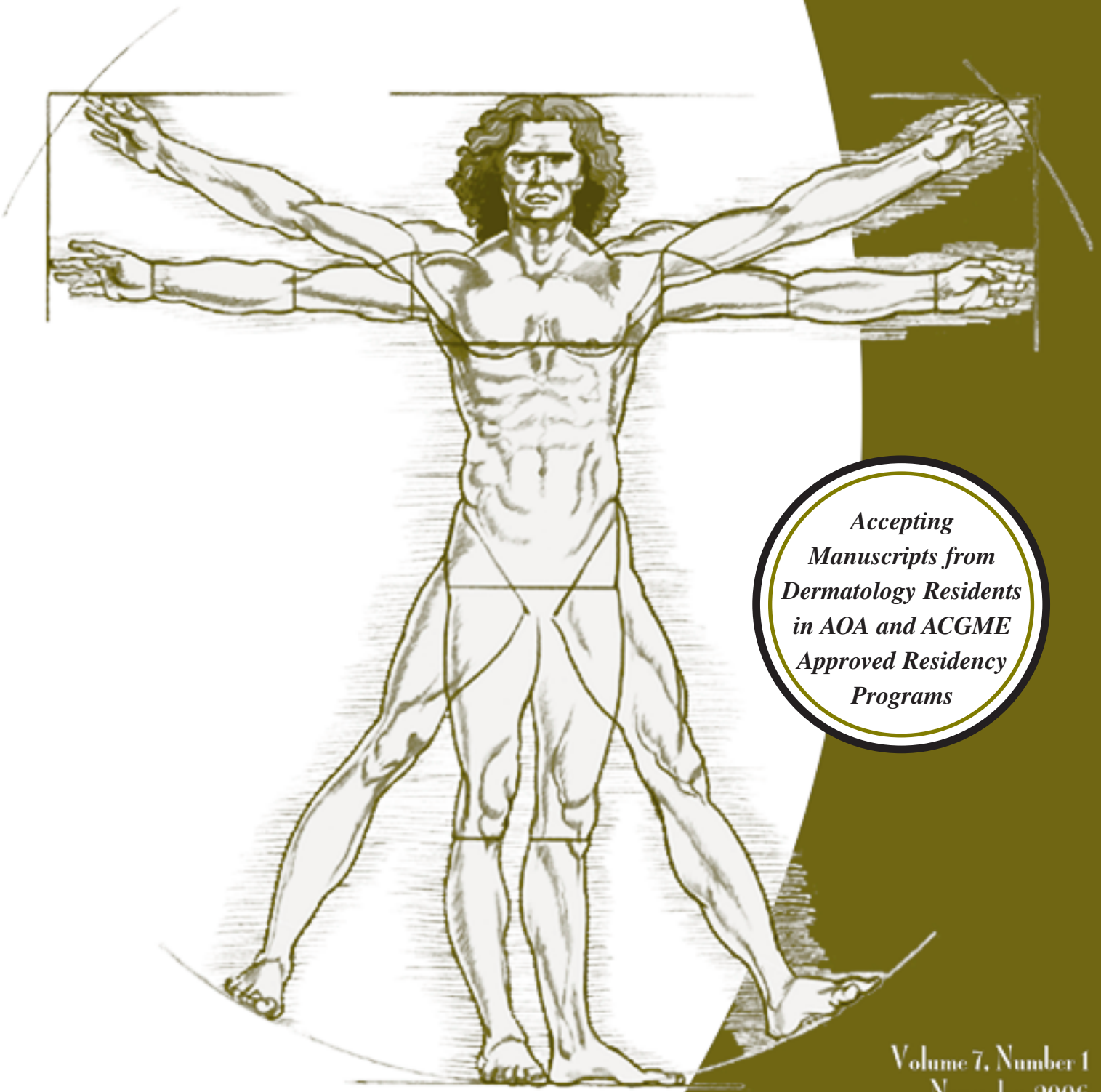
Journal of Resident Dermatology

A Publication of the American Osteopathic College of Dermatology

AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY · FOUNDED 1958 · AOCD



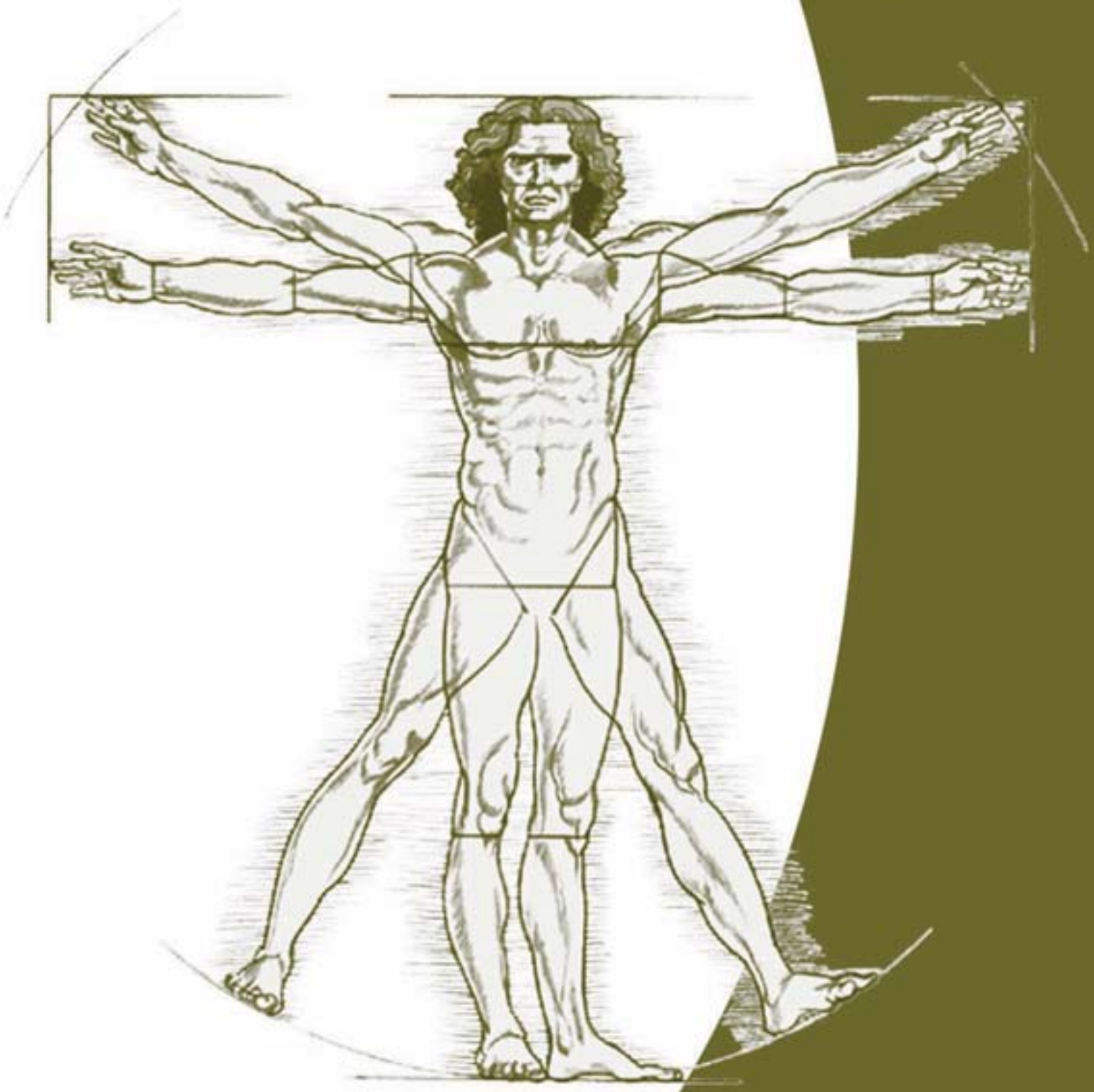
Accepting Manuscripts from Dermatology Residents in AOA and ACGME Approved Residency Programs

Volume 7, Number 1
November 2006
www.aocd.org

Journal of Resident Dermatology

A Publication of the American Osteopathic College of Dermatology

American Osteopathic College of Dermatology · AOCD · Founded 1958



Journal of Resident Dermatology

A Publication 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 7 , NUMBER 1 NOVEMBER 2006

Journal of RESIDENT DERMATOLOGY

A PUBLICATION OF THE AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY

CONTENTS

Letter From The Editors

Jay S. Gottlieb, D.O.

Stanley E. Skopit, D.O.

James Q. DelRosso, D.O.

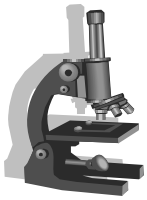
We are sure by now that you have noticed a major change in this journal! We have officially changed the name of the journal to Journal of Resident Dermatology-A publication of the American Osteopathic College of Dermatology. All of the changes that have been made have helped to improve the quality of the manuscripts, grow the journal and increase the distribution. We have gone from a distribution of 450 to just less than 2000! The Journal of Resident Dermatology is getting to be known in the dermatology profession as 'the little journal that grew!'

We recognize that without our Founding Sponsors, none of this would be taking place. Our Founding Sponsors have come to the plate and have committed to the resident physicians in our dermatology training programs. We applaud and thank **Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory, Medicis-The Dermatology Company** and **Stiefel Laboratory**. They are all committed to the dermatology profession and serve to inspire us to be better physicians.

Unlike the healthcare insurance industry, our Founding Sponsors still refer to us as doctors and not healthcare providers. They speak of the dermatology profession and not the healthcare industry. Most importantly, they talk about helping patients and not degrading them to the status of healthcare recipients. The bottom-line is that they see us as the caring professionals that we take pride in being.

Julie Layton of Freelance Proofreading and Editing continues to work closely with us. She remains committed to improving the JAOCD in every way possible.

We encourage every program director to work with their residents to assure that the papers being submitted for consideration for publication are of the highest possible quality.



JAOCD
Founding Sponsor

Again we extend our sincere appreciation for the continued support to our **Founding Sponsors:** ***Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services, Medicis-The Dermatology Company*** and ***Stiefel Laboratory.***

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

Poulos

Barnhill

Hanly

Dermatopathology

Nationwide

24 Hour Turn Around

GLOBAL PATHOLOGY

LABORATORY SERVICES

866 - 825 - 4422

Not Much of a Stretch to GETTING PUBLISHED!

The editors of the Journal of the American Osteopathic College of Dermatology (JAOCD) welcome all dermatology residents in AOA and ACGME residency programs to enjoy this issue of the JAOCD. The JAOCD was developed as a journal for and by residents in dermatology. The editors of the JAOCD welcome input from all dermatology residents, program chairman, program directors and practicing dermatologists. Our editorial review board is open to new members. Our goal is to become a quarterly publication within 1 year and then become a bimonthly publication soon thereafter.

We encourage all dermatologists to participate in this effort. Seasoned practitioners have time-tested wisdom to impart on dermatology residents. When residents are excited about specific cases, they like to share with their co-residents. Original research is the lifeblood of our profession and is always encouraged. Clinical, surgical as well as office management pearls have been topics covered in past issues.

For more information about becoming involved with the JAOCD or submitting manuscripts for consideration for publication, visit www.aocd.org and click on the JAOCD icon or feel free to contact the editors at jaocd@aol.com

Letter from the President

of the AOCD

Richard Miller, President

Dear fellow AOCD members,

It has been my privilege to represent you this past year as President. We have continued to revise and refine our training programs. As a program director, I am acutely aware of the need to maintain a high quality of education, interest and instruction at every level of the residency program and to constantly challenge our residents with new and exciting learning opportunities. It is this constant review and improvement that makes our programs so highly sought after and is such an integral part of the training of the osteopathic dermatologist.

The development of our AOCD Journal and its eventual evolution to the Journal of Resident Dermatology has proven to be a valuable tool in our resident training. I would like to congratulate all those involved in the development and refinement of this journal and would especially like to acknowledge Dr. Jay Gottlieb, the driving force behind this publication. As the journal becomes the Journal of Resident Dermatology it will offer residents another avenue for potential publication of their medical text. In my opinion the skill necessary to produce a viable medical article is becoming a lost art and without the perpetuation of quality medical writing our specialty will certainly suffer. I believe in the adage, publish or perish and those of us involved in post graduate medical education need to encourage and assist our trainees in this endeavor. These papers can vary from interesting case presentation to in-depth review or research articles. The quality and writing detail must be closely assessed prior to submission of these articles and this duty often times should fall on the desk of the program director and his or her co-trainers. The final review would obviously lie with the editorial board. As the journal continues to progress, the quality and quantity of publishable articles will grow. I look forward to reading future editions and will work closely with my residents to create informative and quality work. Our residents are extremely fortunate to have this wonderful journalistic avenue available to them.

I am honored to have served the college as President and plan to remain actively involved in the AOCD. I would like to congratulate my successor Dr. Bill Way on his appointment to the office of President and I know the college will benefit from his contributions.

Hypopigmented Mycosis Fungoides: A Case Presentation and Review of the Literature

Kristen Marie Aloupis, D.O., M.P.H.,* Stanley Skopit, D.O., F.A.O.C.D., Brian Portnoy, D.O., F.A.O.C.D.*****

**1st year resident Nova Southeastern University/BGMC*

***Program Director Nova Southeastern University/BGMC*

****Associate Director Nova Southeastern University/BGMC*

ABSTRACT

Hypopigmented mycosis fungoides (MF) is a rather uncommon variant of cutaneous T-cell lymphoma. Distinguishing features of this variant are the earlier age of onset and its occurrence almost exclusively in individuals of a darker skin type. This is a report of one case of hypopigmented MF that was recently diagnosed in a young black male at the Nova Southeastern University clinic. In addition, clinical and histologic features of hypopigmented MF are reviewed. When considering the differential diagnosis of pigmentary disorders such as vitiligo, tinea versicolor, pityriasis alba, leprosy, post-inflammatory hypopigmentation, sarcoid, and syphilis, it is important as diagnosticians that hypopigmented MF be included as well.

Case Presentation

The patient is a 30-year-old black male with a three-month history of developing multiple white lesions on his face and bilateral forearms. The eruption was not pruritic in nature. His past medical history is significant for cerebral palsy, mental retardation, and Down's syndrome. Family history is negative for any history of autoimmune conditions or malignancies. The patient takes no medications and denied any allergies to medications.

Physical examination reveals a mentally retarded black male in a wheel chair in no acute distress, very pleasant in nature. Comprehensive cutaneous examination revealed multiple hypopigmented macules of the patient's face and bilateral dorsal forearms (Figures 1 and 2). There was no evidence of scale, excoriation, or secondary infection. Approximately 5% of his total body surface area was affected. No lymphadenopathy or organomegaly was appreciated.

Initial laboratory data included a normal CBC and LFTs. The clinical differential diagnosis of the hypopigmented macules included vitiligo, tinea versicolor, nummular eczema, pityriasis alba, and hypopigmented MF. Histopathology of a representative biopsy of a hypopigmented macule revealed a band-like infiltrate of lymphoid cells within the papillary dermis that passes into a non-spongiotic epidermis. Epidermotropic features with Pautrier's microabscesses are observed (Figures 3 and 4). Additional immunogenotyping analysis involving PCR-based amplification of the TCR-gamma genes helped confirm this diagnosis.

Treatment options for the patient who has been presented are currently being considered; they include PUVA versus external beam radiation therapy.

Discussion:

The most common of the T-cell lymphomas, mycosis fungoides, is a non-Hodgkin's peripheral T-cell lymphoma of the skin with a wide spectrum of potential clinical manifestations. This discussion and review of the literature will be limited to the subtype hypopigmented MF. Hypopigmented macules have been reported with increasing frequency as the initial presentation of MF over the last two decades. Though it affects predominantly dark-skinned individuals, as in our patient, a few Caucasian patients have been reported as well.[1,2,3] The age of onset in patients with hypopigmented MF is younger than typical patch and plaque stage MF, in which approximately 80% of patients present at 45 years or older.[6] Patients present with asymptomatic or slightly pruritic non-scaly patches with irregular borders. In some instances, typical patches, plaques, or tumors may accompany the hypopigmented lesions.[14] If this is not the case, MF is rarely suspected, as the differential diagnosis includes pityriasis versicolor, vitiligo, p. alba, leprosy, sarcoid, and post-inflammatory hypopigmentation.

Similar to the more common forms of MF, immunophenotypic analysis of the infiltrating lymphoid cells in hypopigmented MF shows a predominance of CD4+ T cells.[3,4,6] Some studies have shown a predominance of suppressor T cells in MF lesions, which is suggestive of a benign inflammatory dermatosis. Rustin et al. suggest that T-suppressor lymphocytes must play an immunoregulatory role in the disease before the onset of more aggressive disease.[5]

The mechanism of the hypopigmentation in this relatively uncommon subtype of MF remains to be seen. It has been theorized by Breathrauch et al.[7] that atypical lymphoid cells infiltrating the epidermis causes melanocytic degeneration. No evidence of a block in transference of melanosomes from melanocytes to keratinocytes was found. A nonspecific response to cell injury associated with inflammation is likely the cause of hypopigmentation in this subtype of MF. This may be due to ischemia secondary to disruption of normal epidermal architecture

Figure 1

Figure 2

by the accumulation of edema found within the skin in MF lesions. Other authors point out that the degenerative changes seen are not specific to MF and also have been observed in association with halo nevi, idiopathic guttate hypomelanosis, leprosy, and pityriasis versicolor.[3,5] Flaxman et al.[12] noted more melanosomes within keratinocytes in the skin of patients with MF after treatment with topical nitrogen mustard. Others have reported an increased number of Langerhans

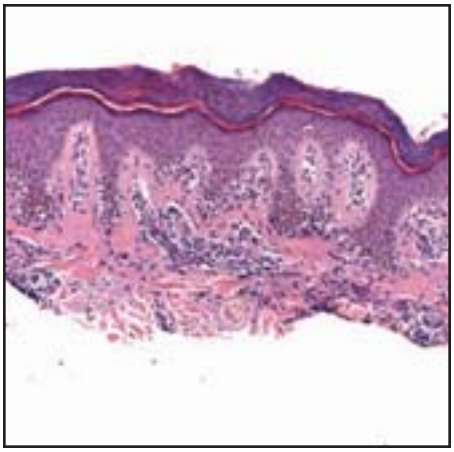


Figure 3

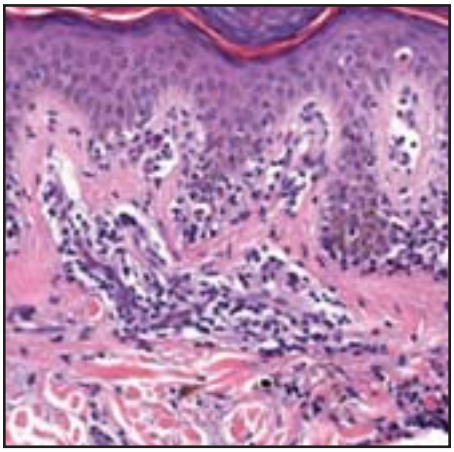


Figure 4

cells in the epidermis from biopsies of patients with hypopigmented MF.[4,5] The relationship between melanocytic dysfunction, the increased number of Langerhans cells and T lymphocyte subsets in the cellular infiltrate remains speculative.

The biologic behavior of hypopigmented MF is similar to that of the nonhypopigmented early stages of the disease. Similar to nonhypopigmented MF, this variant also has a long latent period, a tendency to relapse, and behaves in an indolent fashion in most cases.[11] Overall, patients with hypopigmented MF have an earlier age of onset, slow progression, and a good prognosis compared with MF patients overall.2,13 The histologic findings as well as clinical course and prognosis in hypopigmented MF are similar to those of the classical patch-stage disease.15 Further studies are needed to fully elucidate the clinical and biologic behaviors of this seemingly uncommon variant of MF.

Treatment options for patch-stage MF, which includes subtype hypopigmented MF, include topical mechlorethamine, UVB, PUVA, and topical carmustine.8,9 Given that multiple skin sites are often involved, the initial treatment choices are usually either topical, intralesional corticosteroids or phototherapy with PUVA or UVB.10 Second-line therapy for early-stage disease is often topical chemotherapy using nitrogen mustard or carmustine, frequently utilized in conjunction with retinoids.10

The patient we have presented is currently being considered for treatment with PUVA or external beam radiation therapy.

In summary, hypopigmented MF is being recognized with increasing frequency over the past 20 years. It is still considered a less common presentation of the disease. Distinguishing features of this variant are the earlier age of onset and its occurrence almost exclusively in individuals with darker skin types. It is important as clinicians that we include mycosis fungoides in our differential diagnosis of hypopigmented macules.

References:

1. Robert C, Bahlouli Z, Chemaly P, et al. Hypopigmented mycosis fungoides. Ann Dermatol Venereol. 1995; 122: 704-706.
2. Amichai B, Grunwald MH, Avinoach I, et al. Hypopigmented mycosis fungoides in a white female. J Dermatol. 1996;23:425-426.
3. Sigal M, Grossin M, Laroche L et al. Hypopigmented mycosis fungoides. Clin Exp Dermatol. 1987;12:453-454.
4. Misch KJ, Maclennan KA, Marsden RA. Hypopigmented mycosis fungoides. Clin Exp Dermatol. 1987;12:53-55.
5. Rustin MHA, Griffiths M, Ridley CN. The immunopathology of hypopigmented mycosis fungoides. Clin Exp Dermatol. 1986;11:332-339.
6. Whitemore SE, Simmons-O'Brien E, Rotter FS. Hypopigmented mycosis fungoides. Arch Dermatol. 1994;130:476-480.
7. Breathnauch SM, Mckee PH, Smith NP. Hypopigmented mycosis fungoides: report of five cases with ultrastructural observations. Br J Dermatol. 1982;106:643-649.
8. Heald PW, Edelson RL. Lymphoma, pseudolymphoma and related conditions. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, editors. Dermatology in general medicine. 4th ed. New York: McGraw-Hill; 1993. p. 1285-307.
9. Ramsay DL, Lish KM, Yolowitz CB, Soter NA. Ultraviolet B phototherapy for early stage cutaneous T-cell lymphoma. J Am Acad Dermatol 1992; 128:931-3.
10. Prince HM, McCormack C, Ryan G, O'Keefe R, Seymour JF, Baker C. Management of the primary cutaneous lymphomas. Australasian Journal od Dermatology 2003; 44: 227-240.
11. Akaraphanth R, Douglass MC, Lim HW. Hypopigmented mycosis fungoides treatement and a 6(1/2)- year follow-up of 9 patients. J Am Acad Dermatol 2000; 42:33-39.
12. Goldberg DJ, Schinella RA, Kechijian P. Hypopigmented mycosis fungoides: speculations about the mechanism of hypopigmentation. Am J Dermatopathology. 1986;8:326-330.
13. Handfield-Jones SE, Smith NP, Breathnauch SM. Hypopigmented mycosis fungoides. Clin Exp Dermatol. 1992;17:374-375.
14. Girardi M, Heald PW, Wilson LD. Medical Progress: The Pathogenesis of Mycosis Fungoides. The New England Journal of Medicine. 2004;350;1978-1988.
15. Lamborza E, Cohen SR, Phelps R, et al. Hypopigmented variant of mycosis fungoides: demography, histopathology, and treatment of seven cases. J Am Acad Dermatol. 1995;32:987-993.

Treatment of Rhinophyma with Electrosurgery

Valerie Johnson, D.O.,* Risa Ross, D.O., David Dorton, D.O., F.A.O.C.D.*****
** Third-year dermatology resident at Sun Coast Hospital, Largo, Florida*
*** Intern at Sun Coast Hospital, Largo, Florida*
**** Assistant clinical professor of dermatology, Sun Coast Hospital, Nova Southeastern University, Largo, Florida*

ABSTRACT

Rhinophyma is a severe, disfiguring form of rosacea that affects mostly men.[1,2,3] A red-to-violaceous, bulbous swelling or mass of the lower nose occurs slowly over many years due to sebaceous gland hyperplasia, ectatic vessels, excessive connective tissue, and fibrosis. Treatment of rhinophyma usually requires surgical removal of the excess tissue. Various modalities have been used for this purpose, including cryosurgery,[4] dermabrasion,[2] scalpel excision,[5] electrosurgery[6,7,8] and laser ablation.[9] We present a case report of severe rhinophyma treated in an outpatient setting with electrosurgery using the Ellman Surgitron device. Mild scarring and hypopigmentation of the central nose occurred; but overall, the patient was satisfied with the results. This surgical technique yields good cosmetic results with a relatively bloodless field.

Background:

Rhinophyma is the hyperplasia of sebaceous glands, connective tissue, and blood vessels of the nose.[10] The word comes from the Greek roots "rhino" and "phyma," meaning "nose" and "swelling, mass, or bulb," respectively. Rhinophyma is the most common type of phymatous rosacea,[1] although phymas can occur in multiple locations including the chin, forehead, ears, and eyelids. Although rosacea is more common in women, rhinophyma occurs almost exclusively in males.[1,2,3] Histologic features include a chronic inflammatory process with hypertrophy of the subcutaneous and sebaceous tissues with dialated ducts occluded with debris, bacteria, and sebum.[7] Some believe that rhinophyma may be affected by alcohol, spicy foods, or caffeine; however there are conflicting reports in the literature.[3] Rhinophyma can be quite disfiguring, cosmetically unappealing, and can even cause nasal obstruction. For these reasons, medical and surgical treatments are continuously being explored.

Four different forms of rhinophyma have been classified: glandular, fibrous, fibroangiomatous, and actinic. The characteristics of glandular form include various size and shape tumors of the nose with a pitted surface. There is immense sebaceous-gland hyperplasia and increased sebum excretion. Demodex folliculorum mites have also been identified in the substance easily expressed from the surface of the nose. The fibrous form is characterized by extensive connective-tissue hyperplasia. The presence and degree of sebaceous-gland hyperplasia differs among patients. The fibroangiomatous form is differentiated by an edematous nose of substantial size with a unique crimson color and large, ectatic vessels. The symptoms of the actinic form resemble those seen in individuals with a considerable amount of sun exposure in the past, including nodular masses of elastic tissue on the nose.[11]

Methods

A 54-year-old Caucasian male presented to our clinic to discuss treatment options for his severe disfiguring rhinophyma. The patient had a longstanding history of rosacea and slow, indolent swelling and overgrowth of his nasal tip. He had tried many topical therapies and oral antibiotics without improvement. Treatment options were reviewed with the patient, which included referral to plastic surgery, laser resurfacing with CO2 laser, and electrosection resurfacing with the Ellman Surgitron. The patient opted for electrosection resurfacing and was scheduled for the procedure. The risks, benefits, and options related to the procedure were discussed with the patient, including pain, infection, bleeding, ecchymosis, swelling, scarring, recurrence and need for further surgery. The patient consented to the procedure.

On physical exam, the patient had irregular, hypertrophied nasal tissue with a bulbous extension of the nose tip resulting in a clown-like appearance to the nose. Mild erythema of the nose with few telangiectasias was noted, and his cheeks were essentially normal (Figures 1a, 2a). Our patient most likely had the fibrous form of rhinophyma. The patient was prepped and draped in a sterile manner. Nerve blocks were performed using lidocaine 1% with epinephrine in the supraorbital, infraorbital and paranasal areas bilaterally. In addition, a topical anesthetic consisting of betacaine 20%, lidocaine 6% and tetracaine 4% was applied to the nose for 30 minutes prior to the procedure. The nose was then cleansed and infiltrated directly with 15cc of lidocaine 1% with epinephrine. The hypertrophied nasal tissue was then debulked in thin layers down to the level of normal-appearing skin using the 3/8-inch wire loop electrode and partial rectification mode. Loop passages were short and quick to minimize heat production, therefore limiting tissue destruction. Care was taken to reshape and meticulously contour the nose

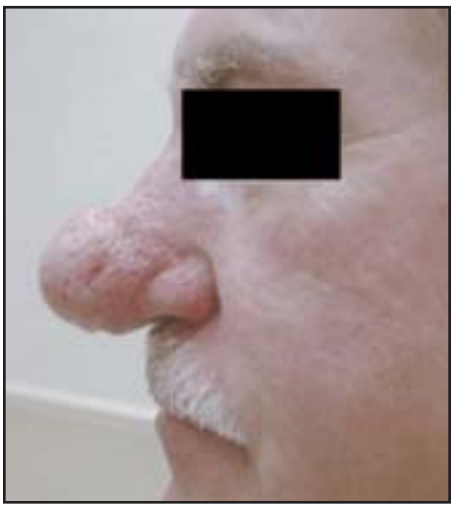


Fig 1a Severe rhinophyma, pre-operative

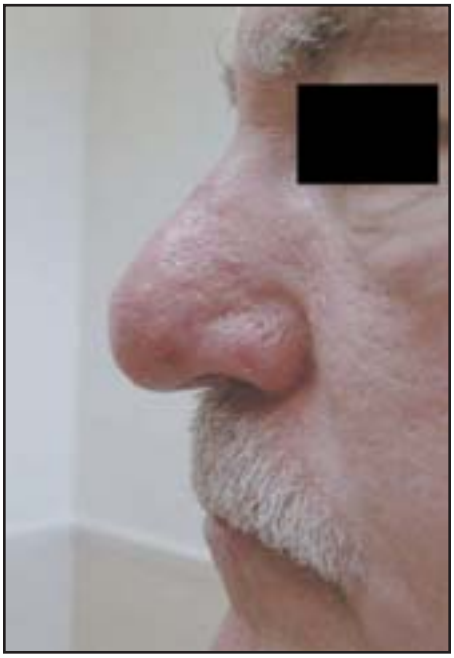


Fig 1b Six weeks post-operative

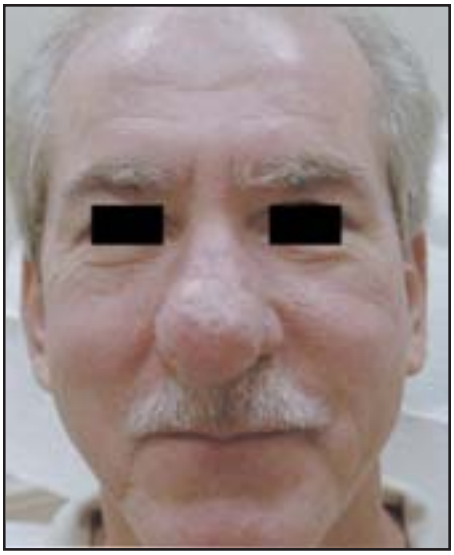


Fig 2a Severe rhinophyma, pre-operative

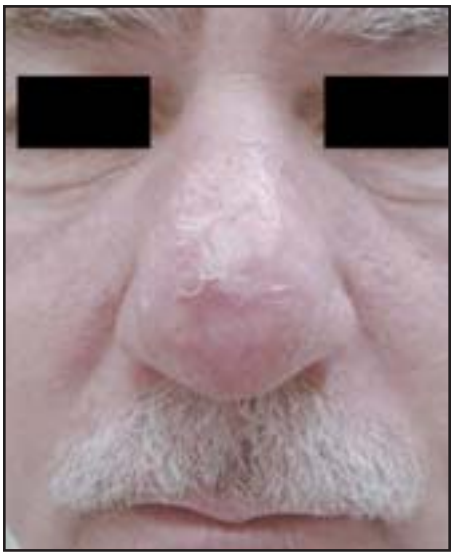


Fig 2b Six weeks post-operative; mild scarring and hypopigmentation

while preserving the pilosebaceous units. Bleeding was controlled using a ball electrode to carefully cauterize the vessels. An approved vacuum device was used to evacuate the plume. White petrolatum and a pressure dressing were applied to the nose post procedure. Post care instructions included applying white petrolatum to the treated area four to five times daily, taking cephalexin 500mg twice daily for 10 days, applying mupirocin cream to the surgery site twice daily for 10 days, and taking propoxyphene 65mg one every four to six hours as needed for pain. The patient was also placed on prophylactic valacyclovir 500mg twice daily for seven days as he had a history of oral herpes labialis.

Results:

The patient had regular follow-up visits at post-operative days two, seven, nine, 13, 21, and 42, with photographs taken at each visit. At the two-day post-operative evaluation, the patient had mild periorbital edema and swelling of the nose with serous drainage from the surgical site. At the 13-day post-operative visit, the patient's nose was almost completely re-epithelialized. At six weeks, the patient was noted to have mild scarring and hypopigmentation at the nasal tip (Figure 2b). Overall, the contour and shape of the nose was significantly improved, and the patient was extremely satisfied with the results (Figure 1b).

Discussion:

Rhinophyma is a severe form of rosacea with complications that include severe disfigurement, occlusion of nasal passages, and low patient self-esteem. The social stigma of rhinophyma includes an alleged association with alcoholism ("whisky nose" or "rum nose").[12] One study from the United Kingdom showed no greater alcohol consumption in rhinophyma patients than the general population surveyed.[3] Spontaneous regression of severe rhinophyma is unlikely, although it has been shown to decrease nasal size in younger patients.[13,14] Medical treatment with isotretinoin has limited value in severe cases. The most effective results in treating rhinophyma have involved surgical debulking using various methods including CO2 laser,[9] electrosurgery[,6,7,8] tangential excision combined with dermabrasion,[2] ultrasonic scalpel,[5] and radiotherapy.[15]

We present an interesting case of severe disfiguring rhinophyma treated with electrosurgery using the Ellman Surgitron device. This device uses low-voltage current with minimal thermal damage while controlling blood loss, all in an effort to maintain the surgical visual field. The depth of debulking is important -- to minimize scarring, the pilosebaceous unit must be preserved to allow for re-epithelialization. In addition, short, quick passages prevent overheating of tissue and help minimize scarring risk. Our patient had mild scarring and hypopigmentation of the nasal tip but overall was extremely satisfied. This technique yields life-changing results and can be performed in an outpatient setting.

References

1. Powell, Frank C. Rosacea New England Journal of Medicine. February 24, 2005; 352 (8):793-803.
2. Curnier, A, Choudhary, S. Triple Approach to Rhinophyma Annals of Plastic Surgery August 2002; 49(2):211-214.
3. Curnier A, Choudhary, S. Rhinophyma: Dispelling the Myths Plastic & Reconstructive Surgery Aug 2004; 114(2):351-354.
4. Sonex TS, Dawber RPR. Rhinophyma treatment by liquid nitrogen spray cryosurgery. Clin Exp Dermatol 11:284-288, 1986.
5. Dufresne R., Zienowicz R., Rozelle A., Whalen J. An Introduction of the Ultrasonic Scalpel: Utility in Treatment of Rhinophyma. Plast. Reconstr. Surg. 1996; 98: 160-162
6. Rex J, Ribera M, Bielsa I, Paradelo C, Ferrandiz C. Surgical Management of Rhinophyma: Report of Eight Patients Treated with Electrosection. Dermatol Surg 2002;28:347-349.
7. Aferzon, M, Millman, B. Excision of Rhinophyma With High Frequency Electrosurgery. Dermatologic Surgery 2002; 28:735-738.
8. Bridenstine J., Use of Ultra-High Frequency Electrosurgery (Radiosurgery) for Cosmetic Surgical Procedures. Dermatol Surg 24:397-400; 1998
9. Lloyd K., Surgical Correction of Rhinophyma. Arch. Dermatol. 1990;126:721-723.
10. Gupta AK, Chaudhry MM. Rosacea and its management: an overview Journal of European Academy of Dermatology and Venereology 2005; 19:273-285.
11. Freedberg IM, Eisen AZ, Wolff K, Austen KF, et al, editors. Fitzpatrick's Dermatology in General Medicine. McGraw Hill Publishing 6th Ed, Vol I; 74:693
12. Matton, G., Pickrell K., Huger W., et al. The surgical management of rhinophyma. Plast. Reconstr. Surg. 30: 403, 1962.
13. Irvine C, Kumar P, Marks R. Isotretinoin in the treatment of rosacea and rhinophyma. In: Marks R, Plewig G, editors. Acne and related disorders: proceedings of an international symposium. London: Martin Dunitz; 1988:301-5
14. Schmidt JB, Gebhart W, Raff M, Spona J. 13-cis-Retinoic acid in rosacea. Clinical and laboratory findings. Acta Derm Venereol. 1984;64:15-21
15. Skala M, Delaney G, Towell V, Vladica N. Rhinophyma treated with kilovoltage photons. Australasian Journal of Dermatology. 2005;46:88

The Treatment of Chondrodermatitis Nodularis Helicis Using Intralesional Etanercept

David B. Roy D.O.,* Don A. Anderson D.O., F.A.O.C.D., F.A.S.M.S., Jason Mazzurco D.O.,*** Johnny Gurgen D.O.******

** First-year Dermatology Resident (corresponding author), Midwestern University of Health Sciences, Kingman Regional Medical Center, Kingman, AZ*

*** Program Chairman, Midwestern University of Health Sciences, Kingman Regional Medical Center, Kingman, AZ*

**** First-year Family Practice Resident, Ohio University College of Osteopathic Medicine, O'Bleness Memorial Hospital, Athens, OH*

***** Intern, NOVA Southeastern College of Osteopathic Medicine, Suncoast Hospital, Largo, FL*

ABSTRACT

Chondrodermatitis nodularis helicis (CNH) is a chronic, painful, inflammatory disorder of the ear typically presenting after age 40. Although the etiology of this disease is unknown, a consistent histological finding is degenerated dermal collagen with surrounding granulation tissue. In spite of the nomenclature "chondrodermatitis," changes in the underlying cartilage are at times absent. Multiple treatments have been reported including topical and intralesional corticosteroids, curettage, CO2 laser, behavior modification, collagen injection, and various surgical approaches. Recurrence is frequent regardless of the modality chosen. For this reason, conservative management should be considered first line. We report the successful treatment of three patients with CNH using intralesional etanercept 1mg/ml as monotherapy.

Case Reports

Case 1: A 52-year-old female with a two-year history of a painful nodule of her left helix presented for a second opinion and treatment. Prior biopsies demonstrated changes consistent with CNH. Surgical excision by her previous physician yielded complete resolution of her pain. Unfortunately, six months later the symptoms returned. Topical and intralesional corticosteroids were of no benefit. A second excision involving the involved skin and cartilage was performed. This led to another brief period of remission. Upon the return of her symptoms, the patient refused any further surgery or corticosteroids. With the informed consent of the patient, 0.2ml of etanercept 1mg/ml was administered intralesionally at the level of the dermis. A complete resolution of her symptoms was noted at one month. At four months, the patient complained of only minimal, intermittent pain for which she desired no treatment. Near complete resolution was noted clinically in both erythema and lesion size.

Case 2: A 71-year-old male presented with a three-month history of a painful, erythematous nodule of his right helix. A shave biopsy was performed to rule out malignancy and demonstrated changes consistent with CNH. A trial of intralesional corticosteroids yielded no relief. After obtaining informed consent, a single intralesional injection of 0.2ml of etanercept 1mg/ml was administered. At one month follow-up, the patient stated his pain had completely resolved. Clinically, no erythema remained. Three months later, the patient remained pain free.

Case 3: A 50-year-old male presented with a one-year history of a painful, rough nodule of his right ear. Physical examination revealed a 3mm erythematous nodule with central crust. A clinical diagnosis of CNH was made, informed consent was obtained, and a single intralesional injection of 0.2ml of etanercept 1mg/ml was administered. At one month follow-up, the patient was asymptomatic. At three months, the lesion was no longer clinically apparent, and the patient remained pain-free.

All patients noted above denied any history of known malignancy, neurological diseases, tuberculosis, or active infection.

Discussion

Chondrodermatitis nodularis helicis was first described by Winkler in 1915.[1] While dermatologists frequently encounter this troublesome condition, little is known regarding its etiology. By definition, CNH is a benign entity; however, the sometimes intense discomfort that accompanies these lesions can be a cause of great concern for patients and of frustration for clinicians. Frequently attributed to trauma, chronic pressure, actinic damage, and cold exposure, it has also been reported to occur following radiation therapy and in association with certain systemic diseases including diabetes mellitus, systemic sclerosis, and dermatomyositis.[2-4] Typically presenting after age 40, CNH has also been observed in children. Pediatric cases include patients with and without associated systemic disease.[5-6]

CNH is classically described as a small, tender nodule of the ear, frequently with crust and ulceration. Two-thirds of patients presenting with this condition are male. The helix is the most commonly affected area in men, whereas women more often present with lesions of the antihelix. Bilateral involvement has been reported.[7-8]

Histological findings demonstrate degenerated collagen in the dermis surrounded by granulation tissue and a lymphohistiocytic infiltrate. The epidermis may exhibit a combination of parakeratosis, hypergranulosis, acanthosis, ulceration, and crust. Evidence of actinic damage is common. There is often an invagination of the epidermis filled with a keratotic plug. The perichondrium is usually thickened with variable findings of the underlying cartilage. In his initial description, Winkler attributed lesions of CNH to degenerative changes within the cartilage.[1] However, some reports have shown lesions to be free of any cartilaginous changes.[9]

Increasing evidence suggests that the primary event leading to CNH likely occurs in the dermis. Magro et al. reported a possible association between CNH and systemic diseases involving microvascular injury, such as diabetes mellitus. They hypothesized that some cases may develop secondary to ischemic changes of the dermal collagen.[2] The necrobiotic distortion of collagen often seen in lesions of CNH is similar to that observed in other necrobiotic processes such as granuloma annulare and necrobiosis lipoidica. Evidence of transepidermal elimination of necrobiotic material has also been reported in some lesions of CNH, leading various authors to propose the reclassification of CNH as a perforating dermatosis.[10-12]

The treatment of CNH is diverse. Topical and intralesional corticosteroids, curettage, CO2 laser, behavior modification, collagen injection, and various surgical approaches are described in the literature with variable rates of success.[13-24] Due to the nonmalignant nature of this condition and the high recurrence rate, conservative treatment should be first line. Anti-tumor necrosis factor therapy has been reported effective in the treatment of certain granulomatous diseases including granuloma annulare, necrobiosis lipoidica, and granulomatous cheilitis.[25-28] Etanercept is an easily administered anti-tumor necrosis factor medication. As such, etanercept was a logical choice as a novel therapeutic modality.

The use of etanercept in CNH is not without risk. Although the safety profile of this medication is well established, the use of anti-tumor necrosis factor therapy for necro-

biotic and granulomatous processes is found in only scattered case reports. The consequences of such treatments are unclear. The development of interstitial granulomatous dermatitis following anti-TNF therapy has been reported.[29] Injection-site reactions are common with etanercept, and the use of this medication intralesionally could lead to an exaggerated inflammatory reaction at the injection site. None of the patients discussed herein reported any adverse events.

References

1. Winkler, M. (1915). Arch. Derm. Syph. (Berl.); 121, 278.
2. Magro CM, Frambach GE, Crowson AN. Chondrodermatitis nodularis helicis as a marker of internal disease associated with microvascular injury. J Cutan Pathol. 2005 May; 32(5):329-33. Erratum in: J Cutan Pathol. 2005 Oct; 32(9):646.
3. Bottomley WW, Goodfield MD. Chondrodermatitis nodularis helicis occurring with systemic sclerosis--an underreported association? Clin Exp Dermatol. 1994 May; 19(3):219-20.
4. Pandya AG, Kettler AH, Hoffmann TJ et al. Chondrodermatitis helicis arising after radiation therapy. Arch Dermatol. 1988 Feb; 124(2):185-6.
5. Rogers NE, Farris PK, Wang AR. Juvenile chondrodermatitis nodularis helicis: a case report and literature review. Pediatr Dermatol. 2003 Nov-Dec; 20(6):488-90.
6. Sasaki T, Nishizawa H, Sugita Y. Chondrodermatitis nodularis helicis in childhood dermatomyositis. Br J Dermatol. 1999 Aug; 141(2):363-5.
7. Oelzner S, Elsner P. Bilateral chondrodermatitis nodularis chronica helicis on the free border of the helix in a woman. J Am Acad Dermatol. 2003 Oct; 49(4):720-2.
8. Cannon CR. Bilateral chondrodermatitis helicis: case presentation and literature review. Am J Otol. 1985 Mar; 6(2):164-6.
9. Lever WF. Histopathology of the Skin. Lippincott 1949; 107.
10. Santa Cruz DJ. Chondrodermatitis nodularis helicis: a transepidermal perforating disorder. J Cutan Pathol. 1980 Apr; 7(2):70-6.
11. Goette DK. Chondrodermatitis nodularis chronica helicis: a perforating necrobiotic granuloma. J Am Acad Dermatol. 1980 Feb; 2(2):148-54.
12. Goette DK. Chondrodermatitis nodularis chronica helicis. A transepithelial elimination disorder. Dermatologica. 1980; 161(2):101-11.
13. Taylor MB. Chondrodermatitis nodularis chronica helicis. Successful treatment with the carbon dioxide laser. J Dermatol Surg Oncol. 1991 Nov; 17(11):862-4.
14. Greenbaum SS. The treatment of chondrodermatitis nodularis chronica helicis with injectable collagen. Int J Dermatol. 1991 Apr; 30(4):291-4.
15. Lawrence CM. The treatment of chondrodermatitis nodularis with cartilage removal alone. Arch Dermatol. 1991 Apr; 127(4):530-5.
16. Karam F, Bauman T. Carbon dioxide laser treatment for chondrodermatitis nodularis chronica helicis. Ear Nose Throat J. 1988 Oct; 67(10):757-8.
17. Kromann N, Hoyer H, Reymann F. Chondrodermatitis nodularis chronica helicis treated with curettage and electrocauterization: follow-up of a 15-year material.Acta Derm Venereol. 1983; 63(1):85-7.
18. Rex J, Ribera M, Bielsa I et al. Narrow elliptical skin excision and cartilage shaving for treatment of chondrodermatitis nodularis. Dermatol Surg. 2006 Mar; 32(3):400-4.
19. Jain PK, Jain S. Use of disposable curette in the treatment of Chondrodermatitis Nodularis Helicis. Clin Otolaryngol. 2005 Feb; 30(1):75-6.
20. Moncrieff M, Sassoon EM. Effective treatment of chondrodermatitis nodularis chronica helicis using a conservative approach. Br J Dermatol. 2004 May; 150(5):892-4.
21. Ormond P, Collins P. Modified surgical excision for the treatment of chondrodermatitis nodularis. Dermatol Surg. 2004 Feb; 30(2 Pt 1):208-10.
22. de Ru JA, Lohuis PJ, Saleh HA et al. Treatment of chondrodermatitis nodularis with removal of the underlying cartilage alone: retrospective analysis of experience in 37 lesions. J Laryngol Otol. 2002 Sep; 116(9):677-81.
23. Cox NH, Denham PF. Intralesional triamcinolone for chondrodermatitis nodularis: a follow-up study of 60 patients. Br J Dermatol. 2002 Apr; 146(4):712-3.
24. Timoney N, Davison PM. Management of chondrodermatitis helicis by protective padding: a series of 12 cases and a review of the literature. Br J Plast Surg. 2002 Jul; 55(5):387-9.
25. Hertl MS, Haendle I, Schuler G et al. Rapid improvement of recalcitrant disseminated granuloma annulare upon treatment with the tumour necrosis factor-alpha inhibitor, infliximab. Br J Dermatol. 2005 Mar; 152(3):552-5.
26. Kolde G, Muche JM, Schulze P et al. Infliximab: a promising new treatment option for ulcerated necrobiosis lipoidica. Dermatology 2003; 206: 180-1.
27. Barry O, Barry J, Langan S et al. Treatment of granulomatous cheilitis with infliximab. Arch Dermatol. 2005 Sep; 141(9):1080-2.
28. Shupack J, Siu K Resolving granuloma annulare with etanercept. Arch Dermatol. 2006 Mar; 142(3):394-5.
29. Deng A, Harvey V, Sina B et al. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol. 2006 Feb; 142(2):198-202.

Facial Orf in a Healthy 33-year-old Man

Shino bay Aguilera, D.O.,* Les Rosen, M.D., F.A.A.D., Brad Glick, D.O., F.A.O.C.D.,*** Phillip Tallman, M.D., F.A.A.D.****

** 3rd year Resident, Wellington Regional Medical Center, Wellington, Florida*

*** Assistant Professor, Dermpath Diagnostics, Pompano Beach, Florida*

**** Program Director, Wellington Regional Medical Center, Wellington, Florida*

***** Private Practice, Billings, Montana*

ABSTRACT

The orf virus is a DNA parapoxvirus that infects sheep, goats and humans. Transmission to humans occurs from infected lesions on animals or from fomites such as wire fencing, barn doors, feeding troughs or shears. It is essential for dermatologists and other health-care providers to be knowledgeable about the clinical and histopathologic features of this infection, which may mimic cutaneous infections like anthrax, tularemia and tuberculosis in addition to neoplasms. The objective of this case report and discussion is to facilitate the recognition of the clinical and histopathologic features, disease-prevention methods, and therapeutic modalities of orf.

Introduction

The orf virus is a self-limited viral infection that is typically observed on the hands of individuals handling infected sheep or goat flesh. It is also known as ecthyma contagiosum.[1] Clinically, it may resemble a variety of cutaneous lesions such as pyogenic granuloma, squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, melanoma, cutaneous anthrax and tularemia.

While the incidence of orf is high, it is infrequently mentioned in the medical literature. This may be due to the fact that it heals spontaneously, a phenomenon that is well-known among infected individuals, who usually do not seek treatment.

We present a case of facial orf-virus infection occurring in a young male rancher from Montana exposed to cattle and sheep. We review the literature on cutaneous orf infections in humans and immuno-modulation of the host immune response by the virus. This common infection is under-represented in the medical literature, and over-treatment by healthcare professionals is a frequent occurrence.

Case Report

A 33-year-old, previously healthy white male rancher with an occupational exposure to cattle, sheep and sun presented to his primary care physician with a rapidly growing, painless, erythematous, cutaneous nodule with ulceration and edema on his right cheek for three weeks (Figure 1). The patient complained of "swollen glands" in his neck region and cervical lymphoadenopathy was confirmed clinically. The patient was given amoxicillin 875 mg and clavulanic acid (as potassium) 125 mg tablets twice a day for 10 days, and a dermatology consult was requested immediately.

During the patient's initial dermatological evaluation, a 2.2 cm by 2.0 cm, eroded, well-demarcated, erythematous nodule with some purulent exudate was noted on the right cheek. No cervical lymphadenopathy or tenderness was appreciated, suggesting that the patient may have responded to the therapeutic trial of antibiotics.

Due to the duration of the lesion and patient's occupational history, an incisional biopsy was performed to rule out a neoplastic process (versus an infectious process). The clinical differential diagnosis included squamous cell carcinoma, kerathoacanthoma, orf, milker's nodule, atypical mycobacteria infection, melanoma, cutaneous anthrax, tularemia, tuberculosis and glanders.

Hematoxylin-eosin staining of the specimen revealed pseudoepitheliomatous hyperplasia with pale, vacuolated cytoplasm containing inclusion bodies and granulation tissue with acute and chronic inflammation consistent with orf (Figures 2 and 3). The PAS, Fite and Gram stains were all negative for organisms.

The patient was allowed to finish his course of amoxicillin 875 mg and clavulanic acid 125 mg tablets twice a day for 10 more days, and the lesion was left to heal by second intention. Three weeks later, at follow-up, the lesion had resolved, and a dense, fibrous scar replaced the subcutaneous tissue.

Discussion

Orf is a cutaneous lesion that is caused by a viral infection from species of the parapoxvirus genus of the poxviridae family. This infection is commonly seen on the hands of people handling sheep and goats. It has been reported in shepherds, veterinary surgeons, butchers, and Muslim communities.

Orf is characterized by six distinct stages which typically last six days each, and it heals uneventfully in three to six weeks.[2] The first stage presents with one to four papules, usually on the hands, and later progresses to more of a maculopapular process. In the second stage, targetoid lesions with a

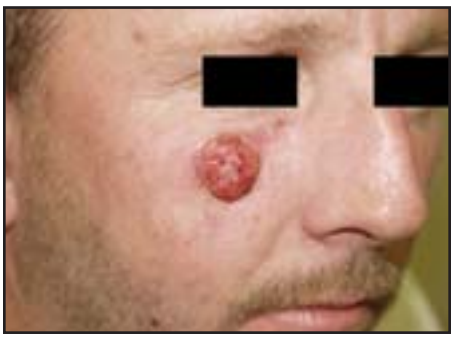


Figure 1. Ulcerated, erythematous nodule on right cheek

red center, a white middle ring and a red halo develop in about 10 to 14 days.[3] The third stage demonstrates lesions that advance to an acute weeping process, later followed by a fourth, regenerative, dry stage with black dots.[3] Next, 28 to 35 days following infection, a fifth, papillomatous stage is appreciated. The last and final transformation, or sixth stage of orf virus infection, is a regressive stage with a dusky crust and eventual shedding of the scab.[3] Lymphangiitis, lymphadenitis, malaise and fever may accompany the skin lesion.

Orf virus may replicate in the presence of an active host immune and inflammatory response.[4] This observation has prompted investigators to use animal models to understand the ability of this virus to attenuate the host immunity and prevent the potent antiviral effect of apoptosis.

The orf virus is an epitheliotropic entity that replicates in the cytoplasm of host cells and therefore encodes its own machinery for DNA transcription and replication.[4] This ingenious virus genome contains several virulence and immuno-modulation genes. The first to be described was a gene that codes for a viral orthologue of mammalian vascular endothelial growth factor (VEGF), which is thought to stimulate epidermal keratinocyte hyperplasia and inhibits apoptosis to provide more target cells for virus replication.[5] The orf virus also contains an early viral gene

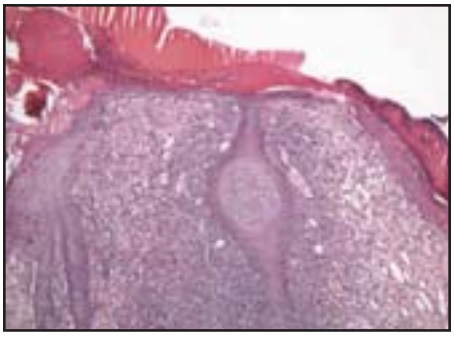


Figure 2. Skin biopsy showing pseudoepitheliomatous hyperplasia with pale, vacuolated inclusion bodies and granulation tissue (hematoxylin-eosin stain; original magnification 100X)

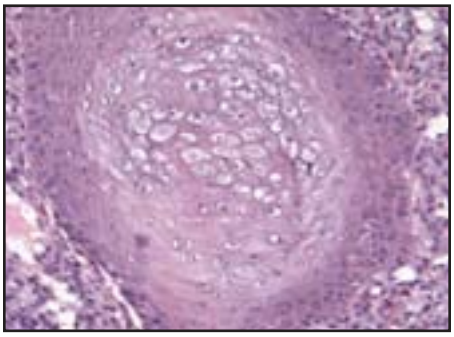


Figure 3. Inclusion bodies (hematoxylin-eosin stain; original magnification 400X)

encoding an interferon resistance factor (OVIFNR), which binds to double-stranded RNA (dsRNA), preventing the activation of PKR kinase. This inhibits protein synthesis as part of the interferon-induced antiviral state in cells. In addition, orf virus encodes an orthologue of mammalian IL-10, which works as an immuno-regulatory, anti-inflammatory cytokine. Viral IL-10 (vIL-10) inhibits tumor necrosis factor alpha (TNF alpha) and IL-8 production from macrophages and keratinocytes.[4] Finally, orf virus encodes for granulocyte macrophage colony stimulating factor (GM-CSF) inhibitory factor (GIF), which suppresses the stimulation of neutrophils, monocytes/macrophages and eosinophils from their hemopoietic progenitor cells.[6] The study of these immuno-modulator proteins provides insight into disease pathogenesis and important elements of a host-protective response.

Although orf virus infection is usually contracted occupationally in people from rural areas, there are reports of individuals living in urban cities who have contracted this infection. For example, Muslim communities congregating in urban cities of the United States and Europe that engage in the celebration of "Eid-ul-Adha" – a ritual commemorating the day that God terminated all human sacrifices when he asked Abraham to sacrifice a sheep instead of his only son Isaac -- are required to handle livestock such as sheep for sacrifices. This practice may increase the chance of contracting the virus.[7,8]

Health-care professionals working in urban areas may have limited experience in managing this condition and may be inclined to aggressively over-treat this self-limited infection with antibiotics or surgical excision. However, members of Muslim communities, like those individuals handling livestock in rural areas, generally tend to underrate orf infection and manage it themselves.

With this in mind, one is able to understand why such a common infection is underrepresented in the medical literature. Once this disease is known by one member of a family or a colleague on a ranch that handles sheep or goats, the other members or ranchers do not consult for this disease. Only a complication such as bacterial super-infection or polymorphous erythema will prompt a consultation with a physician.[7]

In sum, the resemblance of orf to other cutaneous lesions including squamous cell carcinoma, cutaneous anthrax, pyogenic granuloma or even malignant melanoma may result in aggressive over-treatment of this infection. The use of parenteral antibiotics, primary excision, graft or flap repairs are unnecessary and unacceptable both medically and financially.

Conclusion

Facial orf lesions can resemble other skin neoplasms. Therefore, it is imperative that health-care providers have a complete understanding of the clinical features as well as the prevalence of this infection among those who handle sheep and goats. In addition, a careful history and physical examination is necessary to diagnose and treat this infection appropriately.

Although orf-virus infection may confer lasting immunity in humans, cross-immunity for variola or other orthopoxviruses does not result.[1]

A study of virus immuno-modulator proteins would provide insight into the disease pathogenesis of orf and perhaps open the doors to the creation of new anti-viral agents that are more effective and have fewer side-effect profiles to treat this and other viral infections that affect both humans and animals.

References

1. Tyring, S. Mucocutaneous manifestations of viral diseases, Marcel Deker, Inc. 2002: 53-55.
2. Revenga F., Paricio J.F., del Agua C., Facial orf. J Eur Acad Dermatol Venereol. 2001; 15; pg 80.
3. Bolognia J. Dermatology, Mosby publishing 2003; 1; 1266-1267.
4. Haig, D.M., Thomson, J., McInnes, C., McCaughan, C., Imlach, W., Mercer, A., Fleming, S., Orf virus immunomodulation and the host immune response. Vet Dermatol. 2002; 87, 395-399.
5. Savory, L., Stacker, S., Fleming, S.B., Niven, B.E., Mercer, A.A., Viral vascular endothelial growth factor plays a critical role in orf virus infection. J. Virol. 2000; 74, 10699-10706.
6. Haigh, D.M., Percival, A., Mitchell, J., Green, I., Sargan, D., The survival of growth of ovine afferent lymph dendritic cells in culture depends on tumor necrosis factor alpha and is enhanced by granulocyte-macrophage colony stimulating factor but inhibited by interferon gamma. Vet Immunol. Immunopathol. 1995; 45, 221-236.
7. Ghislain, P.D., Dinet, Y., Delescluse, J., Orf contamination may occur during religious events. J Am Acad Dermatol 2000; 42:848.
8. Guibal, F., Cosnes, A., Wechsler, J., Miseri E., Revuz, J., Chosidow, O. Religious ritual practices as a contamination mode for human orf. Eur J Dermatol. 1996; 6: 41-42.

Surgical Pearls
How we did it…

Jay S. Gottlieb, D.O., F.A.O.C.D., Sandy R. Goldman, D.O., A.O.C.D., Amy D. Gottlieb, PA-C

Resection of a tumor on the mid nasal dorsum. Repair of the resulting defect.

Tumor: Basal Cell Carcinoma
Procedure: Resection with frozen sections for pathologic evaluation of margins
Flap: Bilateral Pedicle Advancement Flaps

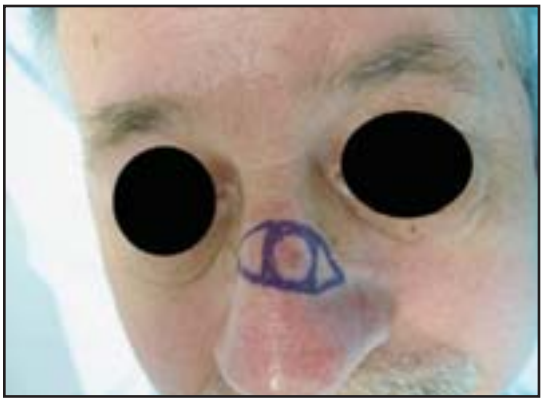


Figure 1 Planned Resection

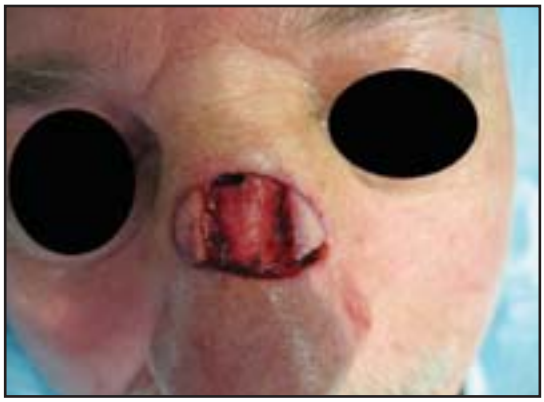


Figure 2 Resection/Pedicle Flaps

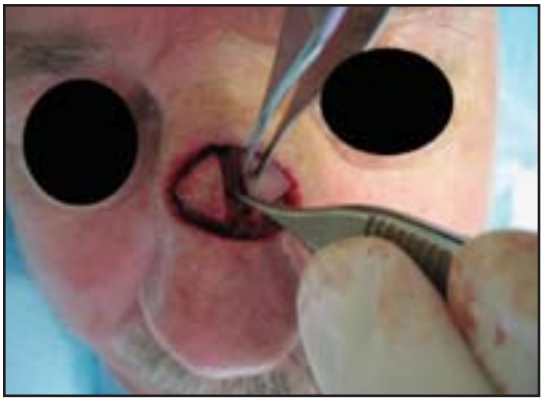


Figure 3 Advancement of Flaps

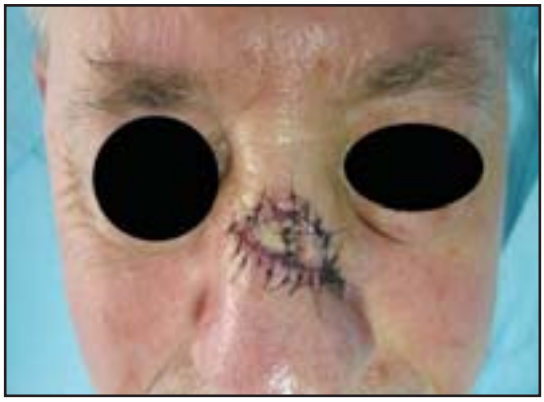


Figure 4 Immediate Closure

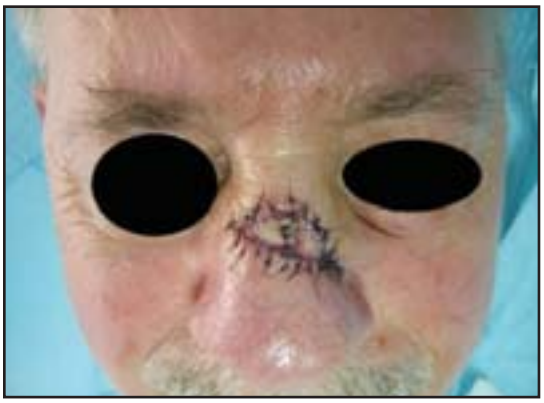


Figure 5 3 Weeks Post Op

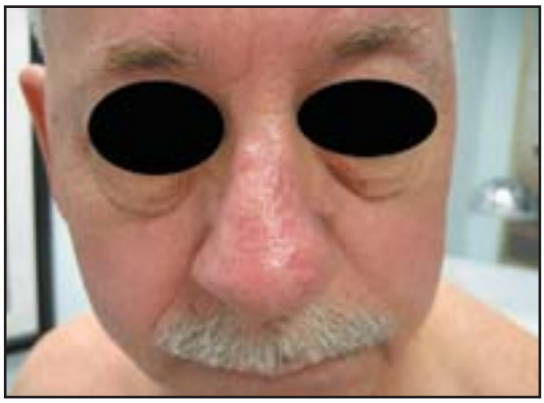


Figure 6 16 Weeks Post Op

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.

Merkel Cell Carcinoma in a Renal-Transplant Patient

Jennifer Bucci, D.O.,* Jennifer Popovsky, M.D., Schield Wikas, D.O.*****
** 3rd Year Dermatology Resident, Cuyahoga Falls General Hospital, Cuyahoga Falls, Ohio*
*** University Dermatology, Inc, Fairlawn, Ohio*
**** Program Director, Cuyahoga Falls General Hospital, Cuyahoga Falls, Ohio*

ABSTRACT

Transplant patients have an increased incidence of skin cancer compared to the general population. This is a case report of a man with known history of non-melanoma skin cancer developing a Merkel cell carcinoma after being re-transplanted with a kidney from a live organ donor. This paper reviews histologic, immunohistochemical, and electron microscopic findings of Merkel cell carcinoma. Current recommendations for therapy including surgical excision, radiation, and chemotherapy are also reviewed.

In transplant patients, skin cancers tend to behave more aggressively than in the general population. Transplant patients require regular routine evaluations, early diagnosis of skin cancers, and effective management when possible.

Introduction

Since Toker's first description in 1972, more than 600 cases of Merkel cell carcinoma (MCC) have been reported in the literature. A surprisingly large number of tumors have been in organ allograft recipients with sequential immunosuppression. According to Dreno et al.,[1] skin cancer prevalence in transplant patients increased with the duration of immunosuppression with a mean of 10% at 10 years, 40% at 20 years, and 42% at 14 years. Risk factors for skin carcinomas include ultraviolet light, immunosuppression, age, fair skin type, genetic factors, and human papilloma virus infection. In contrast to the general population, in organ-transplant recipients, squamous cell carcinomas are more frequent than basal cell carcinomas. The ratio of post-transplant melanoma to MCC is 6 to1, whereas in the general population, the ratio is 65 to 1.[2]

Case Report

This is a case of a 55-year-old man with post renal transplant status and a history of multiple squamous cell carcinomas. After initial transplant, patient again experienced renal failure and was scheduled for re-transplant with a living donor. Prior to re-transplantation, an erythematous nodule was noted on his central forehead. Biopsy showed folliculitis, and subsequently, the patient was allowed to proceed with his transplant.

The man was next seen four weeks after transplantation with a 5 cm to 6 cm, reddish-blue, shiny plaque on the central forehead with multiple satellite nodules. His right cheek was also noted to have a similar-appearing plaque. Biopsy of the forehead revealed primary neuroendocrine carcinoma of the Merkel cell type. Biopsy of the right cheek revealed metastatic neuroendocrine carcinoma, also Merkel cell (Figure 1, 2).

Further work-up was preformed. Routine labs were normal. Kidney function tests revealed good function of the new kidney. No liver abnormalities were detected. PET (positive electron tomography) scans and magnetic resonance imaging of the head and neck showed metastatic and in-transit disease of the head and neck with no tumor beyond the cervical chain. The patient underwent Mohs micrographic surgery to clear this tumor burden (Figure 3). Later, the patient underwent bilateral, radical neck dissections.

Months after original diagnosis, resection, and lymph node dissection, the patient experienced tumor recurrence (Figure 4). He refused any further treatment except debulking of the tumor masses, as they got too large for him to handle at home. He used Cansema salve, a homeopathic remedy containing zinc chloride paste, to "draw out the tumor." The patient expired approximately six months following diagnosis.

Discussion

In the general population, 97% of patients with MCC are Caucasian, and the gender incidence is equal. There may be a trend for female patients, however, to have a better outcome. In transplant recipients, male cases of MCC outnumber female cases 2.4 to 1. This may reflect the increased ratio of males undergoing transplantation, however.

Penn et al.2 looked at 41 cases of MCC in transplant recipients being reported to the Cincinnati Transplant Tumor Registry (CTTR) from 1968 to 1998. In transplant patients, they found the mean age at diagnosis to be 53 years, and 29% of organ recipients were less than 50 years old.2 The tumor appeared a mean of 91.5 months after transplantation. This is strikingly different from the general population, where only 5% of cases of MCC occur at less than 50 years old.

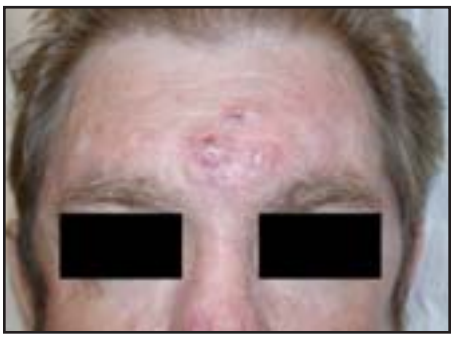


Figure 1
Merkel cell carcinoma pre-op Mohs

Figure 2
Merkel cell carcinoma pre-op Mohs, close-up

Penn et al.[2] found 20 of the 41 organ-recipient patients diagnosed with MCC also had 22 other malignancies. Of these other malignancies, 91% were cutaneous cancers. Therefore, ultraviolet light is implicated as a possible etiologic factor for the development of MCC; however, tumors occurring in unexposed sites such as the genitalia and oral mucosa illustrate the importance of other factors as well.

Ott et al.[3] identified two statistically significant, independent predictors of disease-free survival in the general population when they looked at medical records of 33 patients diagnosed with MCC: location of the lesion and regional node status at the time of diagnosis. Lesions occurring on the trunk had an extremely poor prognosis,

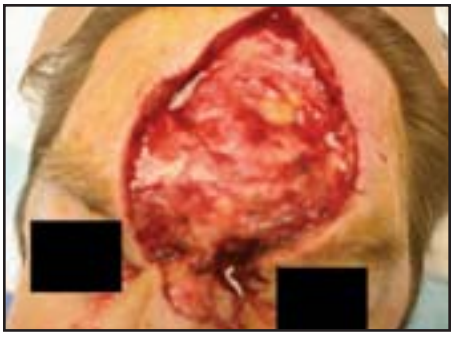


Figure 3
Post-op Mohs

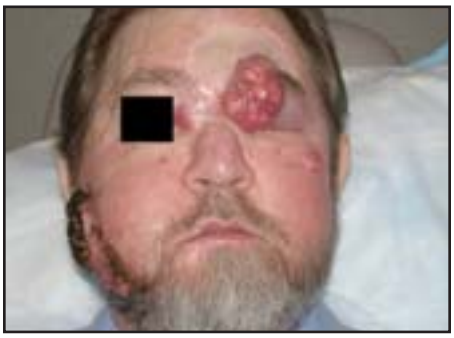


Figure 4
Recurrent merkel cell carcinoma

with six out of seven deaths occurring in this group. Of the eight patients with positive regional nodes at the time of presentation, only four survived. Two of these four survivors received radiation therapy (XRT) to the nodal bed, one received XRT and a therapeutic lymph-node dissection, and one received only a therapeutic lymph-node dissection. Of the four patients with positive lymph nodes who did not survive, none received adequate XRT to the nodal bed in the immediate post-operative period. Adequate XRT was defined as 45 Gy or more to the primary site and/or regional nodes. The average tumor size studied varied from 0.5 cm to 15 cm (median 2 cm) and did not affect outcome.

When Penn et al.[2] reviewed 41 cases of MCC in transplant patients, tumor distribution was similar to that seen in the general population: 36% head and neck involvement, 32% upper extremity, 16% truncal, and 9% unknown.

It is important that clinical suspicion be high in transplant patients. Penn et al.[2] looked at 4,406 organ recipients who developed various skin cancers, 0.9% (39) of whom developed MCC. In one case, the tumor was misdiagnosed as a sebaceous cyst. Yiengpruksawan et al.4 looked at 70 patients treated for MCC at Memorial Sloan-Kettering Cancer Center between 1969 and 1989 and found 61 patients (88%) presented with symptomatic skin nodules, four (6%) with an ulcerating mass, and five (7%) with enlarged metastatic lymph nodes and unidentified primary tumors.

On histologic evaluation, this mostly dermal tumor consists of clusters of medium-sized monomorphic cells, either loose or more cohesively arranged with possible extension into the subcutis (Figure 5A, 5B). Recently, intraepithelial development of MCC has been described with no dermal component.[5,6] Several cases with intraepidermal spread and dermal tumor have been reported.7,8 Microscopic features also show round-to-oval nuclei with scant cytoplasm, finely granular nuclear chromatin and numerous mitotic figures ranging from 1 to 10 per high-power field (Figure 6). Gould et al.[9] recognized three different types of MCC: the trabecular type, which is the most well-differentiated variant; the intermediate cell type, which occurs most frequently; and the small cell type, which behaves very aggressively.

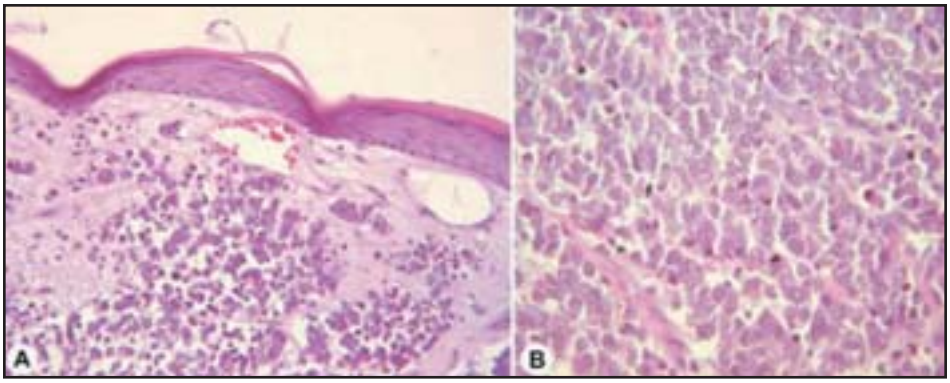


Figure 5 A
Histologic evaluation of merkel cell carcinoma low power
Figure 5 B
Histologic evaluation of merkel cell carcinoma high power
wjso.com/content/ 3/1/58/figure/F4

Merkel cell tumors express various neuroendocrine and epithelial markers, as do normal Merkel cells. Immunohistochemical findings possibly support an epithelial origin for Merkel cells. Merkel cell tumors are positive for epithelial membrane antigen (EMA), which is present in 93% of all epithelial tumors and absent from neuroectodermal tumors. MCC tumors also stain positive for low-molecular-weight cytokeratins (CK) 8, 18, and 20, as well as chromogranin (Figure 7). Neuroendocrine differentiation in a tumor of epithelial origin is supported by the presence of immunoreactivity for neuron-specific enolase, calcitonin, gastrin, and somatostatin. MCCs are usually negative for S100.

Electron-microscopic analysis of MCC demonstrates electron-dense neurosecretory granules, paranuclear bundles of intermediate filaments, and primitive junctional complexes. Normal Merkel cells and Merkel cell tumors contain keratin filaments. Neurofilaments are intermediate filaments with cytoskeletal function. These intermediate filaments are present in Merkel cell tumors and were largely thought not to be found in normal Merkel cells until Narisawa et al.[10] and Fantini et al.11 revealed their presence in normal Merkel cells as well. Neurofilaments were observed in all of the tumors investigated by Drijkoningen et al.[12] The exceptional staining pattern of the tumor cells for neurofilaments is correlated with the presence of bundles and whorls of intermediate filaments in the perinuclear area, as demonstrated by electron microscopy.

It is essential to make sure the tumor is not a metastasis with a primary somewhere else, such as small cell carcinoma of lung or neuroendocrine tumor of the gut. Patients are typically staged at presentation according to the absence (stage I) or presence (stage II) of positive regional lymph nodes and by the presence of systemic metastasis (stage III). Laboratory examination should include a complete blood count, erythrocyte sedimentation rate, liver enzymes and lactate dehydrogenase. In previous case reports, older imaging tests at diagnosis incorporated chest X-rays, abdominal and regional nodal sonography, and, in the case of high risk tumors, computer tomography (CT) of the brain and skeletal scintigraphy. [13] We believe newer imaging modalities, such as CT/PET scan, are better for detection of soft-tissue metastatic disease as detected by high metabolic rate.

Ott et al.[3] recommends aggressive treatment for MCC. Recommendations are based on a retrospective review of 33 patients treated at Massachusetts General Hospital from 1997 to 1980. Optimal treatment for primary MCC when anatomically possible is wide local excision with frozen section examination to ensure adequate margins of at least 2 cm; some authors suggest 3-cm margins. This reduces the incidence of local recurrence, but it does not improve survival.

Our patient was treated with Mohs micrographic surgery, which may prove to be the treatment of choice. Merkel cell carcinomas do not develop in contiguous fashion like basal cell and squamous cell carcinomas. In-transit metastasis may be centimeters away from uninvolved skin. Therefore, rather than taking a predicted surgical margin of several centimeters, it may make sense to minimize the size of

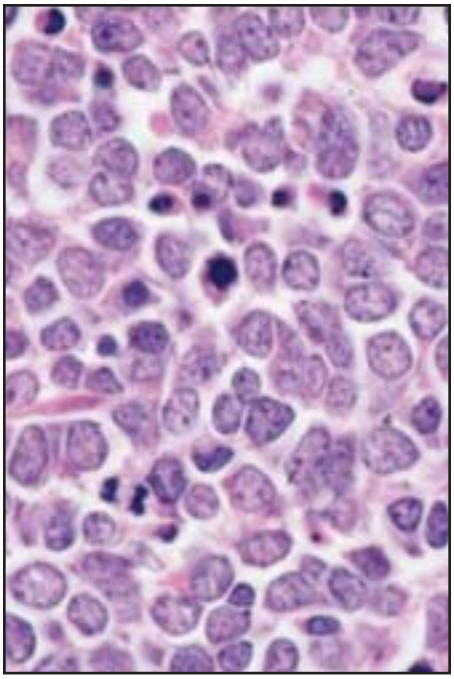


Figure 6
High power microscopic evaluation of merkel cell carcinoma

dermatopathology.stanford.edu/ services/

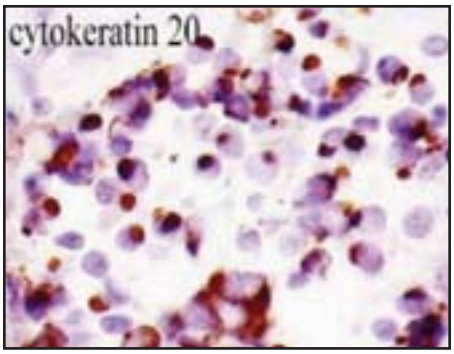


Figure 7
Positive cytokeratin stain in a merkel cell carcinoma

members.tripod.com/ ~dermpath/dpqz22contpg2.html

each surgical basin and treat with Mohs micrographic surgery. Controlled studies are needed to better determine patient outcome with various surgical margins.

Radiation therapy to the primary site is recommended post-operatively if wide margins cannot be obtained due to the anatomic site or if the primary lesion is located on the trunk. Radiation therapy provides local control and long-term improved survival in these instances. Head and neck tumors have been reported to respond to radiation therapy alone.

Regional lymph node status requires determination at the time of local excision. A meta-analysis of all case series in the English literature from 1976 to 2001 by Mehrany et al.[14] proved sentinel lymph node positivity is strongly predictive of a significantly increased short-term risk of recurrence or metastasis in patients with MCC. Forty of 60 patients (67%) had a biopsy-negative sentinel lymph node (SLN); 97% of this group had no recurrence at 7.3 months median follow-up. Twenty patients (33%) had a biopsy-positive SLN; 33% of this group experienced local, regional, or systemic recurrence at 12 months median follow-up. Risk of recurrence or metastasis was 19-fold greater in biopsy-positive patients. None of the 15 biopsy-positive patients who underwent therapeutic lymph node dissection experienced a regional recurrence; three of four who did not receive therapeutic lymphadenectomy experienced regional recurrence. Sentinel-node mapping techniques are therefore as applicable as in melanoma. Positive nodes should undergo formal nodal dissection followed by radiation to the nodal bed. If radical nodal dissection, however, is refused by the patient, then radiation to affected regional nodes should be performed, especially if the primary MCC is a truncal lesion.

Local recurrence was not found to be a predictor of survival.[4] Patients with MCC of the head and neck in this study had the highest rate of local recurrence (37% of patients) but also had the best overall survival rate at five years (91%). Local regional recurrence correlates with inadequate margins and lack of XRT, but remission is possible with multimodality therapy. Recurrent MCC requires a combined modality of re-excision, lymphadenectomy, radiation and, unless contraindicated, chemotherapy. The combination of wide local excision, regional lymphadenectomy, and postoperative XRT has the potential to achieve cure in greater than 90% of patients. Eng et al.[15] studied 46 cases of patients with nodal or local recurrence of MCC. The mean survival after combination therapy (chemotherapy, radiation, and/or surgery) was 36.5 months as compared with 17.5 months for those treated with a single modality.

Distant metastasis occurred in 29% of patients studied.[4] In all but one patient in this study, systemic disease was associated with antecedent regional lymph node metastasis. The most frequent site was the retroperitoneal lymph nodes, with or without peritoneal carcinomatosis. Other sites were the mediastinal lymph nodes, neck, chest wall, liver, stomach, brain, kidney, and ovary.

Chemotherapy should seriously be considered for MCC patients at high risk for developing distant metastasis, including patients with truncal lesions or positive nodes. Chemotherapy can be used in patients with local or distant metastasis. Chemotherapeutic agents used are similar to those used to treat small cell carcinoma of the lung. Various combinations of cyclophosphamide, doxorubicin, vincristine, and various platinum-based drugs are used. Yiengpruksawan et al.4 found the highest response rate was associated with the regimen of cyclophosphamide and doxorubicin hydrochloride and, more recently etoposide and cisplatin. All patients with systemic disease reviewed from Memorial Sloan-Kettering ultimately died of their disease, with the median interval from discovery of distant metastasis to death being five months.

Some authors, including Dreno et al.,[1] argue that immunosuppressive treatment should be reduced or even stopped, given the risk of disease progression and the fact that chemotherapy is relatively ineffective at the metastatic stage. In organ transplant recipients, Penn et al.16 advise the level of immunosuppressive therapy be kept as low as is compatible with good allograft function. If aggressive skin tumors are not controlled, transplant patients will not survive.

In the general population, MCC has a high propensity for local recurrence (26%-75%), regional lymph node metastasis (31%-80%), distant metastases (26%-75%), and death (33%). In review of the CTTR, 28 of 41 patients (68%) had tumor metastasis to lymph nodes, and 56% died from their malignancy despite treatment.[2] Treatment included wide local excision, radical lymph node dissection, radiation therapy, and chemotherapy depending on the stage at presentation. At the completion of case review with a short follow-up, Penn et al. reported 33% of patients surviving with active cancer.[2] Euvrard et al.[17] reported a higher percentage of post-transplant MCC patients who died, 56%, within a two-year period.

Our patient would not have received retransplantation of a living donor's kidney had the diagnosis of MCC been made prior to his surgery. In the April 2004 Dermatology Surgery18 journal, guidelines are provided by the International Skin Transplant Coalition for skin cancer screening and the treatment of aggressive skin cancers in transplant patients. Transplant patients are best cared for in a multi-specialty center. I refer readers to this supplement for further information.

The number of organ transplant recipients is growing steadily due to improvements in organ preservation, transplantation surgery, and immunosuppressive treatments. The significant occurrence of this aggressive tumor in renal transplant patients underscores the importance of routine surveillance in all transplant patients and aggressive intervention if any new skin lesions appear. This requires not only regular examination of the skin, but also strict advice about protection from sun exposure, treatment of warts that might be conducive to the development of skin cancer, and excision of any suspect lesion.

References

1. Dreno, Manstat, Legoux, Litoux. Skin Cancer in transplant patients. Nephrology Dialysis Transplant 1998; 13: 1374-1379
2. Penn, First. Merkel Cell Carcinoma in Organ Recipients: Reports of 41 Cases. Transplantation. December 1999; 68:1717-1721, No 11
3. Ott, Tanabe, Gadd, Stark, Smith, Finkelstein, Souba. Multimodality Management of Merkel Cell Carcinoma. Archives Surgery 1999; 134:388-393
4. Yiengpruksawan, Coit, Thaler, Urmacher, Knapper. Merkel Cell Carcinoma Prognosis and Management. Archives Surgery 1991, 126
5. Brown HA, Sawyer DM, Woo T. Intraepidermal Merkel cell carcinoma with no dermal involvement. Am J Dermatopathology 2000; 22: 65-69
6. Hashimoto K, Lee MW, D'Annuunzio DR, et al. Pagetoid Merkel cell carcinoma: epidermal origin of this tumor. J Cutaneous Pathol 1998; 25:572-579
7. LeBoit, Crutcher, Shapiro. Pagetoid intraepidermal spread in Merkel cell (primary neuroendocrine) carcinoma of the skin. Am J Surg Pathol 1992; 16: 584-592
8. Smith KJ, Skelton HG 3rd, Holland TT, et al Neuroendocrine (Merkel cell) carcinoma with an intraepidermal component. Am J Dermatopathology 1993; 15: 528-533
9. Gould VE, Moll R, Moll I et al: Neuroendocrine (Merkel) cells of the skin: hyperplasias, dysplasia, and neoplasms. Lab Invest 1985; 52:334
10. Narisawa Y, Hashimoto K, Kohda H. Immunohistochemical demonstration of the expression of neurofilament proteins in Merkel cells. Acta Dermatol Venereol 1994; 74: 441-443
11. Fantini, Johansson. Neurochemical markers in human cutaneous Merkel cells. An immunohistochemical investigation. Exp Dermatology 1995; 4:365-371
12. Drijkoningen, Wolf-Peeters, Van Limbergen, Desmet. Merkel Cell Tumor of the Skin: An Immunohistochemical Study. Human Pathology 1986; 17: No 3
13. Krasagakis, Tosca. Overview of Merkel cell carcinoma and recent advances in research. International Journal of Dermatology 2003, 42: 669-676
14. Mehraney, Otley, Weenig, Phillips, Roenigk, Nguyen. A meta-analysis of the Prognostic Significance of Sentinel Lymph Node Status in Merkel Cell Carcinoma. Dermatology Surgery 2002; 28:113-117
15. Eng, Naguib, Fuller, Jones, Herman. Treatment of Recurrent Merkel Cell Carcinoma: An Analysis of 46 Cases. American Journal of Clinical Oncology 2004; 27 (6) 576-583
16. Penn. Incidence and Treatment of Neoplasia After Transplantation. The Journal of Heart and Lung Transplantation 1993; Volume 12, Number 6, Part 2
17. Euvrard, Kanitakis, Claudy Neoplastic. Skin Diseases in Organ Transplant Recipients American Journal Cancer 2002; 1 (2):109-120
18. Dermatologic Surgery April 2004 Part 2, Vol 30 Issue 4p2

Questions

1. True or False: Cytokeratin 20 (CK 20) stain is positive in Merkel cell carcinoma.

a. True

b. False

ANSWER: a. True

REFERENCE:

McKee, Calonje, Granter. Pathology of the skin .Third edition, Volume 2. Pages1230-1238.

2. Which stains are positive for Merkel cell carcinoma?

a. Neuron-specific enolase

b. Keratin filament markers

c. Epithelial membrane-like antigen

d. All of the above

ANSWER: d. All of the above

REFERENCE:

Drijkoningen, Wolf-Peeters, Van Limbergen, Desmet. Merkel Cell Tumor of the Skin: An Immunohistochemical Study. Human Pathology 1986; 17: No 3.

Hitchcock. Neuroendocrine (Merkel Cell) Carcinoma of the Skin. Annals of Surgery February 1988.

3. True or False: Organ transplant recipients have an increased risk of developing skin cancer.

a. True

b. False

ANSWER: True

REFERENCE:

Penn. Incidence and Treatment of Neoplasia After Transplantation. The Journal of Heart and Lung Transplantation. December 1993. Vol 12, No 6, Part 2.

Dermatologic Surgery. April 2004. Part 2, Vol 30 Issue 4 p2.

Linear IgA Bullous Disease: Challenge in Clinical Diagnosis

Danielle DeGennaro, D.O.,* Navid Nami, D.O., Leila Ettefagh, M.D.,*** Layne Nisenbaum, D.O.******
**4th Year Medical Student, Nova Southeastern University*
***3rd Year Dermatology Resident, Columbia Hospital / Nova Southeastern University*
****Clinical Instructor, University of California Irvine / Island Dermatology*
*****Program Director, Columbia Hospital West Palm Beach*

ABSTRACT

Background: *Linear IgA bullous disease (LABD) is a rare autoimmune disorder that can affect both adults and children. It is characterized by subepidermal blister formation and linear IgA deposits along the basement membrane zone (1). This is a case report of LABD misdiagnosed as dermatitis herpetiformis (DH).*

Introduction:

LABD is a rare autoimmune bullous disease that affects adults and has a childhood form known as chronic bullous disease of childhood (CBDC). It is characterized by subepidermal blister formation with linear IgA deposits along the basement membrane zone.[1] The IgA autoantibodies target a 97 kDa antigen in the lamina lucida or, less commonly, anchoring fibrils (collagen VII) in the sublamina densa.[2,3]

Case:

A 64-year-old man presented with a diagnosis of dermatitis herpetiform (DH). The lesions were originally pruritic, pink papules on the buttocks, thighs and axilla (Figure 1). The biopsy showed features consistent with DH. No immunofluorescent studies had been performed at that time. The patient's treatment regimen included a gluten-free diet, dapsone 150mg daily, topical clobetasol, and intramuscular corticosteroids as needed. The patient was continuing to have recurrent flares despite this regimen. In addition, three to four months after his original diagnosis he developed blisters on his oral mucosa.

On examination, the patient had multiple polymorphous, erythematous, crusted papules and plaques on the trunk and extremities. There were also erosions and vesicles on the dorsal surface of the tongue. A repeat biopsy showed a neutrophil-rich, subepidermal blister with smooth epidermal undersurface consistent with an autoimmune subepidermal bullous disease. The histologic differential included DH, LABD and bullous lupus erythematosus. Immunofluorescent studies showed strong, thick, linear IgA deposition along the epidermal basement membrane zone. Salt-split skin showed IgA deposition only at the dermal side (sublamina densa) of the artificial blister. This immunofluorescent pattern was consistent with LABD – lamina densa type (a.k.a. epidermolysis bullosa acquisita variant).

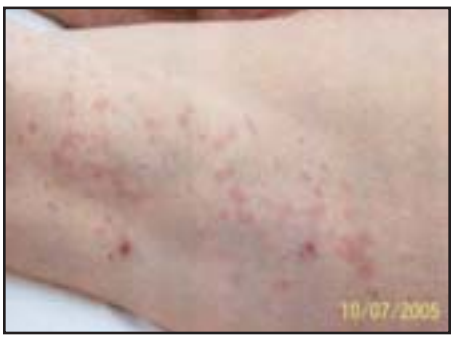


Figure 1

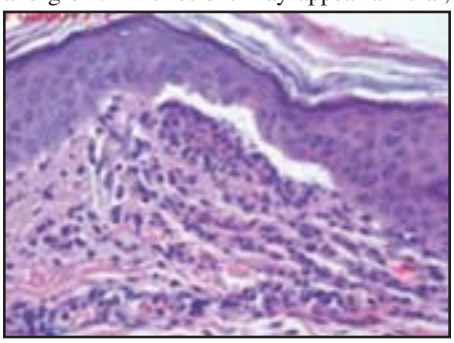


Figure 2

Discussion

There are three clinical variants of LABD: adult, childhood and drug-induced. Each variant has a unique clinical presentation with similar immunohistopathologic findings. The adult form occurs after puberty with pruritic, tense bulla on the trunk and extensor surfaces. Lesions are often secondarily infected due to rupture of the bulla. Mucosal lesions including vesicles, ulcers, erosions, desquamative gingivitis, or erosive cheilitis have also been described. Ocular findings include subconjunctival fibrosis, shrinkage of the fornices, symblepharon formation, or cicatricial ectropion with trichiasis.

The childhood variant, CBDC, affects children between the ages of six months and 10 years old. A recent report has described CBDC presenting in a one-day-old baby boy.[4] Lesions present as an abrupt onset of tense vesicles or bulla classically in the flexural areas, mostly the lower trunk, thigh and groin. The lesions may appear annular, and they may have a smaller cluster of vesicles at the periphery. This has been described as a "cluster of jewels" or "string of pearls." Mucosal lesions may be present, as in the adult form, although with less frequency. One study showed mucosal disease in 64% of patients with CBDC and in 80% of patients with LABD.[5]

A third variant of LABD is drug-induced and mostly seen in the adult population. Vancomycin is the most commonly described offending agent, with many other medications as possible culprits (see Table 1). Lesions occur soon after the initial dose and resolve upon withdrawal of the offending agent. Mucosal lesions are often not present with this variant.

There are also reports of LABD associated with malignancies, including B-cell lymphoma, chronic lymphocytic leukemia and carcinoma of the bladder, thyroid and esophagus.[6]

Histopathology:

Classic early histologic findings in LABD can be similar to DH, with a neutrophilic infiltrate at the papillary tips that evolves into subepidermal bulla (Figure 2).[7,8] This similarity in histology demonstrates the importance of immunofluorescent studies to confirm a final diagnosis.

Immunoflourscence:

The immunoflourscence of LABD shows a homogenous linear deposition of IgA at the basement membrane zone (Figure 3). Other immunoreactants such as IgG and C3 have been identified in some cases. Immunoelectron microscopic studies have revealed three target sites within the dermal-epidermal junction of the immunoreactants. First, there is the more commonly seen lamina lucida region, which is similar to the pattern in bullous pemphigoid. Deposits can also be found at and below the lamina densa, which is similar to the pattern seen in epidermolysis bullosa acquisita (EBA) (Figure 4). This

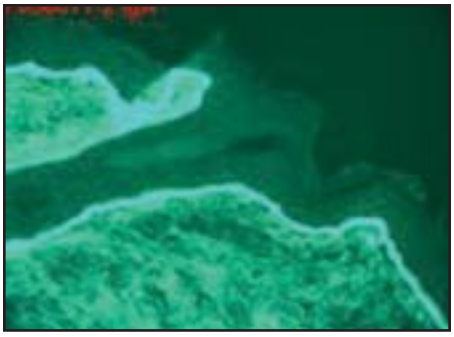


Figure 3

Figure 4

Table 1
DRUG-INDUCED LINEAR IGA BULLOUS DISEASE

Amiodarone	Lithium
Atorvastatin	Penicillin-G
Captopril	Phenytoin
Carbamazepine	Piroxicam
Cefamadole	Rifampicin
Diclofenac	Somatostatin
Furosemid	Topical Iodine
Interferon-gamma	Vancomycin

is the pattern found in our patient. A third pattern can be observed where the deposits are above and below the lamina densa.

Treatment

LABD is a chronic skin condition that requires systemic therapy, though some cases can spontaneously resolve. The rate of remission has been reported to be higher for CBDC at 64% as compared to LABD at 48%.[5]

The first-line drug in the management of LABD is dapsone. Other systemic medications include sulfapyridine, systemic steroids, colchicine, cyclosporine, tetracycline combined with niacinamide, and high-dose IVIG.[9] Dapsone is also the first drug of choice in the treatment of DH. DH patients usually have a good response to dapsone, unlike the patient presented in this case. The average dosage of dapsone required for the treatment of LABD is 100mg daily, but doses as high as 300mg may be needed for a less responsive disease. Occasionally, immunosuppressive doses of prednisone may also be needed.

Although dapsone is a very effective medication used in many dermatologic, neutrophil-rich disorders, its use must not be taken lightly, and close patient follow-up is of utmost importance. The most commonly discussed adverse effects of dapsone include hemolysis and neuropathy.

Dapsone-induced hemolysis may be dose related. A mild hemolytic process occurs in almost every patient. A screening test for glucose-6-phosphate dehydrogenase must be completed prior to initiation of therapy. This is particularly relevant in African-Americans, Asians and Mediterraneans, as these populations are at risk for more severe hemolytic disease. Other reported hematologic side effects of dapsone include methemoglobinemia, leucopenia and agranulocytosis. Laboratory tests (including complete blood count and complete chemistry panel) must be performed prior to initiation of therapy and monitored weekly for the first month, then monthly and eventually every six months. Dapsone-induced peripheral neuropathy is also dose related and is classically described as a motor neuropathy in the distal extremities.

Dermatologic eruptions have also been described in patients taking dapsone. These include erythema nodosum, phototoxicity, fixed drug eruption, erythema multiforme and toxic epidermal necrolysis.

Conclusion

This case illustrates the significance of a proper work-up and accurate diagnosis for any chronic skin disease that may require chronic therapy with systemic medications that have potential toxicities. A good clinician must be able to correlate clinical, histologic and immunohistologic findings when making a diagnosis.

LABD was originally considered a variant of DH. Later, it was recognized as a separate disease entity based on its unique immunohistopathology, immunogenetics, and lack of consistent association with a gluten-sensitive enteropathy.[2,3,4] As compared to LABD, the classical clinical findings in DH are severe pruritic and/or burning urticarial crusted papules or vesicles. The lesions may be in groups or isolated and usually are symmetrically distributed. One unique feature of DH is its association with gluten-sensitive enteropathy and small-bowel lymphoma. Histology of DH reveals subepidermal clefts of evolving vesicles, microabscesses with neutrophils and, less often, eosinophils in the dermal papillae. The direct immunofluorscence findings for DH typically show granular or fibrillar IgA depositions in the dermal papillae of peri-lesional skin (see Table 2 for a comparison of LABD and DH).

Appropriate work-up and close follow-up in patients with chronic autoimmune bullous disease is vital and likely would have helped this patient at an earlier time.

Table 2
LINEAR IGA BULLOUS DISEASE VS. DERMATITIS HERPETIFORMIS

Feature	*Linear IgA Bullous Disease*	*Dermatitis Herpetiformis*
Age of Onset	Adults 18-83 yo Childhood 6 mos-10 yo	Any age Mostly between 20-40 yo
Pruritic	Yes	Yes
Lesion	Vesicles / Bulla	Grouped Urticarial Papules & Vesicles (+/-) Excoriations
Distribution	Symmetrical Extensor Surfaces	Symmetrical Extensor Surfaces
Mucosal	Common	Rare
Associations	Medications / Malignancy	Celiac Enteropathy / Lymphoma Hypothyroidism
Histopathology	Neutrophilic infiltrate at the papillary tips which evolve into subepidermal bulla.	Subepidermal clefts of evolving vesicles, microabscesses with neutrophils and eosinophils in the dermal papillae.
DIF	Linear IgA at Basement Membrane Zone	Granular or fibrillar IgA at Dermal Papillary Tips
Dapsone Response	Excellent	Good

References:

1. Cauza, Karla, Hinterhuber G, Sterniczky B, Brugger K, Pieczkowski, F, Karlhofer F, Wolff K, Foedinger D. Unusual clinical manifestations of Linear IgA dermatosis: a report of two cases. J Am Acad Dermatol. 2004 Aug; 51:
2. Zone JJ, Taylor TB, Kadunce DP, Meyer LJ. Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunoglobulin A bullous dermatosis. J Clin Invest. 1990; 85:812-20.
3. Gammon WR, Fine JD, Forbes M, et al. Immunofluorescence on split skin for the detection and differentiation of basement membrane zone autoantibodies. J Am Acad Dermatol. 1992; 27:79-87.
4. Kishida Y; Kameyama J; Nei M; Hashimoto T; Baba K. Linear IgA bullous dermatosis of neonatal onset: case report and review of the literature. Acta Paediatr. 2004 Jun 01; 93(6): 850-2.
5. Wojnarowska F, Marsden RA, Bhogal B, Black MM. Chronic bullous disease of childhood, childhood cicatricial pemphigoid, and linear IgA disease of adults. A comparative study demonstrating clinical and immunopathologic overlap. J Am Acad Dermatol 1988 Nov: 19:792-805.
6. McEnvoy MT, Connolly SM. Linear IgA dermatosis: association with malignancy. J Am Acad Dermatol. 1990; 22:59-63.
7. Blenkinsopp WK et al: Histology of linear IgA disease, dermatitis herpetiformis and bullous pemphigoid. Am J Dermatopathol 1983, 5:547.
8. Smith SB et al: Linear IgA bullous dermatosis v dermatitis herpetiformis: Quantitative measurements of dermoepidermal alterations. Arch Dermatol 1984, 120:324.
9. Mutasim, Diya F. Management of autoimmune bullous diseases: Pharmacology and therapeutics. J Am Acad Dermatol 2004, 51:6.

Familial Occurrence of Gianotti-Crosti Syndrome and Unilateral Laterothoracic Exanthem

Tara H. Lawlor, D.O.*, Donald J. Adler, D.O., Stephen M. Purcell, D.O.*****
** 3rd-year resident, Lehigh Valley Hospital-Muhlenberg/PCOM Dermatology Residency, Allentown, PA*
***Clinical Faculty Member, Lehigh Valley Hospital-Muhlenberg/PCOM Dermatology Residency, Doylestown, PA*
****Program Director, Lehigh Valley Hospital-Muhlenberg/PCOM Dermatology Residency, Allentown, PA*

ABSTRACT

We report the simultaneous occurrence of Gianotti-Crosti syndrome and unilateral laterothoracic exanthem in two young siblings. Both patients had signs and symptoms of an upper respiratory infection prior to the onset of their skin eruption. Since both Gianotti-Crosti syndrome and unilateral laterothoracic exanthem have been associated with viral etiologies, it seems likely that a common virus caused these two distinctive exanthems in our patients.

Case Report 1

A 16-month-old, Caucasian male presented during the springtime with a chief complaint of a 10-day history of a skin eruption that involved his face, trunk and extremities. He had a family history of atopic dermatitis, melanoma, diabetes and heart disease. He had no known drug allergies. Mild upper-respiratory symptoms, including low-grade fever and rhinopharyngitis, were present prior to the onset of the exanthem. The child was otherwise reported in good health. Oral diphenhydramine was prescribed for the treatment of mild pruritus associated with the eruption. On physical examination, an erythematous, monomorphous eruption consisting of 2-to-3-mm, edematous papules was scattered symmetrically over his cheeks, extremities and trunk. The clinical impression of his exanthem was Gianotti-Crosti syndrome. Reassurance without specific treatment was recommended.

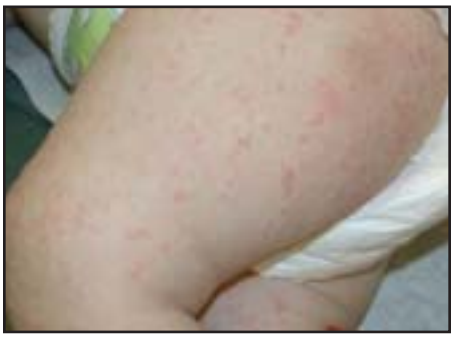


Figure 1a

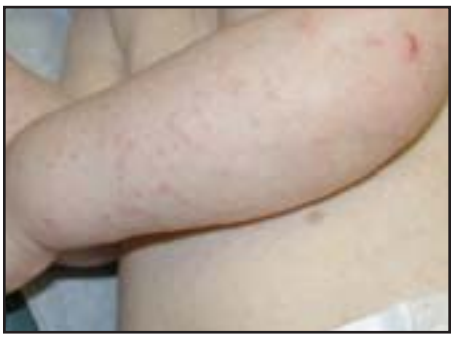


Figure 1b

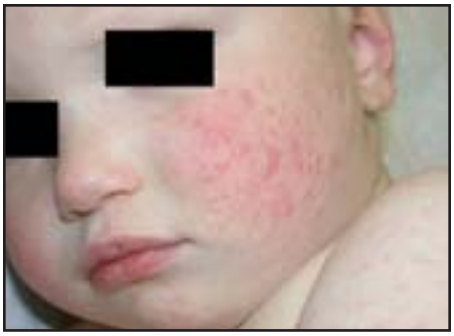


Figure 1c

Figure 1a,b,c: Erythematous, 2-to-3-mm, edematous papules symmetrically distributed over extremities and cheeks

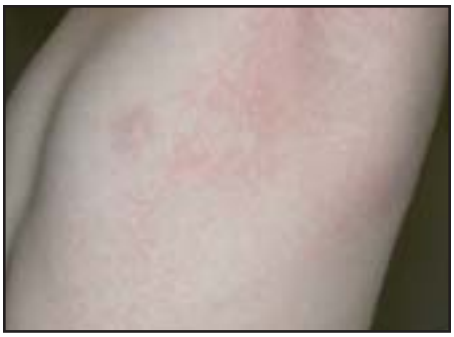


Figure 2a

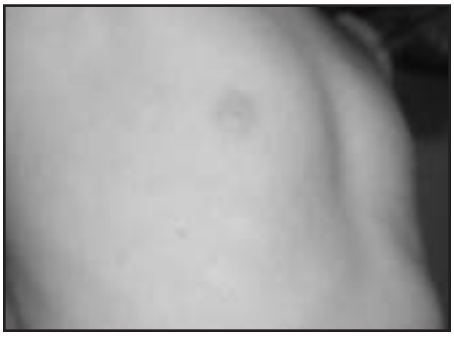


Figure 2b

Figures 2a,b: Multiple, erythematous, coalescing papules on the left axilla, abdomen and chest wall; right trunk is spared

Case Report 2

Several days after the onset of the male child's exanthem, his 3-year-old sister developed a skin eruption on the left side of her trunk. She also had similar, pre-eruption upper-respiratory symptoms, which included a low-grade fever and rhinopharyngitis. She had no known drug allergies and a personal history of atopic dermatitis. Physical examination revealed multiple discrete, erythematous and coalescing papules involving the left axilla, abdomen and chest wall. The remainder of her examination was normal, and no lymphadenopathy was appreciated. The clinical impression was unilateral laterothoracic exanthem. Reassurance without specific treatment was recommended.

Discussion

Gianotti-Crosti syndrome (GCS) is a distinctive exanthem seen mostly in children. It has been referred to as papular acrodermatitis of childhood as well as papulovesicular acrolocated syndrome. No distinguishing clinical features separate the two entities. This led to the recommendation for the unifying title of Gianotti-Crosti syndrome.[1,2] It was first described by Gianotti in 1955 and by Gianotti and Crosti in 1956.1 The pathogenic mechanism of the exanthem is unclear, and cases tend to occur worldwide more commonly in the spring and early summer. The mean age of affected children is two years. Numerous adult cases, mainly in women, have been reported.[1,3] GCS is often preceded by multiple symptoms including lymphadenopathy, low-grade fever, rhinitis, cough and diarrhea. Hepatic involvement is rare. This syndrome is usually asymptomatic at the time of cutaneous presentation. Acute onset of skin findings consist of 1.5-mm, monomorphic, pink-to-reddish-brown, edematous papules symmetrically distributed on the face, extensor extremities and buttocks. The trunk is generally spared, and mucous membranes are not affected.[3] Vesicles and purpuric lesions are rarely encountered. In one report, Epstein Barr Virus (EBV)-proven GCS was limited to a localized facial erup-

tion alone.[4]

GCS is most commonly associated with EBV.[3] Most cases associated with positive Hepatitis B surface antigen have been reported from Japan and Italy.[1] Other proposed causes include unrelated viruses, bacteria and various immunizations. In addition to Hepatitis B virus (HBV) and EBV infection, cytomegalovirus (CMV), parainfluenza virus, respiratory syncytial virus and coxsackievirus infections have been confirmed to be associated with GCS. Often, only mild respiratory symptoms are encountered clinically. This has lead to speculation that in many cases of GCS, a more serious EBV disease trigger goes undiagnosed.[1] EBV is seen worldwide and is easily transmissible, making it a common infection in young children. Recently, a family history of atopic dermatitis has been found in a significant number of children with GCS. This has lead to speculation that genetic factors and/or immunologic imbalances play a role in the pathogenesis of this disease.[3] The differential diagnosis of GCS includes drug hypersensitivity, papular urticaria, viral exanthem, erythema multiforme and molloscum contagiosum. Histopathological findings are generally nonspecific but commonly show epidermal acanthosis, hyperkeratosis and a dermal lymphohistiocytic perivascular infiltrate with dilated capillaries. Electron microscopy and immunohistochemistry have failed to show associated viral particles or antigens in the skin of GCS patients.[3]

GCS generally does not require treatment, although cases that exhibit pruritus are often treated symptomatically. Topical corticosteroids may help suppress the clinical appearance of the eruption. An evaluation to explore viral etiology may be performed if malaise or hepatomegaly is present. This work-up typically would include Hepatitis B surface antigen, EBV and CMV titres. Spontaneous resolution generally occurs within three-four weeks.

Unilateral laterothoracic exanthem (ULE), or asymmetric periflexural exanthem of childhood (APEC), is also a condition characteristically encountered in children.[5,6,7,8,9] ULE was first described by Brunner et al. in 1962, but the actual term was first suggested by Bodemer and de Prost.[6] Cases have been reported in adults, but the majority of cases involve children ranging in age from four months to 15 years.[5,7] The eruption begins unilaterally on the trunk, close to or involving the axilla. It then often spreads centrifugally to the ipsilateral trunk, arm and thigh and displays erythematous papules with or without pale halos. Early on, the exanthem is morbilliform, and later it takes on an eczematous appearance with peak involvement at two to three weeks from onset.[10] The eruption may spread to the contralateral side but often with much less frequency.[8] Most commonly, a history of unilateral involvement aids in making the diagnosis. Some reports claim no right- or left-side dominance, while others note that the left side is more frequently affected.[5] Females predominate in a 2:1 ratio.[10] ULE may be preceded by nonspecific upper respiratory tract or gastrointestinal symptoms including mild fever, rhinitis or diarrhea. In one study, these prodromes were reported in 60% of patients.[7] Pruritus, with or without lymphadenopathy, occurs in two-thirds of all cases.[7,11] The etiology is unknown, but an infectious cause seems likely. The disease exhibits a seasonal occurrence pattern (late winter and early spring) with infectious-type prodromal symptoms, reported familial cases and a lack of response to antibiotics.[5,8] No consistent viral agent has been identified, however. One case reports a child's eruption with ULE at the same time her mother had pityriasis rosea.[9] Another case reports a father with a unilateral, axillary eruption two weeks prior to his child's eruption with ULE.[10] Familial occurrence has been reported in twin sisters who developed the eruption within 10 days of one another.[8] The differential diagnosis includes contact dermatitis, tinea corporis, viral exanthem, drug hypersensitivity, atypical pityriasis rosea, miliaria, scabies and GCS. Histopathological findings are generally nonspecific, consisting of a superficial perivascular lymphocytic infiltrate with or without perieccrine inflammation, epidermal spongiosis, and exocytosis of lymphocytes into the epidermis. Laboratory evaluation is unnecessary in most cases, and spontaneous resolution within three to six weeks without recurrence is expected.[5,11]

Conclusion

We report a case of GCS and ULE that presented in siblings within days of each other. This is of great interest as both diseases have often been reported to be caused by viruses. Our cases seem to fit a viral etiology since both children had onset of their eruptions after experiencing multiple, nonspecific, upper-respiratory symptoms. Since both children share the same household and shared similar symptoms prior to their respective exanthems, we propose this is the first reported case of both entities presenting simultaneously from the same viral etiology.

References:

1. Hofmann, B et al. Gianotti-Crosti syndrome associated with Epstein Barr virus infection. Pediatr Dermatol 1997;14(4):273-77.
2. Caputo R et al. Gianotti-Crosti syndrome: a retrospective analysis of 308 cases. J Am Acad Dermatol 1992;26:207-10.
3. Brandt O et al. Gianotti-crosti syndrome. J Am Acad Dermatol 2006;54:136-45.
4. Yoshida M et al. Five patients with localized facial eruptions associated with Gianotti-Crosti syndrome caused by primary Epstein Barr virus infection. J Pediatr 2004;145(6):843-44.
5. Nahm, WK et al. Asymmetric periflexural exanthema of childhood: A case involving a 4-month old infant. Pediatr Dermatol 2002;19(5):461-62.
6. Coustou D et al. Asymmetric periflexural exanthema of childhood: Microbiologic case-control study. Pediatr Dermatol 2000;17(3):169-73.
7. Coustou D et al. Asymmetric periflexural exanthem of childhood: a clinical, pathologic, and epidemiologic prospective study. Arch Dermatol 1999;135(7):799-803.
8. Bodemer C, de Prost Y. Unilateral laterothoracic exanthema in children: a new disease? J Am Acad Dermatol 1992;27(5):693-96.
9. Ta^{a}eb A et al. Asymmetric periflexural exanthema of childhood. J Am Acad Dermatol 1993;29:391-93.
10. McCuaig C et al. Unilateral laterothoracic exanthema. J Am Acad Dermatol 1996;34:979-83.
11. Brunner MJ, Rubin L, Dunlap F. A new papular erythema of childhood. Archives Dermatol 1962;85:539-40.

A Case of Cutaneous Angiosarcoma of the Scalp

Piyush Raman, D.O.,* Michael Mahon, D.O., F.A.O.C.D.**
**3rd year Dermatology Resident/ Pontiac Osteopathic Hospital/ Michigan State University/ Pontiac, Michigan*
***Program Director/ Pontiac Osteopathic Hospital/ Michigan State University/ Pontiac, Michigan*

ABSTRACT

Cutaneous angiosarcoma is an aggressive, malignant tumor with a high propensity for both local recurrence and distant metastases. It is a rare, difficult to treat, lethal tumor. Due to its aggressive behavior, early recognition is the best approach to increase survival in these patients. We describe an 87-year-old woman with cutaneous angiosarcoma of the scalp and review the available literature.

Case Report

An 87-year-old, white female presented with a four-week history of a rapidly enlarging, crusted plaque of the right temporoparietal scalp. It was initially attributed to trauma, as she had a recent history of falls. The patient had a previous diagnosis of Alzheimer's and hypothyroidism, but no previous history of cancer. She denied any history of radiation to the area. During the first week, the patient was treated with mupirocin ointment, without benefit. The lesion persisted and began growing rapidly over the next three weeks before her presentation to the dermatology clinic.

Physical examination revealed an 8x6-cm, crusted plaque with surrounding necrosis, erythema, and edema (Figure 1). There was slight tenderness to palpation. There was no head or neck lymphadenopathy. Two punch biopsy specimens were obtained. The clinical diagnosis of angiosarcoma was confirmed by histopathology (Figures 2a and 2b). The patient was sent to an oncology center for further evaluation and treatment. Computer tomographic (CT) scan of the head showed no evidence of underlying bone involvement. The patient and her family elected for treatment by palliative radiotherapy.

Discussion

Angiosarcoma (AS), also known as malignant hemangioendothelioma and lymphangiosarcoma, is a rare, malignant tumor arising from vascular endothelium and/or lymphatic cells. It was first identified as a distinct clinical entity by Wilson-Jones in 1964.[1] Approximately half of all angiosarcomas occur in the head and neck, but they account for less than 0.1% of head and neck malignancies.[2]

Different clinical settings of cutaneous AS have been recognized. There are three main subtypes: idiopathic cutaneous angiosarcoma of the head and neck, angiosarcoma complicating lymphedema, and postirradiation angiosarcoma. The most common form primarily affects the scalp and upper face of individuals in the sixth through eighth decades of life, with men more frequently affected than women.[3] Less commonly, AS may arise in the maxilla, mandible, pharynx, tongue, and larynx.[4-6] Stewart and Treves described AS arising in an area of chronic lymphedema, usually in an arm following radical mastectomy for breast cancer.[7] Angiosarcomas that affect the lymphedematous lower limbs have been described.[8] Chronic lymphedema resulting from other insults, such as trauma or infection, may also predispose to AS.[9,10] Postirradiation angiosarcomas are rare and have been documented after radiotherapy for a variety of benign and malignant conditions, but the relationship has not been explained.[11,12] Angiosarcoma metastasis to the skin is rare, but it can herald the presence of an occult tumor from an internal site such as the heart and aorta.[13,14] Recently, an aggressive variant known as epithelioid angiosarcoma has been described.[15,16]

Little is known about the cause of angiosarcomas. A common theory proposes that some form of previous connective-tissue damage may be a pathogenic factor. Actinic damage has been suggested; however, the role of chronic sun damage has been questioned because many lesions arise from the scalp of patients with a full head of hair.[17] The reports of AS complicating xeroderma pigmentosum[18] support the possibility that UV-induced DNA damage may be involved in the pathogenesis of AS. Both ionizing irradiation and UV irradiation cause DNA damage. One of the major pathways reported for the development of AS is the occurrence of a p53 mutation.[19,20] This tumor-suppressor protein is a crucial player in preventing cells or tissues from undergoing transformation or tumorigenesis. In addition, several malignancies carry a risk for subsequent sarcoma formation, independent of the use of radiation therapy. Wilms' tumor, retinoblastoma, and neurofibromatosis are examples.[21,22] Other risk factors include hormonal influences resulting from pregnancy, use of anabolic steroids or exposure to thorium dioxide, vinyl chloride, and insecticides.[21,23,24]

Figure 1
Angiosarcoma: lesion of the right temporoparietal scalp

Clinically, the appearance of cutaneous angiosarcomas is quite variable. The lesions usually have an insidious onset, remaining minimally symptomatic for an extended period of time. The characteristic appearance is that of a red, dusky patch with poorly defined margins; therefore, the tumor is frequently mistaken for a bruise or hemangioma, delaying diagnosis. Some patients with angiosarcoma may present with edema or ulceration, suggesting an infectious process.[3] With time, blue or violaceous plaques and nodules develop. Occasionally, the lesions may infiltrate the deeper dermis and subcutis and appear almost colorless or light red. Satellite nodules may be separated from one another by clinically normal skin. The propensity for horizontal spread within the dermis makes gross assessment of surgical margins difficult. There may be an extensive cicatricial alopecia. In the great majority of cases, the lesions are painless.[25] Aguila and Sanchez reported a case of angiosarcoma of the face resembling rhinophyma.[26] Mentzel and Kutzner reported a patient with angiosarcomas of the face that clinically resembled rosacea.[27]

The classic forms of angiosarcoma grow relentlessly and almost always recur following resection because of their vague circumscription. Involvement of the cranial bones may occur, and metastasis to the

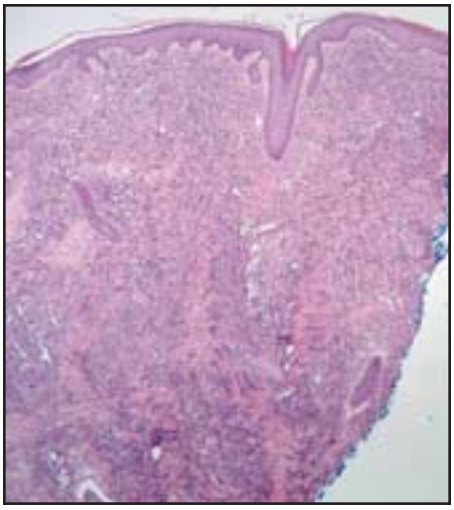


Figure 2a
Low-power view of a highly cellular and vascular tumor in the dermis (Hematoxylin-eosin; magnification 40X)

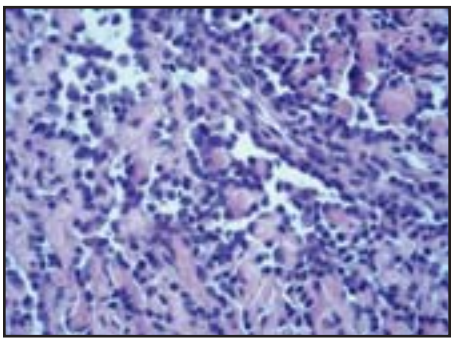


Figure 2b
On higher magnification, the vascular channels are lined by prominent endothelial cells that protrude into the lumen. The endothelial cells show moderate pleomorphism and hyperchromatic nuclei. (Hematoxylin-eosin; magnification 400X)

regional lymph nodes, liver, and lungs is frequent.[21] Involvement of the spleen, bone, kidneys, intestines, retroperitoneum, and heart also has been reported.[3] The cause of death is attributed to local tissue invasion or to metastatic involvement of the cardiorespiratory system.

Angiosarcoma is a poorly circumscribed dermal tumor which may occupy the breadth of the dermis, with some of the larger tumors extending into the subcutaneous fat or fascia. Three distinct patterns of proliferation have been described: angiomatous, spindled, and undifferentiated. Tumors can be composed of varying proportions of each pattern. In the angiomatous pattern, the tumor consists of an anastomosing network of endothelial-lined, variably slit-like to medium-sized sinusoidal to larger, blood-filled cystic spaces. The endothelial cells may be larger than normal and contain hobnailed, hyperchromatic, round to oval nuclei with condensed chromatin. The second major type of microscopic growth pattern consists of islands and diffuse sheets of spindled cells with little intervening stroma. Less-differentiated tumors show solid sheets of epithelioid cells with abundant acidophilic cytoplasm and large, atypical nuclei that expand the dermis. Intralesional hemorrhage may be prominent in this subtype.

Many immunohistochemical markers for endothelial cell differentiation have been used. Studies have indicated that the antibodies to CD31 and Ulex europaeus lectin 1 are more reliable markers for routine use than the antibodies to factor VIII and CD34.[28] In poorly differentiated lesions, there can be loss of one or more of these antigens. Furthermore, the immunohistochemical pattern of AS can vary within tumors, suggesting mixed differentiation of both vascular and lymphatic endothelium.

Tumors that can be mistaken clinically and histologically for angiosarcoma include angiosarcoma-like squamous cell carcinoma, malignant melanoma, pyoderma gangrenosum, Kaposi's sarcoma, and hemangiopericytoma.

Because of the fact that AS is extremely aggressive, only early detection and treatment can modify the prognosis. The prognosis for angiosarcoma is poor, with frequent local recurrence and early metastasis. The reported median survival range is 15 to 20 months, and the five-year survival rate ranges from 10% to 35% in different series.[2,3,29,30] In the series by Holden et al., only 12% of patients survived five years or more in a study of 72 patients with AS of all sites.[3] Mark and Poen reported two-year and five-year actuarial survivals of 44% and 24%, respectively.[21] Studies have shown that prognosis correlates with tumor size. Smaller tumors carry a better prognosis. Holden et al. reported that a tumor size of less than 10 cm correlated with a favorable prognosis.[3] Maddox and Evans concluded that a tumor size of less than 5 cm probably offers an even greater prognostic benefit.[2] In a recent case series, tumor diameter, tumor depth of invasion, margin status, tumor recurrence, and metastases emerged as the most important determinants of outcome.[31]

Given the rarity of the tumor, optimal management of cutaneous angiosarcoma has not been defined. Treatment options include standard surgical excision, Mohs surgical excision,[32,33] radiation, and chemotherapy. Although surgical resection remains the cornerstone therapy, the clinically undetectable spread means that achieving negative margins often is impossible.[25] Routine exploration of the neck is not recommended,[34] but some authors recommend regional cervical-node dissection at the time of primary excision for high-risk larger tumors.[35]

In recent years, there has been an increased use of more limited surgery followed by multimodal therapy involving radiation and chemotherapy. In general, the role of chemotherapy for head and neck angiosarcomas has not been established, but case reports describe efficacy of doxorubicin.[36-38] Interferon alpha 2b and interleukin 2 have also been used.[39] Response to treatment with paclitaxel has been reported by several authors, unfortunately without prolonged survival benefit.[40,41] Although some authors report that radiation therapy provides no benefit,[1,42] others suggest that surgery combined with radiation therapy offers the best prognosis.[3,25,43,44]

Conclusion

Cutaneous angiosarcoma is a highly aggressive neoplasm that poses numerous challenges to the managing team of physicians. The extraordinary variability in the way the tumor presents often results in a great delay in diagnosis that deters early and possibly successful treatment. A high index of suspicion of bruised or indurated lesions on an elderly patient's scalp or face should promote early biopsy. In addition, there is a serious need for the development of new approaches, including more effective local and systemic therapies. Finally, long-term follow-up is essential, given the tumor's propensity for recurrence and metastasis, even after years of disease-free states.

References:

1. Wilson-Jones E. Malignant angioendothelioma of the skin. Br J Dermatol. 1964;76:21-39.
2. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer. 1981;48:1907-21.
3. Holden, CA, Spittle MF, Wilson-Jones E. Angiosarcoma of the face. Prognosis and treatment. Cancer 1987; 59:1046.
4. Frick WG, McDaniel RK. Angiosarcoma of the tongue: report of a case. J Oral Maxillofac Surg. 1988;46:496-8.
5. Lanigan DT, Hey JH, Lee L. Angiosarcoma of the maxilla and maxillary sinus: report of a case and review of the literature. J Oral Maxillofac Surg. 1989;47:747-53.
6. McRae RD, Gatland DJ, McNab Jones RF, Khan S. Malignant transformation in a laryngeal hemangioma. Ann Otol Rhinol Laryngol. 1990;99:562-5.
7. Stewart FW, Treves N. Lymphangiosarcoma in post-mastectomy lymphedema. Cancer 1948;1:64-81.
8. Alessi E, Sala F, Berti E. Angiosarcomas in lymphedematous limbs. Am J Dermatopathol. 1986;8:371-8.
9. Shirger A. Postoperative lymphedema: etiology and diagnostic factors. Med Clin North Am. 1962;46:1045-8.
10. Fitzpatrick PJ. Lymphangiosarcoma and breast cancer. Can J Surg. 1969;12:172-7.
11. Cabo H, Cohen ES, Casas GJ, Allevato M, Woscoff A. Cutaneous angiosarcoma arising on the radiation site of a congenital facial hemangioma. Int J Dermatol. 1998;37:638-9.
12. Goette DK, Detlefs RL. Postirradiation angiosarcoma. J Am Acad Dermatol. 1985;12:922-6.
13. Val-Bernal JF, Figols J, Arce FP, Sanz-Ortiz J. Cardiac epithelioid angiosarcoma presenting as cutaneous metastases. J Cutan Pathol. 2001;28:265-70.
14. Rudd RJ, Fair KP, Patterson JW. Aortic angiosarcoma presenting with cutaneous metastasis: case report and review of the literature. J Am Acad Dermatol. 2000;43:930-3.
15. Marrogi AJ, Hunt SJ, Cruz DJ. Cutaneous epithelioid angiosarcoma. Am J Dermatopathol. 1990;12:350-6.
16. Prescott RJ, Banerjee SS, Eyden BP, Haboubi NY. Cutaneous epithelioid angiosarcoma: a clinicopathological study of four cases. Histopathology. 1994;25:421-9.
17. Requena L, Sangueza 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;38:143-75.
18. Marcon I, Collini P, Casanova M, Meazza C, Ferrari A. Cutaneous angiosarcoma in a patient with xeroderma pigmentosum. Pediatr Hematol Oncol. 2004;21:23-6.

19. Zietz C, Rossle M, Haas C, Sendelhofert A, Hirschmann A, Sturzl M, Lohrs U.MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. Am J Pathol. 1998;153:1425-33.
20. Naka N, Tomita Y, Nakanishi H, Araki N, Hongyo T, Ochi T, Aozasa K. Mutations of p53 tumor-suppressor gene in angiosarcoma. Int J Cancer. 1997;71:952-5.
21. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer. 1996;77:2400-6.
22. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RD, Marsden B, et al. Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol. 1985;3:532-8.
23. Falk H, Thomas LB, Popper H, Ishak KG. Hepatic angiosarcoma associated with androgenic-anabolic steroids. Lancet. 1979;2:1120-3.
24. Hoch-Ligeti C. Angiosarcoma of the liver associated with diethylstilbestrol. JAMA. 1978;240:1510-11
25. Pawlik TM, Paulino AF, McGinn CJ, Baker LH, Cohen DS, Morris JS, Rees R, Sondak VK. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer. 2003;98:1716-26.
26. Aguila LI, Sanchez JL. Angiosarcoma of the face resembling rhinophyma. J Am Acad Dermatol. 2003 Sep;49(3):530-1.
27. Mentzel T, Kutzner H, Wollina U. Cutaneous angiosarcoma of the face: clinicopathologic and immunohistochemical study of a case resembling rosacea clinically. J Am Acad Dermatol. 1998;38:837-40.
28. Orchard GE, Zelger B, Jones EW, Jones RR. An immunocytochemical assessment of 19 cases of cutaneous angiosarcoma. Histopathology. 1996;28:235-40.
29. Hodgkinson DJ, Soule EH, Woods JE. Cutaneous angiosarcoma of the head and neck. Cancer. 1979;44:1106-13.
30. Panje WR, Moran WJ, Bostwick DG, Kitt VV. Angiosarcoma of the head and neck: review of 11 cases. Laryngoscope. 1986;96:1381-4.
31. Morgan MB, Swann M, Somach S, Eng W, Smoller B. Cutaneous angiosarcoma: a case series with prognostic correlation. J Am Acad Dermatol. 2004;50:867-74.
32. Mikhail GR, Kelly AP Jr. Malignant angioendothelioma of the face. J Dermatol Surg Oncol. 1977;3:181-3.
33. Goldberg DJ, Kim YA. Angiosarcoma of the scalp treated with Mohs micrographic surgery. J Dermatol Surg Oncol. 1993;19:156-8.
34. Lydiatt WM, Shaha AR, Shah JP. Angiosarcoma of the head and neck. Am J Surg. 1994;168:451-4.
35. Aust MR, Olsen KD, Lewis JE, Nascimento AG, Meland NB, Foote RL, Suman VJ. Angiosarcomas of the head and neck: clinical and pathologic characteristics. Ann Otol Rhinol Laryngol. 1997;106:943-51.
36. Bong AB, Bonnekoh B, Schon MP, Gollnick H. Treatment of scalp angiosarcoma by controlled perfusion of A. carotis externa with pegylated liposomal doxorubicin and intralesional application of pegylated interferon alfa. J Am Acad Dermatol. 2005;52:20-3
37. Jackel A, Deichmann M, Waldmann V, Bock M, Naher H. Regression of metastatic angiosarcoma of the skin after systemic treatment with liposome-encapsulated doxorubicin and interferon-alpha. Br J Dermatol. 1999;140:1187-8.
38. Eiling S, Lischner S, Busch JO, Rothaupt D, Christophers E, Hauschild A. Complete remission of a radio-resistant cutaneous angiosarcoma of the scalp by systemic treatment with liposomal doxorubicin. Br J Dermatol. 2002;147:150-3.
39. Ulrich L, Krause M, Brachmann A, Franke I, Gollnick H. Successful treatment of angiosarcoma of the scalp by intralesional cytokine therapy and surface irradiation. J Eur Acad Dermatol Venereol. 2000;14:412-5.
40. Fakih MG, Defrances MC, Ohori NP, Ramanathan RK. Unusual tumors involving the head and neck region: case 1. Angiosarcoma of the scalp. J Clin Oncol. 2001;19:4173-4.
41. Fata F, O'Reilly E, Ilson D, Pfister D, Leffel D, Kelsen DP, Schwartz GK,Casper ES. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer. 1999;86:2034-7.
42. Girard C, Johnson WC, Graham JH. Cutaneous angiosarcoma. Cancer. 1970;26:868-83.
43. Morales PH, Lindberg RD, Barkley HT Jr. Soft tissue angiosarcomas. Int J Radiat Oncol Biol Phys. 1981;7:1655-9.
44. 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.

Tumid Lupus Erythematosus: A Case Report and Review of the Literature

Matthew T. Smetanick, D.O.,* Stephen M. Purcell, D.O.**
**Second-year Dermatology Resident, Department of Dermatology, Frankford Hospitals/PCOM, Philadelphia, PA*
***Program director, Dermatology Residency, Department of Dermatology, Frankford Hospitals/PCOM, Philadelphia, PA*

ABSTRACT

The classification and exact identity of tumid lupus erythematosus remains a topic of debate. The clinical and/or histopathologic differential diagnosis may include discoid lupus erythematosus, subacute cutaneous lupus erythematosus, polymorphous light eruption, lymphocytic infiltrate of Jessner, pseudolymphoma, reticulated erythematous mucinosis, and deep gyrate erythema. Herein, we present a case report of tumid lupus erythematosus and review the literature in order to elucidate its main features and provide insight into how to distinguish this entity from the aforementioned conditions.

Case Report

A 53-year-old, white male presented to the office with a three-year history of a persistent, pruritic rash on the upper chest and back (Figure 1), which worsened with sun exposure. Review of systems was otherwise unremarkable. Past medical history included basal cell carcinoma, retinal detachment, and cataract surgery. Family history was remarkable for breast cancer (mother). Physical exam revealed erythematous, edematous, confluent papules and plaques on the chest (V-distribution), shoulders, and upper back (V-distribution). No oral mucosal lesions were observed.

A punch biopsy from the right chest demonstrated a prominent perifollicular, superficial and deep perivascular lymphocytic infiltrate (Figures 2,3). Interstitial mucin was also observed (Figure 4). A second punch biopsy from the upper back also demonstrated a superficial and deep perivascular infiltrate as well as interstitial mucin; however, minimal changes at the dermal-epidermal junction were also noted. Direct immunofluorescence studies from a biopsy of the lower back were negative.

Laboratory studies, including ANA, histone antibody, and Sjögren antibodies, were negative.

The clinical, histopathologic, and serologic findings were all consistent with the diagnosis of tumid lupus erythematosus. The patient refused a trial of hydroxychloroquine as well as other systemic therapies. Treatment, therefore, was limited to topical agents such as pimecrolimus 1% cream and desoximetasone 0.25% cream, which yielded limited improvement of his disease.

Background

The classification and exact identity of tumid lupus erythematosus (TLE) remains a topic of debate. The relatively few published reports suggest that TLE is a distinct subset of chronic cutaneous lupus erythematosus, although several other dermatologic conditions outside the lupus spectrum share similar, often indistinguishable features. Recent studies in the literature have attempted to characterize the specific clinical and histopathologic details of TLE in order to differentiate it from other conditions and classify it as a unique disease entity.

TLE was first reported by Erich Hoffman in 1909 at a meeting of the Berlin Dermatological Society.[1] He described two patients with erythematous, indurated facial lesions with little-to-absent epidermal changes. TLE was later introduced in the literature by Gougerot and Bournier in 1930, who characterized the lesions as erythematous, infiltrated, smooth plaques on the head and neck.[2] They observed that some lesions demonstrated a fine scale. In addition, Gougerot and Bournier noted the spontaneous resolution of the plaques and the tendency for recurrence of these lesions in their original distribution.

Epidemiology

The demographic data in the literature regarding TLE is somewhat conflicting and inconclusive. Goerz et al. observed a slight male predominance.[3] Kuhn et al.[4] also reported a slight male predominance (55%) amongst 40 patients, with a mean age of onset of 36.4 years and a mean duration of disease of 7.8 years. However, in a study of 15 TLE patients, Alexiades-Armenakas et al.[1] reported a slight female predominance (8:7), a mean age of onset of 47 years, and a mean duration of disease of seven years. Choonhakarn et al.[5] and Ruiz et al.[6] also observed a female predominance -- 10 out of 15 patients and four out of four patients, respectively. Hsu et al.[7] assert that most patients with TLE are young women, based on a report of four white patients with ages ranging from 22 to 48 years. As stated, most cases in the literature seem to indicate predominance in Caucasian patients; however, a few reports have described TLE in African-American and Hispanic patients.[1,2]

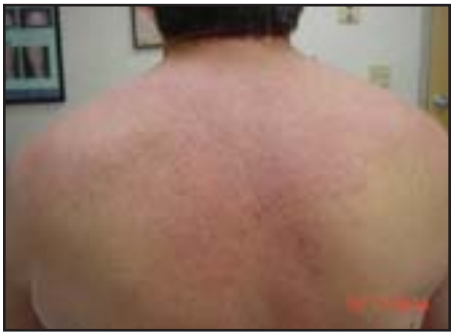


Figure 1
Erythematous, edematous, urticarial-like plaques of tumid lupus erythematosus, in a V-distribution on the back

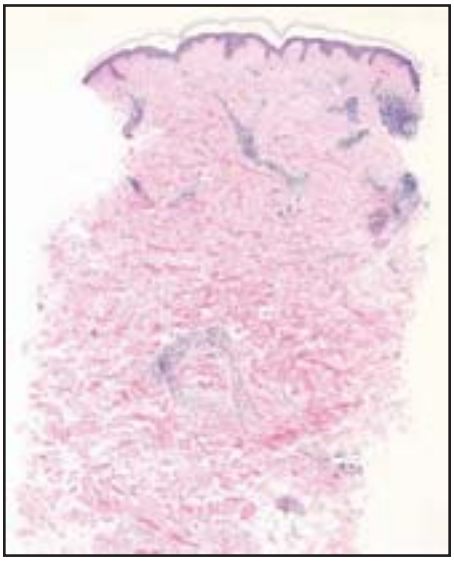


Figure 2
H&E stain (4X), punch biopsy specimen from the chest

Clinical Manifestations

The clinical manifestations of TLE have been described by Kuhn et al.[4] as non-scarring, erythematous, urticarial-like, single-to-multiple plaques with absent surface changes. These lesions have a predilection

Table 1
The differential diagnoses of tumid lupus erythematosus (TLE) and their distinguishing features

Diagnosis	Histopathology	Mucin	DIF	Serology	Antimalarial Tx
TLE	± Epidermal involvement; absent interface changes; CD4>CD8 infiltrate	+	±	± ANA	90% Effective
DLE	Hyperkeratosis; follicular plugging; DE changes	+	+	± ANA ± Ro/La	50% Effective
SCLE	Epidermal thinning; vacuolar degeneration	+	+	± ANA ± Ro/La	80% Effective
PMLE	CD8>CD4 infiltrate	-	-	-	No Improvement
Infiltrate of Jessner	CD8>CD4 infiltrate	-	-	-	No Improvement
Pseudolymphoma	B/T cell infiltrate	-	-	-	No Improvement
REM	CD4 infiltrate	+	±	-	Usually Effective
Deep Gyrate Erythema	Coat-sleeve perivascular infiltrate; focal spongiosis	-	-	-	No Improvement

Adapted from Kuhn et al.[4] an Alexiades-Armenakas et al.d[1]

for sun-exposed surfaces, the face and back being the two most common regions. Other preferred sites include (in decreasing frequency) the arms, V-neck, shoulders, hands, and scalp. No lesions, however, were found to occur below the waist. Provocative phototesting with UVA and/or UVB irritation reproduced lesions in 70% of their patients.

As part of their proposed criteria for classification of TLE, Alexiades-Armenakas et al.[1] reported that 15 out of 15 studied patients manifested papules, plaques, or nodules, absence of surface changes, and absence of scarring. Pink-to-violaceous coloration and a chronic course (>5 months) was observed in 93% of patients. Photodistribution was noted in 86.6% of their patients.

The general consensus in the literature seems to indicate that TLE lacks epidermal changes (i.e. scale); however, Dekle et al.[2] reported three patients with scaly plaques and histopathologic findings consistent with TLE. They subsequently suggest, though, that one may use the possible absence of surface changes to differentiate TLE from papulosquamous diseases such as psoriasis, pityriasis rosea, pityriasis rubra pilaris, and pityriasis lichenoides. Gougerot and Bournier also noted the possible existence of fine scale on lesions of TLE.[2]

Histopathology

The histopathology of TLE generally involves a perivascular and periadnexal lymphocytic infiltrate, prominent interstitial mucin, absence of epidermal changes (such as follicular plugging or atrophy), a lack of interface changes at the dermal-epidermal junction, and occasional neutrophils.[4] However, Alexiades-Armenakas et al.[1] observed focal interface changes at the dermal-follicular junction in two of 15 patients and focal interface changes at the dermal-epidermal junction in three of 15 patients. This perhaps raises the question of whether TLE may be an early manifestation of discoid lupus erythematosus (DLE) or subacute cutaneous lupus erythematosus (SCLE).

Direct immunofluorescence (DIF) findings reported in the literature are equivocal. Kuhn et al.[4] failed to observe significant deposition of IgG, IgM, IgA, C3, or C4 in five out of five patients. In a later study, though, Kuhn et al.[8] performed DIF on both primary and UV-induced skin lesions of 35 TLE patients. Five specimens from primary lesional skin demonstrated deposition of IgG in a band-like pattern, and one patient displayed IgM deposition, also in a band-like pattern. Choonhakarn et al.[5] demonstrated negative DIF results in 15 out of 15 patients. Conversely, Alexiades-Armenakas et al.[1] observed positive DIF findings in five out of 10 patients, demonstrating mostly linear IgG and granular deposits of IgM at the basement membrane zone. Dekle et al.2 also found IgG and C3 (granular pattern) at the basement membrane in one out of four patients.

Alexiades-Armenakas et al.[1] performed immunohistochemical analysis in six patients, verifying a CD3+ (T cell) predominant infiltrate and a CD4+ predominant (>68%) infiltrate. They also observed a CD4:CD8 ratio greater than 2:1 in 83% of patients. These findings were also included in their proposed criteria for the classification of TLE.

Serology

Kuhn et al.[4] measured antinuclear antibody (ANA) titers greater than 1:160 in 10% of patients, Sjögren antibodies (anti-Ro, anti-La) in 5%, and anti-double-stranded DNA antibody (dsDNA) in 3%. They also found decreased C3 levels in 28% and decreased C4 levels in 5% of patients. Alexiades-Armenakas et al.[1] detected ANA titers ranging from 1:40 to 1:160 in 46% of patients and the absence of both dsDNA and Sjögren antibodies. Hsu et al.[7] observed negative ANA, dsDNA, and Sjögren antibodies in all four of their TLE patients.

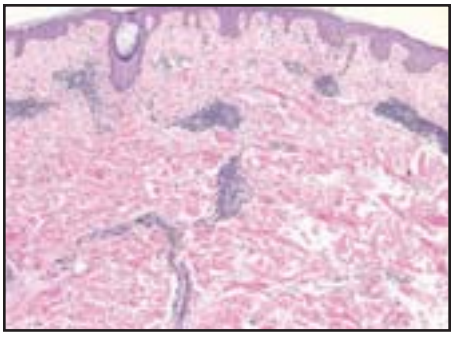


Figure 3
H&E stain (10X), punch biopsy specimen from the chest; perivascular lymphocytic infiltrate apparent

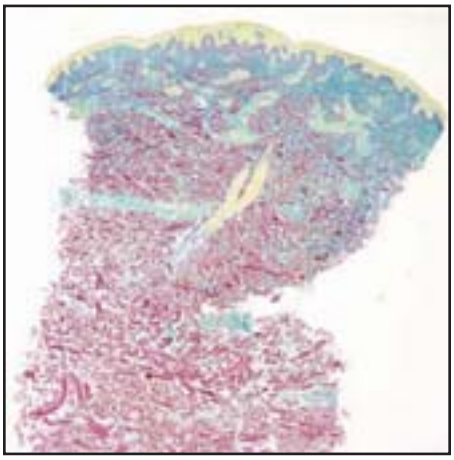


Figure 4
Colloidal iron stain, punch biopsy specimen from the chest; prominent interstitial mucin demonstrated.

Differential Diagnoses

The clinical and/or histopathologic differential diagnosis of TLE may include DLE, SCLE, polymorphous light eruption (PMLE), lymphocytic infiltrate of Jessner, pseudolymphoma, reticulated erythematous mucinosis (REM), and deep gyrate erythema.[1,4,7]

TLE is considered to be more common than the few case reports and studies in the literature seem to indicate.[7] Some believe that TLE has been inadvertently described in the past as lymphocytic infiltrate of Jessner or REM. Dekle et al.[2] have postulated that the Jessner infiltrate and TLE may be the same entity. Ackerman and colleagues consider TLE to be a variant of DLE.[7]

Table 1 demonstrates the main features of the aforementioned differential diagnoses,

which, in general, might be helpful in differentiating them from TLE.

The general lack of interface changes and the typically negative serologic and immunofluorescence findings seem to distinguish TLE from the other entities in the lupus spectrum, although variations or inconsistencies regarding these characteristics have been demonstrated.

DLE typically demonstrates hyperkeratosis, follicular plugging, and subsequent central scarring, whereas SCLE manifests epidermal atrophy and central hyperpigmentation.[4] Lesions of TLE lack scarring, even in those lesions that recur in the same location for many years. DLE and SCLE also demonstrate focal interface changes at the dermal-epidermal junction, unlike the typical histopathologic presentation of TLE.

Kuhn et al.[4] also emphasized the differences in DIF and serologic findings between the forms of cutaneous lupus. DLE demonstrates positive immunoglobulin and complement deposits at the dermal-epidermal junction in 90% of lesional skin, low-titer ANA levels in 30% to 40%, and occasional Sjögren antibodies. SCLE demonstrates positive DIF results in 60% of lesional skin, positive ANA levels in 60% to 81%, anti-Ro antibody in 40% to 100%, and anti-La antibody in 12% to 42%.

PMLE and lymphocytic infiltrate of Jessner are characterized by a lack of mucin, a CD8+ predominant infiltrate, and negative DIF findings. PMLE may be associated with low-titer ANA levels but negative Sjögren antibodies. Provocative phototesting with UVA/UVB produces lesions after several hours in 75% of PMLE patients. However, 70% of TLE patients were found to develop skin lesions several days post-UV exposure. PMLE also is typically characterized by prominent papillary dermal edema and absence of mucin in the reticular dermis. The lymphocytic infiltrate of Jessner is not reproducible through provocative phototesting.

Pseudolymphoma and deep gyrate erythema also differ from TLE based on absence of mucin. As Kuhn et al. emphasized, pseudolymphoma typically demonstrates a top-heavy, wedge-like, lymphocytic infiltrate accompanied by plasma cells and eosinophils. Pseudolymphoma also is not reproducible through photoprovocation.

Interestingly, REM has many similar features to TLE and is considered by some authors to be a variant of DLE or TLE.[4] REM demonstrates a CD4+ T-cell infiltrate, prominent interstitial mucin, and variable DIF findings. Lesions of REM may be induced by sunlight, but results of provocative phototesting are often negative.

Course of Disease

Alexiades-Armenakas et al.[1] observed no evidence of systemic involvement in 14 of 15 TLE patients over a follow-up period ranging from two to 15 years. However, coexisting systemic lupus erythematosus (SLE) was found in one patient at the time of diagnosis. In addition, one patient developed a lesion of DLE on the cheek. Choonhakarn et al.[5] also observed one of 15 patients with concomitant DLE, in addition to two of 15 patients who developed systemic involvement four to six months after diagnosis of TLE. Ruiz et al.[6] found DLE lesions in four of four patients with TLE, three of which also fulfilled the criteria for SLE. These findings would suggest the possibility that TLE is the initial phase in a continuum, preceding DLE (or SCLE), with SLE as a final endpoint. DLE has been reported to demonstrate systemic involvement in 5% to 10% of cases, compared to 50% in SCLE patients (with severe SLE in only 10%).

Contrary to these limited findings, Kuhn et al.[4] reported no systemic involvement in 40 TLE patients after 15 years of follow-up.

Treatment Options

Kuhn et al.[4] observed complete resolution of skin lesions in 45% of those receiving management with only topical corticosteroids or sunscreen (SPF≥15). The remaining 55% of patients were treated with antimalarials, starting with chloroquine phosphate at a daily dose of 3.5 mg/kg to 4.0 mg/kg. Skin lesions resolved in four to six weeks in all but 8% of patients. These remaining patients reportedly cleared with hydroxychloroquine sulfate at a daily dose of 6.0 mg/kg to 6.5 mg/kg.

Alexiades-Armenakas et al.[1] also reported success with hydroxychloroquine (200 mg, twice daily); however, they observed a slower response, with resolution over the course of months compared to weeks as reported by Kuhn et al. Alexiades-Armenakas et al.[1] suggest that a slower response to antimalarials is more consistent with those responses observed in treating the other types of chronic cutaneous lupus erythematosus.

Response to antimalarial therapy may serve as a useful criterion for differentiating TLE from some of the other diseases in the differential. Antimalarials are 90% effective in treating TLE, 50% effective in treating DLE, and 80% effective in treating SCLE, according to Kuhn et al.[4] Antimalarials are also reported to be usually effective for the treatment of REM. However, they fail to improve lesions of PMLE, lymphocytic infiltrate of Jessner, pseudolymphoma, and deep gyrate erythema.

Management of TLE may also involve use of topical or systemic corticosteroids and immunosuppressive agents such as methotrexate, thalidomide, cyclophosphamide, and azathioprine.[9] In addition, patients should be counseled on proper sun avoidance and protection (sunscreens, clothing, and hats).

As evidenced by the variable reports in the literature, the true identity of TLE remains elusive. REM shares many clinical and histopathologic features with TLE but differs slightly in its response to photoprovocative testing. The reports of concomitant DLE and SLE in patients with lesions of TLE, although limited, would suggest that TLE is more likely to be part of the spectrum of chronic cutaneous lupus erythematosus. This concept is also supported by the occasional findings of focal interface changes, positive DIF, and positive serologies, although Kuhn et al. contend that these characteristics of TLE should be absent. Only larger case studies and reports will possibly elucidate the true nature of TLE and reveal whether it is a disease outside the lupus spectrum (such as REM), a variant of DLE, or its own distinct entity amongst the subtypes of chronic cutaneous lupus erythematosus.

References:

1. Alexiades-Armenakas MR et al. Tumid lupus erythematosus: Criteria for classification with immunohistochemical analysis. Arthritis Rheum 2003; 49:494-500.
2. Dekle CL et al. Lupus tumidus. J Am Acad Dermatol 1999; 41:250-3.
3. Goerz G et al. Lupus erythematodes (LE). Z Hautkr 1990; 65:226-34.
4. Kuhn A et al. Lupus erythematosus tumidus. A neglected subset of cutaneous lupus erythematosus: Report of 40 cases. Arch Dermatol 2000; 136:1033-41.
5. Choonhakarn C. et al. Lupus erythematosus tumidus. Int J Dermatol 2004; 43:815-18.
6. Ruiz H, Sanchez J. Tumid lupus erythematosus. Am J Dermatopathol 1999; 21:356-60.
7. Hsu S et al. Tumid lupus erythematosus. Cutis 2002; 69:227-30.
8. Kuhn A et al. Histopathologic findings in lupus erythematosus tumidus: Review of 80 patients. J Am Acad Dermatol 2003; 48:901-908.
9. Werth V. Current treatment of cutaneous lupus erythematosus. Dermatology Online Journal 2001; 7(1):2

Impressive results.
Less irritation.

Whether used alone[1,2] or with a retinoid,[3] Duac® Topical Gel provides proven efficacy with superior tolerability.

For topical BPO/antibiotic acne therapy,

Your Choice is Clear™

once-a-day Duac® topical gel

(clindamycin, 1% - benzoyl peroxide, 5%)

Make the Clear Choice™

IMPORTANT SAFETY INFORMATION
Duac Topical Gel is indicated for the topical treatment of inflammatory acne. Duac Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops.

Please see accompanying Brief Summary of Prescribing Information.

STIEFEL®
Research in Dermatology™
www.stiefel.com

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Duac® Topical Gel
(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.
Not for Ophthalmic Use.

Rx Only

INDICATIONS AND USAGE
Duac Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Duac Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS
Duac Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or 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 *Clostridium 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 *Clostridium difficile* colitis.

PRECAUTIONS
General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients: Patients using Duac Topical Gel should receive the following information and instructions:

1. Duac Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.
4. Patients should report any signs of local adverse reactions to their physician.
5. Duac Topical Gel may bleach hair or colored fabric.
6. Duac Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.
7. Before applying Duac Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.
8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with Duac Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with Duac Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Duac Topical Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with Duac Topical Gel or benzoyl peroxide. It is also not known whether Duac Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Duac Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether Duac Topical Gel is secreted into human milk after topical application. 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 this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS
During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

Local reactions with use of Duac Topical Gel
% of patients using Duac Topical Gel with symptom present
Combined results from 5 studies (n = 397)

	Before Treatment (Baseline)			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

(Percentages derived by # subjects with symptom score/# enrolled Duac subjects, n = 397).

HOW SUPPLIED
Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.

Dispensing Instructions for the Pharmacist: Dispense Duac Topical Gel with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."

Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent Nos. 5,466,446, 5,446,028, 5,767,098, and 6,013,637
Patent Pending

STIEFEL®

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

833185 Rev. 0504

REFERENCES: 1. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *Am Acad Derm.* 1997;37:590-595. **2.** Tanghetti EA, Gold MH. A Two-center patient preference study comparing two benzoyl peroxide/clindamycin gels in acne vulgaris patients. Presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA. Poster 108. **3.** Tanghetti EA, Abramovits W, Solomon B. et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel group trial. Presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA. Poster 147.

Multiple Keratoacanthomas Treated with Acitretin: A Case Report and Review of the Literature

Andrea Passalacqua, D.O. ,* Ronald Liskanich, D.O. , David C. Horowitz, D.O. *****

1st year Resident, Western University/Pacific Hospital of Long Beach, Long Beach, CA

****Dermatology Residency Co-Program Director at Western University/Pacific Hospital of Long Beach, Long Beach, CA***

*****Dermatology Residency Program Director at Western University/Pacific Hospital of Long Beach, Long Beach, CA***

ABSTRACT

An 85-year-old woman with an eruption of multiple keratoacanthomas (KAs) on her lower extremities was successfully treated with acitretin. The treatment resulted in clearing 9 out of 10 keratoacanthomas and has prevented new lesions from developing. We review the clinical and histologic features of the various subtypes of keratoacanthomas and various treatment options.

Case Report

An 85-year-old Caucasian female developed over one month an eruption of hyperkeratotic erythematous nodules on her lower extremities. Patient denied pain, pruritus, bleeding, and any recent trauma to her lower extremities. Past medical history included the development of squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and other solitary keratoacanthomas starting in her early eighties, in addition to gastric lymphoma, breast cancer, esophageal strictures, depression, and hypertension. Patient had no significant family history of skin disease.

On physical exam, the patient was found to have 10 scattered hyperkeratotic erythematous nodules with a central core ranging in size from 0.5 mm to 1 cm on her lower extremities (Figure 1).

A skin biopsy showed an exo-endophytic lesion with crateriform architecture and overhanging buttresses, an epithelial proliferation consisting of uniform cells with abundant pale-staining cytoplasm, many horn pearls resulting from premature cornification, and intraepithelial micro-abscesses.

Complete blood count, basic metabolic panel, and liver function tests were all within normal limits. Her cholesterol and triglyceride levels were noted to be slightly elevated.

Histologically, our clinical impression of multiple keratoacanthomas was confirmed. Because of the multiplicity of lesions and their location on the lower extremities, which can be slower areas to heal in an elderly patient, we decided on a trial of acitretin 25mg daily. Acitretin was then administered for a total of three and a half months. During that time, 9 out of the 10 completely cleared (Figure 2). The remaining lesion was biopsied, and again the histology confirmed the diagnosis of keratoacanthoma.

Discussion

Keratoacanthoma is a relatively common squamous neoplasm that often develops on sun-exposed skin of both sexes equally and peaks during the fifth to seventh decade of life. These lesions are characterized by rapid growth within a few weeks, histologic features similar to squamous cell carcinoma, and a tendency to spontaneously regress.[1] Controversy has surrounded the relationship of keratoacanthomas to SCC.[2] Many have viewed keratoacanthomas as a benign entity; however, now it is often considered a low-grade malignancy that is a variant of squamous cell carcinoma.[3-4]

The exact etiology is uncertain, but it has been postulated that different factors are involved in the development of keratoacanthomas. Exposure to UV light is a well-documented contributing factor, since KAs often appear on the sun-exposed regions of fair-skinned individuals.[1] Other factors include chemical carcinogens, genetic predisposition, infectious etiology, immunosuppression, dysregulation of suppressor gene p53 and trauma.[4-5]

Clinically, keratoacanthomas present as domed-shaped, erythematous or flesh-toned papules up to 2 cm with central keratotic cores. A solitary lesion is the most common presentation, but multiple lesions may occur. Variants of multiple keratoacanthoma include generalized eruptive keratoacanthomas of Grzybowski, multiple keratoacanthomas of Ferguson-Smith type, and multiple eruptive keratoacanthomas of Witten and Zak.[6] Multiple KAs have also been noted to be associated with Muir-Torre syndrome.1 This patient's presentation, however, was not consistent with these three variants.

Generalized eruptive keratoacanthoma of Grzybowski is a rare condition. Less than 31 cases have been reported since the first description by Grzybowski in 1950. Males and females are affected equally in their fifth to seventh decade of life.[7] It is characterized by the eruption of thousands of follicular, keratotic, pruritic papules all over the body with a predilection for sun-exposed areas. If facial involvement occurs, it is usually severe, and coalesced lesions around the eye may cause ectropion.[8]

Multiple keratoacanthoma of the Ferguson-Smith type is a rare, autosomal-dominant disorder that affects both males and females equally during adolescence and early adulthood. It is characterized by hundreds of KAs in sun-exposed areas that typically regress over weeks to months, but rare examples of metastases have been reported.[9]

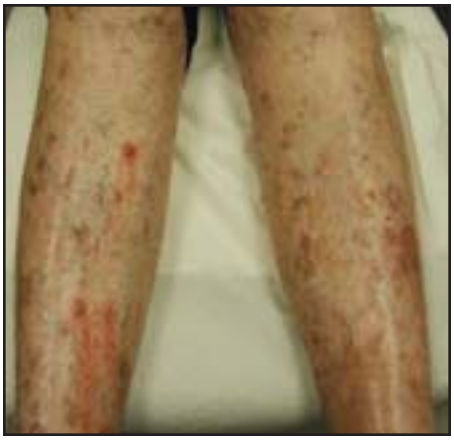


Figure 1

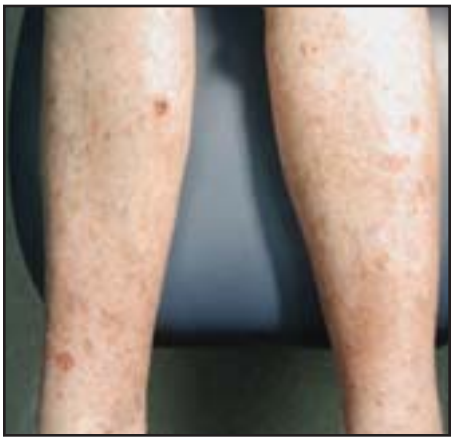


Figure 2

Multiple eruptive keratoacanthoma of Witten and Zak is a rare disorder characterized by numerous large and miliary-type lesions. Affected patients have features of Grzybowski-type and Ferguson-Smith type keratoacanthomas.[10]

Histologically, a keratoacanthoma is characterized by a large central core of keratin surrounded by well-differentiated prolifera-

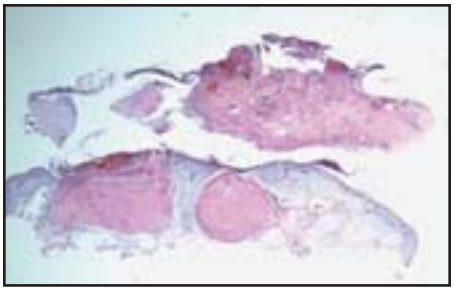


Figure 3

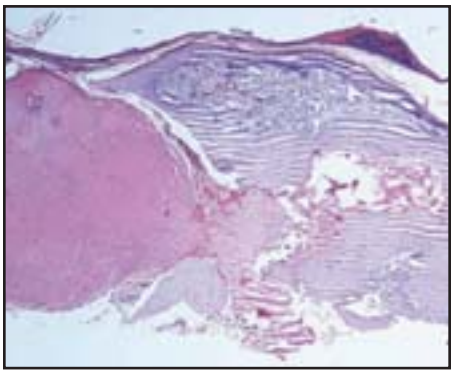


Figure 4

tion of squamous epithelium. A distinct crateriform appearance is achieved by epithelial lipping over the central core[9] (Figure 3). There are many horn pearls resulting from premature cornification, and intraepithelial microabscesses may be present. Proliferating at the base are aggregates of atypical keratinocytes with a glassy appearance and mitoses into the dermis.[1,6]

Treatment of solitary keratoacanthomas is primarily surgical excision. Alternatives include Moh's micrographic surgery, curettage and electrodesiccation, and cryotherapy with liquid nitrogen. Medical treatment options can be reserved for individuals with multiple keratoacanthomas, lesions not ideal for surgery because of size or location, and poor surgical candidates. [4,7]

Systemic retinoids, such as isotretinoin and acitretin, are an alternative approach in patients with multiple KAs. By decreasing sebaceous-gland size and sebum production, they provide efficacious treatment of KAs; however, as in the case we presented, the KAs may not completely clear. Systemic retinoids may also inhibit sebaceous differentiation and abnormal keratinization.[4] They have been shown to aid in the involution of keratoacanthomas.[11-13] Scarring and recurrences can often occur.[7]

Other treatment options that have been successful include intralesional and topical 5-fluorouracil, intralesional glucocorticoids, topical imiquimod, intralesional methotrexate, and intralesional bleomycin. Keratoacanthomas respond well to low doses of radiation, which may be useful in patients with large tumors, recurrent tumors following excision, and poor medical condition. When other approaches fail, then surgical removal is the only option.[4] It is important to remind patients to avoid exposure to UV light since keratoacanthomas have a predilection to erupt on sun-exposed areas.

References:

1. Cerroni L., Helmut K. Keratoacanthoma. In Freedberg IM et al editors. Fitzpatrick's Dermatology in General Medicine 6th edition. New York. McGraw-Hill; 2003. pp. 760-766.
2. Chu D, Hale EK, Robbins P. Generalized eruptive keratoacanthoma of Grzybowski- case reports. J Drugs Dermatol 2003;2: pp. 318-319.
3. Leonard A, Hanke W. Treatment of giant keratoacanthoma with intralesional 5-fluorouracil. J Drugs Dermatol 2006;5:454-456.
4. Chuang T, Brashear R. Keratoacanthoma. eMedicine: http://www.emedicine.com/derm/topic206.htm, Accessed May 16, 2006.
5. Pattee SF, Silvis NG. Keratoacanthoma developing in sites of previous trauma: a report of two cases and review of literature. J Am Acad Dermatol 2003;48(suppl):S35-S38.
6. Dessoukey MW, Omar MF, Abdel-Dayem H. Eruptive keratoacanthomas associated with immunosuppressive therapy in a patient with systemic lupus erythematous. J Am Acad Dermatol 1997;37;478-480.
7. Wee SA. Multiple eruptive keratoacanthomas, de novo. Dermatology Online Journal 10(3):19.
8. Chu DH, Hale EK, Robins P. Generalized eruptive keratoacanthomas. Dermatology Online Journal 9(4);36.
9. Bolognia JL, et al. Keratoacanthoma. Dermatology 1st edition. London. Mosby; 2003. pp.1680.
10. Street ML, White JW, Gibson LE. Multiple keratoacanthomas treated with oral retinoids. J Am Acad Dermaol 1990;23(5 Pt 1):862-866.
11. Kossard S, Thompson C, Duncan GM. Hypertrophic lichen planus-like reactions combined with infundibulcystic hyperplasia. Arch Dermatol 2004;140:1262-1267.
12. Farro P, et al. Unusual association between acrokeratosis verruciformis of Hopf and multiple keratoacanthomas. Successful therapy with acitretin. J Dtsch Dermatol Ges 2004;2:440-442.
13. Levine N, Miller RC, Meyskens FL. Oral isotretinoin therapy. Use in patient with multiple cutaneous squamous cell carcinomas and keratoacanthomas. Arch Dermatol 1984;120:1215-1217.

Acquired Bullous Diseases of Childhood

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

Linear IgA dermatosis is NOT synonymous with acquired bullous diseases of childhood. It is synonymous with the specific disease: chronic bullous disease of childhood. We present a case of a ten year old boy who presented to our clinic with a subepidermal blistering disease who on immunofluorescence studies failed to demonstrate positive antibodies. He was managed as if his process was autoimmune and subsequently showed dramatic improvement with therapy. The differential diagnosis included chronic bullous disease of childhood (CBDC), bullous pemphigoid (BP), and epidermolysis bullosa acquisita (EBA) which are reviewed in detail.

Introduction

Acquired immunobullous diseases are rare in childhood, but the one most commonly seen is chronic bullous disease of childhood (CBDC)[1,2,3,4] , followed by bullous pemphigoid (BP) and epidermolysis bullosa acquisita (EBA), which are much more rare. Their immunohistopathological features are identical to those seen in adults.[5,6,7] Clinically, these diseases are often indistinguishable, and histologically, they each demonstrate subepidermal blistering. In addition, immunopathological studies can show considerable overlap, necessitating the use of immunoblot (IB) and immunoprecipitation studies, direct and indirect immunoelectron microscopy, and Western blot analysis.[3,8-11]

We present a case of a preadolescent boy with clinical and histological features of an acquired immunobullous disease who, despite showing negative immunofluorescence studies, responded dramatically to systemic steroids and antibiotics. Our observations in this case support the claim that bullous disorders in childhood seem to be associated with a very good prognosis when compared to bullous disorders occurring in adults.

Case Report

A 10 year old black male presented to our clinic with his mother complaining of painful blisters that started on his legs but were now spreading all over his body, including his mouth. He had presented to the emergency department one week prior and was given oral clindamycin with the presumptive diagnosis of bullous impetigo. According to his mother, he had been getting these blistering episodes roughly three times per year over the last five years, but the episodes were now becoming more generalized and resistant to antibiotic therapy such as amoxicillin and clarithromycin. There was no family history of blistering disorders, and there was no personal history of recent trauma, fever, malaise, arthralgia, medication use, vaccinations, or gastrointestinal disturbances. In addition, the lesions had never been cultured or biopsied. He was otherwise in good health and was not on any other chronic medications.

On physical examination, he was afebrile, overweight and tall for his stated age, and he did not appear to be in any apparent distress. There were multiple tense vesicles and bullae, some on inflamed bases, clustered along his arms, legs, and ankles (Fig 1, 2). The lesions ranged in size from 0.3 to 2.5cm in diameter. Most of the blisters were filled with clear fluid and a few of them appeared to be hemorrhagic. The Nikolsky and Absoe-Hansen signs were negative giving us further evidence that the pathologic process was occurring at the least, at the level of the dermo-epidermal junction (DEJ). Upon examination of his mouth, we found a single erosion on the surface of his buccal mucosa (Fig 3). There were no urticarial papules or plaques noted, nor were there any hyperpigmented macules or patches.

We performed two 4mm punch biopsies on his lower leg. The first biopsy was of an intact vesicle that was sent for hematoxyllin and eosin (H&E) staining and the second was of perilesional skin that was sent to the New York University immunofluorescence lab for direct immunofluorescence (DIF) studies. He was instructed to finish the course of oral clindamycin.

At one week follow up, he completed his course of antibiotics but he complained of new blisters occurring on his back, arms, and legs. On physical examination, there were several urticarial plaques with central vesiculation scattered over his back and flank (Fig 4, 5). There were also new bullae on his arms and legs. The erosion in his mouth had resolved completely and there were no other new lesions. Histopathological studies revealed a subepidermal blister with an inflammatory infiltrate composed primarily of mononuclear cells and eosinophils (Fig 6).

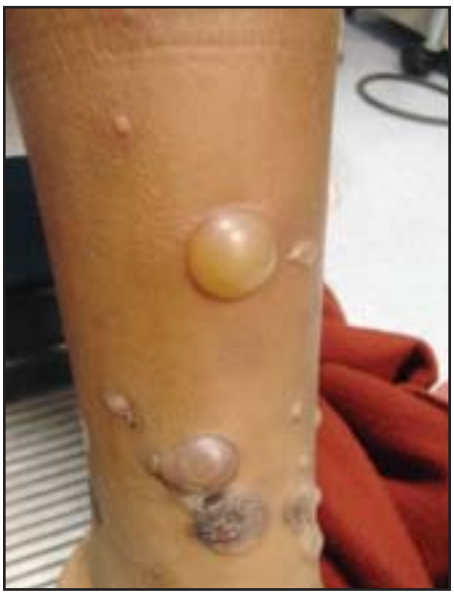


Figure 1
Tense blisters on the lower leg

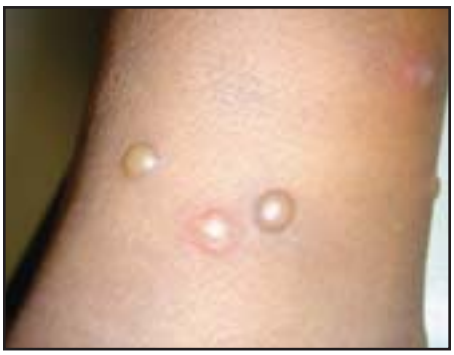


Figure 2
Tense blisters on inflamed and non-inflamed bases

There were only a few neutrophils present and there was no evidence of epidermal necrolysis (Fig 7). Histological studies and culture of blister fluid failed to reveal pathogenic bacteria, fungi, or viral organisms. Direct immunofluorescence studies were negative for deposits of IgG, IgA, IgM, C3,

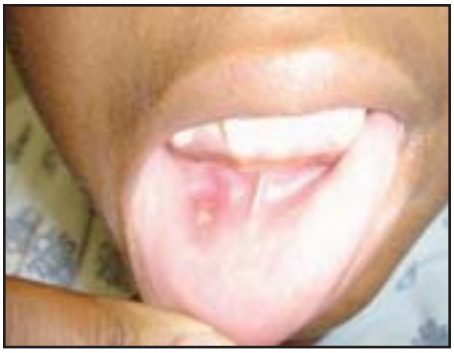


Figure 3
Erosion on the buccal mucosa of the mouth

Figure 4
Urticarial papules on the back and flank

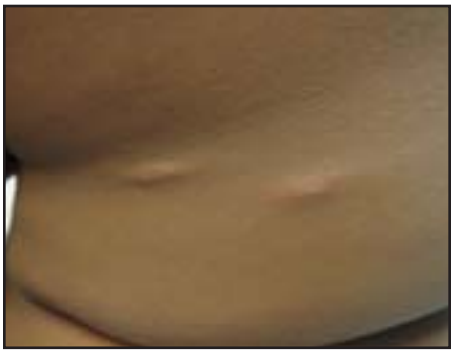


Figure 5
Urticarial plaques with central vesiculation

or fibrin along the epidermis, basement membrane zone (BMZ), and blood vessels. At this point, neither BP nor IgA bullous disease could be ruled out and a repeat perilesional biopsy was suggested. Laboratory studies revealed a normal white count, hematocrit, platelet, eosinophil count, liver and kidney functions, G6PD level, and a negative anti-nuclear antibody (ANA). His mother had refused a repeat biopsy and he was

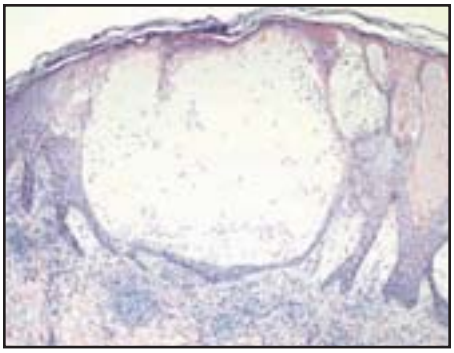


Figure 6
Subepidermal blister with a dense mixed infiltrate on H&E

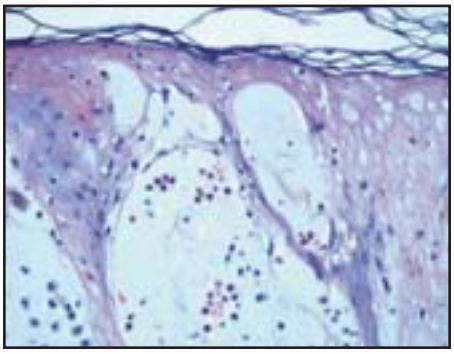


Figure 7
Infiltrate composed mainly of eosinophils and few neutrophils

started on oral prednisone 0.5mg/kg/d and oral erythromycin 1g/d and was instructed to follow up in a week.

At follow up, he stopped getting new lesions and the old lesions were beginning to resolve (Fig 8). The prednisone was stopped without taper and the erythromycin dose was decreased to 750mg/d. At seven weeks post presentation, the blisters had completely resolved and he was placed on an erythromycin taper. At seven months post presentation, he continues to be lesion-free and in remission.

Discussion

The differential diagnosis for acquired subepidermal blistering diseases occurring in childhood where immunopathological features are present includes CBDC, BP, EBA, bullous systemic lupus erythematosus (BSLE), dermatitis herpetiformis (DH), cicatricial pemphigoid (CP), and erythema multiforme (EM) (Table 1). Subepidermal blistering diseases that characteristically do not present with immunopathological features include bullous urticaria pigmentosa (BUP) and toxic epidermal necrolysis (TEN) (Table 2). We will discuss CBDC, BP and EBA since they represent our differential for this case presentation, and because oftentimes, they exhibit identical and overlapping clinical, histological, and immunopathological features which can make arriving at an

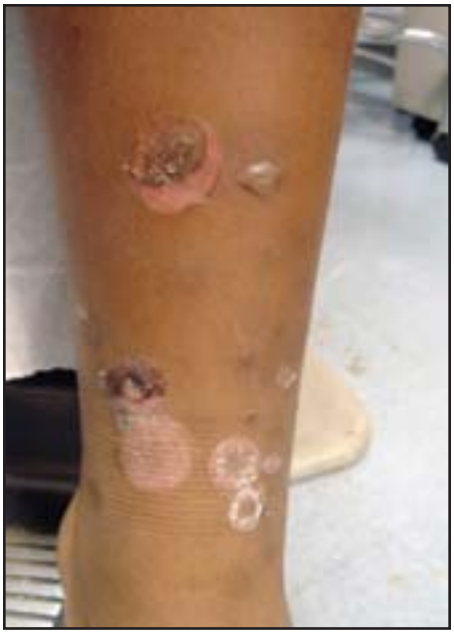


Figure 8
Resolving blisters after 1 week of systemic prednisone and erythromycin therapy

accurate diagnosis extremely challenging. In addition, based on our clinical findings, we believe that our patient's pathologic process is immunologically mediated despite the negative immunofluorescence studies since these may have represented false-negative results which has been found to occur in up to one-third of biopsy specimens taken from the lower leg.[12,13]

Chronic bullous disease of childhood

Chronic bullous disease of childhood is the most common subepidermal autoimmune blistering disease seen in childhood[1,2,3,4] occurring typically between the third and fifth year of life.[14] Clinical findings include vesiculobullous eruptions arranged in annular or polycyclic patterns that are characteristically located on the trunk, neck, face, scalp, flexural, and periorificial areas.[4,9,15] Involvement of the mucous membranes has been reported in up to 91% of cases, affecting mainly the oral, ocular, nasal, and genital areas.[8,14] Histopathological examination reveals a subepidermal blister with neutrophils characteristically being the predominant inflammatory cell[3], although authors have reported that eosinophils may also predominate.[8] The inflammatory cells often line the DEJ and can accumulate at the papillary tips.[4,15]

Direct immunofluorescence studies show deposition of linear IgA in 50-70% of cases, and less often C3 and IgM[8,9,14], along the cutaneous BMZ. [16,17] Indirect immunofluorescence (IIF) studies demonstrate the same linear deposits of circulating anti-BMZ antibodies in 40-70% of children.[8,9,14] Indirect immunofluorescence studies using salt-split

skin (SSS) typically show IgA antibodies localizing to the epidermal side of the blister. With the use of Western blot analysis, it has been shown that IgA autoantibodies recognize most frequently both a 97kDa protein[3,18] and a 285kDa protein.[3,19] Only one autoantibody isotype is usually found in each patient, and with CBDC, it is usually IgA, compared to BP, EBA, and CP, where the isotype is characteristically IgG.[2]

Many reports in the literature have shown overlapping immunopathological findings between CBDC and BP of childhood[2,20-23]. In a study by Powell et al[2], they looked at eight children who fit the diagnosis for CBDC but had both linear IgG in addition to linear IgA demonstrated on IIF and /or DIF. They also found that in six of their cases of well-defined BP, half of these demonstrated a circulating antiepidermal BMZ IgA autoantibody which bound to the BP antigens, BP180 and BP230, and to a 270-280kDa epidermal protein. Immunoblotting analysis in these same patients also showed IgA targeting the 97kDa antigen and IgG targeting laminin 5 in one patient. In addition, Arechalde et al[20] reported three cases of children with clinical and immunopathological features characteristic of CBDC that showed via IB studies, IgA antibodies targeting BP180 or BP230. Several other studies in the literature have reported similar findings.[21-23] The presence of these overlapping features that have been noted in both BP and CBDC makes it difficult to pinpoint one target antigen underlying each disorder. Some have proposed that if there is in fact, only one target antigen involved, it may be that it is heterogeneous and occupying sites in both the lamina lucida and lamina densa.[2]

There has been some evidence suggesting antigenic cross-reactivity between BP180 and the CBDC 97kDa antigen[2], and some studies indicate that the CBDC antigen corresponds to a portion of the extracellular domain of BP180. [20,24] The CBDC 97kDa antigen is an anchoring filament-associated protein that has been thought to be a molecular marker for CBDC[18,25]. If these findings are confirmed, they may provide an explanation for the overlap between BP and CBDC.

The standard treatment for CBDC is dapsone[8,26] at 2mg/kg/d.[27] Corticosteroids may sometimes be necessary and are given at a dosage of 0.5-2.0mg/kg/d[14]. There have been reports of good response to sulphonamides[2], erythromycin[2], colchicine[28], dicloxacillin[29], and 'oxacilline'[30]. Remission is usually induced after six to twelve months of therapy[15] and relapses are uncommon.[8,9,14] The disease typically remits by age 6-8 years and the majority of cases resolve by adolescence.[4,15]

Childhood bullous pemphigoid

Bullous pemphigoid is an acquired immunobullous disease that usually affects the elderly and occurs only rarely in childhood.[31] It was first described as a clinical and histopathologic entity distinct from pemphigus vulgaris by Lever in 1953[32], and in 1970, the first case of immunofluorescence-proven BP was described.[33]

The childhood form of BP is similar to the adult variant with characteristic clinical, histopathologic, and immunopathologic features.[31] It has been reported to occur in children between the ages of two months and 16 years[34,35] and nearly 25% of these cases occurred in children less than one year old.[31,36]

There are some clinical findings that distinguish the childhood form from the adult form. Like the adult form, childhood BP begins as urticarial irregularly bordered plaques that become tense, non-grouped, and variably sized bullae that arise on both erythematous and clinically unaffected skin.[31] Sites of predilection include the inner thighs, flexural surfaces of the forearms, axillae, lower abdomen, groin, and palmar and plantar surfaces. Mucous membrane involvement is a frequent finding in childhood BP [31] and it is more commonly seen in the childhood form compared to the adult variant.[32] Also, there is often marked involvement of acral sites such as the palms and soles, which is a hallmark clinical presentation in the pediatric age group.[31] In addition, facial involvement has also been reported to be more common in childhood BP.[32]

The histopathological findings include a subepidermal bulla with an inflammatory infiltrate characteristically composed of eosinophils. Practically all patients demonstrate linear deposition of IgG at the BMZ of perilesional skin on DIF studies and C3 deposition is found in virtually all BP skin lesions.[31] IgA, IgM, and IgE may also be found but this occurs less frequently.[31] Indirect immunofluorescence studies show circulating IgG antibodies against the BMZ in 70-80% of patients[31,37,38] but in contrast to pemphigus, this titer does not reflect disease activity.[31,39,40] In IIF studies utilizing SSS, IgG autoantibodies are typically found on the epidermal side of cleavage and this is seen in 71% of cases.[1] These autoantibodies may also be present on both sides of the split and this occurs in 17% of cases.[1] Much less commonly, these autoantibodies can also occur on the dermal side alone.[1]

Immunoblot studies have demonstrated BP180 and BP230 to be the target antigens involved in BP which are molecules of the hemidesmosome and lamina lucida. [41] Although these are the autoantigens classically associated with BP, the target antigens seen in both BP and CBDC can overlap considerably as mentioned previously.

Bullous systemic lupus erythematosus and EBA are other subepidermal blistering diseases that may also mimic BP. Similar to EBA, scarring and milia formation has been reported in cases of IIF-positive cases of BP.[31] EBA may be differentiated from BP by IIF studies performed on SSS which characteristically reveal antibodies found only on the dermal side of cleavage in cases of EBA.[31] On DIF, while both BSLE and BP demonstrate linear deposition of IgG and C3 at the DEJ[31], BSLE may be differentiated from BP by immunoelectron microscopy[31] and by the presence of a positive ANA.

A cause for BP is often searched for but presently, there are no associated neoplasms or consistently reported classes of drugs that have shown to trigger BP.[31]

The mainstay of treatment is corticosteroid therapy. There have been reports of mild and localized disease responding adequately to topical steroids alone.[42] For moderate disease, the initial treatment of choice is prednisone at a dose of 1-2mg/kg/d which usually rapidly clears preexisting lesions and halts the formation of new ones.[31] Dapsone alone has been shown to be effective in some cases.[43] In severe cases, the addition of dapsone or sulfapyridine as adjunctive therapy may be beneficial[31,44-47] especially in cases with a predominance of neutrophils.[31] Erythromycin used as an adjunct for its antichemotactic effects on neutrophils, has also been reported to result in good outcomes.[31] Other options include nicotinamide, azathioprine, and other immunomodulatory therapy for resistant cases.[42,48] With treatment, BP often follows a benign course and the disease duration is typically one year or less.[1,31]

Childhood epidermolysis bullosa acquisita

Childhood EBA, like the adult form, is an acquired autoimmune chronic bullous disease which is characterized by the presence of IgG autoantibodies reacting with type VII collagen of the anchoring fibrils beneath the epidermal BMZ.[49] The same pattern is seen in IIF studies in 50% of cases.[15] The incidence of childhood EBA is ten times less frequent than childhood BP[10,50] making it an extremely rare disease.[50-53]

There are two main phenotypes; the first is the classic non-inflammatory mechanobullous type that presents with marked skin fragility, blisters and erosions at sites of trauma, and healing with scarring and milia formation.[52] Mucosal involvement may be present in half of cases[54] and it may be severe and resemble CP.[51] The inflammatory type is oftentimes clinically indistinguishable from CBDC and BP.[52] This difficulty in differentiating the inflammatory type from BP and CBDC may signify that EBA may not be as rare as once thought.

As with the other blistering diseases, the laboratory findings may vary and overlap with other diseases. Histopathological findings reveal a subepidermal blister with a cell-poor or cell-rich infiltrate typically of neutrophils but occasionally composed of

eosinophils. The EBA antigen is collagen VII, a 290 kDa molecule which is the main component of anchoring fibrils in the sublamina densa zone.[49,55] This autoantigen is also seen in BSLE but a positive ANA is often helpful in differentiating the two. Indirect immunofluorescence studies on salt-split skin showed binding of the IgG autoantibody exclusively to the dermal side of cleavage.[52] More recently, IB studies confirming the diagnosis of EBA adds to the belief that EBA may be more common in children than is generally appreciated[9] and this has been suggested previously by other authors.[6,50,56]

Therapeutic options for EBA include prednisone and dapsone.[57] There are documented reports of good responses and disease remission within months of starting systemic therapy.[10] The long term prognosis is good in childhood[9,10] with an average disease duration of three years.[9]

Conclusion

Acquired bullous diseases of childhood often have overlapping features that contribute to the diagnostic dilemma that is frequently encountered. While they may present with severe and debilitating lesions, the overall prognosis and outcome is generally favorable. Treatment strategies include corticosteroids, antibiotics, and dapsone and investigations for disease and/or drug associations is generally unnecessary.

References:

1. Voltan A, Maeda JY, Silva MA, et al. Childhood bullous pemphigoid- report of three cases. J Dermatol 2005; 32:387-92.
2. Powell J, Kirtschig G, Allen J, et al. Mixed immunobullous disease of childhood: a good response to antimicrobials. Br J Dermatol 2001; 144:769-74.
3. Trueb RM, Didierjean L, Fellas A, et al. Childhood bullous pemphigoid: report of a case with characterization of the targeted antigens. J Am Acad Dermatol 1999; 40:338-44.
4. Thappa DM, Jeevankumar B. Chronic bullous dermatosis of childhood. Postgrad Med J 2003; 79:437.
5. Bean SF. Childhood bullous pemphigoid. Clin Dermatol 1987; 5:13-17.
6. Rubenstein R, Esterly NB, Fine JD. Childhood epidermolysis bullosa acquisita. Arch Dermatol 1987; 123:772-6.
7. Oranje AP, van Joost T. Pemphigoid in children. Pediatr Dermatol 1989; 6:267-74.
8. Wojnarowska F, Marsden RA, Bhogal B, et al. Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults. A comparative study demonstrating clinical and immunological overlap. J Am Acad Dermatol 1988; 19:792-805.
9. Kirtschig G, Wojnarowska F, Marsden RA, et al. Acquired bullous diseases of childhood: re-evaluation of diagnosis by indirect immunofluorescence examination on 1 M NaCl split skin and Immunoblotting. Br J Dermatol 1994; 130:610-16.
10. Edwards A, Wakelin SH, Wojnarowska F, et al. Bullous pemphigoid and epidermolysis bullosa acquisita: presentation, prognosis, and immunopathology in 11 children. Pediatr Dermatol 1998; 15:184-90.
11. Nagano T, Masahiro T, Adachi A, et al. Childhood bullous pemphigoid: immunohistochemical, immunoelectron microscopic, and Western blot analysis. J Am Acad Dermatol 1994; 30:884-8.
12. Koch CA, Mazzaferri EL, Larry JA, et al. Bullous pemphigoid after treatment with furosemide. Cutis 1996; 58:340-4.
13. Weigand DA. Effect of anatomic region on immunofluorescence diagnosis of bullous pemphigoid. J Am Acad Dermatol 1985; 12:274-8.
14. Braun-Falco O, Plewig G, Wolff HH, et al. Blistering Diseases. In: Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC, eds. Dermatology. Second, completely revised edition. Berlin: Springer, 2000:649-95.
15. Marinovic B and Jukic IL. Autoimmune blistering skin diseases in childhood. Acta Dermatovenerol Croat 2002; 10:33-7.
16. Chozelski TP, Jablonska S, Beutner EH, et al. Linear IgA bullous dermatosis. In: Immunopathology and the skin (Beutner EH, Chorzelski TP, Bean SF, eds). New York: John Wiley & Sons, 1979: 315-23.
17. Jablonska S and Chorzelsky T. Dermatose a IgA lineaire. Ann Dermatol Venereol 1979; 106:651-5.
18. Zone JJ, Taylor TB, Kadunce DP, et al. Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunoglobulin A bullous dermatitis. J Clin Invest 1990; 85:812-20.
19. Wojnarowska F, Whitehead P, Leigh IM, et al. Identification of the target antigen in chronic bullous disease of childhood and linear IgA disease of adults. Br J Dermatol 1991; 124:157-62.
20. Arechalde A, Braun RP, Calza AM, et al. Childhood bullous pemphigoid associated with IgA antibodies against BP180 or BP230 antigens. Br J Dermatol 1999; 140:112-118.
21. Kanitakis J, Mauduit G, Cozzani E, et al. Llinear IgA bullous dermatosis of childhood with autoantibodies to a 230kDa epidermal antigen. Pediatr Dermatol 1994; 11:139-44.
22. Berard F, Kanitakis J, DiMaio M, et al. Dermatose bulleuse a IgA lineaire de l'enfant avec autoanticorps diriges contre l'antigene 180kDa de la pemphigoide. Arch Pediatr 1996; 3:345-7.
23. Ghohestani RF, Nicolas JF, Kanitakis, et al. Linear IgA bullous dermatosis with IgA antibodies exclusively directed against the 180 or 230kDa epidermal antigens. J Invest Dermatol 1997; 108:854-8.
24. Zone JJ, Taylor TB, Meyer LB, et al. The 97kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180kDa bullous pemphigoid antigen, BPAG2. J Invest Dermatol 1998; 110:270-310.
25. Marinkovich P, Taylor T, Keene D, et al. LAD-1, the linear IgA bullous dermatosis autoantigen, is a novel 120kDa anchoring filament protein synthesized by epidermal cells. J Invest Dermatol 1996; 106:734-8.
26 .Marsden RA. The treatment of benign chronic bullous dermatosis of childhood and bullous pemphigoid beginning in childhood. Clin Exp Dermatol 1982; 7:653-63.
27. Diaz LA and Giudice GJ. End of the century overview of skin blisters. Arch Dermatol 2000; 136:106-12.
28. Ang P and Tay YK. Treatment of linear IgA bullous dermatosis of childhood with colchicine. Pediatr Dermatol 1999; 16:50-2.
29. Skinner RB, Rotondo CK, Schneider MA, et al. Treatment of chronic bullous dermatosis of childhood with oral dicloxacillin. Pediatr Dermatol 1995; 12:65-6.
30. Denguelzi M, Nejma B, Nouira R, et al. La dermatose bulleuse a IgA lineaire de l'enfant. Une serie de 12 amlades Tunisiens. Ann Dermatol Venereol 1994; 121:888-92.
31. Nemeth AJ, Klein AD, Gould EW, et al. Childhood bullous pemphigoid. Clinical and immunologic features, treatment, and prognosis. Arch Dermatol 1991; 127:378-86.
32. Lever WF. Pemphigus. Medicine 1953; 32:1-123.
33. Bean SF, Good RA, Windhorst DB. Bullous pemphigoid in an 11 year old boy. Arch Dermatol 1970; 102:205-8.
34. Cunha PR, Thomazeski PVG, Hipolito E, et al. Bullous pemphigoid in a 2 month old infant. Int J Dermatol 1998; 37:934-48.
35. Geyer AS, Zillikens D, Skrobek C, et al. Vesicular pemphigoid in a 16 year old boy. J Am Acad Dermatol 2003; 49:722-4.
36. Elias M, Suarez J, Medina S, et al. Penfigoide ampolloso de la infancia: A proposito de dos nuevos casos. Med Cut I L A 1992; 20:73-6.
37. Chimanovitch I, Hamm H, Georgi M, et al. Bullous pemphigoid of childhood: autoantibodies target the same epitopes within the NC 16 A domain of BP180 as autoantibodies in bullous pemphigoid of adulthood. Arch Dermatol 2000; 136:527-32.
38. Mutasim DF and Adams B. Immunofluorescence in dermatology. J Am Acad Dermatol 2001; 45:803-22.
39. Thivolet J and Barthelemy H. Bullous pemphigoid. Seminars in dermatology 1988; 7:91-103.
40. Hadi SM, Barnetson RStC, Gawrodger DJ, et al. Clinical, histological, and immunological studies in 50 patients with bullous pemphigoid. Dermatologica 1988; 176:6-17.
41. Giudice GJ, Emery DJ, Zelickson BD, et al. Bullous pemphigoid and herpes gestationis autoantibodies recognize a common non-collagenous site on the BP180 ectodomain. J Immunol 1993; 151:5742-50.
42. Wojnarowska F, Kirtschig G, Highet AS, et al. Guidelines for the management of bullous pemphigoid. Br J Dermatol 2002; 147:214-21.
43. Motegi S, Abe M, Tamura A, et al. Childhood bullous pemphigoid successfully treated with diaminodiphenyl sulfone. J Dermatol 2005; 32:809-12.
44. Jablonska S, Chorzelski T, Beutner EH, et al. Juvenile dermatitis herpetiformis in the light of immunofluorescence studies. Br J Dermatol 1971; 85:307-13.
45. Chorzelski TP, Jablonska S, Beutner EE, et al. Juvenile dermatitis herpetiformis versus 'benign chronic bullous dermatosis of childhood': are these immunologic diseases? J Invest Dermatol 1975; 65:447-50.
46. Piamphongsant T, Chaikittisilpa S, Kullavanijaya P. Bullous pemphigoid in childhood: report of three cases and a review of the literature. Int J Dermatol 1977; 16:126-33.
47. Chorzelski TP and Jablonska S. IgA linear dermatosis of childhood (chronic bullous disease of childhood). Br J Dermatol 1979; 101:535-42.
48. Fontaine J, Joly P, Roujeau JC. Treatment of bullous pemphigoid. J Dermatol 2003: 30:83-90.
49. Woodley DT, Burgeson RE, Lunstrum G, et al. Epidermolysis bullosa acquisita antigen is the globular carboxyl terminus of type VII procollagen. J Clin Invest 1988; 81:683-7.
50. Inauen P, Hunziker TH, Gerber, et al. Childhood epidermolysis bullosa acquisita. Br J Dermatol 1994; 131:898-900.
51. Callot-Mellot C, Bodemer F, Caux F, et al. Epidermolysis bullosa acquisita in childhood. Arch Dermatol 1997; 133.
52. Gammon WR, Briggaman RA, Inman AO, et al. Differentiation anti-lamina lucida and anti-sublamina densa BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. J Invest Dermatok 1984; 82:139-44.
53. Trigo-Guzman FX, Conti A, Aoki V. Epidermolysis bullosa acquisita in childhood. J Dermatol 2003; 30:226-29.
54. Zierhut M, Thiel HJ, Weidle EG, et al. Ocular involvement in epidermolysis bullosa acquisita. Br J Dermatol 1988; 118:7-15.
55. Saki LY, Keene DR, Morris NP. Type VII collagen is a major structural component of anchoring fibrils. J Cell Biol 1986; 103:1577-86.
56. Palestine RF, Kossard S, Dicken OH. Epidermolysis bullosa acquisita: a heterogeneous disease. J Am Acad Dermatol 1981; 5:43-53.
57. Borok M, Heng MCY, Ahmed AR. Epidermolysis bullosa acquisita in an 8 year old girl. Pediatr Dermatol 1986; 3:315-22.

Poulos

Barnhill

Hanly

Dermatopathology

Nationwide

24 Hour Turn Around

GLOBAL PATHOLOGY

LABORATORY SERVICES

866 - 825 - 4422

Park Avenue Dermatology, PA

is looking for a full time BC/BE Dermatologist to work along side a professional team in a new state of the art building in the Greater Jacksonville area in North East Florida.

Benefits include:

Base Salary $300,000
40% Bonus after Expenses
3% Matching Fund on our 401k Program
Malpractice Insurance (250/750k)
Health Insurance (Premiums paid by the Company)
Health Insurance Deductible Paid by the Company (HSA Account)
Long Term Disability (Premiums paid by the Company)
$2500 CME Per Year (If not used will be paid out)
Two Weeks Vacation
Three Personal Days
Two Sick Days
Seven Holidays (Includes Good Friday)

For more information please contact
Jose Paredes Practice Administrator at 904-644-0204
or email your resume/cv to jpcheito1@aol.com.

Wanted: Dermatologist

Northern Virginia. Family oriented dermatology practice in a suburb of Washington DC. Seeking a dermatologist to join a staff of 2 physicians. General and cosmetic dermatology practice utilizing lasers. Part-time initially with potential full-time. E-mail inquiries/resume to info@exceldermatology.com or fax to 703-827-7011.

Histological Findings in POEMS Syndrome

Shaheen Oshtory, D.O.,* Roger Sica, D.O., Jay Dennett, D.O.,* Cindy Hoffman, D.O.,* Damian DiCostanzo, M.D.*****
** Lutheran Medical Center, Brooklyn, New York, USA*
*** Suncoast Hospital, Tampa, Florida, USA*
**** Dermpath Diagnostics Pathology Associates, Port Chester, New York, USA*

ABSTRACT

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes is known as POEMS syndrome. This is a rare, multi-system disorder first described by Crowe in 1956. It is usually associated with plasma cell dyscrasia. Fukase reported a patient with similar clinical features in 1968. POEMS syndrome is also known as Crow-Fukase syndrome. We report a case of a 46-year-old male patient who presented to our dermatology clinic with a previous diagnosis of POEMS syndrome. Further work-up demonstrated distinct clinical and pathological features consistent with this syndrome. The microscopic evaluation demonstrated a vascular pattern not commonly associated with the syndrome.

Introduction

POEMS syndrome is a rare, multisystem disorder first described by Crowe in 1956. It is usually associated with plasma cell dyscrasia and characterized by the combination of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.[1] In 1980, the acronym POEMS was coined by Bardwick and colleagues[2] based on these five features. The combination of signs and symptoms is complex; currently, no specific case definition for POEMS exists, and no single test establishes the diagnosis. Patients are relatively young, predominantly male, and usually have neurological symptoms.[3] Cytokines such as TNF·, IL-1,, vascular endothelial growth factor (VEGF), and IL-6 are frequently elevated, and levels may correspond to disease activity.[4,5,6] The cause of POEMS syndrome is still unknown.

We report a case of a 46-year-old male patient who presented to our dermatology clinic with clinical manifestations and a prior diagnosis of POEMS syndrome. A skin biopsy revealed an interesting vascular pattern not commonly associated with POEMS syndrome and rarely reported.

Case Report

A 46-year-old male, originally from Ecuador, presented with a 10-year history of progressive peripheral neuropathy. In 1992, he was unable to play soccer professionally because of weakness in his lower extremities. He was diagnosed with peripheral neuropathy of unknown etiology and treated with prednisone. His neuropathy eventually spread to involve all four of his extremities with vibratory, sensory and motor loss, leaving him confined to a wheelchair. His disease progressed, and he sought treatment in the United States in 1985. Initial radiographic studies revealed thickened bone trabeculae and bony destruction involving his left hip and spine. He underwent spinal surgery, and a bone-marrow biopsy revealed osteosclerotic myeloma. Physical examination and laboratory studies revealed splenomegaly, peripheral edema, hypothyroidism, plethora, and anemia. The combination of features was consistent with POEMS syndrome. He was subsequently treated with chemotherapy (chlorambucil), radiation therapy to his left hip, and interferon therapy within the course of a year. He returned to Ecuador and was lost to follow-up until 2005. He then presented to our dermatology clinic. He had been diagnosed with colitis, renal failure, hypertension, cardiomegaly, and COPD. Dermatological evaluation revealed hypertrichosis, mainly on his face, generalized hyperpigmentation, skin thickening primarily of his hands, Terry's nails, and peripheral clubbing of his fingers. A biopsy was performed on the hyperpigmented area of the skin. Microscopic evaluation demonstrated a diffuse vascular proliferation, not commonly seen in POEMS syndrome.

The patient was referred to endocrinology and was diagnosed with hypothyroidism, adrenal insufficiency, and hypogonadism. He was treated medically and symptomatically for his various conditions. Shortly after he was seen in our clinic, he was admitted to the intensive care unit with respiratory failure and died in January of 2006.

Discussion

POEMS syndrome, a unique syndrome with various clinical symptoms, consists of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. The first Japanese patient with clinical features similar to this syndrome was reported by Fukase et al. in 1968,[7] and POEMS syndrome has therefore also been called Crow-Fukase syndrome.1 POEMS syndrome affects men twice as often as women and is more common in

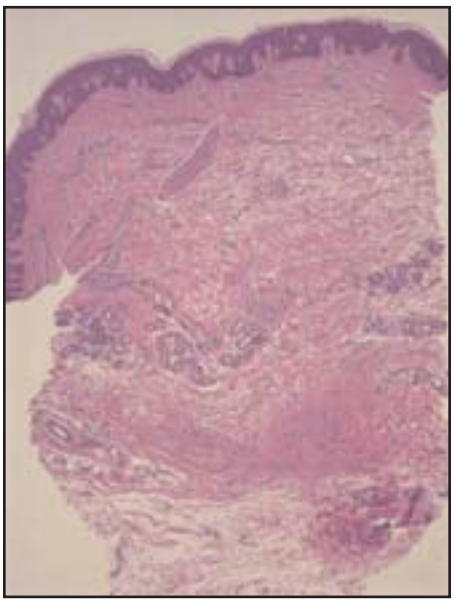


Figure 1
3 mm punch biopsy showing diffuse dermal vascular proliferation in a background of slight fibroplasia

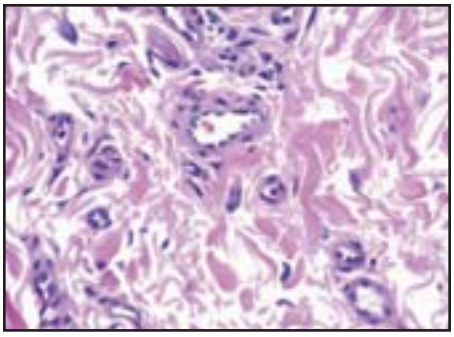


Figure 2
Interstitial proliferation of small, uniform vascular spaces without endothelial cell atypia

Japanese populations, with 165 patients being reported in Japan from 1968 to 1991.[8] The mean age of onset is 51 years. The disease tends to be slowly progressive and affect diverse populations, and the mechanisms responsible for its various clinical manifestations are still unknown.

The most common feature is an ascending, symmetrical, sensorimotor polyneuropathy with either an insidious or rapidly progressive onset. The neuropathy is usually not painful, and autonomic involvement is rare. It is typically a chronic, large-fiber, sensorimotor neuropathy.[9] Organomegaly may include hepatomegaly, splenomegaly, and lymphadenopathy. An array of endocrine abnormalities may occur and can be the defining feature of the syndrome.[2] Primary and secondary hypothyroidism, hypogonadism, adrenocortical insufficiency, and diabetes mellitus have all been described.10 Patients can have a monoclonal gammopathy of undetermined significance (MGUS) or a plasmacytoma with osteolytic, osteosclerotic, or mixed lesions.[10]

Various dermatologic changes have also been associated with POEMS syndrome. The most common skin changes include hyperpigmentation, cutaneous sclerosis, angiomatous lesions, hypertrichosis, hyperhidrosis, and edema.[10, 11] Other skin changes include whitening of the proximal nail (Terry's nails), peripheral edema, clubbing of the fingers, and Raynaud's phenomenon.[11]

The pathophysiology of POEMS syndrome is not well understood. In all patients, a plasma cell disorder underlies the development of the syndrome; however, the mechanism by which this occurs is still unknown.10 Cytokines have been implicated in the pathogenesis of the disease, and POEMS appears to be mediated by an imbalance of proinflammatory cytokines. IL-1,, IL-6, and TNF· inconsistently have been reported to be increased in association with the syndrome,[4,5,6] and recent studies have speculated that a high level of vascular endothelial growth factor is responsible for many symptoms seen in POEMS syndrome. VEGF is detected in platelet cells and has been reported to be produced by plasma cells.[12] Since patients with POEMS syndrome usually suffer from plasmacytomas, and therefore have an outgrowth of plasma cells, increased VEGF levels are expected and have been reported in serum and ascitic fluid.[14] Physiologically, VEGF induces a rapid and reversible increase in vascular permeability, is a growth factor for endothelial cells and is important in angiogenesis. The characteristic features of POEMS syndrome, such as ascites, pleural effusions, edema, organomegaly and neuropathy, may be induced by increases in serum VEGF levels, and a high level of VEGF has also been implicated in some of the skin changes noted in the disease.[13]

Histopathology

Skin biopsy may show inflammation, fibrosis, or nonspecific changes. There is an association with various angiomatous lesions, including glomeruloid hemangioma, which many consider a specific cutaneous marker for POEMS syndrome since it has not been reported in many patients without this syndrome.14 A skin biopsy of our patient involved hyperpigmented skin and revealed a diffuse and interstitial proliferation of small-caliber blood vessels within the dermis and subcutis. These vessels were relatively uniform in size and lined by flattened, monomorphous endothelial cells. There was neither atypia nor mitosis. This proliferation was set in a background of slight dermal and subcuticular fibroplasias (Figures 1 and 2). This histological pattern is not commonly associated with POEMS syndrome and is rarely reported.

Conclusion

The clinical course of POEMS syndrome is chronic in many cases, and median survival is approximately 165 months. Many studies have demonstrated that survival is not affected by the number of POEMS features, and most patients die not of plasmacytomas but from cardiorespiratory failure and pneumonia.[10] Because the pathogenesis of this multisystem disorder is unclear, treatment is not standardized and is based on the stage and severity of the disorder. Most patients are treated with a combination of medical, surgical, and adjuvant therapies. The most effective treatment for POEMS syndrome is surgical excision or localized irradiation for plasmacytomas. Radiation therapy to limited areas can also improve osteosclerotic lesions.[10] Besides radiation, many strategies have been used, including plasmapheresis, intravenous immunoglobulin, interferon alpha, corticosteroids, alkylators, azathioprine, autologous stem cell transplantation, tamoxifen, and transretinoic acid.[10,15] Melphalan and steroids are often used to treat patients, and cycophosphamide and vincristine are sometimes used as well.[16]

Our patient had many of the criteria needed to establish a diagnosis of POEMS syndrome, and in particular he had interesting histological findings. He was treated with multiple modalities including chemotherapy, surgery, radiation therapy, and interferon, which helped prolong his survival. He eventually died of respiratory failure 10 years after receiving his diagnosis of POEMS syndrome.

Fortunately, the future for patients with POEMS syndrome is promising. With recent advancements in therapy and further understanding of the pathogenesis of the disease, survival for patients is better than previously reported. Radiation and chemotherapy remain as first-line treatment for the disease, but ultimately, manipulation of the cytokine environment may be the treatment of choice.

References:

1 Nakashani T, Sobue I, Toyokura Y, et al. The Crow-Fukase Syndrome: a study of 102 cases in Japan. Neurology. 1984; 34:712-720.

2 Bardwick PA, Zvaifler NJ, Gill GN, et al. Plasma cell dyscrasia with polyneuropathy, organomegaly, Endocrinopathy, M protein and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine (Baltimore). 1980; 59:311-322.

3 Singh D, Wadhwa J, Kumar L. POEMS Syndrome: Experience with Fourteen Cases. Leukemia and Lymphoma. 2003; 44: 1749-1752.

4 Rose, C, Mahieu, M, Hachulla, E, et al. POEMS syndrome. Rev. Med. Interne, 1997; 18: 553-562.

5 Feinberg L, Temple D, deMarchena E, et al. Soluble immune mediators in POEMS syndrome with pulmonary hypertension: case report and review of literature. Crit. Rev. Oncogol, 1990; 10: 293-302.

6 Kyle, R. POEMS Syndrome. Clinical Lymphoma. 2003; 4 (3): 186.

7 Fukumasu H, Nishitani H, Fukase M, et al. Solitary plasmacytomas with polyneuritis and endocrine disturbances. Nippon Rinsho. 1968; 26: 2444-2456.

8 Takatsuki K, Matsuzaki H. Japanese clinical statistical data of patients with plasma cell dyscrasia with polyneuropathy and endocrine disorder. Nippon Rinsho. 1992; 50 suppl: 855-863.

9 Dispenzieri A, Kyle R, Lacy M, et al. POEMS syndrome: definitions and long-term outcome. Blood. 2003; 101: 2496-2506.

10 Goldstein M, Bandyopadhyay T. POEMS Syndrome. Connecticut Medicine. 2004; 68: 431-433.

11 Chang, Sung E, Choi J. POEMS Syndrome With Xanthomatous Cells. The American Journal of Dermatopathology. 1999; 21; 567-570.

12 Hideaki M, Fukashi U, Tamotsu K. POEMS Syndrome Demonstrating VEGF Decrease by Ticlopidine. Internal Medicine, 2004; 43: 1082-183.

13 Minamitani S, Ohfuji S, Nishiguchi S. An Autopsy Case of POEMS Syndrome with a High Level of IL-6 and VEGF in the Serum and Ascitic Fluid. Internal Medicine. 2002; 41: 233-236.

14 Velez D, Delgado-Jimenez Y, Fraga J. Solitary Glomeruloid Hemangioma without POEMS Syndrome. J Cutan Pathol. 2005; 32: 449-452.

15 Rotta F, Bradley W. Marked Improvement of Severe Polyneuropathy Associated With Multifocal Osteosclerotic Myeloma Following Surgery, Radiation, and Chemotherapy. Muscle and Nerve. 1997; 20: 1035-1037.

Rosai-Dorfman Disease: Case Report and Review of the Literature

Adriana Ros, D.O.,* David Kessler, D.O., Marvin Watsky, D.O.,*****
**1st year resident, St. John's Episcopal Hospital, South Shore, Department of Dermatology, Far Rockaway, NY*
***Attending, St. John's Episcopal Hospital, South Shore, Department of Dermatology, Far Rockaway, NY*
****Program Director, St. John's Episcopal Hospital, South Shore. Department of Dermatology – Far Rockaway, NY*

ABSTRACT

Rosai-Dorfman disease is an uncommon, histiocytic, proliferative disorder. It was first described in 1969 by Rosai and Dorfman, and so far only 600 cases have been reported worldwide. It is also known as sinus histiocytosis with massive, painless lymphadenopathy (SHML), but may also solely include skin manifestations. Cutaneous lesions are the most common extranodal site. The etiology of this disease is unknown, although a viral pathogenesis has been postulated. Treatment should be based on clinical manifestations. In this paper, we describe a patient with SHML presenting with cervical and inguinal lymphadenopathy with skin involvement. This case report and a review of the literature are presented below.

Case Report

A 29 year-old, healthy-appearing, Hispanic male suddenly developed a lesion on his right cheek, which was not pruritic or painful, two months before presenting at our clinic. This was his first occurrence, and he did not have a history of skin conditions. He denied any systemic symptoms of fever, weight loss, sore throat, or sinus pain. His past medical history included varicella at 21 years of age and a possible tick bite at age 14. He denied using any medications or having any allergies. He was born and lived in rural El Salvador on a chicken farm, but moved to New York 11 years ago. At the time of presentation, he worked in a deli and was married with no children. He denied any history of drug use but said he occasionally smoked cigarettes. His family history was insignificant. On physical examination, he was a healthy-appearing male with an 8-mm, soft, reddish-yellow, dome-shaped papule with telangiectasia on his right lateral cheek. He had left posterior cervical chain lymphadenopathy with no associated tenderness. His right inguinal lymph nodes were slightly enlarged. The remainder of the physical examination was within normal.

A shave biopsy was performed of the papule on the right cheek. The pathology report showed a nodular proliferation of foamy histiocytes admixed with an infiltrate of neutrophils, lymphocytes, eosinophils, and plasma cells. Some of the histiocytes displayed phagocytosis of inflammatory cells (emperipolesis). Occasional histiocytes showed slightly pleomorphic nuclei. Immunohistochemical stains of histiocytes were positive for S-100 stain, focal staining with CD-68, and scattered dermal dendritic cells stained with factor XIIIa. It was negative with stains for CD1-A.

At this time, this patient's laboratory values were assessed. Complete blood count was within normal range except for elevated absolute eosinophils of 2109.

HSV 1 was elevated to 3.71. HSV 2 was elevated at >5.00. EBV IgM Ab was 0.02 (negative). EBV IgG Ab was 6.35 (positive). EBV nuclear AG (IgG) was >5.00 (positive). ESR and immunoglobulins (G,A,M,E) were in range. Lyme disease screen was negative.

Discussion

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a well-established clinicopathologic entity. A small number of patients with skin or soft-tissue manifestations have been described. There is widespread geographic distribution of the disease, but it is more prevalent in Africa and the West Indies. It is more common in children and young adults than in older people. There appears to be both a male and a black race predilection.

The etiology of Rosai-Dorfman disease (SHML) remains uncertain. There are two main theories. One is primary infectious, and the other is a disturbance in cell-mediated immunity. The infectious causes include: Epstein-Barr virus (most frequently cited; results inconclusive),[7] herpes simplex virus, rubella, cytomegalovirus, brucella, klebsiella rhinoscleroma, and nocardia. Conceivably, these infections create an immunological environment resulting in activation of the histiocyte-macrophage system.[7] Disturbance in cell-mediated immunity can be an intrinsic cellular defect. There have been reports of both normal and decreased blast transformation of lymphocytes to phytohemagglutinin, concanavalin A, or pokeweed mitogen in patients with SHML, making a uniform defect in lymphocyte-mediated cellular immunity unlikely. Moreover, SHML does not seem to be an antibody-mediated disorder because macrophages retain the property of phagocytosis of other cells and micro-organisms in vitro in the absence of specific stimulation.1

The key clinical features of Rosai-Dorfman disease are massive, painless, bilateral cervical lymphadopathy with any extranodal site being involved. Extranodal disease has been reported in 28% to 32% of cases with SHML.[1] Involvement of extranodal sites include the skeleton, salivary glands, central nervous system, eyes, upper respiratory tract, and skin. The cutaneous lesions are the most common extranodal site and are varied in appearance. They can be nodules up to 4 cm or more, erythematous or xanthomatous papules, plaques or pigmented macules, or a transient panniculitis. The majority of lesions are multiple, and in at least one case the nodules have been painful. Patients may also experience fever, anemia, elevated sedimentation rate, and hypergammaglobulinemia.

The most common laboratory values are leukocytosis, neutrophilia, elevated erythro-

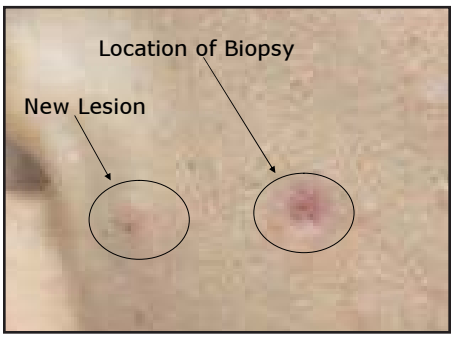


Figure 1
Biopsy location – right cheek

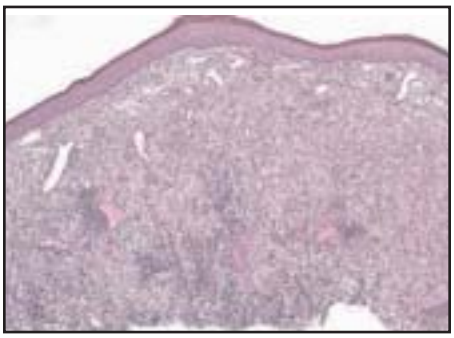


Figure 2
Histology of Biopsy

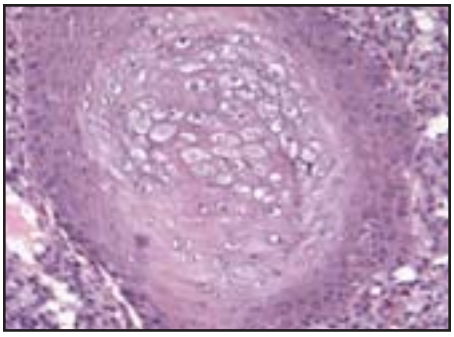


Figure 3
Histology of Biopsy-Higher Magnification

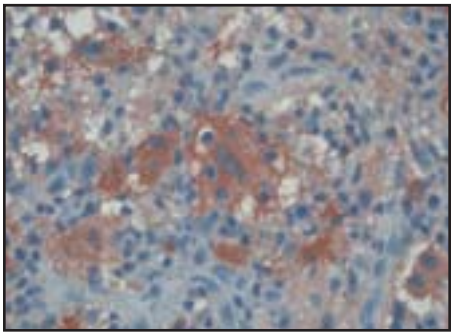


Figure 4
Histology of Biopsy-S100 stain

cyte sedimentation rate, chronic anemia (most often normochromic, normocytic), hypergammaglobinemia (usually polyclonal), and elevated antibody titers to Epstein-Barr virus.[2] Other abnormalities include elevated HSV titers, abnormal urine analysis and culture, abnormality of HHV-6 by PCR DNA testing, and positive direct Coomb's test.

Histopathology of Rosai-Dorman disease displays expansion of sinuses of lymph nodes by large, foamy histiocytes admixed with plasma cells. Skin specimens are nonspecific but usually show dense dermal infiltrate of large histiocytes with abundant, lightly eosinophilic cytoplasm and vesicular nuclei. There can be scattered multinucleated cells, touton giant cells, and collection of neutrophils. There are plasma cells and Russell bodies. Nodular lymphoid aggregates, fibrosis, increased vascularity, and focal necrosis can also be seen. Phagocytosis of plasma cells and lymphocytes, called emperipolesis, is characteristic.

Histiocytes express positivity for S-100 antigen, CD 14, CD 68, CD 11c, laminin 5, lysozyme, alpha 1-antitrypsin, Mac-387, and factor XIIIa (dendrocyte marker). It is negative for CD1a (OKT6).

The course and prognosis of Rosai-Dorfman disease (SHML) is indolent and protracted, with frequent exacerbations and remissions. Many lesions are asymptomatic and heal spontaneously. Twenty percent of cases have been reported to undergo spontaneous regression.[7] Patients require hematology/oncology follow-up. CT scans are done to search for other extranodal disease. Unfortunately, there have been 14 documented deaths in the SHML patient registry. Either of these patients died of unusual infections or immunologic disorders. Two died of extranodal involvement of the CNS and kidneys. The remaining four had prominent SHML infiltrates, but the cause of death was not related to their disease. All of these 14 patients had received multiple modalities of treatment without any benefit.[2] Unfavorable prognostic signs include disseminated nodal disease or involvement of the liver, kidney, or lower respiratory tract.

Because Rosai-Dorfman disease involves clinically non-specific cutaneous lesions, the differential diagnosis includes several other disorders. This includes other histiocytoses, infectious processes, sarcoidosis, Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, metastases, and Kikuchi's disease. While the lymph node swelling and fever seen in Kikuchi's disease may mimic that seen in Rosai-Dorfman disease, patients with Kikuchi's disease have a normal white blood cell count, ESR, and hemoglobin.8

Treatment options are based upon clinical manifestations. If the lesions are destructive, disseminated, or causing physical compromise, then radiotherapy, surgical excision, systemic steroids, or chemotherapeutic regimens are used. Antibiotics are of no benefit because resolution of the infection does not modify the course of the skin lesions. Chemotherapeutic regimens that have been used include thalidomide, vinblastine and a combination of methotrexate, 6-thioguanine, leukovorin, and prednisone.3456

In conclusion, our patient is one of few with cutaneous Rosai-Dorfman disease. He developed painless lymphadenopathy in the cervical and groin area along with a dome-shaped papule on his left cheek. He tested positive for EBV and HSV 1 and 2.

He is being followed by hematology/oncology, and a consultation has been requested with infectious disease for his eosinophilia. Currently, there is no physical compromise, and he is refusing a second biopsy. For this patient, a wait-and-see approach is being implemented because of his low morbidity.

References:

1 Olsen EA, Crawford JR, Vollmer RT. Sinus Histiocytosis with massive lymphadenopathy: case report and review of a multisystemic disease with cutaneous infiltrates. JAAD 1998;18:1322-32

2 Lazar AP, Esterly NB, Gonzalez-Crussi F. Sinus Histiocytosis clinically limited to the skin Pediatric dermatology 1987;4:247-53.

3 Lopez P, Estes ML. Immunohistochemical characterization of the histiocytes in sinus histiocytosis with massive lymphadenopathy: analysis of an extranodal case. Hum Pathol 1989;20:711-5

4 Penneys NS, Ahn YS, McKinney EC et al. Sinus histiocytosis with Massive Lymphadenopathy: a case with unusual skin involvement and a therapeutic response to vinblastine-loaded platelets. Cancer 1982;49:1994-8

5 Scheel M Md, Monica, et al. Sinus Histiocytosis with massive lymphadenopathy: Presentation of giant granuloma annulare and detection of HHV 6. JAAD 1997;37:643-6.

6 Viraben RDupre A, Gorguet B. Pure Cutaneous Histiocytosis resembling sinus histiocytosis. Clin Exp Derm 1988:13:197-93.7 Perez A, Rodriguez M, Febrer I , et al. Sinus Histiocytosis Confined to the Skin: Case Report and Review of Literature. The American Journal of Dermatopathology 1995; 17:387.

8 Bolognia L, Jean, Jorizzo L, Joseph et al. Dermatology Mosby; 2003; volume 2:1441-1443.

Lever E. David, et al. Lever's Histopathology of the Skin. Lippincott Williams and Williams; 2005: 693-694.

Levine PH, Jahan N, Murari P, et al. Detection of human herpesvirus 6 in tissues involved by sinus histiocytosis with massive lymphadenopathy . J. Infectious Disease 1992;166:291-5.

Axillary Granular Parakeratosis: A Case Report

Asfa S. Akhtar, D.O. *, Evangelos G. Poulos, M.D. **, Stanley Skopit, D.O., F.A.O.C.
**3rd year resident, NSU/BGMC, Department of Dermatology, Fort Lauderdale, FL*
*** Dermatopathologist, Global Pathology, Miami, FL*
**** Assistant Clinical Professor, Director –Dermatology Residency Program, NSU/BGMC, Fort Lauderdale, FL*

ABSTRACT

Axillary granular parakeratosis (AGP) is an uncommon, acquired, idiopathic disorder of keratinization with distinct histologic characteristics. Histologic examination reveals acanthosis, papillomatosis and parakeratosis with basophilic keratohyaline granules within the stratum corneum. The same histopathologic features have been seen in benign cutaneous eruptions of non-axillary intertriginous areas, and the term intertriginous granular parakeratosis (GP) has been proposed to cover this entity. The following is a case of AGP in a young patient.

Case Report

An 18-year-old female presented to the dermatology clinic for the evaluation of a mildly pruritic eruption in the axillae bilaterally of several months duration. The patient stated that she had noticed a darkening of the skin in the axillary areas after repeated use of antiperspirants. The patient denied severe pruritus or trauma to the affected areas. She also noted no involvement of other intertriginous areas. The patient's past medical history was non-contributory. She recalled no family history of skin diseases or current use of any medications.

Physical exam revealed a well-developed, well-nourished female in no acute distress. Examination of the axillary vaults bilaterally revealed mildly erythematous, hyperpigmented keratotic plaques. There were no satellite lesions noted. Examination of the inframammary and inguinal areas revealed no abnormal lesions. A complete physical exam revealed no other abnormal-appearing lesions. The differential diagnosis included post-inflammatory hyperpigmentation, acanthosis nigricans, tinea, inverse psoriasis, Hailey-Hailey disease, Darier-White disease, contact dermatitis and irritant dermatitis. A Wood's lamp exam was negative for erythrasma. A KOH prep was negative. A biopsy from one axilla revealed slight epidermal hyperplasia, dilated capillaries and a thickened cornified layer with retention of keratohyalin granules. The presence of nucleated cornified cells containing basophilic granules was noted in the thickened cornified layer, establishing the diagnosis of axillary granular parakeratosis (Figure 1-3). A Periodic acid-Schiff stain was negative for hyphae. The patient partially improved with topical corticosteroids in a four-week period. She was lost to follow-up.

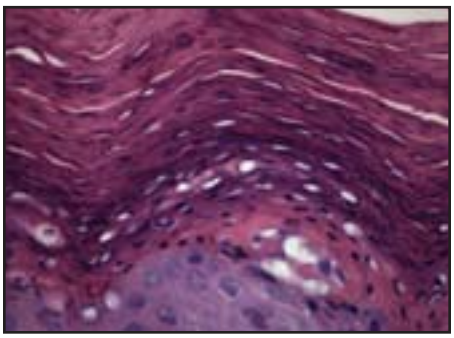


Figure 1

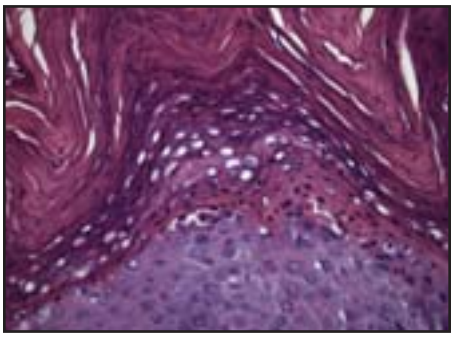


Figure 2

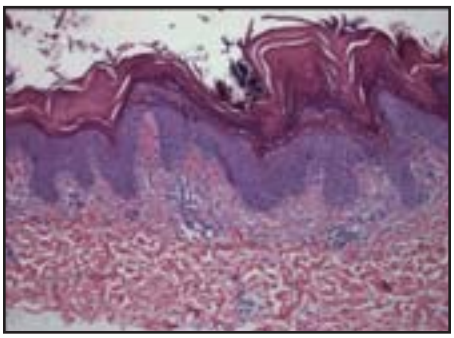


Figure 3

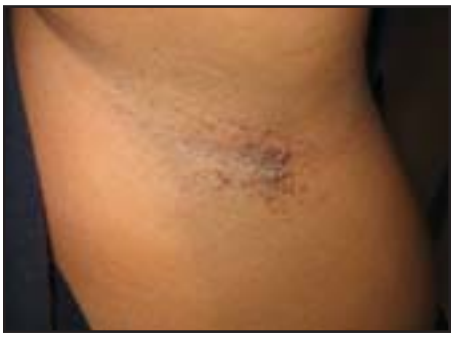


Figure 4

Discussion:

The term axillary granular parakeratosis is a benign condition with distinct histopathologic features. In 1991 Northcutt, Nelson, and Tschen[1] described four patients with a well-demarcated axillary eruption that was clinically similar to Hailey-Hailey disease. Biopsy specimens, however, exhibited an unusual parakeratosis with retention of keratohyalin granules throughout the stratum corneum. A similar eruption was described by Mehregan et al. [2]

The cause of axillary granular parakeratosis is not known. In some of the previously reported cases, it has been speculated that an antiperspirant or deodorant was altering the normal maturation of keratinocytes and causing corneocytes to retain keratohyaline granules abnormally. Several authors have postulated that, in AGP, a basic defect exists in the processing of profliggrin to filaggrin which maintains the keratohyaline granules in the stratum corneum during cornification. Proflaggrin is a high molecular weight constituent of keratohyalin granules that normally undergo dephosphorylation to release filaggrin, a matrix protein that promotes cross-linking and aggregation of cytoplasmic keratin filaments in the stratum corneum. The reduced degradation of profilaggrin and decreased release of filaggrin leads to abnormal aggregation of keratin filaments in the stratum corneum. Because AGP has been associated with excessive use of topical preparations, an occlusive environment, increased sweating, and sometimes local irritation, some suggest that it is an allergic contact or irritant reaction. AGP has been seen in a unilateral distribution and has also been linked with a lack of change upon cessation of the offending agent. Patch testing in some subjects has been negative. There have been cases where there was no history of using any products prior to the appearance

of the lesions. This process is probably a disorder of cornification. The predominant change is alteration in the stratum corneum, which is much thicker than normal, and there is broad parakeratosis containing keratohyaline granules.

Axillary Granular parakeratosis presents as erythematous, red and/or brown scaly or keratotic papules that can be confluent, discrete or reticulated (Fig4). Numerous reports have subsequently noted the existence of GP occurring on the groin, abdomen and lumbosacral areas thus limiting the use of the body region qualifier "axillary" to pertinent cases only.[1-16] The axilla is the most commonly affected sight, whether unilateral or bilateral.

Axillary granular parakeratosis can occur for patients of all ages and both sexes although it seems more common in women. In reported cases, patients range from 6 months to 83 years of age. It has been reported in whites, blacks and hispanics. It does not appear to have any systemic associations but some think it is more common in patients who are obese. In 2002,Trowers et al reported the first case of an infant with granular parakeratosis(GP).[12] Excessive washing was found in 4 children manifesting with GP[4]. Two clinical patterns in infancy have been described-Geometric scaling erythematous plaques and discrete linear warty plaques in the inguinal folds. Patients with GP usually present with a 1 to 12-month history of an axillary or intertriginous bilateral or unilateral brown erythermatous or red-scaly or hyperkeratotic patches, papules, or plaques. Some cases of GP are pruritic.

The classic histology of GP is of a thickened stratum corneum with retention of keratohyalin granules.There is acanthosis, papillomatosis and vacuolization of keratinocytes.The upper dermis may reveal a scattered lymphohistiocytic inflammation and mild vascular proliferation. Under Electron microscopy, the viable cell layers and cell organelles appear almost normal. Electron dense granules of variable sizes are noted within flattened corneocytes which account for the basophilic granules in the stratum corneum as seen by light microscopy. A review of these 18 cases by Scheinfeld and Mones demonstrated the classic histology in all cases with some variations.[17]

In 2003, Resnik and DiLeonardo described follicular granular parakeratosis that was granular parakeratosis confined to the follicle.[18] In 2004, Resnik et al described dermatophyte-related granular parakeratosis.[19]

Although, few patients with this condition have been reported, successful medical treatment of patients with AGP has been inconsistent. Response to topical or systemic steroids, antibiotics, retinoids and antimycotics has been variable. Some reports have cited the use of topical calcipotriene and ammonium lactate to effectively treat this condition. Some patients demonstrated spontaneous resolution of the lesions over a course of weeks to months. The goals of pharmacotherapy are to reduce pruritus and to improve the appearance of the eruption. Patients should avoid excessive washing of intertriginous areas. They should also minimize the use of roll on anti-perspirants/ deodorants.

Dermatologists and dermatopathologists must be aware of this condition so that they can correctly diagnose AGP and accurately treat patients who have this disorder. The study by Schienfeld and Mones suggests that AGP is uncommonly recognized by clinicians. It also demonstrates that there are histopathologic variants of AGP. Advising patients on the benign nature of this condition is vital in establishing a strong patient-physician relationship.

References:

1. Northcutt AD, Nelson DM, Tschen JA. Axillary granular parakeratosis. J Am Acad Dermatol 1991;24:541-544.
2. Scheinfeld NS. Axillary granular parakeratosis. Emedicine 2003. Available from: URL:http://www.emedicine.com/derm/topic923.htm. Accessed March 30, 2004.
3. Mehregan DA, Vandersteen P, Sikorski L, Mehregan DR. Axillary granular parakeratosis. J Am Acad Dermatol 1995;33:373-375.
4. Patrizi A, Neri I, Misciali C, Fanti PA. Granular parakeratosis: four paediatric cases. Br J Dermatol 2002;147:1003-1006.
5. Contreras ME, Gottfried LC, Bang RH, Palmer CH. Axillary intertriginous granular parakeratosis responsive to topical calcipotriene and ammonium lactate. Int J Dermatol 2003;42:382-383.
6. Metze D, Rutten A. Granular parakeratosis—a unique acquired disorder of keratinization. J Cutan Pathol 1999;26:339-352.
7. Mehregan DA, Thomas JE, Mehregan DR. Intertriginous granular parakeratosis. J Am Acad Dermatol 1998;39:495-496.
8. Wallace CA, Pichardo RO, Yosipovitch G, Jancox J, Sangueza OP. Granular parakeratosis: a case report and literature review. J Cutan Pathol 2003;30:332-335.
9. Brown SK, Heilman ER. Granular parakeratosis: resolution with topical tretinoin. J Am Acad Dermatol 2002;47:S279-S280.
10. Barnes CJ, Lesher JL Jr, Sangueza OP. Axillary granular parakeratosis. Int J Dermatol 2001;40:439-441.
11. Webster CG, Resnik KS, Webster GF. Axillary granular parakeratosis: response to isotretinoin. J Am Acad Dermatol 1997;37:789-790.
12. Trowers AB, Assaf R, Jaworsky C. Granular parakeratosis in a child. Pediatr Dermatol 2002;19:46-47.
13. Rodriguez G. Axillary granular parakeratosis. Biomedica (Bogota) 2002;22:519-523.
14. Brady SP. Parakeratosis. J Am Acad Dermatol 2004;50:77-84.
15. Kurtis B, Guillen D, Cockerell C. Granular parakeratosis in submammary distribution: a case report of a unique histological and clinical phenomenon. [abstract] J Cutan Pathol 2004;31:112.
16. Malhotra R, Amin M, Bhanot P, Singer R. Axillary granular parakeratosis: a report of two additional cases. [abstract] J Cutan Pathol 2004;31:116.
17. Noah S. Scheinfeld, Joan Mones. Granular parakeratosis: Pathologic and clinical correlation of 18 cases of granular parakeratosis. Journal of the American Academy of Dermatology (JAAD) May 2005, part 1 • Volume 52 • Number 5 :863- 867.
18. Resnik KS, DiLeonardo M. Follicular granular parakeratosis. Am J Dermatopathol 2003;25:428-429.
19. Resnik KS, Kantor GR, DiLeonardo M. Dermatophyte-related granular parakeratosis. Am J Dermatopathol 2004;26:70-71.

Spontaneously Regressing Merkel Cell Carcinoma: A Case Report and Review of the Literature

Brett B. Bender, DO,* Lynn Sikorski, DO**
**1st year dermatology resident, POH Medical Center, Pontiac, MI*
***Attending dermatologist, POH Medical Center, Pontiac, MI*

ABSTRACT

Merkel cell carcinoma is a rare, highly aggressive tumor of the elderly usually located on the head and neck. Spontaneous regression is a sparsely occurring event in these lesions. In this paper, a case of a partially regressed Merkel cell carcinoma (MCC) in a 90-year-old female is presented along with a review of the current literature on this topic.

Introduction

Merkel cells are unique cells found within the basal layer of the epidermis that play a role as mechanoreceptors and as secretory neuroendocrine cells.[1] Merkel cell carcinoma, also known as neuroendocrine carcinoma of the skin or trabecular carcinoma, first appeared in the literature in 1972 as described by Toker.[2] MCC usually presents as a rapidly enlarging, erythemetous nodule on a sun-exposed surface, the head and neck being the most common sites, followed by the extremities.[3] Male or female predominance is debated, and incidence in children is exceedingly rare.[4] The course of MCC is rapid, and mortality after metastasis is high. In 1986, the first reported case of a spontaneously regressed MCC was published.5 Since then, less than 15 cases in total have been described.[3,6-12] In this paper, a case of a partially regressed MCC of the lower extremity in an elderly female will be presented. This is a unique entity since only one other case of a spontaneously regressing MCC on an extremity has been reported; all others have been from the head and neck.[13]

Case Report

A 90-year-old female presented to the office with a large, erythemetous, friable nodule on her left anterior thigh that had been present for approximately three months. She stated that the lesion had rapidly grown but over the last month had become somewhat smaller. She denied any pain, previous trauma to the site, fevers or any previous history of skin cancer. Her past medical history was significant for colon cancer, which was resected in 1976, along with chronic obstructive pulmonary disease, hypothyroidism, hypertension, chronic hearing loss, and spinal stenosis, which has caused her to become wheelchair bound. Medications included prednisone, furosemide, levothyroxine, lisinopril, atenolol, risedronate, potassium and multiple inhalers.

Physical exam of the left anterior thigh revealed a large, erythemetous nodule, 3.5 cm in its largest diameter. No significant regional adenopathy was appreciated. A 3 mm punch biopsy was taken from the inferolateral margin of the lesion and sent for histopathological examination. Differential diagnosis at this time included angiosarcoma, cutaneous metastasis, lymphoma, atypical mycobacteria and amelanotic melanoma.

Histology revealed a diffuse proliferation of variously sized and shaped aggregations of large, round, basophilic neoplastic cells with finely granular nuclei and scant cytoplasm in the dermis. Many mitotic figures, apoptotic cells and necrotic cells were present, along with a patchy, lymphocytic infiltrate. Immunoperoxidase stains were positive for CK 20, chromogranin and synaptophysin and negative for TTF-1, LCA and S100. A diagnosis of Merkel cell carcinoma was made.

The patient was seen in follow-up approximately two weeks later for suture removal, and the lesion then measured in its greatest diameter 2.5 cm (Figure 1). After discussion of treatment options with the patient, she was referred to surgical oncology for wide excision of her tumor. The tumor was removed with 1.5 cm to 2 cm margins, and a sentinel lymph node biopsy was performed. Pathologic analysis showed clear tumor margins and a negative sentinel lymph node. In a subsequent CT scan of the chest for staging purposes, a lung nodule of unknown origin was discovered. The patient has since declined post-operative radiation therapy or further work-up. A six-month follow-up visit with her surgeon revealed no recurrence of the primary tumor.

Discussion

Merkel cell carcinoma is an uncommon, aggressive malignancy with an approximate incidence in the United States of 0.42 cases per 100,000.[3] As stated previously, patients are usually elderly individuals who present with a rapidly enlarging, painless, ulcerative mass on a sun-exposed site, most commonly the cheek.[14] Predisposing conditions to the development of MCC have been postulated to include PUVA therapy, arsenic exposure, chronic immunosuppression as seen in HIV, leukemia, and patients post solid organ transplant.[15]

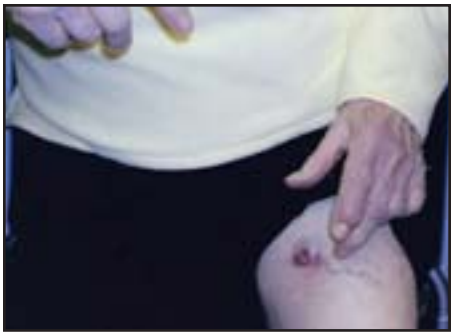


Figure 1
2.5 cm nodule on left anterior thigh two weeks post biopsy

Treatment options for MCC are based upon the stage of the tumor. Stage I is defined as localized disease, stage II as nodal metastatic disease and stage III as distant metastasis. Current recommendations for stage I and II disease is wide local excision (2 cm to 3 cm margins) with adjuvant radiation therapy and possibly systemic chemotherapy if there is a high risk for metastasis. Treatment for stage III disease is strictly palliative. The use of Mohs surgery is controversial but in one study has shown similar results in comparison to wide local excision for primary treatment.[9]

Spontaneous regression of any cancer is a rare event, but it is not totally uncommon in dermatology as cases of regressed melanoma, keratoacanthoma and basal cell carcinoma have been reported.[3] Since its first description by O'Rourke and Bell in 1986, only 12 cases of spontaneously regressed MCC have been reported.3,5-13 The overwhelming majority of these cases have been on the face, while only one case of a regressed tumor on an extremity has been reported.[13] Of the patients in the literature, approximately 60% had a spontaneous and complete remission of the tumor post biopsy within four weeks to five months of diagnosis. The other cases of spontaneous regression occurred after recurrence of the primary tumor or with a metastatic lesion.3 Whether or not the surgical procedure (biopsy or excision) was instrumental in initiating the

process of regression is a matter of debate.

Common histological features in the reported cases of spontaneously regressed MCC include numerous apoptotic tumor cells and a marked lymphocytic infiltrate of predominately CD8+ T cells but also CD4+ T cells and NK cells.[6,10,12] The dense, inflammatory infiltrate suggests that cell-mediated immunity plays an important role in the regression of these tumors, although other mechanisms yet identified surely contribute to the process.[7]

In summary, a case of a partially spontaneously regressed MCC of the lower extremity in an elderly female was presented in this case report. The histologic features of apoptosis and a lymphocytic infiltrate surrounding neoplastic cells in our specimen are consistent with the previous reported cases. The precise nature of this immune response has yet to be elucidated, but one can speculate another possible use of immune therapy in the treatment of this aggressive tumor. Whether or not our patient would have achieved a complete regression of her tumor without surgical intervention should not be debated. The risk of observing such an aggressive carcinoma far outweighs any potential benefit.

References:

1. Halata Z, Grim M, Bauman KI. Freidrich Sigmund Merkel and his "Merkel cell", morphology, development and physiology: review and new results. Anat Rec 2003; 271:225-369.
2. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972; 105:107-10.
3. Junquera L, et al. Complete spontaneous regression of merkel cell carcinoma. Ann Otol Rhinol Laryngol 2005; 114:376-79.
4. Moya CE, Guarda LA, Dyer GA, et al. Neuroendocrine carcinoma of the skin in a young adult. Am J Clin Pathol 1982; 78:783-85.
5. O'Rourke MG, Bell JR. Merkel cell tumor with spontaneous regression. J Dermatol Surg Oncol 1986; 12:994-6, 1000.
6. Kayashima K, Ono T, Johno M, Kojo Y, Yamashita N, Matsunaga W. Spontaneous regression in merkel cell (neuroendocrine) carcinoma of the skin. Arch Dermatol 1991; 127:550-3.
7. Yanguas I, Goday JJ, Gonzalez-Guemes M, Oleaga JM, Lozano M, Soloeta R. Spontaneous regression of merkel cell carcinoma of the skin. Brit J Dermatol 1997; 137:296-8.
8. Duncan WC, Tschen JA. Spontaneous regression of merkel cell (neuroendocrine) carcinoma of the skin. J Am Acad Dermatol 1993; 29:653-4.
9. Brown TJ, Jackson BA, MacFarlane DF, Goldberg LH. Merkel cell carcinoma: spontaneous resolution and management of metastatic disease. Dermatol Surg 1999; 25:23.
10. Inoue T, Yoneda K, Manabe M, Demitsu T. Spontaneous regression of merkel cell carcinoma: a comparative study of TUNEL index and tumor-infiltrating lymphocytes between spontaneous regression and non-regression group. J Dermatol Sci 2000; 24(3):203-11.
11. Connelly TJ, Cribier B, Brown TJ, Yanguas I. Complete spontaneous regression of merkel cell carcinoma: a review of the 10 reported cases. Dermatol Surg 2000; 26:853.
12. Takenaka H, Kishimoto S, Shibagaki R, Nagata M, Yasuno H. Merkel cell carcinoma with partial spontaneous regression: an immunohistochemical, ultrastructural and TUNEL labeling study. Am J Dermpath 1997; 19(6):614-18.
13. Sais G, Admella C, Soler T. Spontaneous regression in primary cutaneous neuroendocrine (merkel cell) carcinoma: a rare immune phenomenon? J Eur Acad Dermatol Venereol 2002; 16:82-3.
14. Eng T, Boersma MGK, Fuller CD, Cavanaugh SX, Valenzuela F, Herman TS. Treatment of merkel cell carcinoma. Am J Clin Onc 2004; 27(5):510-15.
15. Urbatsch A, et al. Merkel cell carcinoma occurring in renal transplant patients. J Am Acad Dermatol 1999; 41:289.

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

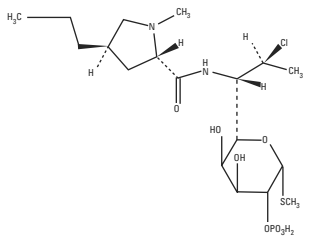
FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

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

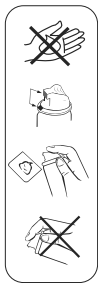
Topically applied Evoclin may be absorbed in sufficient amounts to produce systemic effects (see WARNINGS).

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®

Pityriasis Rubra Pilaris: Case Report and Review of the Literature

Piyush Raman, D.O.,* Michael Mahon, D.O., F.A.O.C.D.**
**3rd year Dermatology Resident, Pontiac Osteopathic Hospital, Michigan State University, Pontiac, Michigan*
***Program Director, Pontiac Osteopathic Hospital, Michigan State University, Pontiac, Michigan*

ABSTRACT

Pityriasis rubra pilaris refers to a group of chronic, papulosquamous dermatosis of unclear etiology characterized by reddish-orange, scaly plaques, palmoplantar keratoderma, and keratotic follicular papules. The case of a 52-year-old man with pityriasis rubra pilaris is presented. In addition, history, histology, clinical presentation, its different classified forms, treatments, and differential diagnoses are reviewed.

Case Report

A 52-year-old Turkish male initially presented in our office with a two-month history of a mildly pruritic rash of the scalp, face, trunk, lower extremities, and the palmer/plantar surface (Figures 1 and 2). He was otherwise healthy and denied any medical problems except for a history of "eczema." There was no family history of psoriasis, ichthyosis, palmoplantar keratoderma, or other skin diseases.

Physical examination revealed reddish-orange, slightly scaly patches and thin plaques of the face, trunk, and extremities. Subtle follicular prominences were present in the lesions. The scalp had yellowish scale. The hands showed hyperkeratosis and fissures. The feet showed hyperkeratotic plaques of the soles in a sandal-like distribution. Examination of the nails revealed onychodystrophy and subungual hyperkeratosis. Mucous membranes were normal, and there was no pruritus. There was neither head nor neck lymphadenopathy.

A punch biopsy revealed an epidermis with acanthosis, elongation of rete ridges, and overlying, alternating, compact orthokeratosis and parakeratosis. The papillary dermis showed mild edema and scattered lymphocytes and histiocytes. Deeper portions of dermis and subcutaneous tissue included in the biopsy were unremarkable. Clinical and histologic findings were consistent with a diagnosis of pityriasis rubra pilaris (PRP), type I (classic adult). He was placed on isotretinoin with clinical improvement.

Discussion

Pityriasis rubra pilaris was first described by Devergie in 1856.[1] It is a rare, chronic, papulosquamous disorder of unknown etiology characterized by reddish-orange, scaly plaques, palmoplantar keratoderma, and keratotic follicular papules. It has a bimodal age of onset. The first is during the first and second decades, and the second is during the sixth decade. The disease affects males and females equally. All races are affected.

The etiology of PRP is unknown. The therapeutic success of various retinoids has suggested a possible dysfunction in keratinization or vitamin A metabolism. Most cases are sporadic and acquired, but a familial form exists which is transmitted as an autosomal dominant trait. One hypothesis is that PRP may be related to an abnormal immune response to an antigenic trigger.[2] A viral etiology has been suggested, although a virus has never been isolated.

PRP usually begins as an asymptomatic, seborrheic dermatitis-like rash on the face or scalp that rapidly spreads downward. Truncal lesions develop as small, follicular papules with perifollicular erythema. This results in rough papules, especially on the dorsal aspect of the fingers, that have been described as a "nutmeg grater." As the involvement becomes even more extensive over the trunk, the skin assumes an orange or salmon-toned hue. A characteristic finding is truncal involvement that occurs in a manner such that some areas of the skin are spared, producing uninvolved islands of normal skin, the so-called "islands of sparing." When the disease is generalized, it is difficult to differentiate PRP from other diseases that eventuate in an exfoliative reaction. There is orange-red, waxy keratoderma of the palms and soles. This peculiar appearance on the soles is referred to as "keratodermic sandals." It is sharply demarcated at the juncture of the volar and glabrous skin. The keratoderma becomes dry and fissured, and these areas are extremely painful. Nail changes include thickening of the nail plate, subungual hyperkeratosis, yellow-brown discoloration, and splinter hemorrhages, but there is no pitting or onycholysis.[3] The mucous membranes are rarely involved, but they may show features similar to oral lichen planus, such as a diffuse whitish appearance of the buccal mucosa as well as lacy white plaques and erosions.[4] Patients with extensive disease may develop ectropion and may have reported blurred vision and dryness. Pruritus, although not a major symptom, may occur in the early stages of the disease. The general health in most patients is not affected, although occasionally arthritis may accompany the eruption.[5,6] A number of cases of associated malignancy have been reported.[7,8] Several human immunodeficiency virus (HIV) infected patients with PRP have been described.[9-11] It remains to be established whether these are true associations or chance findings.

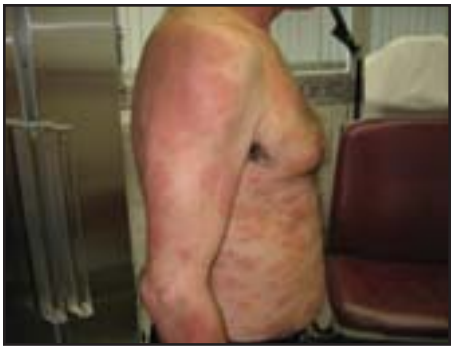


Figure 1

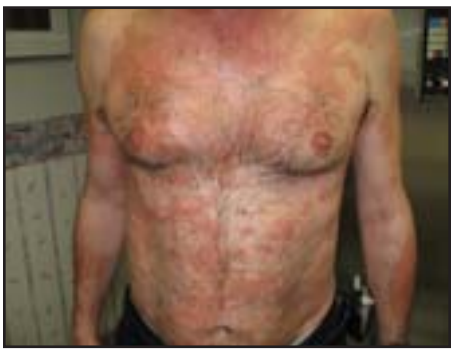


Figure 2

Five types of pityriasis rubra pilaris have been described, which differ with respect to age, clinical features, course, and prognosis. Griffiths[12,13] divided PRP into five categories: classic adult type, atypical adult type, classic juvenile type, circumscribed juvenile type, and atypical juvenile type. More recently, an HIV-associated type has been added to this classification system (Table 1).

Type I (classic adult) PRP is the most

common form, accounting for more than 50% of all cases of PRP. It usually begins in the head and neck region and then progressively advances caudally. The features are classic, including erythroderma with islands of sparing, palmoplantar keratoderma, and follicular hyperkeratosis. This type of PRP has the best prognosis. It is typically self-limited, clearing within three years in 80% of patients.

Type II is atypical adult PRP. This form accounts for about 5% of all cases of PRP. The disease shows atypical morphological features and starts in adult life. It is characterized by ichthyosiform lesions and alopecia. The orderly caudal progression seen in type I does not occur, and there is a lesser tendency for the disease to become erythrodermic. In addition, only 20% of type II patients experience resolution within three years.

Types III through V are seen in juveniles. Type III is the classic juvenile PRP. This form accounts for about 10% of all cases of PRP. It shows all the features of type I PRP; however, its onset is within the first three years of life. Spontaneous clearing is common within one to two years.[14,15] Type IV is circumscribed juvenile PRP. This form accounts for about 25% of all cases of PRP. It is characterized by sharply demarcated areas of follicular hyperkeratosis and erythema of the knees and elbows.[16] Some cases also show marked palmoplantar keratoderma. The prognosis is uncertain, but circumscribed PRP shows no tendency toward progression. Type V is atypical juvenile PRP. This form accounts for about 5% of all cases of PRP. Most cases of familial PRP belong to this group.[17] It has an early onset and runs a chronic course. It is characterized by prominent follicular hyperkeratosis and scleroderma-like changes on the palms and the soles. There is little tendency for the disorder to clear spontaneously.

Type VI has been proposed for those with HIV infection who develop PRP.[9-11] Patients with HIV may have nodulocystic and pustular acneiform lesions[18] as well as elongated follicular plugs or lichen spinulosus–type lesions. Patients' conditions tend to be resistant to standard treatments, but they may respond to highly active antiretroviral therapies (HAART).

No specific laboratory tests are available to confirm the diagnosis of PRP. Hematological and laboratory tests are normal. The diagnosis is usually made on the basis of a correlation between clinical findings and histologic findings. PRP may be difficult to diagnose with complete confidence in its early or later stages, when some of the distinctive signs may be lacking. Repeated observation and a number of biopsies may be necessary in these cases.

The histological changes seen in PRP are consistent but not specific. There is irregular hyperkeratosis and alternating vertical and horizontal parakeratosis ("checkerboard pattern"). In addition, there is focal or confluent hypergranulosis; follicular plugging with perifollicular parakeratosis forming a shoulder effect; thick suprapapillary plates; broad rete ridges; narrow dermal papillae; and sparse, superficial, dermal lymphocytic perivascular infiltration, sometimes containing eosinophils or plasma cells. Acantholysis has recently been reported as an additional histologic finding in PRP.[19-22] The presence of acantholysis, hypergranulosis, follicular plugging, and the absence of dilated capillaries and epidermal pustulation may help distinguish PRP from psoriasis.[23] The neutrophils and Munro's microabscesses of psoriasis are usually absent. Features on electron microscopy include a decreased number of keratin filaments and desmosomes, enlarged intercellular spaces, parakeratosis with lipid-like vacuoles, large numbers of lamellar granules, and focally split basal lamina.[24]

Pityriasis rubra pilaris is frequently misdiagnosed. Confusion with psoriasis presents the major diagnostic problem. Early PRP of the scalp can mimic seborrheic dermatitis. Children with acute-onset PRP may be misdiagnosed as having Kawasaki disease; and occasionally, PRP can be confused with symmetric progressive erythrokeratodermia. Phrynoderma,[25,26] caused by vitamin A deficiency, gives a somewhat similar appearance to the skin as PRP, as may eczematous eruptions caused by vitamin B deficiency. Both dermatomyositis[27] and subacute cutaneous lupus erythematosus[28] may present with similar cutaneous findings. In children, the usual working diagnosis is atopic dermatitis. Because PRP may develop into a generalized exfoliative reaction, a host of other diseases must be differentiated. These include drug reactions, contact dermatitis, and cutaneous T-cell lymphoma.

Because of the relative rarity of PRP, the ability to perform randomized, double-blind, placebo-controlled trials assessing treatment options (Table 2) is limited. In addition, the value of treatment is difficult to assess, as the clinical course is so variable for each of the different types of PRP. In general, the inherited forms of PRP tend to persist throughout life, while the sporadically acquired forms tend to resolve spontaneously. Topical medications such as emollients may be used to relieve symptoms of dryness and cracking. As a rule, topical corticosteroids are not very effective in general treatment, although they may be effective in reducing pruritus. In severe cases, acitretin or isotretinoin may be useful. Isotretinoin in doses of 0.5 to 1.5 mg/kg/day may induce prolonged remissions or cures. In these cases, it may take six to nine months for full involution to occur, and tapering of the drug may prevent recurrence.[29,30] Acitretin in doses of 10 to 75 mg/day is also effective over a course of several months.[31,32] However, results with retinoids are unpredictable, with some patients showing dramatic clearing while others appearing to be resistant to systemic retinoids. Methotrexate has been reported to lead to significant clinical improvement in doses of 2.5 to 30mg/week either alone or in combination with oral retinoids. In general, the response to methotrexate takes approximately six to eight weeks, and full remission is seen in three to four months. Variable results are seen with topical calcipotriol,[33] extracorporeal photochemotherapy,[34,35] azathioprine,[36] infliximab,[37] and cyclosporine A.[38-40] While systemic steroids can reduce inflammation and may be helpful in the early part of the disease, they are required at levels that usually lead to side effects. Although ultraviolet light runs the risk of exacerbating the disease,[41-43] there are some reports of success with narrowband UVB, UVA1, or PUVA alone or in combination with an oral retinoid.[44,45]

Conclusion

Pityriasis rubra pilaris is a rare group of hyperkeratotic, papulosquamous diseases that can be acquired or inherited. The variability in the way this disease presents often results in a delay in diagnosis that deters appropriate treatment. Fortunately, the majority of patients presenting with PRP have a favorable prognosis. Our case demonstrates many of the features of classic PRP. Further research is needed to better understand the etiology of this condition, and randomized, double-blind, placebo-controlled trials are needed to better assess the various treatment options.

References:

1. White, K.L. (2003). Pityriasis rubra pilaris. Online Journal of Dermatology. 2003;9:6.
2. Betlloch I, Ramon R, Silvestre JF, Carnero L, Albares MP, Banuls J. Acute juvenile pityriasis rubra pilaris: a superantigen mediated disease? Pediatr Dermatol. 2001;18:411-4.
3. Lambert DG, Dalac S. Nail changes in type 5 pityriasis rubra pilaris. J Am Acad Dermatol.1989;21:811-2.
4. Baden HP, Roth SI. Oral lesions in pityriasis rubra pilaris. Oral Surg Oral Med Oral Pathol. 1968;25:691-4.
5. Lister RK, Perry JD, Cerio R. Pityriasis rubra pilaris and a seronegative polyarthritis. Br J Dermatol. 1997;137:318-9.
6. Nakafusa J, Misago N, Narisawa Y. Pityriasis rubra pilaris in association with polyarthritis. Dermatology. 2002;205:298-300.
7. Sanchez-Regana M, Lopez-Gil F, Salleras M, Umbert P. Pityriasis rubra pilaris as the initial manifestation of internal neoplasia. Clin Exp Dermatol. 1995;20:436-8.
8. Reinhardt LA, Rosen T. Pityriasis rubra pilaris as the initial manifestation of leukemia. Cutis. 1983;31:100-2.
9. Miralles ES, Nunez M, De Las Heras ME, Perez B, Moreno R, Ledo A. Pityriasis rubra pilaris and human immunodeficiency virus infection. Br J Dermatol. 1995;133:990-3.
10. Auffret N, Quint L, Domart P, Dubertret L, Lecam JY, Binet O. Pityriasis rubra pilaris in a patient with human immunodeficiency virus infection. J Am Acad Dermatol. 1992;27:260-1.
11. Blauvelt A, Nahass GT, Pardo RJ, Kerdel FA. Pityriasis rubra pilaris and HIV infection. J Am Acad Dermatol. 1991;24:703-5.
12. Griffiths WA. Pityriasis rubra pilaris - an historical approach. Trans St Johns Hosp Dermatol Soc.

1975;61:58-69.
13. Griffiths WA. Pityriasis rubra pilaris--an historical approach. 2. Clinical features. Clin Exp Dermatol. 1976;1:37-50.
14. Gelmetti C, Schiuma AA, Cerri D, Gianotti F. Pityriasis rubra pilaris in childhood: a long-term study of 29 cases. Pediatr Dermatol. 1986;3:446-51.
15. Griffiths A. Pityriasis rubra pilaris. Etiologic considerations. J Am Acad Dermatol. 1984;10:1086-8.
16 Arnold AW, Buechner SA. Circumscribed juvenile pityriasis rubra pilaris. J Eur Acad Dermatol Venereol. 2004;18:705-7.
17. Vanderhooft SL, Francis JS, Holbrook KA, Dale BA, Fleckman P. Familial pityriasis rubra pilaris. Arch Dermatol. 1995;131:448-53.
18. Martin AG, Weaver CC, Cockerell CJ, Berger TG. Pityriasis rubra pilaris in the setting of HIV infection: clinical behaviour and association with explosive cystic acne. Br J Dermatol. 1992;126:617-20.
19. Hoover WD Jr, Maize JC. Focal acantholytic dyskeratosis occurring in pityriasis rubra pilaris. Am J Dermatopathol. 1990;12:321-3.
20. Kao GF, Sulica VI. Focal acantholytic dyskeratosis occurring in pityriasis rubra pilaris. Am J Dermatopathol. 1989;11:172-6.
21. Howe K, Foresman P, Griffin T, Johnson W. Pityriasis rubra pilaris with acantholysis. J Cutan Pathol. 1996;23:270-4.
22. Cowen P, O'Keefe R. Pityriasis rubra pilaris and focal acantholytic dyskeratosis. Australas J Dermatol. 1997;38:40-1.
23. Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris. A comparative analysis with psoriasis. J Cutan Pathol. 1997;24:416-24.
24. Kanerva L, Lauharanta J, Niemi KM, Lassus A. Ultrastructure of pityriasis rubra pilaris with observations during retinoid (etretinate) treatment. Br J Dermatol. 1983;108:653-63.
25. Nakjang Y, Yuttanavivat T. Phrynoderma: a review of 105 cases. J Dermatol. 1988;15:531-4.
26. Niemi KM, Kousa M, Storgards K, Karvonen J. Pityriasis rubra pilaris. A clinico-pathological study with a special reference to autoradiography and histocompatibility antigens. Dermatologica. 1976;152:109-18.
27. Requena L, Grilli R, Soriano L, Escalonilla P, Farina C, Martin L. Dermatomyositis with a pityriasis rubra pilaris-like eruption: a little-known distinctive cutaneous manifestation of dermatomyositis. Br J Dermatol. 1997;136:768-71.
28. Boyd AS, Zemtsov A, Neldner KH. Pityriasis rubra pilaris presenting as subacute cutaneous lupus erythematosus. Cutis. 1993;52:177-9.
29. Goldsmith LA, Weinrich AE, Shupack J. Pityriasis rubra pilaris response to 13-cis-retinoic acid (isotretinoin). J Am Acad Dermatol. 1982;6:710-5.
30. Dicken CH. Isotretinoin treatment of pityriasis rubra pilaris. J Am Acad Dermatol. 1987;16:297-301.
31. Blanchet-Bardon C, Nazzaro V, Rognin C, Geiger JM, Puissant A. Acitretin in the treatment of severe disorders of keratinization. Results of an open study. J Am Acad Dermatol. 1991;24:982-6.
32. Dicken CH. Treatment of classic pityriasis rubra pilaris. J Am Acad Dermatol.1994;31:997-9.
33. Van de Kerkhof PC, Steijlen PM. Topical treatment of pityriasis rubra pilaris with calcipotriol. Br J Dermatol. 1994;130:675-8.
34. Haenssle HA, Bertsch HP, Emmert S, Wolf C, Zutt M. Extracorporeal photochemotherapy for the treatment of exanthematic pityriasis rubra pilaris. Clin Exp Dermatol. 2004;29:244-6.
35. Hofer A, Mullegger R, Kerl H, Wolf P. Extracorporeal photochemotherapy for the treatment of erythrodermic pityriasis rubra pilaris. Arch Dermatol. 1999;135:475-6.
36. Hunter GA, Forbes IJ. Treatment of pityriasis rubra pilaris with azathioprine. Br J Dermatol. 1972;87:42-5.
37. Liao WC, Mutasim DF. Infliximab for the treatment of adult-onset pityriasis rubra pilaris. Arch Dermatol. 2005;141:423-5.
38. Wetzig T, Sticherling M. Juvenile pityriasis rubra pilaris: successful treatment with ciclosporin. Br J Dermatol. 2003;149:202-3.
39. Rosenbach A, Lowe NJ. Pityriasis rubra pilaris and cyclosporine. Arch Dermatol. 1993;129:1346-8.
40. Meyer P, van Voorst Vader PC. Lack of effect of cyclosporin A in pityriasis rubra pilaris. Acta Derm Venereol. 1989;69:272.
41. Iredale HE, Meggitt SJ. Photosensitive pityriasis rubra pilaris. Clin Exp Dermatol. 2006;31:36-8.
42. Khoo L, Asawanonda P, Grevelink SA, Taylor CR. Narrowband UVB-associated lesional blisters in pityriasis rubra pilaris. J Am Acad Dermatol. 1999;41:803-4.
43. Yaniv R, Barzilai A, Trau H. Pityriasis rubra pilaris exacerbated by ultraviolet B phototherapy. Dermatology. 1994;189:313.
44. Kirby B, Watson R. Pityriasis rubra pilaris treated with acitretin and narrow-band ultraviolet B (Re-TL-01) Br J Dermatol. 2000;142:376-7.
45. Herbst RA, Vogelbruch M, Ehnis A, Kiehl P, Kapp A, Weiss J. Combined ultraviolet A1 radiation and acitretin therapy as a treatment option for pityriasis rubra pilaris. Br J Dermatol. 2000;142:574-5.

Osteopathic Manipulation in Dermatology

Stephen C. Verral, D.O., MPH,* Reagan B. Anderson, D.O., M.P.H., M.C.S., Steven K. Grekin, D.O., F.A.O.C.D.***
**Oakwood Southshore Medical Center, Trenton, Michigan*
***Lieutenant, First Reconnaissance Battalion Surgeon-DMO, Camp Pendleton, California*

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. government.

ABSTRACT

While there are numerous publications and reviews of the use of osteopathic manipulation in various medical specialties, to date, there are no published articles on the use of osteopathic manipulation in the field of dermatology. The authors present an argument for pursuing an evidenced-based approach to osteopathic manipulation in dermatology as well as case reports on the use of osteopathic manipulation in a clinical dermatology setting.

Introduction

Since its inception, osteopathy has been a unique conceptualization of medical intervention. Andrew Taylor Still pioneered a revolutionary and novel approach to health during a time when medicine often did more harm than good.[1] Today, both allopathic and osteopathic medicine seek to increase the safety and efficacy of disease treatments through evidence-based medicine (EBM).[2,3]

While osteopathic physicians should embrace this trend in medicine, it is important that we remember the heritage from which our practice springs. Our foundations are epistemologically distinct from every other healthcare profession. Ours is one of finding and encouraging the health in our patients and not simply diagnosing and treating disease.[4] The osteopathic heritage has equipped its practitioners with a myriad of tools that can be used to encourage the patient's health as well as treat the disease process. Osteopathic physicians now have the opportunity to employ every efficacious and safe treatment modality that currently exists or is yet to be discovered. Our potential is unlimited.

Due to the steadfast efforts of current and past osteopathic physicians, the inherent validity of the practice of osteopathic medicine is accepted in the U.S. medical system. Now that the fight is over, there is freedom to branch out and determine if our unique philosophy of medical care can be validated scientifically as well as improve the quality of care we offer.

The osteopathic and allopathic practices of dermatology are often very similar. While dermatologic osteopathic physicians are thoroughly acquainted with the concepts of structure and function and the ability of the body to heal itself, there is little to no EBM to support osteopathic manipulative medicine (OMM) in dermatologic practice. However, the wisdom of a mind, body, and spirit approach is rapidly gaining acceptance even in allopathic circles; and there is a palpable thirst in society for alternative approaches to medicine.[5,6,7]

The use of complementary or alternative medicine has drastically increased in the last decade. One study found that in 1998, Americans spent $27 billion on alternative medicine and $29.3 billion for all traditional-physician services.[5] Another study demonstrated that 26% of patients with psoriasis, 22% with eczema, and 20% with unknown "rash" sought alternative treatments in England. In the latter study, osteopathy was third in the list of alternative practices most utilized.[6] Alternative treatments, such as osteopathy, are not only well received but are also increasingly being pursued by the patient population.[8] However, the research has not yet been done to support the use of an osteopathic manipulative touch in dermatologic care.

Evidence-based Medicine

Evidence-based medicine (EBM) is the integration of the traditional wisdom of practical experience with reproducible evidence from research.[3] The highest quality of healthcare can be achieved with this approach because it forces physicians to examine practices that are founded on intuition and unscientific methodologies. EBM dictates a standard of care that should be reproducible regardless of where or by whom its findings are implemented.[2,3] Having properly conducted research with statistically relevant outcomes adds validity, projected efficacy, and safety to those treatments.[5,6] This helps to demystify the practice of medicine. EBM is an invaluable tool to help validate clinical experience with the most current and reproducible research, thus offering evidence-informed medicine to our patients.[2,3] It is inaccurate to say that non-EBM approaches are not founded on research; however, it is accurate to say that EBM does demand a better and more reproducible approach to medical care.[2]

Even though the concepts of mind, body, and spirit have crept into mainstream allopathic and osteopathic dermatology, there is a paucity of EBM concerning the efficacy of distinctly osteopathic treatments. The role of the mind and spirit (e.g. stress) affecting multiple disease processes has been well documented. Acne, atopic dermatitis, and psoriasis are just a few of the dermatologic processes which have been linked to stress as an exacerbating factor.[9] The psychoneuroimmunologic and neuroendocrine changes that result from stress have a profound and scientifically supported influence on the severity of multiple disease processes, including numerous immunologically mediated dermatologic diseases.[10,11] However, there is a lack of clinical evidence that OMM can decrease the psychological morbidity and severity of the overall disease process.

A literature search was performed in PubMed for "Dermatology and Osteopathic Manipulation," and no articles were found. Another search was submitted to PubMed for "Dermatology and Manipulation," and 22 articles were found; but none of them related to OMM. "Dermatology and Osteopathic" was entered, and five articles were retrieved; however, they merely came from osteopathic institutions and were not concerning OMM. Finally, one article from 1961 was available that discussed OMM in the treatment of measles.[12] The Osteopathic Literature Database, Ostmed, was also searched, and 18 articles were found. Of those 18, six related to OMM. However, the most recent of these six articles was from 1951.[13,14,15,16,17,18]

Literature searches yield better results when massage therapy is entered in the context of dermatologic issues. Everything from the lymphatic drainage associated with kaposiform hemangioendotheliomas to the reduction of stress improving exacerbations of atopic dermatitis is represented.[9,10,19,20,21,22] While the results of these studies cannot be extrapolated to encompass OMM due to the differences in training and techniques, they do suggest that researching the efficacy of

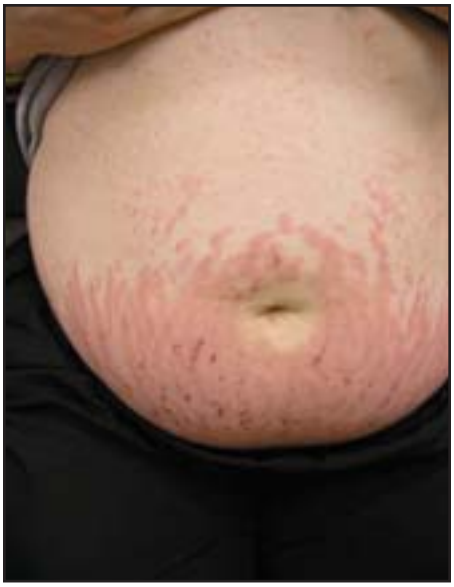


Figure 1a

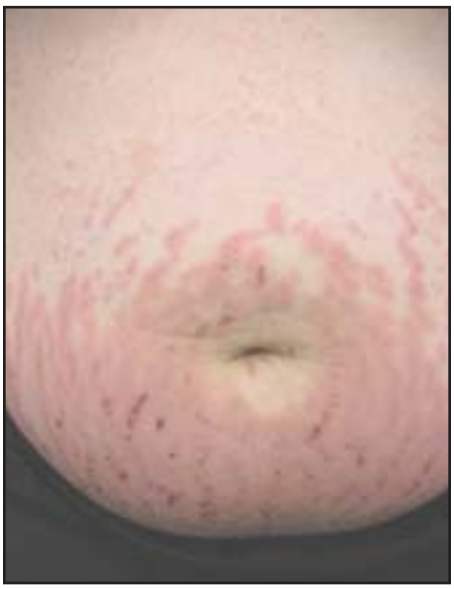


Figure 1b

manipulative therapy for dermatologic conditions is possible.

Osteopathic medicine has been used in many different specialties with varying degrees of success depending on the diagnosis.[23] The justification to perform the needed research to provide EBM is well founded. The OMM success in other clinical specialties, the documented effect of psychoneuroimmunology on many dermatologic conditions, and the successful research of other manipulative specialties all support the potential efficacy of OMM in dermatologic care.

Case Reports

Case Report #1: A 34-year-old, primigravida, white female in her thirty-sixth week of gestation presented with severe itching and red rash on her abdomen. The rash began in her stretch marks, and over three days progressively spread over her abdomen. On physical examination, the patient had erythematous plaques and papules on her abdomen concentrated in the abdominal striae and sparing the peri-umbilical area (Figure 1a). The patient was diagnosed with pruritic urticarial papules and plaques of pregnancy (PUPPP). The patient was in obvious discomfort from the severe pruritus but was resistant to using any medication, oral or topical, because of concerns for her unborn child. In an attempt to offer some relief to the patient, osteopathic manipulation was performed on the patient. The patient was unable to lie comfortably in a supine position, so she was placed in an examining chair slightly reclined and with her knees slightly bent. The thoracic inlet was opened and balanced using an indirect approach. Paraspinal inhibition was performed in an attempt to decrease the patient's sympathetic tone. Upon completion of the prescribed course of manipulation, the patient experienced a decrease in her pruritus as well as a visible decrease in erythema (Figure 1b). The patient was again offered a prescription for topical steroids, which she declined. The patient was able to control her pruritus with over the counter 1% hydrocortisone until delivery.

One of the most promising fields of study is that of the immunologically mediated cutaneous diseases. Using OMM to mitigate the physiologic process by decreasing stress, opening lymphatic drainage, and increasing skin blood flow could potentially improve quality of care. For instance, all of these factors combined might help to decrease the necessity or amount of immunomodulating agents necessary to treat the condition. The patient in Case Report #1 experienced a notable decrease in her discomfort with osteopathic manipulation and was able to tolerate a lower class of topical steroid, decreasing the risk of side effects to herself and her unborn child. While one example is not indicative of a proven approach to treatment, it does demonstrate the potential for osteopathic manipulation as an adjuvant treatment for certain inflammatory disorders.

Case Report #2: A 56-year-old, white female presented three days post wide excision of a squamous cell carcinoma of her left dorsal hand with a complaint of increasing swelling and tightness at the excision site. On physical examination, the patient had significant edema and increased tension at the suture site. There was minimal erythema and a serosanguinous discharge upon palpation (Figure 2a). The patient was experiencing lymphedema secondary to her surgery. Instead of removing the sutures and opening up the excision site, which would have delayed healing and worsened the cosmesis, we elected to perform osteopathic manipulation. The patient was placed in a supine position on the examining table. The thoracic inlet was opened using an indirect technique, and effleurage was performed in the direction of lymphatic flow starting at the excision site. Significant reduction of edema and discomfort was achieved without removal of the sutures (Figure 2b).

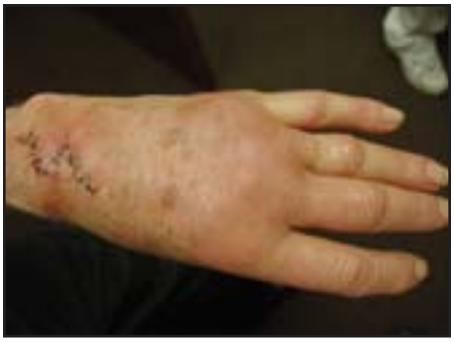


Figure 2a

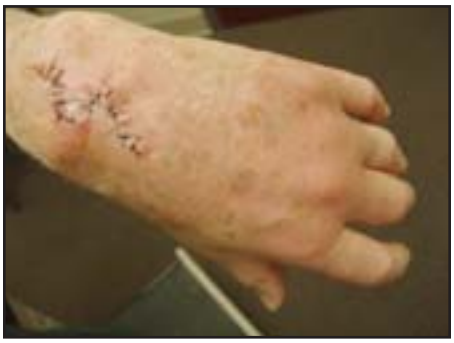


Figure 2b

Through osteopathic manipulation, the patient in Case Report #2 was able to have her symptoms relieved without delaying wound healing, increasing her risk of infection by re-opening the wound or affecting the cosmetic result of the closure. There are numerous publications demonstrating the benefits of osteopathic manipulation in surgical patients.[23] The benefits of osteopathic manipulation can and should be applied to our dermatologic surgeries to improve the care we can give our patients.

Conclusion

From our own clinical practices and the current understanding of disease processes, there is ample justification to actively pursue research into the efficacy of OMM for certain dermatologic conditions. This process will take time but will ultimately strengthen and add validity to the field of osteopathic medicine.

If the studies are done properly, and the results show that OMM does not offer a statistically significant advantage, then our set of dermatologic practices will continue as is, and osteopathic medicine will continue the proud tradition of only offering treatments that do no harm. If, however, the studies show a statistically significant benefit with the addition of OMM to traditional therapy, our patients will receive a higher quality of care.

However, incorporating OMM into daily dermatologic practice may be difficult. Conducting a proper osteopathic examination and treatment takes more time than is reasonable for most busy dermatology clinics. This may be a significant factor for many physicians, and there is no reason that the osteopathic dermatologist has to offer OMM. If EBM suggests that OMM is beneficial for certain dermatologic patients, they can be referred to practitioners who specialize in OMM. Validation of OMM by EBM will be beneficial for our patients and our profession.

References:

1 Andrew Taylor Still Establishes Osteopathy. Retrieved January 18, 2006 from the AOA website http://history.aoanet.org/Osteopathy/osteopathy.htm.

2 Pencheon, D. (2005). What's next for Evidence Based Medicine? Evidence Based Healthcare and Public Health 9(5): 319-21.

3 White, B. Making Evidence Based Medicine Doable in Everyday Practice. Family Practice Management 2004;11(2): 51-8

4 What is Osteopathic Medicine? Retrieved January 19, 2006 from University of North Texas Health Science Center's website http://www.hsc.unt.edu/patientcare/what.cfm.

5 Barrett, B, Marcband, L, Scheder, J., Applebaum, D, Plane MB et al. What Complementary and Alternative Medical Practitioners Say About Health and Health Care. Annals of Family Medicine 2(3):253-9.

6 Baron et al. Use of complimentary medicine among outpatients with dermatologic conditions within Yorkshire and South Wales, United Kingdom. JAAD 2005;52(4):589-94.

7 Body-Mind-Spirit: Index of Articles on Insights to Healthy Living. Retrieved January 18, 2006 from http://www.all-natural.com/art-indx.html.

8 Eisenberg, DM, Davis, RB, Ettner, SL, Appel, S, Wilkey, S, et al. Trends in Alternative Medicine Use in the United States: results of a follow-up national survey. JAMA 1998; 280(18):1569-75.

9 Feldman, S, Behnam, SM, Behnam, SE, Koo, JYM Involving the patient: Impact of Inflammatory Skin Disease and Patient Focused Care. Journal of the American Academy of Dermatology 2005; 53(1s1): S78-85.

10 Gupta, MA. (2005). Psychocutaneous Disease. Dermatologic Clinics 23(4):xiii-xiv.

11 Gupta, MA, Lanius, RA, Van der Kolk, BA. Psychologic Trauma, Post Traumatic Stress Disorder, and Dermatology. Dermatologic Clinics 2005; 23(4): 649-56

12 Purse, FM. Clinical Evaluation of Osteopathic Manipulative Therapy in Measles. Journal of the American Osteopathic Association 1961;61:274-6.

13 Keene, WH. Dermatology: adjustment of lesioned areas assists normal circulation in herpes zoster. The Osteopathic Profession 1951; 18(12): 18-19, 48.

14 Brown, RR. Dermatology: Osteopathic Therapy Scientifically Applied Illustrated in Handling of Acne Vulgaris. The Osteopathic Profession 1947;14(9):20-21, 44.

15 Fleming, TA. Dermatology: Common Skin Conditions of Foot: A Report on Medicinal Aids, Emphasising Therapy in Diabetic Complications. The Osteopathic Profession 1943;10(7): 16-19, 46.

16 Scardino, AE. Dermatology: Discussion of Common Lesions: Chemophysical Therapy and Manipulation Efficacious for Refractory Skin Changes. The Osteopathic Profession 1942; 9(7): 18-21, 42.

17 Hamilton, RE. Drugless Dermatology. The Journal of Osteopathy 1910; 17(1):31-33.

18 Smith, RK, Fox, GA. Drugless Dermatology. The Journal of Osteopathy 1909; 16(12): 900-904.

19 Gruman, A, Liang, MG, Mulliken, JB, Fishman, SJ, Burrows, PE, Kozakewich, HPW et al. Kaposiform hemangioendothelioma without Kasabach-Merrit Phenomena. Journal of the American Academy of Dermatology 2005; 52(4): 616-22.

20 Schachner, L. Atopic Dermatitis Symptoms Decreased in Children Following Massage Therapy. Pediatric Dermatology 1998; 15(5): 390-5.

21 Marshal, M. Stress Management in Dermatology Patients. Nurs. Stand. 1991;5(24): 29-31.

22 Field, T. Massage Therapy for Skin Conditions in Young Children. Dermatologic Clinics 2005; 23(4): 717-21.

23 Ward, R. Section VII: Osteopathic Consideration in the Clinical Specialties. In Foundations of Osteopathic Medicine 1997. Williams and Wilkins:

Multinucleate Cell Angiohistiocytoma: A Case Report and Review of the Literature

James J. Briley, Jr., D.O. *, Marvin S. Watsky, D.O. **, David B. Kessler, D.O. ***
** 1st year dermatology resident, St. John's Episcopal Hospital – South Shore, Far Rockaway, New York*
*** Dermatology Residency Program Director, St. John's Episcopal Hospital – South Shore, Far Rockaway, New York*
**** Massapequa Dermatology, Massapequa, New York*

ABSTRACT

Multinucleate cell angiohistiocytoma (MCAH) was first described by Smith and Wilson-Jones in 1985. This is a rare and benign, fibrohistiocytic, vascular proliferation mainly affecting the acral sites of middle-aged women. We will present an atypical presentation of MCAH in a male – the first reported case of MCAH involving the back and scalp. In addition, we will discuss the clinical presentation, histopathological and immunohistochemical features, and treatment options of MCAH through a review of the literature.

Case Report

History

A 55-year-old, obese, Caucasian male with a past medical history only significant for diabetes type 2 presented with the complaint of violaceous "bumps" grouped together on his back and left posterior shoulder that first appeared several months prior. Since first noticed, the papules had become more confluent, and the affected area had grown slightly larger in diameter according to his wife. Nonetheless, they were completely asymptomatic to the patient. He denied any recent travel, illness, insect bites or trauma in relation to the onset or location of the lesions. His family history was negative for any skin conditions or similar lesions. He was prompted by his wife to seek the advice of a dermatologist.

Physical Exam

Examination revealed a 4.5 cm x 7.0 cm, dusky, red-to-violaceous, sharply demarcated plaque with irregular borders located in the mid back (Figures 1, 2, & 3). Similar, smaller plaques as well as solitary papules were noted on the upper back, posterior left shoulder, and left parietal scalp. These plaques consisted of multiple, solitary and coalescing well-circumscribed papules with a red-to-dusky-brown, violaceous hue. Also noted was superficial scale haphazardly arranged within the plaques and outside the borders of the lesions, negative for fungal elements via light microscopy and potassium hydroxide preparation. The plaques were indurated upon palpation, but blanchable on diascopy. Total body examination was performed and was negative for lymphadenopathy or other vascular-like lesions. Incidentally, the patient was found to have numerous, scattered fibroepithelial polyps on the back, axillae, and neck in addition to a verrucous-like papule of the right temple.

Evaluation and Course

At his next visit, a 4mm punch biopsy of the largest plaque located in the mid back was performed (Figure 1). Our differential diagnosis at this time included: Kaposi's sarcoma, histiocytoma, sarcoidosis, and vascular neoplasm of unknown etiology. While awaiting biopsy results, the patient had a complete blood count, serum chemistry panel, lipid profile and urinalysis, all of which were within normal limits.

Histopathological exam revealed a hyperplastic epidermis with numerous small vascular spaces in the upper two-thirds of the dermis lined with plump endothelial cells along with a perivascular mononuclear cell infiltrate of plasma cells and large numbers of bizarre-shaped multinucleate cells admixed throughout (Figures 4, 5, 6, & 7). These findings were consistent with a diagnosis of multinucleate cell angiohistiocytoma (MCAH). The patient was given treatment options of wide excision, referral for argon laser treatment, or observation. He chose observation because of the lack of symptoms and the benign nature of MCAH, as will be discussed.

Subsequent to the first biopsy, a second punch biopsy of the patient's left parietal scalp was performed two and one-half years later because of changing features and irritation caused by combing his hair. Histopathological exam revealed similar findings as the first biopsy, consistent with MCAH. At this time, the patient decided to use topical steroid treatment to reduce the irritation, followed again by observation only.

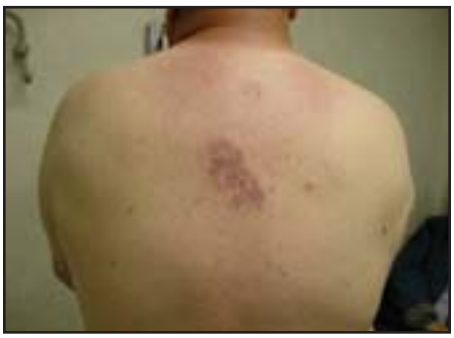


Figure 1

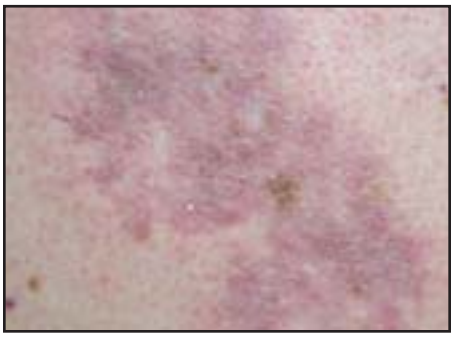


Figure 2

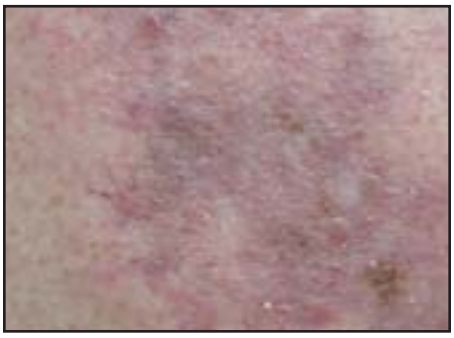


Figure 3

Discussion

Epidemiology

First described by Smith and Wilson-Jones in 1985,[1,2] MCAH is a benign, fibrohistiocytic and vascular proliferation of unknown etiology. It is a rare disorder with fewer than 50 cases reported in the literature as of 2002.[3] In fact, the first well-documented case of MCAH in the United States was not until 1994.[4] Despite such few cases, it is thought to be underdiag-

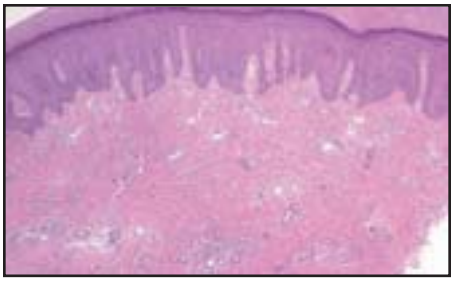


Figure 4

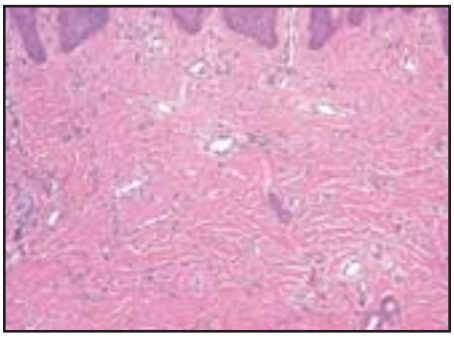


Figure 5

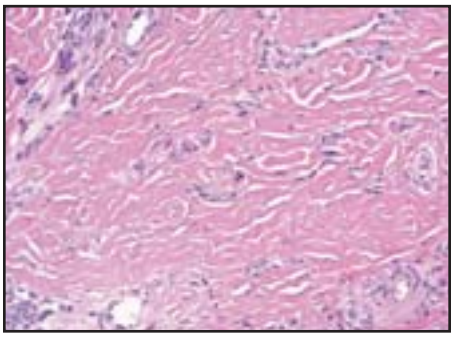


Figure 6

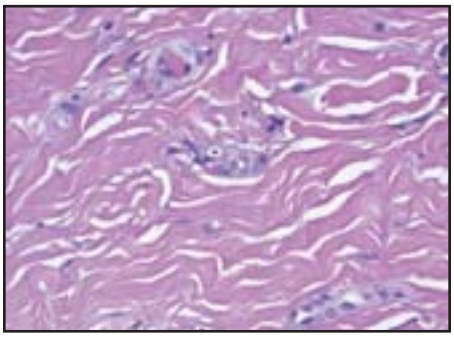


Figure 7

nosed and more prevalent than represented in the literature.

MCAH predominantly affects middle-aged women between the ages of 37 and 66 with an average age of onset of 52 and a female-to-male ratio of approximately 5:1.

Generally, it is an asymptomatic dermatosis that affects the upper and lower extremities, acral sites, and facial structures, either unilaterally or, less commonly, bilaterally.[5] Though typically asymptomatic, pruritis has been reported in two separate cases.[6]

Clinical Presentation

The characteristic lesions of MCAH are described as multiple discrete but grouped, well-circumscribed papules 2 mm to 15 mm in size, either dome-shaped or flat-topped, with a dull, erythematous-to-violaceous hue.[7,8] They are firm in consistency, non-tender to touch, and have been known to exhibit an annular distribution[5,6] or to coalesce to form plaque-like lesions.[9] And though the lesions of MCAH are most often localized in distribution, there has been one case report of generalized MCAH in a 24-year-old male, the youngest person reported to have had MCAH.[10]

Due to the presentation and location, the clinical differential diagnosis of MCAH should include such entities as: granuloma annulare, lichen planus, Kaposi's sarcoma, lupus erythematosus, arthropod reaction, sarcoidosis, fibrous papule, histiocytoma, lymphocytoma, bacillary angiomatosis, and microvenular angioma.[4, 7, 11] However, diagnosis of MCAH remains a histopathological one.

Histopathology

On hematoxylin and eosin, MCAH usually exhibits a hyperplastic epidermis along with classical features of increased blood vessels and multinucleated cells located most prominently in the upper reticular dermis and the subpapillary plexus. The increased vasculature consists of small capillaries, small venules, and few if any small arterioles, all with plump endothelial cells protruding into the vessel lumina and concentrated around more mature blood vessels. The multinucleated cells contain three to eight nuclei, closely aggregated in a ring-like fashion, with scalloped or angulated borders.[3,4] In addition to the characteristic findings, there is often a perivascular infiltrate of lymphocytes, plasma cells and/or neutrophils that is occasionally found in association with an increased number of mast cells and decreased number of elastic fibers.[3,7,12,13]

Although multinucleate cells are one of the most distinguishing features of MCAH, they are not specific to MCAH. They can also be seen in numerous other conditions including pleomorphic lipoma, pleomorphic leiomyoma, desmoplastic Spitz's nevus, ancient schwannoma, giant cell fibroblastoma, and sometimes chronic acrochordons.[14]

Since the diagnosis of MCAH is a histological one, it is important to recognize and be able to differentiate MCAH from other similarly appearing histological lesions, namely angiofibromas and dermatofibromas. In angiofibromas, the collagen fibers are oriented vertically in the upper dermis and have a perifollicular onion-skin effect. Also, angiofibromas contain an increased number of large vessels in the upper dermis. In contrast, MCAH has its collagen bundles arranged in a typically horizontal fashion with an increased number of small vessels in the upper dermis as previously mentioned.[12] In regard to dermatofibromas, they usually have flattened rete ridges and thickened and somewhat-circumscribed collagen bundles and are usually without perivascular infiltrates, whereas the lesions of MCAH often have a hyperplastic epidermis with normal-appearing collagen and a perivascular infiltrate.[4]

Immunohistochemistry

Immunohistochemical staining has shown greater than 50 percent of the mononuclear interstitial cell population in MCAH to be factor XIIIa positive, a marker for fibrohistiocytic differentiated cells. This fact, in conjunction with the marked increase in small vasculature, was used to validate the descriptive term 'angiohistiocytoma' in the naming of MCAH. In contrast to the mononuclear interstitial cells, the bizarre multinucleated cells are factor XIIIa negative but strongly positive for vimentin, an intermediate filament. It is thought that these multinucleate cells in MCAH represent degenerate or "effete" connective tissue cells that, under prolonged, chronic stimulation, have lost their function to mitotically divide. In essence, they have become "sterile" and functionless.[5]

Course and Prognosis

MCAH is a completely benign disorder. In fact, to prove its benign nature, multinucleate cells of MCAH were cultured alongside spindle cells of Kaposi's sarcoma, known to be highly proliferative and invasive as well as capable of replication through multiple cell-culture passages. The cultures of the multinucleate cells of MCAH demonstrated no invasive qualities, as assessed by their inability to traverse the basement membrane. In addition, in vitro amplification of the multinucleate cells of MCAH was unsuccessful, suggesting that these cells are degenerate or effete cells rather than transformed cells, as previously mentioned.[15]

The course of MCAH is an indolent one, progressing slowly over months to years with no tendency of self-resolution.[7] However, spontaneous resolution has been reported in two cases.[4,5] To date, there has been no evidence of associated systemic disease.[7,12]

Treatment

Because of its benign nature, treatment of MCAH is not necessary. However, treatment is often carried out because of cosmetic or functionality issues. Among the different treatment options, surgical excision is the most common modality reported in the literature. The results of surgical excision appear to be long-standing. In fact, one case reported no recurrence subsequent to surgical excision with five years of

follow-up.[5,7]

Other treatment modalities include the use of lasers in the treatment of MCAH. Recently, there have been two reported cases of MCAH successfully treated with CO2 laser therapy.[16] But the most often reported use of laser therapy has been with the argon laser, which emits light in the blue-green portion of the visible spectrum with wavelengths of 475.0 nm to 514.5 nm. With these particular wavelengths, the hemoglobin content within the small-vessel proliferation of MCAH is preferentially targeted as the chromophore, causing red-blood-cell destruction and thrombosis. Post-treatment biopsies have shown blood-vessel thrombosis and damage, with a reduction of inflammatory infiltrate.[11] The use of argon laser therapy has led to complete resolution of lesions of MCAH in several case reports, with good cosmetic results and without noticeable scarring.

Conclusion

MCAH is a rare, benign disorder of fibrohistiocytic and vascular proliferation of unknown etiology. However, it is thought to be more prevalent than reported because its histopathological characteristics were not described until the first reported case by Smith and Wilson-Jones in 1985. Still, more case reports need to be examined and further studies conducted to better understand the etiology and pathogenesis of this disorder. In our report, we add to the list two more sites of involvement of MCAH. Our case represents the first-known reported case of MCAH involving the back and scalp. Hopefully, greater awareness of this disorder by clinicians and pathologists will facilitate diagnosis and appropriate treatment options.

References:

1. Smith NP, Wilson-Jones E. Multinucleate cell angiohistiocytoma: a new entity. Br J Dermatol 1985; 113 (Suppl 29): 15-20.
2. Smith NP, Wilson-Jones E. Multinucleate cell angiohistiocytoma: a new entity. J Cut Pathol 1986; 13: 77.
3. Puig L, Fernandez-Figueras MT, Bielsa I, et al. Multinucleate cell angiohistiocytoma: a fibrohistiocytic proliferation with increased mast cell numbers and vascular hyperplasia. J Cutan Pathol 2002; 29: 232-237.
4. Shapiro PE, et al. Multinucleate cell angiohistiocytoma: A distinct entity diagnosable by clinical and histologic features. J Am Acad Dermatol 1994; 30 (3): 417-422.
5. Wilson-Jones E, Cerio R and Smith NP. Multinucleate cell angiohistiocytoma: an acquired vascular anomaly to be distinguished from Kaposi's sarcoma. Br J Dermatol 1990; 122: 651-663.
6. Cribier B, Gambini C, Rainero M, and Grosshans E. Multinucleate Cell Angiohistiocytoma: A Review and Report of Four Cases. Acta Derm Venereol 1995; 75: 337-339.
7. Smolle J, Auboeck L, Gogg-Retzer I, et al. Multinucleate cell angiohistiocytoma: a clinicopathological, immunohistochemical and ultrastructural study. Br J Dermatol 1989; 121: 113-121.
8. Kamino H and Pui J. Fibrous and Fibrohistiocytic Proliferations of the Skin and Tendons. In: Bolognia JL, Jorizzo JL, Rapini RP et al, editors. Dermatology. Philadelphia: Elsevier 2003. p. 1869.
9. Issa AA, Lui H, Shapiro J, and Trotter MJ. Plaque-Type Multinucleate Cell Angiohistiocytoma. J Cut Med Surg 1998; 3 (2): 112-114.
10. Chang SN, Kim HS, Kim SC, and Yang WI. Generalized multinucleate cell angiohistiocytoma. J Am Acad Dermatol 1996; 35 (2): 320-322.
11. Kopera D, Smolle J, and Kerl H. Multinucleate cell angiohistiocytoma: treatment with argon laser. Br J Dermatol 1995; 133: 308-310.
12. Annessi G, Girolomoni G, Giannetti A. Multinucleate Cell Angiohistiocytoma. Am J Dermatopathol 1992; 14 (4): 340-344.
13. Masouye L. Elastolytic Multinucleate Cell Angiohistiocytoma. Am J Dermatopathol 1997; 19 (4): 429.
14. Aloi F, Solaroli C, Tomasini C, Pippione M. Multinucleate cell angiohistiocytoma: a report of two cases. J Eur Acad Dermatol Venereol 1998; 11 (1): 51-54.
15. Sass U, Noel JC, Andre J, and Simonart T. Multinucleate cell angiohistiocytoma: report of two cases with no evidence of human herpes virus-8 infection. J Cutan Pathol 2000; 27: 258-261.
16. Vakeva L, Saksela O, and Kariniemi AL. Multinucleate Cell Angiohistiocytoma: A Report of Four Cases in Finland. Acta Derm Venereol 2003; 83: 222-223.

Acne Keloidalis Nuchae: A Retrospective Analysis of the Associated Bacteria

Michael R. Hohnadel, D.O.,* Bill V. Way, D.O., F.A.O.C.D.**
**3rd Year Dermatology Resident, North East Regional Medical Center. KCOM Dept of Dermatology, Texas Division*
***Chairman: K.C.O.M. Dept. of Dermatology, TX Division*

ABSTRACT

Acne keloidalis nuchae (AKN) is often associated with inflammatory papules and pustules from which bacteria can be cultured. These bacteria may represent a causative or exacerbating factor in AKN. This document is a retrospective analysis of bacterial culture results of AKN patients seen at the Dermatology Institute from January of 2004 through December of 2005. The types of bacteria present in AKN lesions and their sensitivity to common antibiotics were examined. In addition, the responses of the bacterially infected lesions to both topical and oral antibiotics as well as topical steroids were tabulated. Our results indicate that Staphylococcus aureus is the dominant bacteria in inflamed AKN lesions, followed in frequency by gram-negative organisms. These organisms may be multi-drug resistant. Analysis of treatment data suggests that a combination of antibiotics with a topical steroid is a more effective treatment than antibiotics alone at reducing inflamed lesions of AKN.

Introduction

Acne keloidalis nuchae (AKN) is a relatively rare condition of the posterior neck characterized by follicular papules and pustules, which may evolve into confluent, thickened, hairless plaques (Figure 1). The condition is most prevalent in adult black males between the ages of 20 and 50 years, but it can be seen in females and in other ethnic groups including Caucasians and Hispanics. These papules and plaques can result in physical discomfort and, with increased size, may become a significant cosmetic concern.

Many causes have been surmised for AKN. Originally, seborrheic dermatitis was often linked to exacerbations of this disease. Frequently, mechanical irritation to the posterior neck was cited as an initiating event in this affliction. More recently, an autoimmune-mediated process directed at the follicular unit has gained favor as the etiology of AKN.[1,2,3,4] Bacterial infection has also been implicated as a possible etiology or exacerbating factor in AKN.[1,2,3,4] The inflamed papules or pustules which occur sporadically during the course of the condition are often what leads a patient to seek medical attention. As lesions evolve, they often become keloidal plaques with draining sinuses that are positive for bacterial growth when cultured.

Physicians in our clinic have anecdotally reported achieving some success in controlling AKN lesions with the use of antibiotics. This document seeks to define the types of cultured bacteria associated with inflamed AKN lesions and to characterize their antibiotic sensitivities. The effectiveness of oral and topical antibiotics and topical steroid treatment for inflamed AKN lesions are also examined.

Methods

This study was conducted as a retrospective analysis through an internal chart review of 123 AKN patients treated in our office from January of 2004 through December of 2005. Inclusion criteria consisted of a diagnosis of AKN which was defined as follicular-based papules and pustules located on the posterior scalp and neck only. Exclusion criteria included several types of primary scarring alopecia, such as folliculitis decalvans or dissecting cellulitis, which could be confused with AKN. Patients with localized, simple folliculitis were also excluded.

Subjects who met the inclusion criteria were further characterized by age, race, sex and duration of disease. Aerobic bacterial culture and sensitivity results were recorded from cultures obtained exclusively from actively inflamed papules or pustules.

Subjects were divided into two (2) groups in order to assess the general effectiveness of oral and topical antibiotics versus topical steroids in the treatment of inflamed AKN lesions. The first group included patients who had received oral or topical antibiotics as treatment. The second group included patients who had received oral or topical antibiotics concomitantly with a topical steroid. There were no patients that received only topical steroids. The study subjects were further stratified into subgroups in order to evaluate if the administration of either a topical antibiotic or an oral antibiotic was more effective in treating inflamed AKN lesions. These subgroups included patients who received topical antibiotics alone, an oral antibiotic alone, or both topical and oral antibiotics. A similar set of subgroups of patients who had received topical steroids in addition to oral and/or topical antibiotics was also evaluated.

In order to assess the response to treatment of the AKN lesions, the patients' progress notes from their next scheduled office visit following treatment were examined, and the patients' condition was characterized as either improved or not improved based on the clinician's assessment. Patients were only included in the treatment portion of the study if they returned within two (2) months of receiving their prescribed treatment.

Figure 1

Results

A total of 62 patients met the inclusion criteria of the study. Included were 59 males and three females. Subject ages ranged from 19 to 58 years with an average age of 35 years and a mode of 32 years. Fifty-six (56) of the patients were African American, four (4) were Caucasian and two (2) were Hispanic. The average duration of the AKN lesions prior to seeking treatment was 2.3 years.

A total of 71 cultures, showing the types of bacteria isolated, were taken from 62 patients (Table I). Staphylococcus aureus was found to be the most dominant organism, representing 75% of the organisms cultured. Gram-negative bacteria including Citrobacter koseri, Enterobacter sp., Serratia marcescens and Acinetobacter baumannii represented the second most commonly cultured organisms, with other known pathogens representing 11% of cultures taken. Normal skin flora was cultured in 13% of cases. A number of other organisms were cultured with lower frequencies (Table I). No growth was demonstrated in 4 % of cultures.

Table II illustrates the susceptibility and sensitivity of the isolated bacteria to a commonly utilized panel of antibiotics. In general, the bacteria were found to be resistant to

Table I
Bacterial Organisms Cultured from Inflamed AKN Lesions

Bacteria		*Number of cultures positive*	*Percent of cultures*
Staphylococcus aureus	gm(+)	53	74.6%
Citrobacter koseri	gm (-)	3	4.2%
Enterobacter sp	gm (-)	3	4.2%
Serratia marcescens	gm (-)	1	1.4%
Acinetobacter baumannii	gm (-)	1	1.4%
Normal skin flora	n/a	9	12.7%
Coag-negative Staph	gm(+)	2	2.8%
Group B strep	gm(+)	2	2.8%
No growth	n/a	3	4.2%

Total number of cultures *71*
Note: Several cultures grew more than one organism.

Table II
Antibiotic-sensitivity Data for Aerobic Bacteria Cultured from AKN Lesions

Antibiotic	*Percent of Bacteria Sensitive*
Vancomycin	100.0%
Levofloxacin	100.0%
Rifampin	97.6%
Trimethoprim /Sulfa	95.5%
Clindamycin	91.3%
Ciprofloxacin	90.9%
Gentamicin	90.9%
TCN	80.5%
Cefazolin	78.6%
Erythromycin	77.3%
Amoxicillin/Clavulanic	74.5%
Oxacillin	73.3%
Ampicillin/Sulbactam	70.5%
Azithromycin	68.9%
PCN	15.2%

PCN. Only vancomycin and levofloxacin were found to be effective in 100% of cases cultured.

Table III illustrates the response to therapy of the bacterial isolates when treated exclusively with antibiotics to which the organisms were sensitive. The response of the bacterial isolates when treated with a combination of antibiotics to which the organisms were sensitive and with topical steroids is also found in Table III. Seventy-three percent (73%) of the group treated with an antibiotic alone improved, while 86% of those patients treated with an antibiotic combined with a topical steroid improved. The treatment data was also examined in order to determine if oral or topical antibiotics were more effective at treating inflamed AKN (Table IV). The data suggests that the combination of an oral antibiotic and a topical steroid with or without a topical antibiotic is the most effective treatment for inflamed AKN lesions. The limited size of the data set does limit the ability to draw irrefutable conclusions.

Discussion

A variety of bacteria were isolated from the inflamed AKN lesions of our subjects. The dominant organism isolated was Staphylococcus aureus. This isolate accounted for 75% of the pathogenic bacteria. This finding is not surprising due to the prevalence of Staphylococcus aureus on human skin both as a colonizing and a pathogenic organism. It is unclear whether the presence of Staphylococcus aureus represents the etiology of an AKN lesion, an exacerbating factor or merely a harmless colonizer. It is plausible that a low-grade bacterial infection with the accompanying host inflammatory response could result in and certainly would exacerbate AKN lesions by facilitating follicular inflammation with subsequent fibrosis.

Gram-negative, coliform bacteria with known human pathogenicity were also cultured from the AKN lesions. These include Citrobacter koseri, Enterobacter sp., Serratia marcescens and Acinetobacter baumannii. These organisms are normal residents of the human G.I. tract and frequently colonize other body areas. Although typically harmless to healthy individuals, they can be the etiology of pneumonia, urinary tract septicemia and a host of infections in immunocompromised patients.[5] As is the case with Staphylococcus aureus, the pathogenicity of these gram-negative organisms in AKN is uncertain.

Interestingly, normal skin flora was cultured in 13% of patients, and no growth was seen in 4%. This could indicate that too few bacteria were present in the lesions, that a sampling error occurred, or that poor specimen transport methods and/or poor lab technique were used. Also, these findings could indicate that the inflammatory process resulting in the pustule was independent of bacterial infection, as would be the case with an autoimmune-mediated etiology.

Bacterial sensitivities as shown in table II indicate that most AKN-associated bacteria are resistant to PCN and oxacillin. The bacteria cultured from the AKN lesions were sensitive to ciprofloxacin, clindamycin, gentamicin, levofloxacin, rifampin, trimethoprim/sulfamethoxazole and vancomycin greater than 90% of the time. Other agents listed in Table II were therapeutically less effective, with the bacteria being sensitive to Augmentin®, cefazolin and TCN 75%, 79% and 81% of the time, respectively. Nineteen percent (10 cases) of the 53 patients whose lesions revealed growth of Staphylococcus aureus were of the methicillin-resistant Staphylococcus aureus (MRSA) type. It is noteworthy that in other settings, the types of gram-negative bacteria isolated from these AKN lesions are well known for their multi-drug resistance. A review of the sensitivities from our cases revealed that the majority of the gram-negative organisms cultured were indeed multi-drug resistant.

Our evaluation of the effectiveness of treatment with antibiotics alone or in combination with a topical steroid (Table III) revealed that the combination of antibiotics and steroids was generally more effective (86% of treated cases improved) than antibiotics alone (73% of treated cases improved). Our attempt to determine whether oral antibiotics were more effective than topical antibiotics in the treatment of inflamed AKN lesions was limited by the small data set obtained. Table IV suggests that topical antibiotics are superior to oral antibiotics when utilized as monotherapy. However, the oral-antibiotic group only represented four (4) patients, as compared to the 11 patients in the topical-antibiotic monotherapy group. The combination of oral antibiotics and topical steroids, as well as the combination of oral antibiotics, topical antibiotics and topical steroids, yielded superior efficacy (100%) when compared to the treatment of inflamed AKN lesions with topical antibiotics alone. The small data set available for the topical antibiotics/topical steroid group limits the utility of this data.

The effectiveness data would seem to lend some support to a postulated autoimmune etiology of AKN, as steroids appear helpful in improving inflammatory lesions. However, the addition of a steroid to an antibiotic treatment regimen could simply be improving the underlying inflammation associated with a bacterial infection, resulting in more rapid visible improvement. It is noteworthy that those groups treated with antibiotics as monotherapy comparatively improved with regards to their inflammatory lesions. Whether this represents the removal of inflammation-inducing bacteria or the anti-inflammatory properties inherent to the antibiotics is unclear. No follow-up cultures were obtained in order to determine if the bacteria had been eradicated in the improved AKN lesions.

Several factors limited the utility of the treatment portion of the study. Unfortunately, each data set represented a relatively small group of patients, the examiners were not blinded and no strict criteria were utilized to grade improvement of the lesions at follow-up. Obviously, no placebo treatment group was available for the study. This would have allowed one to determine the rate at which inflamed AKN lesions improved or worsened as part of the natural course of this condition. In all of the reviewed cases, the patients were ultimately placed on antibiotics to which the organisms were sensitive. This eliminated the possibility of having a group of patients treated by antibiotics to which the bacteria were resistant, which would have revealed more information regarding the natural course of this disease. Additionally, there were no cases where steroids alone were utilized. Therefore, it was not possible to ascertain if the steroids alone would have been as effective as the other therapies at reducing the severity of AKN lesions. Further study is warranted to determine the place of antibiotic therapy in AKN lesions.

Conclusions

This study has shown that a large portion of inflamed AKN lesions contain bacteria known to be pathogenic in other settings. Staphylococcus aureus was the dominant pathogenic organism, followed by multiple gram-negative bacteria. These organisms may be multi-drug resistant; therefore, cultures with sensitivities should be obtained to ensure appropriate antibiotic use. The combination of an oral antibiotic with a topical steroid appears to be more effective than antibiotics alone in treating inflamed AKN lesions. Further study, however, is required. It is the recommended that all cases of AKN have aerobic bacterial culture and sensitivity studies performed as part of the routine diagnostic work-up.

Table III
Effectiveness of Treatment on Aerobic Bacteria Cultured from AKN Lesions

	Antibiotics Alone (organism sensitive to agent)*		*Antibiotics* and Topical Steroids***	
# Treated	22	14		
Improved	16	73%	12	86%
Not Improved	6	27%	2	14%

**Antibiotic agents include both topical and oral agents such as clindamycin, TCN, ciprofloxacin, levofloxacin, and cephalosporins.*

***Steroids include topical agents only. Steroids are of classes I-IV.*

Table IV
Effectiveness of Oral versus Topical Antibiotics

Antibiotics Only	Sample Size	# Improved	# Not Improved	% Improved
Topical antibiotic	11	7	4	64%
Oral antibiotic	4	2	2	50%
Oral and topical antibiotics	7	5	2	71%
Antibiotics with Topical Steroids				
Topical antibiotic	4	2	2	50%
Oral antibiotic	6	6	0	100%
Oral and topical antibiotics	4	4	0	100%

References:

1. Sperling, L. An Atlas of Hair Pathology. Parthenon Pub. 2003.
2. Bolognia J. Dermatology. Mosby 2003.
3. Odom R. Andrew's Diseases of the Skin. W.B. Saunders 2000.
4. Weedon, D. Skin Pathology. Elsevier pub. 2002.
5. Guentzel, N. Escherichia, Klebsiella, Enterobacter, Serratia, Citrobacter, and Proteus. Medmicrobook, UTMB. 2004

Lesions Giving the Illusion of Pustulation on the Abdomen of a 37-Year-Old Woman

Peter Saitta, MSIII, B.A.,* Shane A. Meehan, M.D., Amy E. Goldstein, D.O.,*** Regina M. Yavel, M.D.,*****

** School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey*

*** Dermatopathologist, Ronald O. Perelman Department of Dermatology, New York University School of Medicine*

**** Dermatologist, Private Practice, The Skin Institute of New York*

ABSTRACT

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare histiocytic proliferative disorder of unknown etiology. It is traditionally characterized by painless, bilateral, cervical lymphadenopathy and often affects multiple anatomic sites simultaneously, the skin being the most common extranodal site. Lesions resulting from RDD vary greatly and therefore are not diagnostic. Instead, RDD is currently diagnosed by its histopathologic features, namely the prominence of enlarged, foamy histiocytes, which stain strongly for S-100, and the presence of lymphophagocytosis (emperipolesis).

Report of a Case:

A 37-year-old black woman presented with a 10-month history of indurated papules and nodules on the abdomen. The patient reported isolated episodes of nominal bleeding and itching. Her past medical history was significant for non-insulin dependent diabetes mellitus, hypertension and asthma. No significant family history or social history was reported. Her medications included glucophage, lisinopril and bextra. There were no known drug allergies. A review of systems was negative for preceding illness, recent weight loss or constitutional symptoms.

Physical examination revealed a well-appearing patient with an ill-defined, hyperpigmented patch on the abdominal apron that was studded with nontender, firm papules and nodules. Though hyperpigmented at their base, a majority of the papules and nodules were capped with a yellowish-pink hue, giving the illusion of pustulation (Figure 1). No lymphadenopathy was noted.

Microsopic Findings:

Histologic examination of multiple abdominal lesions revealed similar findings. There was a dense, nodular dermal infiltrate of enlarged histiocytes with vacuolated cytoplasm in addition to numerous plasma cells, lymphocytes and scattered eosinophils and neutrophils. Occasional lymphocytes and neutrophils were present within the cytoplasm of some enlarged histiocytes (Figure 2). Immunohistochemical staining for S-100 protein revealed reactivity with the majority of enlarged histiocytes cells in addition to the scattered Langerhans cells in the epidermis (Figure 3). Rare, enlarged histiocytes and scattered, small histiocytes reacted for CD68. Special stains for fungi and acid-fast bacilli were negative. The results of the pathologic examination, coupled with the constellation of clinical features, supported a diagnosis of cutaneous Rosai-Dorfman disease.

Discussion:

RDD was first described by Rosai and Dorfman in 1969. They described classic disease features as including painless, bilateral cervical lymphadenopathy accompanied by fever, leukocytosis with neutrophilia, elevated ESR, and polyclonal hypergammaglobulinemia.[1,2,3] Case reports antedating this initial description highlight a broad clinical spectrum in which any or all of these features may be unapparent at presentation.[4] Extranodal involvement may include almost any anatomic site, but most commonly affects the skin, upper respiratory tract and bone.[3,5] Although cutaneous involvement in RDD is common, purely cutaneous disease is thought to be rare.[3,5]

Cutaneous lesions in RDD exhibit a wide variety of appearances. There seems to be no favored area of distribution, and lesions may be solitary or multiple. Variability also exists in terms of skin coloration, texture and lesion size. The literature presents a host of clinical descriptions, too numerous to list. In one study, however, a central noduloplaque with satellite papules was the most common manifestation, with the lesions being asymptomatic.[6] Furthermore, in terms of color, a 423-patient registry suggests that RDD lesions are most commonly xanthomatous,[3] though the very same registry clearly documents numerous lesions that are red, brown, pink, blue, and purple.[3] Interestingly, some instances of RDD may mimic more common skin disorders. For example, case reports describe cutaneous lesions resembling giant granuloma annulare,[7] pustular and acneiform lesions,[8] telangiectasias,[3] and guttate psoriasis.[9] Rarely, central ulceration or necrosis is present.[3,6] The sizes of lesions are highly variable, with measurements ranging from fractions of centimeters (for non-follicular papules)[10] to 30-cm plaques.[7] The lesions are reported diffusely over anatomic sites including the face, extremities, trunk, axillae, groin, chest, scrotum, back, vulva and buttocks.[3]

Currently, RDD is diagnosed by its

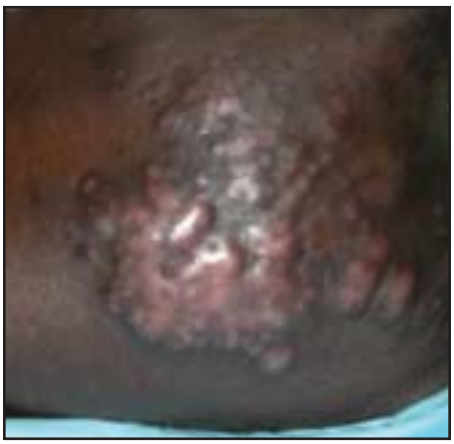


Figure 1

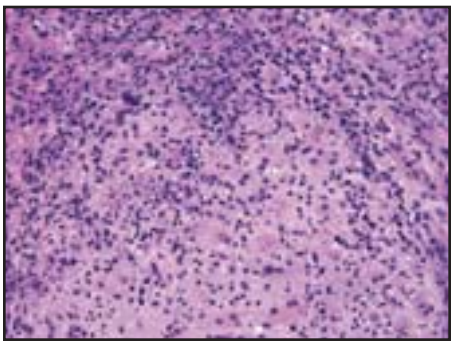


Figure 2

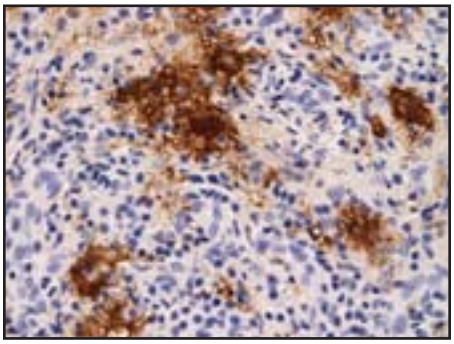


Figure 3

histopathologic features,[5,11] namely the prominence of enlarged, foamy histiocytes that stain strongly for S-100 and the presence of lymphophagocytosis (emperipolesis).[3] The latter is a characteristic finding of RDD but not a specific one -- it may also be seen in certain infectious processes and other lymphoproliferative disorders.[12] In addition, the histiocytes of RDD lack Birbeck granules seen by electron microscopy, [9,13] unlike those of Langerhans cell histiocystosis. In the literature, weakly positive staining for CD68 is often reported; however, this is not a consistent finding.[8,14,15] Furthermore, reports of positive and negative staining for CD1a can be found.[6,8,9,10]

In one patient registry, systemic RDD showed a median age at presentation of 20.6 years, a male predominance (1.4:1) and a predominance of white and black individuals.[3] In contrast, cutaneous RDD has a higher age of presentation, shows a marked female predominance and is commonly reported in white and Asian individuals. It is seldom reported in black individuals.[14] The etiology of RDD has not been delineated. While some reports suggest the involvement of human herpes virus 6 and Epstein-Barr virus,[7,16,17] others do not.

Although RDD is a benign and often self-limiting disorder, it has an unpredictable course. Patients may undergo complete remission, experience recurrent disease with lymphadenopathy secondary to a minor upper respiratory infection, have persistent but stable disease, or succumb to effects of progressive, disseminated disease.[18] In fact, 14 deaths were documented in a series of 217 patients.[18] Potential life-threatening complications include vital organ compression and airway obstruction. Involvement of the kidney, lower respiratory tract and liver correlate with a particularly grave prognosis.[19, 3] Though it may seem unnecessary for cutaneous cases, imaging modalities such as X-ray and computed tomography can help detect the extent of the disease by uncovering extracutaneous organ involvement. It is therefore advisable that patients with a cutaneous histopathologic diagnosis consistent with RDD receive a chest X-ray, computed tomography and histological examination of any enlarged lymph nodes.

Given the clinical heterogeneity of cutaneous lesions seen in RDD, the differential diagnosis should include other histiocytoses, sarcoidosis, infectious processes, and infiltrative disorders. The differential diagnosis of massive lymphadenopathy includes Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, metastasis, and Kikuchi's disease. These diseases may microscopically resemble RDD, but the combination of lymphophagocytosis and the pattern of S-100 staining strongly favor RDD.

There is no established treatment protocol for RDD, and current therapeutic modalities tend to be disappointing. Although purely cutaneous lesions require no treatment and can undergo partial or complete remission, therapy may be desired for cosmesis. Therapeutic modalities for cutaneous lesions have included superficial X-ray, cryotherapy, oral corticosteroids and surgical excision.[6,8,13,20,21] Recently, thalidomide therapy has been implemented with mixed results.[6,9,15] Other reported options include chemotherapy, interferon, oral and topical retinoids, pulse-dye laser and dapsone.[6,21]

References:

1. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a newly recognized benign clinicopathological entity. Arch Pathol. 1969;87:63-70.
2. Rosai J, Dorfman RF. Sinus histiocystosis with massive lymphadenopathy: a pseudolymphomatous benign disorder. Cancer 1972;30:1174-88.
3. Foucar E, Rosai R, Dorman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. Semn Diag Path. 1990;7;19-73.
4. Thawerani H, Sanchez RL, Rosai J, Dorfman RF. The cutaneous manifestations of sinus histiocytosis with massive lymphadenopathy. Arch Dermatol. 1978;114:191-197.
5. Huang HY, Yang CL, Chen WJ. Rosai-Dorfman disease with primary cutaneous manifestations – a case report. Ann Acad Med Singapore 1998;27:589-93.
6. Lu CI, Kuo TT, Wong WR, and Hong HS. Clinical and histopathologic spectrum of cutaneous Rosai-Dorfman disease in Taiwan. J Am Acad Dermatol. 2004;51:931-9.
7. Scheel MM, Rady PL, Tyring SK, Pandya AG. Sinus histiocytosis with massive lymphadenopathy: presentation as giant granuloma annulare and detection of human herpesvirus 6. J Am Acad Dermatol. 1997;37:643-6.
8. Ang P, Tan SH, Ong BH. Cutaneous Rosai-Dorman disease presenting as pustular and acneiform lesions. J Am Acad Dermatol. 1999;41:335-7.
9. Perez A, Rodriguez M, Febrer I, Aliaga A. Sinus histiocytosis confined to the skin: case report and review of the literature. Am J Dermatopathol. 1995;17:384-388.
10. Perrin C, Michiels JF, Lacour JP, Chagnon A, Fuzibet JG. Sinus histiocytosis (Rosai-Dorfman disease) clinically limited to the skin: an immunohistochemical and ultrastructural study. J Cutan Pathol. 1993;20:368-74.
11. Chang LY, Kuo TT, Chan HL. Extranodal Rosai-Dorfman disease with cutaneous, ophthalmic and laryngeal involvement: report of a case treated with isotretinoin. Int J Dermatol. 2002;41:888-91.
12. Kalugina Y, Hall CR, Berk RS, Sturgis CD. Pathologic quiz case: persistent localized inguinal adenopathy in a man. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Arch Pathol Lab Med. 2003 Aug;127(8):1044-6.
13. Salim A, Williamson M, Barker F, Hughes J. Steroid responsive cutaneous Rosai-Dorfman disease associated with uveitis and hypothyroidism. Clin Exp Dermatol. 2002;27:277-9.
14. Brenn T, Calonje E, Granter SR, Leonard N, Grayson W, Fletcher CD, et al. Cutaneous Rosai-Dorfman disease is a distinct clinical entity. Am J Dermatopathol. 2002;24:385-91.
15. Tjiu JW, Hsiao CH, Tsai TF. Cutaneous Rosai-Dorfman disease: remission with thalidomide treatment. Br J Dermatol. 2003;148:1060-1.
16. Requena L, Kutzner H, Escalonilla P, Ortiz S, Schaller J, Rohwedders A. Cutaneous reactions at sites of herpes zoster scars: an expanded spectrum. Br J Dermatol. 1998;138;161-168.
17. Levine P, Jahan N, Murari P, Manak M, Jaffe E. Detection of human herpesvirus 6 in tissues involved by sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). J Infe Dise 1992;166;291-294.
18. Foucar E, Rosai J, Dorman R. Sinus histiocytosis with 19. massive lymphadenopathy: an analysis of 14 deaths occurring in a patient registry. Cancer 1984;54:1834-1839.
19. Bankaci M, Stool SE, Morris RF, Paradise JL. Sinus histiocytosis with massive lymphadenopathy; report of its occurrence in two siblings with retropharyngeal involvement in both. Ann Otol. 1978;87:327-31.
20. Pulsoni A, Anghel G, Falcucci P, Matera R, Pescarmona E, Ribersani M, et al. Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): report of a case and literature review. Am J Hematol. 2002;69:67-71.
21. Olsen EA, Crawford JR, Vollmer RT. Sinus histiocytosis with massive lymphadenopathy. J Am Acad Dermatol. 1988;18:1322-32.

San Diego Plan Ahead!!

Save the dates

September 30-October 4th

2007 AOCD Annual Meeting in San Diego

Program Chairman:

Jay S. Gottlieb, DO, FAOCD

California's second largest city and the United States' seventh largest. San Diego boasts the downtown's historic Gaslamp Quarter, Little Italy, Coronado, La Jolla, Del Mar, Carlsbad, Escondido, La Mesa, Hillcrest, Barrio Logan, Chula Vista just to name a few.

San Diego is renowned for its idyllic climate. In October, expect temperatures of 60 at night and 75 during the day. There is 70 miles of pristine beaches and a dazzling array of world-class family attractions. Popular attractions include the world-famous San Diego Zoo and Wild Animal Park, Sea World San Diego and LEGOLAND California. San Diego offers an expansive variety of things to see and do.

What a place for our annual AOCD meeting!!

The 2007 South Beach Symposium

The SBS is recognized by the AAD for 41 hours of AAD category 1 CME credit and may be used toward the AAD's CME Award.

Loews Miami Beach Hotel
Miami Beach, Florida
February 15~19, 2007

Expect the BEST in education from this exciting South Beach Symposium event!

2007 Symposium Speakers

Diane Baker, M.D.
Brian Berman, M.D., Ph.D.
Eric Bernstein, M.D.
Fredric S. Brandt, M.D.
Jean D. A. Carruthers, M.D.
Wayne Carey, M.D.
Roger Ceilley, M.D.
Joel Cohen, M.D.
James Q. Del Rosso, D.O.
Dirk Elston, M.D.
Steve Fagien, M.D.
Patricia Farris, M.D.
Roy Geronemus, M.D.
Michael H. Gold, M.D.
David J. Goldberg, M.D., J.D.
William Hanke, M.D.
Bruce E. Katz, M.D.
Arnold Klein, M.D.
Mark Lebwohl, M.D.
Amy Lewis, M.D.
Debra B. Luftman, M.D.
Stephen Mandy, M.D.
Gary D. Monheit, M.D.
Mark S. Nestor, M.D., Ph.D.
Michael Nestor, ISD
David Pariser, M.D.
Marta I. Rendon, M.D.
Darrell S. Rigel, M.D.
Eva C. Ritvo, M.D.
Neil S. Sadick, M.D.
Lawrence A. Schachner, M.D.
James M. Spencer, M.D.
Amy Taub, M.D.
Susan Weinkle, M.D.
Robert Weiss, M.D.
...plus many others

SESSION DIRECTORS

Brian Berman, M.D., Ph.D.
Jean D. A. Carruthers, M.D.
James Q. Del Rosso, D.O.
Michael H. Gold, M.D.
Gary D. Monheit, M.D.

SYMPOSIUM CHAIR

Mark S. Nestor, M.D., Ph.D.

SYMPOSIUM HIGHLIGHTS

The 2007 South Beach Symposium will offer cutting-edge medical education and training in clinical and surgical dermatology, aesthetic enhancement and practice management from world leaders in dermatology and aesthetic surgery. Symposium highlights will include:

- Special advanced live-patient certification courses in botulinum toxin and new fillers and techniques, including new hyaluronic acid compounds as well as new novel fillers presented by Drs. Fred Brandt, Jean Carruthers, Arnold Klein, Gary Monheit, and Susan Weinkle.
- One of the most comprehensive laser, light and RF workshops you will ever attend, where over 20 new laser, light and RF devices will be demonstrated in live patient workshops.
- Advanced live patient training in photodynamic therapy techniques.
- Advanced clinical and therapeutic dermatology updates including antibiotics, immune response modulators (IRMs), biological treatments for psoriasis, and combination therapy for acne and psoriasis.
- A special practice management session featuring state-of-the-art information technology, EMR and digital imaging solutions for medical practices, as well as malpractice risk management.

For more information on this event,
visit us at www.southbeachsymposium.org
or contact our office at 850-531-8386

Mycobacterium Marinum: A Case Report and Review of the Literature

Jason Arthur Barr, D.O.*, Don Arlan Anderson, D.O. **
** Third year resident, Midwestern University, Kingman Regional Medical Center, Arizona Desert Dermatology, Kingman, AZ*
***Program Director, Midwestern University, Kingman Regional Medical Center, Arizona Desert Dermatology, Kingman, AZ*

ABSTRACT

Mycobacterium marinum infection is a rare disease that requires a high index of suspicion and knowledge of microbiology to make a diagnosis. The differential diagnosis for the histopathologic findings is extensive. A directed history must be obtained and adequate specimen and culture instructions sent to the lab for diagnosis. There are many therapeutic options reported to be effective. If deeper structures are involved by direct inoculation or cutaneous extension, surgery may be required. Although very rare, disseminated M. marinum infection has been reported in immunosuppressed patients with aquatic or aquarium exposure.

Case Report

A forty-five year old male presented with the chief complaint of two lesions on his right knee (fig. 1-3). He had suffered a below the knee amputation of his left leg twenty five years prior, the result of trauma from a motor vehicle accident. He had an unremarkable medical history, including no history of malignancy or immunosuppression. The painless lesions had been present and slowly enlarging for two years. He had undergone several biopsies, cultures, and courses of topical and systemic antibiotics with no resolution. He is an avid boater on the Colorado River and uses his right knee to pivot when maneuvering in and out of watercraft. The lesions occasionally drain a clear red liquid but never purulent or grainy material.

Exam revealed two 3 to 4cm erythematous scaling nodules of the right knee. No drainage or tenderness was appreciated. Inguinal lymphadenopathy was absent.

Initial punch biopsies revealed acute and chronic perifollicular inflammation with microabscess formation and surrounding granulomatous inflammation. A Steiner stain was negative for bacteria, a GMS stain was negative for fungus, and an AFB stain was negative for mycobacteria. Cultures taken from the tissue were negative. Due to the lack of diagnosis and the fact that the lesions were interfering with the patient's active lifestyle, they were completely excised (Fig. 7) and sent for routine histopathology, special stains, and tissue cultures with emphasis on mycobacterial culture.

Histopathology of the excised lesions (Fig. 4,5,6) revealed epidermal hyperplasia and focal areas of pseudoepitheliomatous hyperplasia. Microabscesses with surrounding granulomatous inflammation and multinucleated histiocytes were noted. Strict caseation was not observed. Again, all stains were negative including an acid fast stain.

Due to the history of repeated aquatic related trauma, the patient was placed on doxycycline 100mg B.I.D. with the presumptive diagnosis of M. marinum infection and the lesions were allowed to heal by second intention. Five weeks after excision, preliminary results of positive mycobacterial culture were received. One week later the organism was identified as M. marinum by conventional biochemical methods. In another week, antibiotic susceptibilities were reported. Doxycycline was continued for 6 months after excision. The patient healed with atrophic scars (Fig. 8) and continued to be disease free for 18 months following excision.

History

Cutaneous mycobacterial infection was first described by Laennec in 1826. Joseph Aronson isolated a mycobacterium causing an epidemic in saltwater fish at the Philadelphia aquarium in 1926 and named it Mycobacterium Marinum. Cutaneous tuberculoid infections in humans using public swimming pools were reported in 1939 in Europe and the early 1950s in the U.S. Linell and Norden isolated and identified a mycobacterium responsible for another swimming pool outbreak in 1954 by self inoculation and subsequent culture. This organism was later identified as the previously described M. marinum.[1] Cutaneous infection with M. marinum was initially named "swimming pool granuloma" because of these outbreaks. Recently, more cases are related to aquarium exposure and the term "fish tank granuloma" has become popular.

Microbiology

Mycobacterium marinum is a free living organism which infects warm, cold, fresh and saltwater fish and frogs in a worldwide distribution. It is a non-tuberculous mycobacterium of the Runyon group I, a photochromogen that produces a vibrant yellow pigment when the culture is exposed to light. It grows best at 30 to 330C and will grow in 7 to 28 days on Lowenstein- Jenson media. It will grow in the presence of thiacetazone and is negative for nitrate reductase, both of which differentiate it from its nearest microbiologic relative, Mycobacterium Kansasii. Infection in fish usually manifests

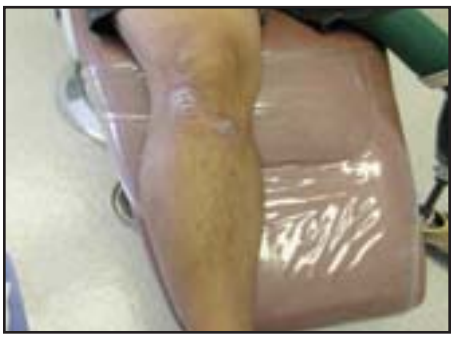


Figure 1

Figure 2

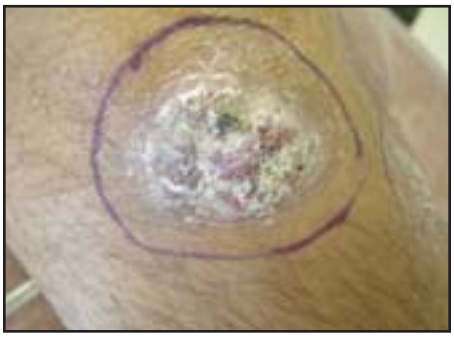


Figure 3

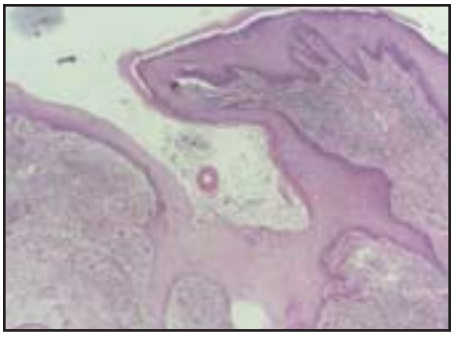


Figure 4

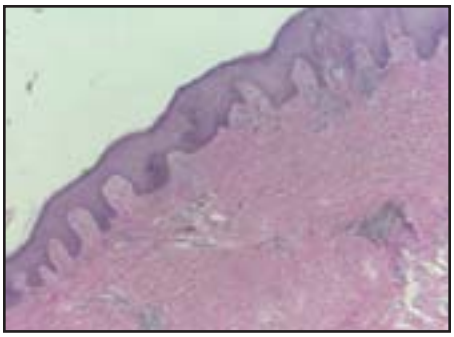


Figure 5

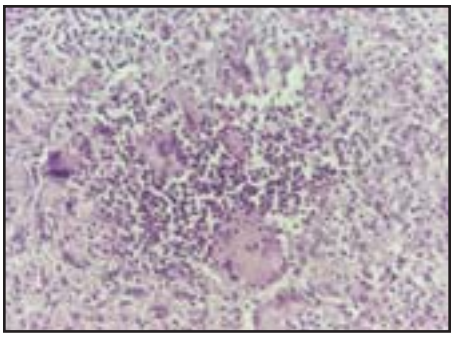


Figure 6

as a latent granulomatous infection in multiple organs which may spontaneously resolve over a period of months to years. The granulomas produced in fish are very similar to human pulmonary M. tuberculosis granulomas. For this reason M. marinum is an excellent model to study mycobacterial granulomas.[2]

Clinical Characteristics

M. marinum infection usually results from direct inoculation following trauma to an extremity. A history of aquatic trauma or aquarium exposure is very common. The lower temperature of the skin correlates to the preferred growth temperature for the organism. After 2-6 week incubation, a painless papulonodular, pustular, or ulcerative lesion appears. There are no systemic symptoms and adenopathy is rare. The lesions often spontaneously resolve over a period of months to years.[3] The lesions are non-contagious. Less commonly, deeper structures may be involved through direct extension or initial inoculation rather than hematogenous spread. Arthritis, tenosynovitis, bursitis, and

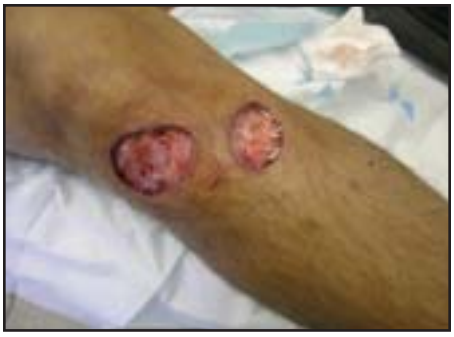


Figure 7

osteomyelitis have been described.[4] Also, a "sporotrichoid" form may be seen, which represents subcutaneous extension and proximal lymphatic spread. Both of these rarer forms are more difficult to treat successfully. Very rarely, disseminated forms have been reported almost exclusively in immunosuppressed patients with aquatic exposure.[4]

Histopathology

During the first six months of M. marinum infection, a mixed neutrophilic predominant non-specific inflammatory infiltrate is produced. Epidermal changes include acanthosis and pseudoepitheliomatous hyperplasia. If there are granulomas during this early stage they are poorly formed. Acid fast bacteria can usually be demonstrated if lesions are biopsied in the early inflammatory stage.[5] By the sixth month mature granulomas form with multinucleated giant cells. There may be central fibrinoid necrosis present within abscesses, but no true caseation.[6] Rarely one may see an occasional acid fast bacterium but usually acid fast stains are negative in the late granulomatous stage. Organisms may be demonstrated by antibody fixation and immunofluorescence, but these are not species specific. In immunosuppressed patients with atypical mycobacterial infection, the inflammatory infiltrate tends to be deeper with more constant abscess formation.[7]

Diagnosis

While M. marinum infection should be considered for any granulomatous lesion with a history of aquatic activity or aquarium exposure it can only be confirmed by culture and identification. As M. marinum is ubiquitous in the environment, false positive results from contaminated lab or surgical equipment or media are possible. False negative cultures may be due to inadequate specimen amount, as many labs will sub-divide any specimen for bacterial and fungal cultures first, leaving "the leftovers" for mycobacterial culture. When suspected, appropriate culture material must be submitted with the suspicion of M. marinum noted, so that appropriate media and incubation times are followed.[4]

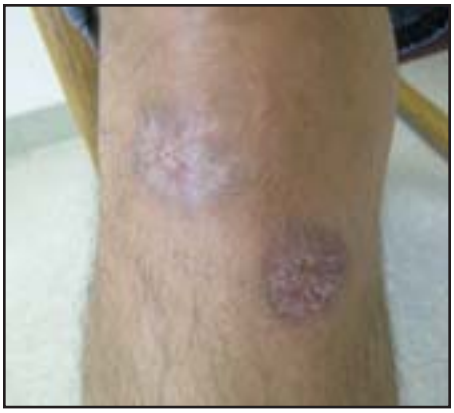


Figure 8

A tuberculin skin test is usually positive in patients with M. marinum infection as there is cross reactivity with M. tuberculosis. Also, many species specific purified protein derivative skin tests have been developed but are of little clinical value due to the cross reactivity and ubiquitous nature of many of the mycobacteria.[4]

The differential diagnosis for typical M. marinum lesions is extensive and includes other mycobacterial infections, including tuberculosis; sporotrichosis; nocardia; leishmaniasis; tularemia; sarcoidosis; candidiasis; coccidioidomycosis; histoplasmosis; blastomycosis; cryptococcosis; syphilis; yaws; foreign body granuloma and cutaneous malignancies.[4,8,9] For diagnosis by conventional techniques (biochemical and HPLC), identification of M. marinum requires days to weeks after successful culture. Recently, identification of M. marinum was demonstrated through PCR-pattern restriction analysis of the heat shock protein (gene hsp65).[10] This method is much faster but not yet widely available.

Treatment

Because of the lack of controlled studies secondary to the rarity of this infection no single "best" therapy exists. Physical modalities used previously include surgical excision, cryotherapy, heat therapy and even radiation therapy.[1] Many antibiotics have also been used successfully. One fact to note is that M. marinum is resistant to isoniazid and this drug has no place in therapy. Antibiotics reported in the literature to be effective include amikacin, kanamycin, tetracyclines, rifampin, ethambutol, trimethoprim/sulfamethoxazole, clarithromycin, azithromycin, and the quinolones.[8,11,12] One recent study from France published in 2002 examined 63 cases of biopsy proven M. marinum infections to determine the most effective therapy.[11] Treatment failures occurred in 13% of cases and were related to deep tissue involvement only. Surprisingly, favorable outcome was not related to antibiotic regimen used. Susceptibilities were performed and ranged from rifampin (0.5 microgram/ml) to the quinolones (range 4-16

microgram/ml). Intermediate M.I.C. antibiotics included clarithromycin, minocycline, doxycycline and ethambutol.

In general, for cutaneous limited infections clarithromycin, minocycline, doxycycline, or TMP/SMX should be given as monotherapy for 3-6 months. Surgical debridement may be used as adjunctive therapy for simple lesions but may be required for deeper structure involvement.[12] If feasible, excision followed by antibiotic therapy may be used. If there is no clinical response after 4 weeks, a different antibiotic should be utilized. For serious or disseminated infections the combination of rifampin 600mg/day and ethambutol 12-25 mg/Kg/day is indicated.[4]

References:

1) Johnston JM, Izumi AK. Cutaneous Mycobacterium marinum infection ("swimming pool granuloma"). Clin Dermatol. 1987 Jul-Sep;5(3):68-75
2) Stamm LM, Brown EJ. Mycobacterium marinum: the generalization and specialization of a pathogenic mycobacterium. Microbes Infect. 2004 Dec;6(15):1418-28.
3) Palenque E. Skin disease and nontuberculous atypical mycobacteria. Int J Dermatol. 2000 Sep;39(9):659-66.
4) Gluckman SJ. Mycobacterium marinum. Clin Dermatol. 1995 May-Jun;13(3):273-6.
5) Elder D, Elenitsas R, Jaworsky C, Johnson B Jr. Lever's Histopathology of the Skin. 9th ed. Lippincott Williams & Wilkins. 2005.
6) Weedon D. Skin Pathology 2nd ed. Churchill Livingstone, 2002.
7) Bartralot R, Pujol RM, Garcia-Patos V, Sitjas D, Martin-Casabona N, Coll P, Alomar A, Castells A. Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28 cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts. J Cutan Pathol. 2000 Mar;27(3):124-9.
8) Edelstein H. Mycobacterium marinum skin infections. Report of 31 cases and review of the literature. Arch Intern Med. 1994 Jun 27;154(12):1359-64.
9) Bolognia J. Dermatology. Mosby 2003.
10) Ena P, Sechi LA, Saccabusi S, Molicotti P, Lorrai MP, Siddi M, Zanetti S. Rapid identification of cutaneous infections by nontubercular mycobacteria by polymerase chain reaction-restriction analysis length polymorphism of the hsp65 gene. Int J Dermatol. 2001 Aug;40(8):495-9.
11) Aubry A, Chosidow O, Caumes E, Robert J, Cambau E. Sixty-three cases of Mycobacterium marinum infection: clinical features, treatment, and antibiotic susceptibility of causative isolates. Arch Intern Med. 2002 Aug 12-26;162(15):1746-52.
12) Lahey T. Invasive Mycobacterium marinum infections. Emerg Infect Dis. 2003 Nov;9(11):1496-8.

Now In 120 g Tube

Class I Strength[1]

- An FDA-approved, super-potent fluocinonide formulation
- QD dosing for atopic dermatitis
- QD or BID dosing for plaque-type psoriasis* and corticosteroid responsive dermatoses
- An elegant cream alternative to ointments, gels, lotions, and foams
- Available in 120 g, 60 g, and 30 g tubes.

Vanos™
(fluocinonide) cream 0.1%

Now approved for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in patients 12 years of age or older.

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 the disease is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

Safety Information

- The most commonly reported adverse events were headache, burning at the application site, nasopharyngitis and nasal congestion.
- Reversible HPA-axis suppression may occur with potential glucocorticosteroid insufficiency after withdrawal of treatment. HPA-axis suppression was demonstrated in two out of 18 adult patients with psoriasis treated twice daily for two weeks and in one out of 31 adult patients with atopic dermatitis treated once daily. HPA-axis suppression has not been evaluated in psoriasis patients who are less than 18 years of age. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a higher risk than adults of HPA-axis suppression and Cushing's syndrome when they are treated with topical corticosteroids.
- VANOS™ Cream should not be used on the face, groin, or axillae; or for treatment of rosacea or perioral dermatitis.
- The safety and efficacy in patients younger than 12 years of age have not been established.
- If irritation develops, VANOS™ Cream should be discontinued and appropriate therapy instituted.

See Full Prescribing Information on next page.

* Twice daily application has been shown to be more effective in achieving treatment success for plaque-type psoriasis.

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

Vanos™
(fluocinonide) cream 0.1%

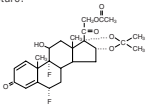
Rx Only

FOR TOPICAL 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-isopropylidenedioxypregna-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

Like other topical corticosteroids, VANOS™ (fluocinonide), has anti-inflammatory, antipruritic, and vasoconstrictive properties. 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. 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 ($ACTH_{1-24}$) (**See PRECAUTIONS: General** and **Pediatric Use**).

HPA-axis suppression has not been evaluated in psoriasis patients who are less than 18 years of age. HPA-axis suppression has been evaluated in pediatric patients with atopic dermatitis 12 to 18 years of age (See **PRECAUTIONS: Pediatric Use**).

CLINICAL STUDIES

Two adequate and well-controlled efficacy and safety studies of VANOS™ Cream have been completed, one in adult patients with plaque-type psoriasis (Table 1), and one in adult patients with atopic dermatitis (Table 2). In each of these studies, patients with between 2% and 10% body surface area involvement at Baseline treated all affected areas either once daily or twice daily with VANOS™ Cream for 14 consecutive days. The primary measure of efficacy was the proportion of patients whose condition was cleared or almost cleared at the end of treatment. The results of these studies are presented in the tables below as percent and number of patients achieving treatment success at Week 2.

Table 1: Plaque-Type Psoriasis in Adults

	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 (5%)

*Cleared or almost cleared

Table 2: Atopic Dermatitis in Adults

	VANOS™ Cream, *once daily* (n = 109)	Vehicle, *once daily* (n = 50)	VANOS™ Cream, *twice daily* (n = 102)	Vehicle, *twice daily* (n = 52)
Patients cleared	11 (10%)	0 (0)	17 (17%)	0 (0)
Patients achieving treatment success*	64 (59%)	6 (12%)	58 (57%)	10 (19%)

*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 the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in patients 12 years of age or older (**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 the disease is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary. Do not use more than half of the 120 g tube per week.

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 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) and 31 adult patients (17 treated once daily; 14 treated twice daily) with atopic dermatitis (2-10% BSA, mean 5% BSA) showed demonstrable HPA-axis suppression in 2 patients with psoriasis (with 12% and 25% BSA) and 1 patient with atopic dermatitis (treated once daily, 4% 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 ($ACTH_{1-24}$) (**See CLINICAL PHARMACOLOGY**).

Controlled clinical efficacy studies of VANOS™ Cream in pediatric patients younger than 17 years of age have not been conducted; (See PRECAUTIONS: **Pediatric Use**).

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

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. It should not be used on the face, groin, and underarms.

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) As with other corticosteroids, therapy should be discontinued when control is achieved. 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.

7) Patients should be informed to not use more than 60g per week of VANOS™ Cream. Do not use more than half of the 120 g tube per week.

8) Patients should inform their physicians that they are using VANOS™ Cream if surgery is contemplated.

9) Patients should wash their hands after applying medication.

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: Safety and efficacy of VANOS™ Cream in pediatric patients younger than 12 years of age have not been established; therefore use in pediatric patients younger than 12 years of age is not recommended.

HPA axis suppression was studied in 4 sequential cohorts of pediatric patients with atopic dermatitis covering at least 20% of the body surface area, treated once daily or twice daily with VANOS™ Cream. The first cohort of 31 patients (mean 36.3% BSA) 12 to < 18 years old; the second cohort included 31 patients (mean 39.0% BSA) 6 to < 12 years old; the third cohort included 30 patients (mean 34.6% BSA) 2 to < 6 years old; the fourth cohort included 31 patients (mean 40.0% BSA) 3 months to < 2 years old. VANOS™ Cream caused HPA axis suppression in 1 patient in the twice daily group in Cohort 1, 2 patients in the twice daily group in Cohort 2, and 1 patient in the twice daily group in Cohort 3. Follow-up testing 14 days after treatment discontinuation, available for all 4 suppressed patients, demonstrated a normally responsive HPA-axis. Signs of skin atrophy were present at baseline and severity was not determined making it difficult to assess local skin safety. Therefore, the safety of VANOS™ Cream in patients younger than 12 years of age has not been demonstrated.

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 adult 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:

Table 3: Most Commonly Observed Adverse Events in Adult Clinical Trials

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. Safety in patients 12 to 17 years of age was similar to that observed in adults.

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

For psoriasis, apply a thin layer of VANOS™ Cream once or twice daily to the affected skin areas as directed by a physician. Twice daily application for the treatment of psoriasis has been shown to be more effective in achieving treatment success during 2 weeks of treatment.

For atopic dermatitis, apply a thin layer of VANOS™ Cream once daily to the affected skin areas as directed by a physician. Once daily application for the treatment of atopic dermatitis has been shown to be as effective as twice daily treatment in achieving treatment success during 2 weeks of treatment (See **CLINICAL STUDIES**).

For corticosteroid responsive dermatoses, other than psoriasis or atopic dermatitis, apply a thin layer of VANOS™ Cream once or twice daily to the affected areas as directed by a physician.

Treatment with VANOS™ Cream should be limited to 2 consecutive weeks, and no more than 60 g/week should be used. Do not use more than half of the 120 g tube per week.

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) 120 g (NDC 99207-525-10)

Store at controlled room temperature: 15º to 30ºC (59º to 86ºF).

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 and Patents Pending

Prescribing information as of July 2006.

IN-5304/S

MEDICIS
The Dermatology Company®