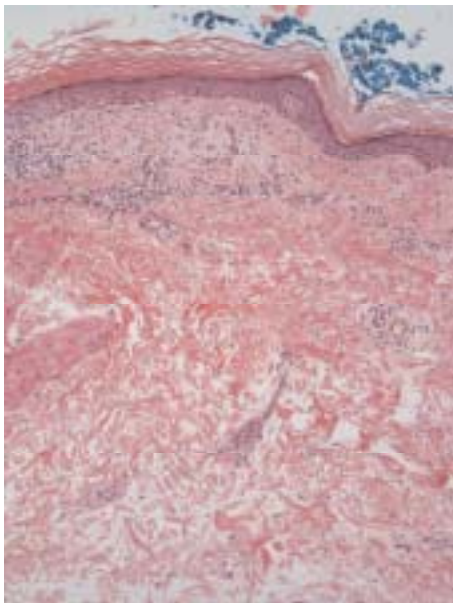


Figure 4

she developed leukopenia and therapy was then interrupted for a period of nine days. She then continued melphalan at 2 mg every other day for a total of 8 cycles. Patient's dose was then reduced to 2 mg given only Mondays and Thursdays for 4 cycles. Finally the melphalan was administered only on a once weekly basis due to bone marrow suppression evidenced on repeat laboratory reports. Darbepoetin alfa support was utilized due to the emergence of anemia.

Concomitantly the patient began IVIG therapy consisting of 5-day infusions given every three weeks. The IVIG was dosed at 30 grams per day for 5 consecutive days. After 12 consecutive cycles, the patient's frequency of administration of drug was reduced to every five weeks. Patient's primary side effect with administration of IVIG was nausea and mild flares of stomatitis. Toward the end of therapy, the patient reported "not feeling well" despite being pre-medicated with 1,000 mg of oral acetaminophen.

The patient has experienced remission with single drug therapy. The patient has remained under the care of the department of hematology and oncology. The patient has successfully continued on melphalan over the past year. We have defined success of therapy based on the reported patient's quality of life. Her lower extremity weakness improved with increased ability to perform activities of daily living (ADLs) previously requiring assistance. The patient now works full-time.

Serum protein electrophoresis has continued to show an elevated M spike throughout the course of therapy. Muscle enzymes, including CPK, previously elevated, returned to normal during the course of systemic chemotherapy.

Discussion:

This case highlights the importance of scleromyxedema as a generalized papular and sclerodermoid form of lichen myxedematosus with systemic, even lethal manifestations. It is distinguished from a localized form that does not run a disabling course. The original description of cutaneous mucinosis was described by Dubreuilh 2 in 1906 and Reitmann 3 in 1908. In 1953 Montgomery and Underwood 4 proposed a clinical classification distinguishing four types of lichen myxedematosus: a generalized lichenoid eruption, a discrete papular form, a generalized or localized lichenoid plaque form and an urticarial form. The term scleromyxedema was first proposed in 1954 by Gottron to denote the generalized lichenoid papular eruption with sclerodermoid features [5]. Scleromyxedema is a generalized variant of cutanoeus mucin deposition with systemic, even lethal, manifestations.

The exact pathogenesis of scleromyxedema is unknown and various etiologic hypotheses exist. A number of immunomodulatory mechanisms have been proposed to attempt to link the monoclonal gammopathy with fibroblast proliferation. The precise relationship between skin changes and paraproteinemia remains unclear. It has been proposed that the paraprotein acts as an autoantibody and directly stimulates fibroblast proliferation and mucin deposition in the skin [6]. Harper and Rispler 7 provided evidence against this hypothesis, showing that the serum of 3 patients containing paraprotein and one patient's serum without paraprotein, stimulated fibroblast DNA synthesis and proliferation in vitro. The paraprotein did not have stimulatory effects when eluted and isolated [8].

Later these same results of a causal relationship between scleromyxedema patients' serum and fibroblast proliferation could not be duplicated by another group of researchers. Instead, Yaron et al demonstrated that serum could induce a 2-fold increase in hyaluronic acid synthesis and a 13-fold increase in prostaglandin E synthesis [9]. These findings possibly suggest a causal relationship between prostaglandin-E synthesis as a mediator that then stimulates synthesis of hyaluronic acid.

Scleromyxedema is an uncommon disease of middle age persons without a sex predilection. The disease presents typically with two components of the skin eruption. The papular component presents as symmetric firm, waxy papules approximately 2 to 3 millimeters in diameter. These papules are found most commonly on the bilateral hands, arms, face, neck, upper trunk, and proximal lower extremities. The papules are typically arranged in a linear pattern. A generalized and woody induration of the skin is the second component and presents in a way similar to scleroderma. The cutaneous involvement typically spares the mucous membranes as well as the scalp. Telangiectasias and calcinosis are always absent.

Patients with scleromyxedema may have significant cutaneous and extracutaneous involvement leading to significant co-morbidity associated with this disease. Scleromyxedema patients can have a paraproteinemia with rare progression to multiple myeloma. Central and peripheral nervous system involvement can include coma following a flu-like illness and paresthesias. Patients may present with varying degrees of proximal muscle weakness. Interestingly, post-mortem examination of patients with known scleromyxedema, revealed no mucin deposition in the brain. Mucin deposition in the muscles was seen in only 2 patients[10]. Pulmonary manifestation may present as obstructive or restrictive lung disease. Patients may experience progressive dysphagia.

Although many patients with scleromyxedema report a wide variety of systemic symptoms, a correlation with mucin deposition infrequently occurs at post-mortem autopsy. [11]. Myopathy is a common finding in patients with scleromyxedema, but upon muscle biopsy mucin deposition is usually not found.[12, 13]. Therefore, something rather than mucin may contribute to the extracutaneous systems involved with this disease process.

Histologically, on biopsy, the skin shows a diffuse deposit of mucin in the upper and mid reticular dermis, an increased collagen deposition and a marked proliferation of irregularly arranged fibroblasts. The epidermis may be either normal or thinned by

the pressure of the underlying mucin and fibrosis. Hair follicles may be atrophic and a slight perivascular, superficial lymphocytic and plasmocytic infiltrate is often present. The elastic fibers are usually fragmented and decreased in number[14].

Due to the rarity of this disease, no prospective controlled therapeutic trials have been reported in the literature. This disorder presents in the skin with systemic involvement and the etiology of this systemic disease is not clearly understood. Therefore, treatment of the cutaneous involvement includes topical, intralesional, and systemic steroids, topical and intralesional hyaluronidase, topical dimethyl sulfoxide, corticotrophin and PUVA, which may decrease skin thickness. Prolonged use of PUVA increases risk of squamous cell carcinoma. Grenz ray, electron beam therapy, retinoids by possibly reducing fibroblast proliferation may be used. Plasmapheresis, dermabrasion and extracorporeal photochemotherapy also have a role in treating this disease.

The underlying disease process; however, may be targeted by drugs used to treat other hematologic disorders such as melphalan and other chemotherapeutic agents. Due to the significant hematologic malignancies and chance of life-threatening infections, these therapies are limited to patients that are severely impacted by the co-morbidities associated with their disease. High-dose immune globulin has also been used after reported success in treating neurologic disease associated with a paraprotein[15]. Limited use with granulocyte colony stimulating factor, cyclosporine, thalidomide, and interferon alfa has been reported in the literature. Treatment is commonly disappointing and the prognosis overall is poor.

References

1,4 Montgomery H, Underwood LJ. Lichen myxedmatosus (differentiation from cutaneous myxedemas or mucoid states). J Invest dermatol 1953; 20:213-36.

2 Dubreuilh W. Fibromes miliares folliculaires: sclerodermie consecutive. Ann Dematol Syph 1906; 37: 569-72.

3 Reitmann K. Uber eine eigenartige, der sklerodermie nahestehende affection. Arch Dermatol Syph 1908; 92: 417-424.

5, 14 Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. Journal Amer Academy Dermatology 02/2001, part1; vol 44

6 Lister R, Jolles S, et al. Scleromyxedema: Response to high-dose intravenous immunoglobulin. Journal Amer Academy Dermatology 08/2000, part 2; vol 43

7, 8 Harper, RA, Rispler J. Lichen myxedematosus serum stimulates human skin fibroblast proliferation. Science 1978; 199: 545-547.

9 Yaron M, Yaron I, Yust I, Brenner S. Lichen myxedematosus serum stimulates hyaluronic acid and prostaglandin E production by human fibroblasts. J Rheumatol 1985; 12: 171-5.

References

10 Rothe MJ, Rivas R, Gould E, Kerdel FA. Scleromyxedema and severe myositis. Int J Dermatology 1989; 28: 657-60

11 Godby A, Bergstresser P, et al. Fatal scleromyxedema: Reprort of a case and review of the literature. Journal A,er Academy Dermatology 02/1998, part2; vol 38

12 Verity MA, Toop J, McAdam LP, Pearson CM. Scleromyxedema myopathy. American Journal Clinical Pathology 1978;69: 446-52.

13 Espinosa A, De Miguel E, Morales C, Fonseca E, Gihon-Banos J. Scleromyxedema associated with arthritis and myopathy: a case report. Clin Exp Rheum 1993;11:545-547.

15 Van Doorn PA, Vermeulen M, BrandA, Mulder PGH, Busch HFM. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: clinical and laboratory characteristics associated with improvement. Arch Neurol 1991; 48:217-20.

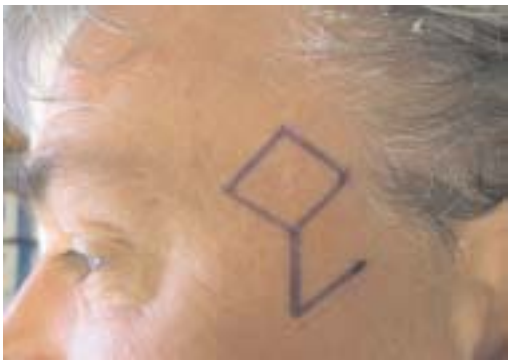
Surgical Pearls

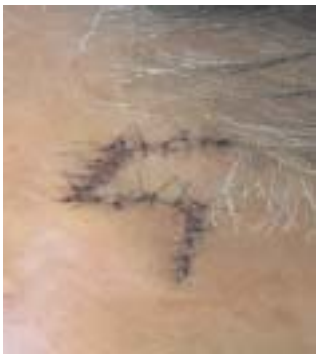
Jay S. Gottlieb, DO, FAOCD, Amy D. Gottlieb, PA-C

How I did it…..

The rhomboid transposition flap is a work-horse for us in the temple area. With precise and delicate technique, an imperceptible surgical scar can be obtained in most patients.

In utilizing a rhomboid flap, it is critical to make sure that all lengths and angles are precise. Plan the donor flap site in a way to insure that the resulting scar is optimally placed. All of the incision lengths are equal in a rhomboid flap. The acute angles are 60 degrees and the obtuse angles are 120 degrees. In a rhomboid, there are two flaps that are created, undermined and transposed. No subcutaneous sutures are required. 5-0 black nylon sutures are used in a simple interrupted fashion. The depth of undermining is just below the reticular dermis, in the subcutaneous plane. In the temple area, care must be taken to avoid injury to the temporal branch of the facial nerve.





January 2004

December 2005

All in incisions are of equal length

The two flaps are transposed

Tungiasis: A Case Report and Review

Lynora Curtis Bassett, D.O.* Brad P. Glick, D.O. Les Rosen, M.D.*****
**2nd Year Resident, Wellington Regional Medical Center/Lake Erie College of Osteopathic Medicine, Dermatology Residency Program, Wellington, FL*
***Residency Director, Wellington Regional Medical Center/Lake Erie College of Osteopathic MedicineDermatology Residency Program Wellington, FL*
****Dermatopathologist, Dermpath Diagnostics Division of AmeriPath Laboratories, Pompano Beach, FL*

ABSTRACT

Tungiasis is an ectoparasitosis caused by the pregnant sand flea Tunga penetrans. Tunga penetrans is endemic in Central and South America, Caribbean, Africa, India, and Pakistan. Prevalence in endemic areas ranges from 15-40%.1 It has become a major health concern in these areas where the incidence of heavy infestations is increasing. Although rare and sporadic in the United States and many other countries, it has been reported in people who have traveled to the endemic areas. This is a case report of Tungiasis in a 45 year old male who traveled to Brazil. Following this case report there is a discussion of Tungiasis, potential complications, treatment alternatives, and preventative measures.

Introduction

Tungiasis is an infestation of the female sand flea, Tunga penetrans. When the female sand flea becomes impregnated it needs the blood supply of a host to mature and release its eggs. It burrows into the epidermis and dermis and maintains an opening to release its eggs outside of the skin. After the eggs are released the flea dies and is shed from the skin. Isolated lesions tend to be self-limited. It is brought to the United States from travelers to the endemic regions.

Case Report

A forty-five year old healthy white male presented with a lesion on the sole of his right foot. The lesion was present for one week. The patient denied any itching or tenderness. He also denied any systemic symptoms including fever, chills, nausea, vomiting, diarrhea, and headache. The lesion was solitary and there was no evidence of any disseminated skin eruption. He recently traveled to Brazil where he spent time walking on the beach in sandals and barefoot.

His dermatologic history was significant for inactive plaque stage mycosis fungoides. He denied any drug allergies. Additional medical and social history was non-contributory.

Physical exam revealed a 4-5mm pink papule on the right plantar foot. Biopsy of the lesion was deferred due to pending knee surgery. On subsequent follow up the patient reported that the lesion slowly increased in size and became pruritic. There was no pain or tenderness. The second physical inspection revealed a 1 cm spongy appearing pinkish, yellow, purple nodule with a deep subcutaneous component. A 3-mm punch biopsy was done. (Figure 1)

The initial histopathologic diagnosis was "arthropod bite reaction", but a second opinion of the slides established the diagnosis of Tungiasis. Hematoxylin-eosin staining demonstrated the body cavity of an insect inserted into the epidermis and dermis, lined by an eosinophilic cuticle. In the cavity were eggs, hollow ring-like components of the tracheal system, and the digestive tract. (Figures 2-3)

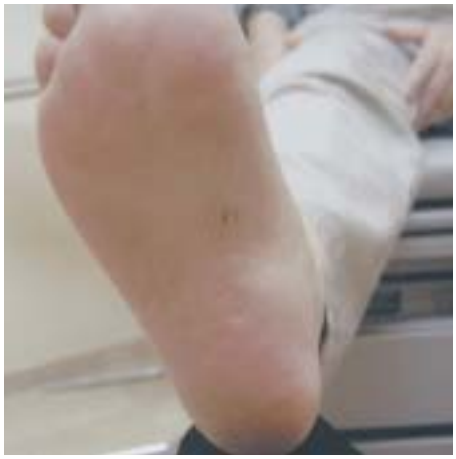


Figure 1

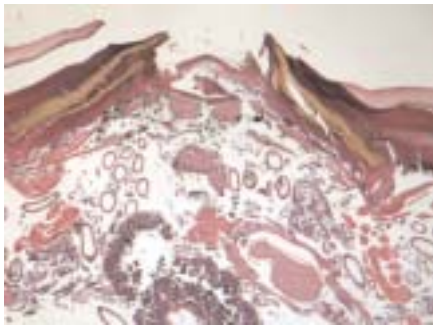


Figure 2

Discussion

Tungiasis is an infestation by the burrowing sand flea Tunga penetrans. It is part of the Arthropoda Phylum, Insecta Class, and Siphonaptera (fleas) Order. In endemic areas Tunga Penetrans is also known as sand flea, chigoe, jigger, pigue, nigua, pico, and bicho de pie.[2] It is the only member of the family Tungidae known to attack humans.[2] It is the smallest known sand flea (1mm). Tungiasis originated in Central and South America and was first reported in Columbus' crewman in 1492.[3] It is endemic in Central and South America, Caribbean, Africa, India, and Pakistan. In endemic areas prevalence ranges from 15-40 %.[2] In the United States and in Europe it is imported from travelers. It has also been reported in the West Indies.

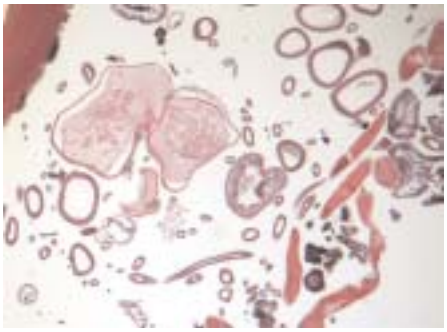


Figure 3

The main habitat of the flea is the warm, dry soil and sand of beaches, stables, and stock farms. The male and non-fertilized female fleas feed intermittently on warm-blooded hosts including cattle, sheep, horses, mules, rats, mice, dogs, pigs, and other wild animals.[2] After copulation, the male sand flea dies.[3] It is the pregnant sand flea, a poor jumper, which burrows into human skin most often on the feet (soles, interdigital, subungual). Other parts of the body can be affected. It is unknown how the flea burrows into the skin, but it is believed to be due to a keratolytic enzyme within the flea because the process is painless.[2]

Early physical exam will show a small, inflammatory papule with a central black dot. The papule slowly enlarges (4-10mm) into a pea-sized nodule with well-defined

borders over a few weeks. It may be pustular or ulcerative. The punctum or ulceration through which it breathes and excretes carries the potential for secondary infection. The lesion can range from asymptomatic to pruritic and/or extremely painful. Multiple or severe infestations could present as a cluster of nodules with a honeycomb appearance.[2]

Physiologically the female sand flea needs a blood supply for the eggs to mature. With its head in the upper dermis, the flea feeds on the blood vessels of its host while its caudal tip of the abdomen at the skin surface forms the punctum. Over the next 1-2 weeks, eggs are released from the opening. After all the eggs are released, and without complications, the flea dies and is shed from the skin of the host. The eggs that have fallen to the ground hatch in 3-4 days, become pupa in 10-14 days, and then become adults in 1-2 weeks. The entire life cycle is one month.[4]

The clinical differential diagnosis of Tungiasis includes: fire ant bite, tick bite, scabies, cercarial dermatitis, early creeping eruption, myiasis, folliculitis, dracunculiasis, and neoplasms. In addition, nodular cutaneous T-cell lymphoma was considered in this patient due to his history.

Complications from heavy infestations may include severe inflammation, ulceration, and fibrosis. There is also the potential for gangrene, sepsis, lymphangitis, lymphadenitis, bone necrosis, autoamputation of the digits, secondary infections (tetanus), cellulitis, erysipelas, superinfections (Staph aureus or gram negative bacteria), and death.[1]

Treatment includes many medical and surgical options. Standard therapy includes removal with a needle or forceps attempted in the first 48 hours followed by disinfection of the site. Occlusive petrolatum suffocates the flea. Electrodessication is good for the intermediate stages of development. When the flea is engorged surgical options include curettage or surgical excision to remove the cavity. Other treatments that have been reported with unknown success include: formaldehyde, chloroform, turpentine, and dichlorodiphenyltrichloroethane (DDT). Topical or systemic antibiotics may prevent secondary infections. In addition tetanus prophylaxis may be indicated. In endemic areas where there is a higher incidence of heavy infestations there is a need for an effective systemic agent. Oral Ivermectin has been investigated, but fails to demonstrate clinically significant efficacy.[5] Our Patient was treated successfully with surgical excision and secondary healing.

In endemic areas prevention of Tungiasis can be achieved by several measures: wearing of shoes, personal cleanliness, disinfection of clothing, linens, furniture, insecticide used on the ground in infested villages, flypaper low to the ground to collect jumping fleas, avoidance of contaminated areas, avoidance of stray animals, treating infected reservoir hosts (livestock and domestic animals), and improving insufficient or non-existent sanitation and garbage disposal.[3] In addition, use of an effective skin repellent may reduce the morbidity associated with heavy infestations.[5]

Conclusion

Tunga penetrans is a serious health threat in endemic, underdeveloped areas with depressed socioeconomic conditions. These resource-poor communities battle with heavy infestations and serious complications. In these areas effective chemotherapy is desperately needed. For the majority of cases outside of the endemic areas standard therapy is sufficient. Isolated, uncomplicated lesions tend to be self-limited. Even though Tungiasis is rare in the United States, physicians should have a high clinical suspicion as more people travel to endemic areas.

References

1. Gibbs N. Tungiasis. www.eMedicine.com 2003 August 13.
2. Tungiasis Biology and Treatment. www.stanford.edu. 2001
3. Samlaska CP. Arthropod Infestations and Vectors of Disease. Military Dermatology. 192-193.
4. Wolf R, Orion E, Matz H. Stowaways with wings: Two cases reports on high-flying insects. DOJ 2003; 9(3):10
5. Heukelbach J, Franck S, Feldmeier H. Therapy of Tungiasis: a Double-blinded Randomized Controlled Trial with Oral Ivermectin. 2004 December. Mem Inst Oswaldo Cruz, Rio de Janeiro, vol 99(8): 873-876.
6. Janvier-Fevrier. Tungiasis. European Journal of Dermatology 1999; 9(1):57-59
7. Feldmeier H, Eisele M, Sabonia-Moura RC, Heukelbach J. Severe Tungiasis in Underprivileged Communities: Case Series from Brazil. Emerging Infectious Diseases [serial online] 2003 August; 9(8). www.cdc.gov
8. Golouh R, Spiler M. A paraungual tumor?-No, just tungiasis. Radiol Oncol 2000: 34(1): 35-39
9. Bertrand R. Parasitic Infections of the Nails. Abstracts of the Fifth Meeting of the European Nail Society: DOJ 9(1):17C

Allergic Contact Dermatitis: Historical Perspective, Clinical Review, and Case Report

Mary Evers D.O.*, Susan T. Nedorost M.D., Monte Fox, D.O., F.A.O.C.D.*****
**2nd year dermatology resident UHHS Richmond Heights Program, Cleveland, Ohio*
***Assistant Professor, Case Western Reserve University Department of Dermatology*
****Program Director UHHS Richmond Heights Program, Cleveland Ohio*

ABSTRACT

Allergic contact dermatitis (ACD) is a common condition seen in the dermatology clinic. First described in 1895 by Jadassohn1, we now have a much better understanding of the immunologic complexity of this delayed type hypersensitivity. Classically, ACD presents as a well-demarcated erythematous, vesicular, and/or scaly patch or plaque with well-defined margins indicating the area of contact. However, clinical presentations of ACD can vary, making the diagnosis challenging. The gold standard for the diagnosis of ACD remains patch testing. The Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test is the only patch test approved by the U.S. Food and Drug Administration10. This test, containing only 23 of the more than 3700 known allergens, is an accurate but insensitive method of detecting ACD10. We present a case of a 22-year-old woman who presented to our contact dermatitis clinic with a fifteen-month history of a pruritic and sometimes-painful rash. Patch testing to a modified North American Screening Series (Chemotechnique Diagnostics AB, Malmö, Sweden) revealed current relevant positive reactions to both Kathon CG and cocamidopropyl betaine.

Historical Perspective

Contact dermatitis was first described by Jadassohn in 1895.[1] Considered the "father" of contact dermatitis, he reported a case of contact allergy to mercury. It was not until well into the 20th century that we began to understand the immunologic complexity of this condition. In 1927, Landsteiner published his initial work on antigens containing "simple chemical compounds".[1] His work with Jacobs in 1935 established that epicutaneous application of allergens could induce contact sensitivity.[2,3] We now know that most contact allergens are small haptens less than 500 Daltons in size that are able to penetrate the skin barrier. A disruption in this barrier, such as a dermatitis or ulceration, places the skin at increased risk of contact sensitivity.

But just where in the skin does sensitization to an allergen occur? Marion Sulzberger, in the 1930's, published a series of articles describing the skin as an originator and site of hypersensitivity.[4] He coined the term Sonderstellung to indicate a specific place in the skin involved in sensitization. In his attempt to locate this site, he showed that intracutaneous injection of a sensitizing material resulted in peripheral sensitization. His research also demonstrated that a hypersensitivity reaction could not be elicited if the antigen is administered by a non-skin route (intravenous, intramuscularly, intraperitoneally, intrapulmonally, intratesticularly, and intracardially). Although a Sonderstellung was never identified, Sulzberger was able to demonstrate that the skin was both a sensitizing organ and an organ that could be sensitized.

It is now known that allergens are taken up by antigen presenting cells, primarily Langerhans Cells (LCs), in the epidermis. As a medical student, Paul Langerhans was the first to identify these cells in 1868.[4] First thought to be of neural origin, it is now believed that LCs are derived from bone marrow.[4,5] Epidermal LCs, like macrophages, are dendritic cells that bear a variety of antigenic determinants on their cell surface.[4] Pehamberger et al demonstrated in 1983 that LCs are required for the generation of contact sensitivity.[6] It is well know that exposure to ultraviolet (UV) radiation will result in a reduction in the density of LCs and inhibition of contact sensitization.[1,7,8]

Following allergen uptake, the LC migrates to the lymph node where presentation to T-lymphocytes occurs. A subset of antigen-specific T-lymphocytes are then produced and migrate to the site of exposure on the skin. In 1942 Landsteiner and Chase first described the relationship of contact allergy and delayed type hypersensitivity.[1] Their work showed that both contact allergy to small molecular antigens and delayed type hypersensitivity to microbial antigens could be passively transferred with lymphocytes in guinea pigs.

Following re-exposure to the allergen, an inflammatory response recognized as an eczematous dermatitis is seen. This response is an acquired hypersensitivity of the delayed type. Prior sensitization is required and may occur following one exposure or even after years of contact to an allergen. This fact is important for the clinician to bear in mind, as patients may not mention products they have used for many years as a potential source of their dermatitis. Although complex, a fundamental knowledge of this immunologic process is essential in the management of patients with contact dermatitis.

Clinical Review

Contact dermatitis (irritant and allergic) is a common condition comprising 6% to 10% of all dermatology clinic visits.[9] A diagnosis of allergic contact dermatitis (ACD) can be difficult to make on clinical grounds alone. Classically, ACD presents as a pruritic well-demarcated erythematous, vesicular, and/or scaly patch or plaque with well-defined margins indicating the area of contact. Atypical presentations may include a patchy or diffuse dermatitis, depending on the nature of the causative allergen. Other less common clinical presentations of ACD include urticaria and photosensitivity reactions.

Biopsy may be helpful to diagnose ACD by excluding other diagnoses such as psoriasis, tinea, and cutaneous T-cell lymphoma. The histology of acute lesions exhibit spongiosis with or without intraepidermal vesiculation and a mixed dermal inflammatory infiltrate. Subacute and chronic lesions can produce confusing histological patterns less diagnostic for ACD.

The gold standard for the diagnosis of ACD remains patch testing. The only patch test approved by the U.S. Food and Drug Administration is the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test.[10] The T.R.U.E. Test contains 23 allergens and a negative control. Although this test only contains approximately 1.4% of the more than 3700 known allergens, it is an accurate but insensitive method of detecting ACD.[10] Among patients tested for ACD, a 23% to 62% detection rate has been reported with the T.R.U.E. Test.[10] In order to demonstrate the reproducibly of a positive reaction in patch testing, Ale and Maibach performed a concurrent right versus left study.[11] Their data suggest that patch test-

ing is a reasonably reproducible test when methodological error is kept to a minimum.

Patch testing is performed by the application of a series of patches to an area completely free of dermatitis, most commonly the back. The patches are left in place for 48 hours then removed. Readings are performed at 48 to 72 hours and again between 72 and 168 hours after placement. Patients are instructed not to get their back wet, shower, or perspire heavily during this entire time period.

Patch test reactions are recorded on a quantitative scale as recommended by the International Contact Dermatitis Research Group1 (Table 1). The absence of a positive reaction may be due to testing error. Wet or loosened patches or removal prior to the 48 hours may result in a false negative reaction. Inadvertent washing of the back can remove grid patterns creating an inability to accurately read any positive reactions. Application of potent topical steroids to the site of testing several days prior or during testing can blunt the immune response. This is also true for doses of systemic corticosteroids greater than 20mg per day.[1] Finally, failure to perform a late reading may miss a delayed positive reaction.

Table 1. Patch test interpretation

-	negative reaction
?	faint macular erythema
+	erythema, possibly papules
++	erythema, papules, vesicles
+++	bullous reaction
IR	irritant reaction
NT	not tested

A negative patch test does not prove the absence of allergy. It is often due to a "missed" allergen. Results of a meta-analysis by Krob et al suggest that the T.R.U.E. Test is, at best, a screening test.[9] The North American Contact Dermatitis Group (NACDG) recognizes that important allergens may be missed by the T.R.U.E. Test.[12, 13] Directed and detailed questioning about the patient's hobbies, personal care products, and work environment is essential and may identify potential allergens not previously tested. A study by Soni and Sherertz found that 27 of 43 patients were found to have additional relevant allergens when further patch testing was performed.[14]

Identifying a positive reaction is only the initial step in the search for the clinical relevance of an allergen. Relevance is classified as possible, probable, certain, or past depending on the clinical situation. There are no absolute rules for determining relevance. It is dependent on the knowledge and experience of the clinician. The most prevalent allergens tested by the T.R.U.E. test are nickel, thimerosal, cobalt, fragrance mix, and balsam of Peru.[9] In comparison, the NACDG patch test results from 2001-2002 reports the 5 most common allergens in patients tested are nickel (16.7%), neomycin (11.6%), balsam of Peru (11.6%), fragrance mix (10.4%), and thimerosal (10.2%). [13]

In summary, when performed and interpreted correctly, patch testing is a reliable method of identifying ACD. It may appear simple to apply and read, but is in fact, a complicated procedure. Identification of a relevant positive allergen requires expertise in contact dermatitis on the part of the clinician. Contact dermatitis education, including patch testing, should be an integral part of every dermatology residency program. A recent survey by High and Cruz report only 27% of programs had rotations dedicated to contact dermatitis and/or patch testing.[15]

Case Report

A 22-year-old woman presented to our Contact Dermatitis Clinic with a fifteen-month history of a pruritic and sometimes-painful rash. The rash started on her dorsal hands bilaterally and symmetrically with spreading to her palms, scalp, posterior neck, and chest (Figure 1-4). She reported her legs were only intermittently involved and it has never affected her feet. She had no significant past medical history and denied a personal history of atopy. Family history was negative for atopy, psoriasis, autoimmune disease, or other skin conditions. Her only medication allergy was to ampicillin, which caused hives. Prior to the onset of the rash, she was a

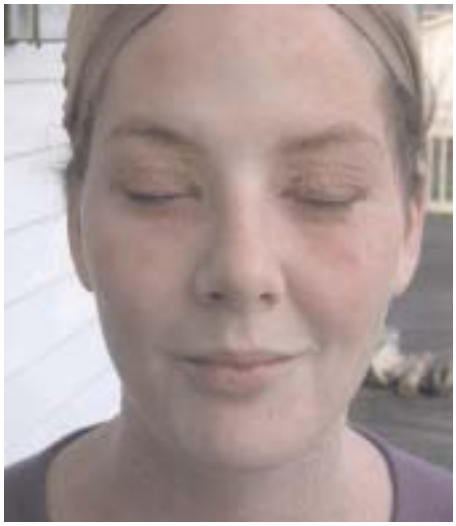


Figure 1

Figure 2

Figure 3

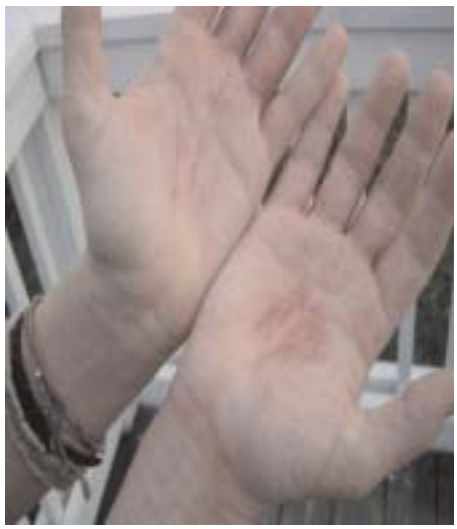


Figure 4

Figure 1-4 Erythematous scaly plaques involving the face, neck, dorsal hands, and palms.

Table 2. University Hospitals of Cleveland Screening Series

*additional allergens added to North American Screening Series (Chemotechnique, Malmö, Sweden)

Benzocaine	Thimerosal (Merthiolate)
2-Mercaptobenzothiazole	Propylene Glycol
Colophony	2-Hydroxy-4-methoxybenzophenone (Benzophenone-3)
4-Phenylenediamine base	4-Chloro-3, 5-xylenol (PCMX)
Imidazolidinyl urea	Ethyleneurea-Melamine formaldehyde mix
Cinnamic aldehyde	2-tert-Butyl-4-methoxyphenol (BHA)
Americhol L 101	Goldsodium thiosulfate
Carba Mix	Ethyl acrylate
Neomycin sulfate	Glyceryl monothioglycolate (Glyceryl thioglycolate)
Thiuram Mix	Toluenesulfonamide Formaldehyde resin
Formaldehyde	Methyl methacrylate
Ethylenediamine dihydrochloride	Cobalt (II) chloride hexahydrate
Epoxy Resin	Tixocortal-21-Pivalate
Quaternium 15	Budesonide
4-tert-Butylphenol formaldehyde resin	Stearyl alcohol*
Mercapto Mix	2-Phenoxyethanol*
N-isopropyl-N-phenyl-4-phenylenediamine	Sorbitan sesquioleate*
Potassium dichromate	Benzyl alcohol*
Balsum Peru	Clioquinol (5-chloro-7-iodo-quinolinol)*
Nickel sulfate hexahydrate	Wool Alcohols (Lanolin)*
2,5-Diazolidinylurea	2-Chloroacetamide*
DMDM Hydantoin	Triethanolamine*
Bacitracin	Abitol (Hydroabietyl alcohol)*
Mixed Dialkyl Thioureas	Dimethylol Dihydroxyethyleneurea (Fix. CPN)*
5-chloro-2-methyl-4-isothiazolinone (Kathon CG, 100ppm)	Dimethylol Dihydroxyethyleneurea, modified (Fix. ECO)*
Paraben Mix	Cocamidopropyl betaine*
Euxyl K400 (methyl diromoglutaronitrile and phenoxyethanol)	Triclosan*
Fragrance Mix	Lidocaine*
Glutaraldehyde	Tea Tree Oil*
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	
Sesquiterpene Lactone mix	

college student but had since withdrawn from school and social activities because of this condition.

Previously, she had been seen by multiple physicians for this condition including internists, dermatologists, rheumatologists, and infectious disease specialists. The differential diagnosis had included lupus erythematosis (possible subacute type), dermatomyositis, eczema, guttate psoriasis and prophyria cutanea tarda. Extensive laboratory testing including ANA, Anti-SM, Anti-RNP, Anti-SSA, Anti-SSB, Anti-Scl-70, Anti-DNA and HIV were negative. Serum aldolase, ESR, IgE, Latex IgE, CBC with differential, BMP (except glucose 120), LFT, lipid profile, plasma prophyrins, SPEP, C3, C4, serum fungal titers, and ASO titer were all within normal limits. UA, UPEP, and CXR were also normal. Previous treatments included topical and oral steroids, topical immunomodulators, oral antihistamines, and oral cyclosporine without complete clearing.

A punch biopsy of skin from the nape of the neck had been performed (Figure 5,6). It demonstrated a spongiotic epidermis with an occasional apoptotic keratinocyte and focal areas of neutrophils in the stratum corneum. Direct and indirect immunofluorencence were negative. These histological features are nonspecific, but most consistent with an eczematous dermatitis with secondary inflammation or impetiginization.

Following consultation at our contact dermatitis clinic, the patient was scheduled for patch testing. She was tested to her hair gel as is and the North American Screening Series (Chemotechnique Diagnostics AB, Malmö, Sweden) modified to include an additional 15 allergens (Table 2). The positive results are shown in Table 3. A 1+ reaction to both cocamidopropyl betaine and Kathon CG at days 4 and 7 were recorded. After 3 weeks of strict avoidance of these allergens, she was completely clear except for one residual patch test site on her left upper back. Other reactions included a 2+ reaction to neomycin and bacitracin (considered to be of past relevance), 1+ reaction to carba mix and mixed dialkyl thioureas, and a questionable reaction to nickel. The patient was instructed to avoid neomycin and bacitracin antibiotic ointments. Nickel and rubber accelerators were relevant to her use of an eyelash curler.

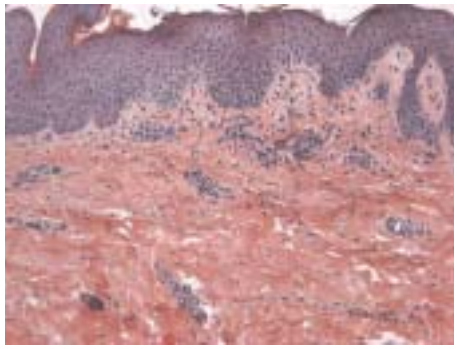


Figure 5

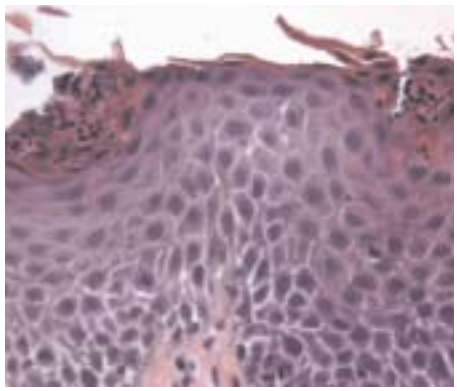


Figure 6

Figure 5,6 A low and high power view magnification demonstrating a spongiotic epidermis with focal areas of neutrophils in the stratum corneum. Within the superficial dermis is a mild lymphocytic perivascular inflammatory infiltrate.

Table 3. Positive patch test results in case presented

ALLERGEN	*REACTION*
Cocamidopropyl Betaine	1+
Kathon CG	1+
Carba Mix	1+
Neomycin	2+
Bacitracin	2+
Mixed Dialkyl Thioureas	1+
Nickel	?

Discussion

Kathon CG was first marketed in 1980.[1] It is an effective preservative with outstanding antimicrobial activity against gram-negative and gram-positive bacteria, yeasts and fungi.[16] The active chemical constituents are 5-chloro-2-methyl-4-isothiazoline-3-one (chloromethylisothiazolinone) and 2-methyl-4-isothiazoline-3-one (methylisothiazolinone) in an approximate 3:1 ratio respectively.[1, 16, 17] Other isothiazolinone biocides are available and marketed under many trade names. Currently, patch testing for Kathon CG allergy is performed with 0.01% aq or 100 ppm.[1]

Kathon CG is present in many rinse-off and leave-on toiletry products such as liquid soaps, shampoos, hair gels, cosmetics, and body lotions.[16] Prevalence of a positive patch test reaction has been reported to be as high as 8% to 8.5%. [1, 16] However, other studies report much lower positive reactions (0.8% to 3.5%)[16, 18, 19] (approximately 4% at our University Hospitals of Cleveland Contact Dermatitis Clinic). The NACDG data from 1998-2000 reported a 1.4% positive reaction to Kathon CG in over 5000 patients tested.[12] This allergen has also been reported to be more prevalent in women, with cosmetics being the principal source of sensitization.[16]

Cocamidopropyl betaine (CABP) is a nonionic surfactant found primarily in personal care products.[1, 20] It is available from many suppliers under more than 50 trade names. CAPB is made by reacting coconut fatty acids (found in coconut oil) with dimethylaminopropylamine (DMAPA) to produce cocamidopropyl dimethylamine, which then reacts with sodium monochloroacetate to form the end product CAPB.[20, 21] Patch testing is preformed with 1% aqueous CAPB.

Allergy to CAPB was first reported in 1983.[21] It is commonly found in over 600 personal care products including shampoos, bath gels, body washes, liquid detergents, pet shampoos, skin lotions, make-up removers, and contact lens cleaners.[1, 20, 21, 22] Allergy to CAPB can present as scalp, facial, eyelid, neck, and/or hand dermatitis. Prevalence of ACD secondary to CAPB ranges from 3.0 to 7.2%21, [23] (approximately 4% at our University Hospitals of Cleveland Contact Dermatitis Clinic). This allergen has been responsible for occupational allergic contact dermatitis in hairdressers and health care workers.[21, 23]

The true allergen in patients with positive patch test to CAPB has been debated in the literature.[21, 22, 23] Amidoamine (AA) and DMAPA, products used in the synthesis/production of CAPB, may be the true contact allergen. Fowler reports European patients are rarely allergic to AA, but test positive to both CAPB and DMAPA.[22] On the other hand, patients in North America are allergic to either CAPB or AA or both, but rarely allergic to DMAPA.[24] Our patient was only tested to CAPB. The difference in the North American studies may be explained by manufacturing and supply variations in North America as compared to other countries.

Conclusion

ACD is a common dermatological condition with significant economic impact and morbidity. A detailed history, including an occupational history, may provide clues to possible allergens. Patch testing is often necessary to make a diagnosis of ACD. Relevance must be determined and additional patch testing may be necessary. Studies have shown that up to 10% of patients patch tested are allergic to cosmetic products or their constituent ingredients.[25] Head and neck dermatitis should raise a clinical suspicion for CAPB allergy. We recommend patch testing for CAPB as part of a standard series.

REFERENCES

1. Rietschel RL and Fowler JF. Fisher's Contact Dermatitis Philadelphia: Lippincott Williams & Wilkins; 2001.
2. Landsteiner K, Jacob J. Studies on the sensitization of animals with simple chemical compounds J Exp Med 1935; 61:643-656.
3. Tamaki K et al. The Role of Epidermal Cells in the Induction and Suppression of Contact Sensitivity J Invest Derm 1981;76(4):275-278.
4. Katz SI. The skin as an immunologic organ J Am Acad Dermatol 1985;13(3):530-536.
5. Volc-Platzer B et al. Cytogenetic Identification Of Allogeneic Epidermal Langerhans Cells In A Bone-Marrow-Graft Recipient NEJM 1984;310(17):1123-1124.
6. Pehamberger H et al. Epidermal Cell-Induced Generation of Cytotoxic T-Lymphocyte Responses Against Alloantigens or TNP-Modified Syngeneic Cells: Requirement for Ia-Positive Langerhans Cells J Invest Derm 1983;81(3):208-211.
7. Freedberg IM et al, editors. Fitzpatrick's Dermatology In General Medicine New York: McGraw-Hill; 1999.
8. Kripke ML et al. Role of DNA damage in local suppression of contact hypersensitivity in mice by UV radiation Exp Dermatol 1996;5(3):173-80.
9. Krob HA et al. Prevalence and relevance of contact dermatitis allergens: A meta-analysis of 15 years of published T.R.U.E. Test data J Am Acad Dermatol 2004;51(3):349-353.
10. Belsito DV. Patch testing with a standard allergen ("screening") tray: rewards and risks Dermatologic Therapy 2004;17:231-239.
11. Ale SI, Maibach HI. Reproducibility of patch test results: a concurrent right-versus-left study using TRUE Test Contact Dermatitis 2004;50(5):304-12.
12. Marks JG et al. North American Contact Dermatitis Group Patch-Test Results, 1998 to 2000 Am J Contact Dermat 2003;14(2):59-62.
13. Pratt MD et al. North American Contact Dermatitis Group patch-test results, 2001-2002 study period Dermatitis 2004;15(4)176-83.
14. Soni BP and Sherertz EF. Evaluation of Previously Patch-Tested Patients Referred to a Contact Dermatitis Clinic Am J Contact Dermat 1997;8(1):10-14.
15. High WA and Cruz PD Jr. Contact dermatitis education in dermatology residency programs: can (will) the American Contact Dermatitis Society be a force for improvement? Am J Contact Dermat 2004;14(4):195-9.
16. Hasson A et al. Patch test sensitivity to the preservative Kathon CG in Spain Contact Dermatitis 1990;22(5):257-61.
17. Bjorkner B et al. Contact allergy to the preservative Kathon CG Contact Dermatitis 1986;14(2):85-90.
18. Hjorth N and Roed-Petersen J. Patch test sensitivity to Kathon CG Contact Dermatitis 1986;14(3):155-7.
19. Shuster S and Spiro J. Measurement of risk of sensitization and its application to Kathon Contact Dermatitis 1987;17(5):299-302.
20. Mowad CM. Cocamidopropyl Betaine Allergy Am J Contact Dermat 2001;12(4):223-224.
21. De Groot AC et al. Contact allergy to cocamidopropyl betaine Contact Dermatitis 1995;33:419-22.
22. Fowler JF Jr. Cocamidopropyl Betaine Dermatitis 2004;15(1):3-4.
23. Brey NL and Fowler JF Jr. Relevance of Positive Patch-Test Reactions to Cocamidopropyl Betaine and Amidoamine Dermatitis 2004;15(1):7-9.
24. Fowler JF Jr et al. Allergy to Cocamidopropyl Betaine and Amidoamine in North America Dermatitis 2004;15(1):5-6.
25. Orton DI and Wilkinson JD. Cosmetic allergy: incidence, diagnosis, and management Am J Clin Dermatol 2004;5(5):327-37.

At the first sign of...

In patients with recurrent genital herpes or herpes zoster

Famvir®

(famciclovir)

Tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Herpes Zoster: Famvir® (famciclovir) is indicated for the treatment of acute herpes zoster (shingles).

Herpes Simplex Infections: Famvir is indicated for:

- treatment or suppression of recurrent genital herpes in immunocompetent patients.
- treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

CONTRAINDICATIONS

Famvir® (famciclovir) is contraindicated in patients with known hypersensitivity to the product, its components, and Denavir® (penciclovir cream).

PRECAUTIONS

General

The efficacy of Famvir® (famciclovir) has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering Famvir to patients with creatinine clearance values <60 mL/min. *(See DOSAGE AND ADMINISTRATION in the full prescribing information).* In patients with underlying renal disease who have received inappropriately high doses of Famvir for their level of renal function, acute renal failure has been reported.

Information for Patients

Patients should be informed that Famvir is not a cure for genital herpes. There are no data evaluating whether Famvir will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

Drug Interactions

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis: Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.5 to 9.0x the human systemic exposure at the recommended daily oral doses of 500 mg t.i.d., 250 mg b.i.d., or 125 mg b.i.d. based on area under the plasma concentration curve comparisons [24 hr AUC] for penciclovir). No increases in tumor incidence were reported in male rats treated at doses up to 240 mg/kg/day (0.9 to 5.4x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.4 to 2.4x the human AUC).

Mutagenesis: Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutations in bacteria *(S. typhimurium* and *E. coli)* and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5,000 mcg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/mL), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir-induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 mcg/mL). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 mcg/mL). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/mL).

Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility: Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.9 to 11.4x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.2 to 1.2x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.4 to 2.4x the human AUC) and 150 mg/kg/day (1.7 to 10.2x the human AUC), respectively.

Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (3.6 to 21.6x the human AUC).

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8-week baseline period and recurrent genital herpes receiving oral Famvir (250 mg b.i.d.) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8-week follow-up.

Pregnancy

Teratogenic Effects–Pregnancy Category B: Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 3.6 to 21.6x and 1.8 to 10.8x the human systemic exposure to penciclovir based on AUC comparisons for the rat and rabbit, respectively) and intravenous doses of 360 mg/kg/day in rats (2 to 12x the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.5 to 9.0x the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.4 to 2.6x the human dose [BSA]) or rabbits (60 mg/kg/day, 0.7 to 4.2x the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to Famvir, Novartis Pharmaceuticals Corporation maintains a Famvir Pregnancy Registry. Physicians are encouraged to register their patients by calling (888) 669-6682.

Nursing Mothers

Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of Famvir in infants.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.

Geriatric Use

Of 816 patients with herpes zoster in clinical studies who were treated with Famvir, 248 (30.4%) were ≥65 years of age and 103 (13%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

ADVERSE REACTIONS

Immunocompetent Patients

The safety of Famvir® (famciclovir) has been evaluated in clinical studies involving 816 Famvir-treated patients with herpes zoster (Famvir, 250 mg t.i.d. to 750 mg t.i.d.); 528 Famvir-treated patients with recurrent genital herpes (Famvir, 125 mg b.i.d. to 500 mg t.i.d.); and 1,197 patients with recurrent genital herpes treated with Famvir as suppressive therapy (125 mg q.d. to 250 mg t.i.d.) of which 570 patients received Famvir (open-labeled and/or double-blind) for at least 10 months. Table 5 lists selected adverse events.

Table 5

Selected Adverse Events Reported by ≥2% of Patients in Placebo-Controlled Famvir® (famciclovir) Trials*

	Incidence					
	Herpes Zoster		Recurrent Genital Herpes		Genital Herpes-Suppression	
Event	Famvir® (n=273) %	Placebo (n=146) %	Famvir® (n=640) %	Placebo (n=225) %	Famvir® (n=458) %	Placebo (n=63) %
Nervous System						
Headache	22.7	17.8	23.6	16.4	39.3	42.9
Paresthesia	2.6	0.0	1.3	0.0	0.9	0.0
Migraine	0.7	0.7	1.3	0.4	3.1	0.0
Gastrointestinal						
Nausea	12.5	11.6	10.0	8.0	7.2	9.5
Diarrhea	7.7	4.8	4.5	7.6	9.0	9.5
Vomiting	4.8	3.4	1.3	0.9	3.1	1.6
Flatulence	1.5	0.7	1.9	2.2	4.8	1.6
Abdominal Pain	1.1	3.4	3.9	5.8	7.9	7.9
Body as a Whole						
Fatigue	4.4	3.4	6.3	4.4	4.8	3.2
Skin and Appendages						
Pruritus	3.7	2.7	0.9	0.0	2.2	0.0
Rash	0.4	0.7	0.6	0.4	3.3	1.6
Reproductive Female						
Dysmenorrhea	0.0	0.7	2.2	1.3	7.6	6.3

*Patients may have entered into more than one clinical trial.

The following adverse events have been reported during post-approval use of Famvir: urticaria, hallucinations and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Table 6 lists selected laboratory abnormalities in genital herpes suppression trials.

Table 6

Selected Laboratory Abnormalities in Genital Herpes Suppression Studies*

Parameter	Famvir® (n=660)† %	Placebo (n=210)† %
Anemia (<0.8 x NRL)	0.1	0.0
Leukopenia (<0.75 x NRL)	1.3	0.9
Neutropenia (<0.8 x NRL)	3.2	1.5
AST (SGOT) (>2 x NRH)	2.3	1.2
ALT (SGPT) (>2 x NRH)	3.2	1.5
Total Bilirubin (>1.5 x NRH)	1.9	1.2
Serum Creatinine (>1.5 x NRH)	0.2	0.3
Amylase (>1.5 x NRH)	1.5	1.9
Lipase (>1.5 x NRH)	4.9	4.7

*Percentage of patients with laboratory abnormalities that were increased or decreased from baseline and were outside of specified ranges.

† n values represent the minimum number of patients assessed for each laboratory parameter.

NRH = Normal Range High.

NRL = Normal Range Low.

HIV-Infected Patients

In HIV-infected patients, the most frequently reported adverse events for famciclovir (500 mg twice daily; n=150) and acyclovir (400 mg, 5x/day; n=143), respectively, were headache (16.7% vs. 15.4%), nausea (10.7% vs. 12.6%), diarrhea (6.7% vs. 10.5%), vomiting (4.7% vs. 3.5%), fatigue (4.0% vs. 2.1%), and abdominal pain (3.3% vs. 5.6%).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].

T2004-06

REV: MARCH 2004 89011404

Manufactured by:
Novartis Farmacéutica S.A.
08210 Barberà del Vallès
Barcelona, Spain

Distributed by:
Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

Act FAST!

In Recurrent Genital Herpes

FAMVIR® stops pain and burning in a median of 2 days or less with episodic therapy*†[1]

- Median time (days) to cessation vs placebo (pain: 2.0 vs 2.4, *P*<.006; burning: 1.7 vs 2.1, *P*<.001)

FAMVIR keeps patients outbreak-free for nearly a year with suppressive therapy[2,3]

- Median time to first recurrence was 336 days with FAMVIR vs 47 days with placebo (*P*<.001)[2]
- The safety and efficacy of FAMVIR for suppressive therapy have not been established beyond 1 year

In Herpes Zoster

Only FAMVIR is proven to shorten the median duration of PHN by 100 days vs placebo‡§[4,5]

- For patients ≥ 50 years

FAMVIR (famciclovir) Tablets are indicated for the treatment or suppression of recurrent genital herpes in immunocompetent patients; the treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients; and the treatment of acute herpes zoster (shingles).

In clinical trials, the most commonly reported adverse events vs placebo were headache (zoster: 22.7% vs 17.8%; episodic: 23.6% vs 16.4%; suppression: 39.3% vs 42.9%); nausea (zoster: 12.5% vs 11.6%; episodic: 10.0% vs 8.0%; suppression: 7.2% vs 9.5%); and diarrhea (zoster: 7.7% vs 4.8%; episodic: 4.5% vs 7.6%; suppression: 9.0% vs 9.5%).

The efficacy of FAMVIR has not been established for initial-episode genital herpes infection, ophthalmic zoster, disseminated zoster, or in immunocompromised patients with herpes zoster.

There is no cure for genital herpes. There is no evidence that FAMVIR can stop the spread of herpes to others.

FAMVIR, Pregnancy Category B, is contraindicated in patients with known hypersensitivity to the product, its components, or DENAVIR® (penciclovir cream).

See brief Prescribing Information on previous page.

*In patients with moderate to severe genital herpes.

†In clinical studies designed for medication to be administered within 6 hours of symptom or lesion onset.

‡No significant difference in overall incidence of PHN for famciclovir vs placebo. In patients <50 years, no statistically significant difference seen in duration of PHN.

§Therapy should be initiated as soon as herpes zoster is diagnosed. The efficacy of treatment started more than 72 hours after rash onset has not been established.

References: 1. Data on file, Novartis Pharmaceuticals Corp. **2.** Diaz-Mitoma F, Sibbald RG, Shafran SD, et al, for the Collaborative Famciclovir Genital Herpes Research Group. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. *JAMA.* 1998;280:887-892. **3.** Tyring SK, Diaz-Mitoma F, Shafran SD, et al. Oral famiciclovir for the suppression of recurrent genital herpes: the combined data from two randomized controlled trials. *J Cutan Med Surg.* 2003;7:449-454. **4.** Tyring S, Barbarash RA, Nahlik JE, et al, and the Collaborative Famciclovir Herpes Zoster Study Group. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.*1995;123:89-96. **5.** Dworkin RH, Boon RJ, Griffin DRG, Phung D. Postherpetic neuralgia: impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients. *J Infect Dis.* 1998;178(suppl 1):S76-S80.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

FAMVIR® famciclovir tablets
125 mg 250 mg 500 mg
FAST THAT LASTS

FAMVIR is a registered trademark of Novartis. www.FAMVIR.com

Printed in U.S.A. 6/05 FVR-AD-0162-A

Diagnostic Pearls- Photos Utilizing Dermoscopy

Jay S. Gottlieb, DO, FAOCD, Amy D. Gottlieb, PA-C

Many times, when we discuss with our patients the need to do a biopsy on a pigmented lesion, we take a digital photo of the lesion and show the patient the picture. We then enlarge the photo and show them the abnormal variation that is cause for concern. This is a good way to educate our patient about changing pigmented lesions and it also puts their mind at ease that there is a real reason to do the procedure. We use a 5.0 megapixel Canon Power Shot 500 Digital Elph camera in our office. As we enlarge the photo, the image quality is diminished, but the abnormality becomes more obvious.

We purchased and began using a 3Gen Dermlite 00 ProHR in April of 2005. Dermoscopy has become a real asset in our practice. We feel much more comfortable now when we make a decision to perform a biopsy on a pigmented lesion. We elected not to spend the money required to purchase a quality dermoscopy camera setup.

Today, we decided to try something new. We took a digital picture of a pigmented lesion through our Dermlite using no special attachments. We were amazed at what we found and what we could now show to our patient. We will be using this procedure regularly in our practice from this point forward. We hope that some readers find it as intriguing as we have!

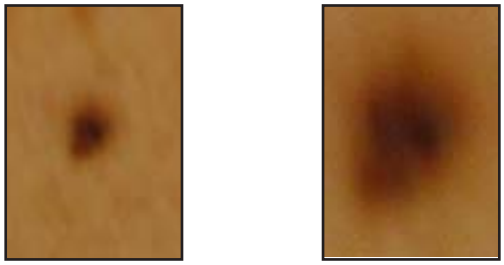


Figure 1 Digital macro photo in normal mode and then a 4X digital enlargement as seen on the screen of the digital camera.

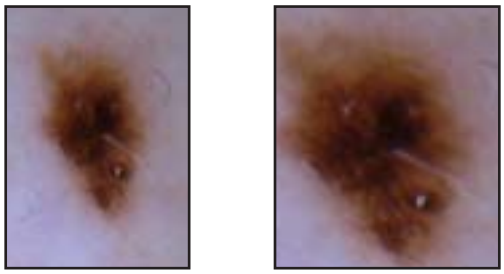


Figure 2 Digital photo of the same lesion in Figure 1 taken by holding our camera against the Dermlite 00 ProHR and then a 4X digital enlargement of the same lesion as seen on the screen of the digital cameral.