Journal of Resident Dermatology

A Publication of the American Osteopathic College of Dermatology

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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.

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)
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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

Not Much of a Stretch to GETTING PUBLISHED!
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

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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 pigmented 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 wheelchair 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. 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. 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. If this is not the case, MF is rarely suspected, as the differential diagnosis includes pityriasis versicolor, vitiligo, p. alba, leprosy, sarcoi, 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. 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.

The mechanism of the hypopigmentation in this relatively uncommon subtype of MF remains to be seen. It has been theorized by Breathrauch et al. 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 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. Flaxman et al. 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...
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.4,5 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. Distinctive 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:
ABSTRACT

Rhinophyma is a severe, disfiguring form of rosacea that affects mostly men. 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, dermabrasion, scalpel excision, electrosurgery, and laser ablation. 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. 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, 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. Histologic features include a chronic inflammatory process with hypertrophy of the subcutaneous and sebaceous tissues with dilated ducts occluded with debris, bacteria, and sebum. Some believe that rhinophyma may be affected by alcohol, spicy foods, or caffeine; however, there are conflicting reports in the literature. 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.

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 CO2 laser, and electrosection resurfacing was performed using the Ellman Surgitron. The patient was satisfied with the results. This surgical technique yields good cosmetic results with a relatively bloodless field.
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”). One study from the United Kingdom showed no greater alcohol consumption in rhinophyma patients than the general population surveyed. Spontaneous regression of severe rhinophyma is unlikely, although it has been shown to decrease nasal size in younger patients. 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, electrosurgery, tangential excision combined with dermabrasion, ultrasonic scalpel, and radiotherapy.

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**


**Results:**

The patient had regular follow-up visits at post-operative days two, seven, nine, 13, 21, 28, 34, 37, and 42. Post-operative edema and swelling of the nose were noted at the two-day evaluation. 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).
The Treatment of Chondrodermatitis Nodularis Helicis Using Intralesional Etanercept

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 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. 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. Typically presenting after age 40, CNH has also been observed in children. Pediatric cases include patients with and without associated systemic disease.

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.

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. However, some reports have shown lesions to be free of any cartilaginous changes.

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. 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.

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. 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. 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. 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
Facial Orf in a Healthy 33-year-old Man

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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. 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 lymphadenopathy 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, keratoacanthoma, orf, milker’s nodule, atypical mycobacteria infection, melanoma, cutaneous anthrax, tularemia, tuberculosis and glinders.

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. 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 red center, a white middle ring and a red halo develop in about 10 to 14 days. The third stage demonstrates lesions that advance to an acuteweeping process, later followed by a fourth, regenerative, dry stage with black dots. 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. 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. 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. 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. The orf virus also contains an early viral gene...
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. 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. 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.

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 under-represented 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.

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.

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

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
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) 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 with a diagnosis of glabellar lines. This is based on the Food and Drug Administration's (FDA) acknowledgement of the association of glabellar lines with forehead and glabellar muscle movement. BOTOX® COSMETIC may be re-administered at non-discounted prices.

**CONTRAINDICATIONS**

BOTOX® COSMETIC is contraindicated in the presence of infection at the proposed injection site 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, use of clinical results observed with the use of BOTOX® also have the potential to be associated with the use of BOTOX® COSMETIC. Risks resulting from administration at higher dosages are not known.

**Hypersensitivity Reactions**

Severe, possibly life-threatening, 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 for BOTOX® and, consequently, the product 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**

Care should be taken 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 clinical doses of the same. In these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

**Cardiovascular System**

Dysphagia is a commonly reported adverse event following treatment of cervical dysphonia patients with BOTOX® COSMETIC. In these patients, these are reports of cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed dysphagia post-BOTOX® treatment within 24 hours of the injection with the dysphagia lasting several months and relating to the finding of dysphagia.

**Cardiovascular System**

There have also been rare reports following administration of BOTOX® COSMETIC of adverse events involving the cardiovascular system, including the rare cases of arrhythmia, stroke and neurovascular embolism. Some of these patients had risk factors including pre-existing cardiovascular disease.

**Human Albumin**

This product is prepared from human 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 agents. In the absence of data regarding its effectiveness in removing viruses, the safety of using this product should be carefully weighed against the potential risks of infection with any virus that may still be present.

**Immunogenicity**

Immunogenicity studies have not been well studied. Co-administration of BOTOX® COSMETIC with other botulinum toxins is contraindicated to reduce the risk of immunization to the botulinum toxin. Additional botulinum neurotoxin type A or B injections are not recommended within the same treatment cycle.

**Use of BOTOX® COSMETIC in Women of Reproductive Age**

Pregnancy:

BOTOX® COSMETIC offers no advantage to women of reproductive age over existing, generally accepted methods of contraception; therefore, all patients should be encouraged to use effective contraception during and following any treatment with BOTOX® COSMETIC. In rabbits, BOTOX® COSMETIC administration produced an increase in the number of resorptions and implantation failures. In a study in which pregnant mice and rats were injected intramuscularly during the period of organogenesis, the following adverse effects were observed:

- Mice:
  - Mortality at 8 U/kg and 16 U/kg
  - Reducing the body weight of the treated fetuses
- Rats:
  - Birth defect incidence and litter size

In general, adverse events occurring with treatment of BOTOX® COSMETIC have been similar to those observed in the clinical trials but are also consistent with the expected pharmacological action of botulinum toxin and with typical adverse reactions. In general, adverse events occur within the first week following injection of BOTOX® COSMETIC and while generally transient may vary in duration from a few days to months. Local pain, injection, infection, tenderness, swelling, erythema and/or bleeding/bluising may be associated with the injection.

**Gelatin Use**

In clinical trials of BOTOX® COSMETIC the most frequently reported adverse events following treatment with BOTOX® COSMETIC were: respiratory infection1; flu syndrome, blepharitis, and nausea.

**Geriatric Use**

The clinical relevance of these adverse events is not known. The effectiveness of BOTOX® COSMETIC was not altered by age in the Phase 3 safety and efficacy trials.

**Adverse Events**

**Percent of Patients Reporting Adverse Events**

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall</th>
<th>BOTOX® Cosmetics (N=405)</th>
<th>Placebo (N=130)</th>
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<tbody>
<tr>
<td><strong>Body System</strong></td>
<td></td>
<td></td>
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<tr>
<td>Body as a Whole</td>
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</tr>
<tr>
<td>Pain in Face</td>
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<td>1</td>
<td>0</td>
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<tr>
<td><strong>Skin and Appendages</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Skin Tightness</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dyspepsia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tooth Disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events Reported at Higher Frequency (+1%) in the BOTOX® COSMETIC Group Compared to the Placebo Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blepharitis</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Musculoskeletal System</strong></td>
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<tr>
<td>Muscle Weakness</td>
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</table>

**Rx Only**

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Based on package insert 71711US13S revised January 2005

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc., 2305 DuPont Dr, Irvine, CA 92612

**Reference:**

Merkel Cell Carcinoma in a Renal-Transplant Patient

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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 to 1, 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, red-dish-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 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,
normal Merkel cells until Narisawa et al. and Fantini et al. revealed their presence in normal Merkel cells as well. Neurofilaments were observed in all of the tumors investigated by Drijkoningen et al. 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. 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. 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...
Mehrany et al. 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. 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. 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. 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. 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., 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. 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. 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. Euvrard et al. reported a higher percentage of post-transplant MCC patients who died, 56%, within a two-year period.

Our patient would not have received re-transplantation 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.

Figure 6
High power microscopic evaluation of merkel cell carcinoma

dermatopathology.stanford.edu/services/

Figure 7
Positive cytokeratin stain in a merkel cell carcinoma

cytokeratin 20.

Figure 8
Positive cytokeratin staining in a merkel cell carcinoma.
References


Questions

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

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:

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

MERKEL CELL CARCINOMA IN A RENAL-TRANSPLANT PATIENT
Linear IgA Bullous Disease: 
Challenge in Clinical Diagnosis

*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. The IgA autoantibodies target a 97 kDa antigen in the lamina lucida or, less commonly, anchoring fibrils (collagen VII) in the sublamina densa.

Case:

A 64-year-old man presented with a diagnosis of dermatitis herpetiformis (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).

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. 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.

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.

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). This similarity in histology demonstrates the importance of immunofluorescent studies to confirm a final diagnosis.

Immunofluorescence:

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

**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Amiodarone</td>
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<tr>
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<td>Interferon-gamma</td>
<td>Vancomycin</td>
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**Table 2**

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

**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%.

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. 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. 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 clefs of evolving vesicles, microabscesses with neutrophils and, less often, eosinophils in the dermal papillae. The direct immunofluorescence 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.

**References:**


Familial Occurrence of Gianotti-Crosti Syndrome and Unilateral Laterothoracic Exanthem

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.

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.1,2 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.1,2 Vesicles and purpuric lesions are rarely encountered. In one report, Epstein Barr Virus (EBV)-proven GCS was limited to a localized facial erup-

ABSTRACT

We report the simultaneous occurrence of Gianotti-Crosti syndrome and unilateral laterothoracic exanthem in two young siblings. 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.

Figure 1a

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

Figure 2a

Figures 2a, b: Multiple, erythematous, coalescing papules on the left axilla, abdomen and chest wall; right trunk is spared
FAMILIAL OCCURRENCE OF GIANOTTI-CROSTI SYNDROME AND UNILATERAL LATEROTHORACIC EXANTHEM

GCS is most commonly associated with EBV. Most cases associated with positive Hepatitis B surface antigen have been reported from Japan and Italy. Other proposed causes include unrelated viruses, bacteria and various immunizations. In addition to Hepatitis B virus (HBV) and EBV infection, cytomegalovirus (CMV), paramfluenza 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. 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. The differential diagnosis of GCS includes drug hypersensitivity, papular urticaria, viral exanthem, erythema multiforme and molluscum contagiosum. Histopathological findings are generally non-specific 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.

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. ULE was first described by Brunner et al. in 1962, but the actual term was first suggested by Bodemer and de Prost. Cases have been reported in adults, but the majority of cases involve children ranging in age from four months to 15 years. 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. The eruption may spread to the contralateral side but often with much less frequency. 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. Females predominate in a 2:1 ratio. 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. Pruritus, with or without lymphadenopathy, occurs in two-thirds of all cases. 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, familial cases and a lack of response to antibiotics. 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. Another case reports a father with a unilateral, axillary eruption two weeks prior to his child’s eruption with ULE. Familial occurrence has been reported in twin sisters who developed the eruption within 10 days of one another. The differential diagnosis includes contact dermatitis, tinea corporis, viral exanthem, drug hypersensitivity, atypical pityriasis rosea, miliaria, scabies and GCS. Histopathological findings are generally non-specific, 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.

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, non-specific, upper-respiratory symptoms. Since both children share the same household and shared similar symptoms prior to their respective exanthem, we propose this is the first reported case of both entities presenting simultaneously from the same viral etiology.

References:
A Case of Cutaneous Angiosarcoma of the Scalp

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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 treatment for palliative radiotherapy.

Discussion

Angiosarcoma (AS), also known as malignant hemangiendothelioma 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.4,5 Stewart and Treves described AS arising in an area of chronic lymphedema, usually in an arm following radical mastectomy for breast cancer.6 Angiosarcomas that affect the lymphedematous lower limbs have been described.7 Chronic lymphedema resulting from other insults, such as trauma or infection, may also predispose to AS.8-10 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 pigmentosum18 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.23,24-26

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.1 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.15 Aguilera and Sanchez reported a case of angiosarcoma of the face resembling rhinophyma.26 Mentzel and Kutzner reported a patient with angiosarcoma 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
Angiosarcoma is a poorly circumscribed and histologically highly aggressive neoplasm that has a variable pattern of differentiation. Many immunohistochemical markers for endothelial cell differentiation have been used. Studies have indicated that the antibodies to CD31 and Ulex europeaus lectin 1 are more reliable markers for routine use than the antibodies to factor VIII and CD34. 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 hemangioendothelioma.

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. 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. Mark and Poen reported two-year and five-year actuarial survivals of 44% and 24%, respectively. 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. Maddox and Evans concluded that a tumor size of less than 5 cm probably offers the best prognosis. The role of chemotherapy for head and neck angiosarcoma remains controversial. Some authors report that radiation therapy provides no benefit, others suggest that surgery combined with radiation therapy offers the best prognosis.

**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 long delay in diagnosis that delays 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**


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

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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 pimecolimus 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. 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 Bourrier in 1930, who characterized the lesions as erythematous, infiltrated, smooth plaques on the head and neck. They observed that some lesions demonstrated a fine scale. In addition, Gougerot and Bourrier 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. Kuhn et al. 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. 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. and Ruiz et al. also observed a female predominance -- 10 out of 15 patients and four out of four patients, respectively. Hsu et al. 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.

Clinical Manifestations

The clinical manifestations of TLE have been described by Kuhn et al. 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

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

Adapted from Kuhn et al.4 and Alexiades-Armenakas et al.1

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.1 performed DIF on both prior 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.3 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.

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 erythematosus mucinosis (REM), and deep gyrate erythema.1,4,5

TLE is considered to be more common than the few case reports and studies in the literature seem to indicate.3 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
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. 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 Sjogren 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 Sjogren antibodies. 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 papillar 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. 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.6 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.4 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.3 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.6 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.

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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.

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2. This medication should not be used for any disorder other than that for which it was prescribed.

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REFERENCES:

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Case Report

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.

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. Controversy has surrounded the relationship of keratoacanthomas to SCC. 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.

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 fairskinned individuals. Other factors include chemical carcinogens, genetic predisposition, infectious etiology, immunosuppression, dysregulation of suppressor gene p53 and trauma.

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. Multiple KAs have also been noted to be associated with Muir-Torre syndrome. 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. 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.

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.

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

Histologically, a keratoacanthoma is characterized by a large central core of keratin surrounded by well-differentiated prolifera-
tion of squamous epithelium. A distinct crateriform appearance is achieved by epithelial lipping over the central core (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.

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.

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. They have been shown to aid in the involution of keratoacanthomas. Scarring and recurrences can often occur.

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. It is important to remind patients to avoid exposure to UV light since keratoacanthomas have a predilection to erupt on sun-exposed areas.

References:
Acquired Bullous Diseases of Childhood

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ABSTRACT

Linear IgA dermatosis is NOT synonymous with acquired bullous diseases of childhood. It is synonymous with the specific diseases: 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 pempigoid (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 pempigoid (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 immunofluorescence microscopy, and Western blot analysis.8,9,10

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 hematoxylin 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 vesication 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 blisterer with an inflammatory infiltrate composed primarily of mononuclear cells and eosinophils (Fig 6).

There were only a few neutrophils present and there was no evidence of epidermal necrosis (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.
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 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 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.12-15

**Chronic bullous disease of childhood**

Chronic bullous disease of childhood is the most common subepidermal autoimmune blistering disease seen in childhood occurring typically between the third and fifth year of life.1-5 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.6-15 Involvement of the mucous membranes has been reported in up to 91% of cases, affecting mainly the oral, ocular, nasal, and genital areas.6-14 Histopathological examination reveals a subepidermal blister with neutrophils characteristically being the predominant inflammatory cell, although authors have reported that eosinophils may also predominate.5 The inflammatory cells often line the DEJ and can accumulate at the papillary tips.5,6

Direct immunofluorescence studies show deposition of linear IgA in 50-70% of cases, and less often C3 and IgM6-15, along the cutaneous BMZ.5,6 Indirect immunofluorescence (IF) studies demonstrate the same linear deposits of circulating anti-BMZ antibodies in 40-70% of children.5,6 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 and a 285kDa protein. 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.

Many reports in the literature have shown overlapping immunopathological findings between CBDC and BP of childhood. In a study by Powell et al., 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 lamin 5 in one patient. In addition, Arechalde et al. 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.

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.

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

The standard treatment for CBDC is dapsone at 2mg/kg/d. Corticosteroids may sometimes be necessary and are given at a dosage of 0.5-2.0mg/kg/d. There have been reports of good response to sulphasalazine, erythromycin, colchicine, dicloxacillin, and oxacillin. Remission is usually induced after six to twelve months of therapy and relapses are uncommon. The disease typically remits by age 6-8 years and the majority of cases resolve by adolescence.

**Childhood bullous pemphigoid**

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

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

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. Sites of predilection include the inner thighs, flexural surfaces of the forearms, axillae, lower abdomen, groin, and palmar and planter surfaces. Mucous membrane involvement is a frequent finding in childhood BP and it is more commonly seen in the childhood form compared to the adult variant. 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. In addition, facial involvement has also been reported to be more common in childhood BP.

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. IgA, IgM, and IgE may also be found but this occurs less frequently. Indirect immunofluorescence studies show circulating IgG antibodies against the BMZ in 70-80% of patients but in contrast to pemphigus, this titer does not reflect disease activity. In IIF studies utilizing SSS, IgG autoantibodies are typically found on the epidermal side of cleavage and this is seen in 71% of cases. These autoantibodies may also be present on both sides of the split and this occurs in 17% of cases. Much less commonly, these autoantibodies can also occur on the dermal side alone.

Immunoblot studies have demonstrated BP180 and BP230 to be the target antigens involved in BP which are molecules of the hemidesmosome and lamina lucida. 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.

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. On DIF, while both BSLE and BP demonstrate linear deposition of IgG and C3 at the DEJ, BSLE may be differentiated from BP by immunoelectron microscopy 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.

The mainstay of treatment is corticosteroid therapy. There have been reports of mild and localized disease responding adequately to topical steroids alone. 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. Dapsone alone has been shown to be effective in some cases. In severe cases, the addition of dapsone or sulfapyridine as adjunctive therapy may be beneficial especially in cases with a predominance of neutrophils. Erythromycin used as an adjunct for its antichemotactic effects on neutrophils, has also been reported to result in good outcomes. Other options include nicotinamide, azathioprine, and other immunomodulatory therapy for resistant cases. With treatment, BP often follows a benign course and the disease duration is typically one year or less.

**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. The same pattern is seen in IIF studies in 50% of cases. The incidence of childhood EBA is ten times less frequent than childhood BP, making it an extremely rare disease.

There are two main phenotypes; the first is the classic non-inflammatory mechnobullous type that presents with marked fragility, blisters and erosions at sites of trauma, and healing with scarring and milia formation. Mucosal involvement may be present in half of cases and it may be severe and resemble CP. The inflammatory type is oftentimes clinically indistinguishable from CBDC and BP. 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...
ACQUIRED BULLOUS DISEASES OF CHILDHOOD

Eosinophils. The EBA antigen is collagen VII, a 290 kDa molecule which is the main component of anchoring fibrils in the sublamina densa zone.5-11 This autoantigen is also seen in BLSE 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.12 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 and this has been suggested previously by other authors.13-16

Therapeutic options for EBA include prednisone and dapsone.1 There are documented reports of good responses and disease remission in children with EBA with an average disease duration of three years.1,4

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:

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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. In 1980, the acronym POEMS was coined by Bardwick and colleagues 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. Cytokines such as TNF-α, IL-1α, vascular endothelial growth factor (VEGF), and IL-6 are frequently elevated, and levels may correspond to disease activity. 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 a previous diagnosis of POEMS syndrome. A 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, and POEMS syndrome has therefore also been called Crow-Fukase syndrome. POEMS syndrome affects men twice as often as women and is more common in

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.
Japanese populations, with 165 patients being reported in Japan from 1968 to 1991.1 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.1 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 gammapathy of undetermined significance (MGUS) or a plasmacytoma with osteolytic, osteosclerotic, or mixed lesions.

Various dermatologic changes have also been associated with POEMS syndrome. The most common skin changes include hyperpigmentation, cutaneous sclerosis, angiomatosus 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, 11 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.15

**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 uncommon 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 pulmonary hypertension.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.16 Besides radiation, many strategies have been used, including plasmapheresis, intravenous immunoglobulin, interferon alpha, corticosteroids, alkylators, azathioprine, autologous stem cell transplantation, tamoxifen, and transretnioic acid.17, 18 Melphalan and steroids are often used to treat patients, and cyclophosphamide and vincristine are sometimes used as well.19

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:**

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 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 telangiectasias 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 (emperiplois). 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), 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. 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.

The key clinical features of Rosai-Dorfman disease are massive, painless, bilateral cervical lymphadenopathy with any extranodal site being involved. Extranodal disease has been reported in 28% to 32% of cases with SHML. 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, neutophilia, elevated erythro-
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. 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 entities. 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.

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 regiments 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.

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 cutaneous and systemic symptoms. Because Rosai-Dorfman disease involves only the skin, treatment usually involves systemic steroids, immunomodulatory agents, or chemotherapeutic regimens. If the disease is widespread or causing physical compromise, chemotherapy is considered. For this patient, a wait-and-see approach is being implemented because of his low morbidity.

References:

2. Laxer AP, Esterly NB, Gonzalez-Crussi F. Sinus Histiocytosis clinically limited to the skin Pediatrdermatology 1987;4:247-53.
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-inflammation 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.

Discussion:

The term axillary granular parakeratosis is a benign condition with distinct histopathologic features. In 1991 Northcutt, Nelson, and Tschén 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. 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 proflaggrin 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 proflaggrin 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 (Fig 4). Numerous reports have subsequently noted the existence of GP occurring on the groin, abdomen and lumbarosacral areas thus limiting the use of the body region qualifier “axillary” to pertinent cases only.1–10 The axilla is the most commonly affected site, 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. 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 erythematous 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 antymycotics 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:
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. 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. MCC usually presents as a rapidly enlarging, erythematous nodule on a sun-exposed surface, the head and neck being the most common sites, followed by the extremities. Male or female predominance is debated, and incidence in children is exceedingly rare. 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. Since then, less than 15 cases in total have been described. 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.

Case Report

A 90-year-old female presented to the office with a large, erythematous, 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, levothyroxi- ne, lisinopril, atenolol, risedronate, potassium and multiple inhalers.

Physical exam of the left anterior thigh revealed a large, erythematous 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. 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. 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.

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.

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. Since its first description by O’Rourke and Bell in 1986, only 12 cases of spontaneously regressed MCC have been reported. 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. 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. 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. 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.

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:
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.2 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.

The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trihydroxy-6-(1-methyl-trans-4-propyl-2-pyridyl)-2-(dihydrogen phosphate). The structural formula is presented below.

Figure 1: Structural Formula

The vehicle foam contains clindamycin phosphate in a foam vehicle, consisting of: water, 90% dehydrated alcohol (38%), polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl octanoate (2 dihexyl glycol).

CLINICAL PHARMACOLOGY
Pharmacodynamics: In an open-label, parallel group study in 24 patients with acne vulgaris, 12 patients (1 male and 11 females) applied 4 grams of Evoclin Foam once daily for twelve weeks and 12 patients (7 male and 5 females) applied 4 grams of Clindagel® (clindamycin phosphate) Topical Gel, once daily for twelve weeks. On day 9 the mean±SD for % of lesions ≥ 1% of subjects

<table>
<thead>
<tr>
<th>Efficacy Parameters</th>
<th>Evoclin Foam N=386</th>
<th>Vehicle Foam N=154</th>
</tr>
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<tbody>
<tr>
<td>Treatment response (ISSA)</td>
<td>31%</td>
<td>18%</td>
</tr>
<tr>
<td>Percent reduction in lesion counts</td>
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<tr>
<td>Inflammatory Lesions</td>
<td>49%</td>
<td>35%</td>
</tr>
<tr>
<td>Neutrophil Leukocytes</td>
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<tr>
<td>Total Lesions</td>
<td>43%</td>
<td>31%</td>
</tr>
</tbody>
</table>

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 its metabolites, a history of regional enteritis or ulcerative colitis, or a history of antibacterial-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 in association with the use of topical formulations of clindamycin and rarely with topical clindamycin (see WARNINGS). Use of topical formulations of 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.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number (%) of Subjects</th>
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<tbody>
<tr>
<td>Headache</td>
<td>12% (11)</td>
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<tr>
<td>Application site burning</td>
<td>27% (14)</td>
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<tr>
<td>Application site pruritus</td>
<td>51% (50)</td>
</tr>
<tr>
<td>Application site dysesthesia</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>3% (3)</td>
</tr>
</tbody>
</table>

In a contact sensitization study, none of the 829 subjects developed evidence of allergic contact sensitization to Evoclin. 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. In a contact sensitization study, none of the 203 subjects developed evidence of allergic contact sensitization to Evoclin.

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 can cap. Align the black mark on the nozzle of the actuator.
3. Hold the can at an upright angle and then press firmly to dispense. Dispose of an amount directly into the cap or onto a cool surface. Dispose of an amount of Evoclin that will cover the affected area. 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 fingers and gently massage into the affected areas until the foam disappears.

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 68322-051-01 and 50 gram can - NDC 68322-051-00.

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.

May be stored above ground.

Do not store near heat or in direct sunlight.

Keep out of reach of children.

Manufactured for
Connetics Corporation
Palo Alto, CA 94304

 Printed in USA
October 2004

For additional information: 1-888-500-8383 or visit www.evoclin.com

AW No: AW-0313-r3

U.S. Patent Pending

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References:

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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 palmar/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 orthokeratotic plaques 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.

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Discussion

Pityriasis rubra pilaris was first described by Devergie in 1856.1 It is a rare, chronic, papulosquamous dermatosis of unclear 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 Several human immunodeficiency virus (HIV) infected patients with PRP have been described.8-11 It remains to be established whether these are true associations or chance findings.

Five types of pityriasis rubra pilaris have been described, which differ with respect to age, clinical features, course, and prognosis. Griffiths6,12 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 erthroderma 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. 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. 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. It has an early onset and runs a chronic course. It is characterized by prominent follicular hyperkeratosis and scieroderma-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. Patients with HIV may have nodulocystic and pustular acneiform lesions as well as elongated follicular plugs or lichen planus–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. The presence of acantholysis, hypergranulosis, follicular plugging, and the absence of dilated capillaries and epidermal postulation may help distinguish PRP from psoriasis. 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.

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 erythrodermatophytoma. Phrynodermia, 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 and subacute cutaneous lupus erythematosus 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.

Acitretin in doses of 10 to 75 mg/day is also effective over a course of several months. 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 30 mg/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, extracorporeal photochemotherapy, azathioprine, infliximab, and cyclosporine A. 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, there are some reports of success with narrow-band UVB, UVA1, or PUVA alone or in combination with an oral retinoid.

**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.

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Osteopathic Manipulation in Dermatology

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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 thrust in society for alternative approaches to medicine.4,5

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.3 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.7 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.7,8 Having properly conducted research with statistically relevant outcomes adds validity, projected efficacy, and safety to those treatments.6,9 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.6

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
her stretch marks, and over three days presenting with severe itching and gravidia, white female in her thirty-sixth week of gestation presented with severe itching and 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).

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. The benefits of osteopathic manipulation can and should be applied to our dermatologic surgeries to improve the care we can give our patients.

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.

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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.

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

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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.

Discussion

Epidemiology

First described by Smith and Wilson-Jones in 1985, 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. In fact, the first well-documented case of MCAH in the United States was not until 1994. Despite such few cases, it is thought to be underdiag-
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.\textsuperscript{7,8} They are firm in consistency, non-tender to touch, and have been known to exhibit an annular distribution\textsuperscript{4,6} or to coalesce to form plaque-like lesions.\textsuperscript{5} 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.\textsuperscript{9}

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.\textsuperscript{6,7,11} 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.\textsuperscript{5,7} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} 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.\textsuperscript{7}

**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 ‘angiomyocytoma’ 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 multinucleated 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.\textsuperscript{9}

**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.\textsuperscript{5}

The course of MCAH is an indolent one, progressing slowly over months to years with no tendency of self-resolution.\textsuperscript{7} However, spontaneous resolution has been reported in two cases.\textsuperscript{6,9} To date, there has been no evidence of associated systemic disease.\textsuperscript{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

**Clinical Presentation**

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.\textsuperscript{5} Though typically asymptomatic, pruritis has been reported in two separate cases.\textsuperscript{6}
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.

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ABSTRACT

Acne keloidal 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 keloidal 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 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.

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...
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 sepsis and a host of infections in immunocompromised patients. 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® 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.

**References:**


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**Table III**

**Effectiveness of Treatment on Aerobic Bacteria Cultured from AKN Lesions**

<table>
<thead>
<tr>
<th>Antibiotics* Alone (organism sensitive to agent)</th>
<th>Antibiotics* and Topical Steroids**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Treated</strong></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>22</td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>86%</td>
</tr>
<tr>
<td>Not Improved</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>14%</td>
</tr>
</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Antibiotics Only</th>
<th>Sample Size</th>
<th># Improved</th>
<th># Not Improved</th>
<th>% Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical antibiotic</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>64%</td>
</tr>
<tr>
<td>Oral antibiotic</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Oral and topical antibiotics</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>71%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics with Topical Steroids</th>
<th>Sample Size</th>
<th># Improved</th>
<th># Not Improved</th>
<th>% Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical antibiotic</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Oral antibiotic</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Oral and topical antibiotics</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>
Lesions Giving the Illusion of Pustulation on the Abdomen of a 37-Year-Old Woman

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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.

Microscopic 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 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.5,6 Although cutaneous involvement in RDD is common, purely cutaneous disease is thought to be rare.7,8

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.9 Furthermore, in terms of color, a 423-patient registry suggests that RDD lesions are most commonly xanthomatous,1 though the very same registry clearly documents numerous lesions that are red, brown, pink, blue, and purple.7 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,6 telangiectasias,5 and guttate psoriasis.5 Rarely, central ulceration or necrosis is present.10 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.7

Currently, RDD is diagnosed by its
histopathologic features,\textsuperscript{8,11} namely the prominence of enlarged, foamy histiocytes that stain strongly for S-100 and the presence of lymphophagocytosis (emperipolysis).\textsuperscript{7} 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.\textsuperscript{22} In addition, the histiocytes of RDD lack Birbeck granules seen by electron microscopy,\textsuperscript{13} unlike those of Langerhans cell histiocytosis. In the literature, weakly positive staining for CD68 is often reported; however, this is not a consistent finding.\textsuperscript{4,11} Furthermore, reports of positive and negative staining for CD1a can be found.\textsuperscript{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.\textsuperscript{1} 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.\textsuperscript{14} The etiology of RDD has not been delineated. While some reports suggest the involvement of human herpes virus 6 and Epstein-Barr virus,\textsuperscript{2,3,16,17} 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.\textsuperscript{15} In fact, 14 deaths were documented in a series of 217 patients.\textsuperscript{16} 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.\textsuperscript{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.\textsuperscript{6,8,11,15,20,21}

Recently, thalidomide therapy has been implemented with mixed results.\textsuperscript{8,11} Other reported options include chemotherapy, interferon, oral and topical retinoids, pulse-dye laser and dapsone.\textsuperscript{22}

References:

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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 4 cm 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 bacteria, a GMS stain was negative for bacteria, a GMS stain was negative for bacteria, a GMS stain was negative for bacteria. 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 an emphasis on mycobacterial culture.

Histopathology of the excised lesions (Fig. 4, 5, 6) revealed epidermal hyperplasia and focal areas of pseudoeitheliomatous 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 tuberculous 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. 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 thiocetazone and is negative for nitrate reductase, both of which differentiate it from its nearest microbiologic relative, Mycobacterium Kansaii. Infection in fish usually manifests
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, purulent, 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. 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 osteomyelitis have been described. 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.

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. By the sixth month mature granulomas form with multinucleated giant cells. There may be central fibrinoid necrosis present within abscesses, but no true caseation. 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.

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.

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.

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. 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). 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. 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. One recent study from France published in 2002 examined 63 cases of biopsy proven M. marinum infections to determine the most effective therapy. 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

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.\textsuperscript{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\textsuperscript{12} 12-25 mg/Kg/day is indicated.\textsuperscript{3}

References:

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

Now
In 120 g
Tube

Class I Strength

- 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.

Vanoss™
(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

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**VANOS™ (fluocinonide) cream 0.1%**

**Rx Only**

**FOR TOPICAL USE ONLY**

**DO NOT USE ORAL, OINT, OR INTRAVENOUS USE**

**DESCRIPTION**

VANOS™ (fluocinonide) Cream, 0.1% contains fluocinonide, a synthetic corticosteroid for topical dermatologic use. Its corticosteroid content is formulated in a ratio of prednisolone and 20-hydroxyproglandin A, forming a physiologically active compound with a molecular weight of 504 Da.

It has the following chemical structure:

Fluocinonide is an almost colorless white to creamy-white crystals powder. It is practically insoluble in water and slightly soluble in ethanol.

Each gram of VANOS™ Cream contains 1 mg of fluocinonide in a cream base of propylene glycol (USP) dimethyl sulfoxide, glycerin (anhydrous) (PEG)-100 steardate, glycerin monostearate NF, purified water USP, carbopol 940 NF, disodiumpropionate, and citric acid.

**CLINICAL PHARMACOLOGY**

Like other topical corticosteroids, VANOS™ (fluocinonide) Cream, has anti-inflammatory, antiproliferative, and antioedematous 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 A₂, inhibiting protein, collectively called lipocortin. It is postulated that these proteins control the biosynthesis and release of the proinflammatory mediators, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Pharmacology studies have demonstrated the absence of topical corticosteroids in many variables including the vehicle and the integrity of the aged barrier. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other dermal provocation may increase percutaneous absorption.

Vehicle control studies performed with VANOS™ Cream, 0.1% in healthy subjects indicate that it is in the super-regional range of potency as compared to other topical corticosteroids. However, similar patching scores do not translate directly into therapeutic efficacy. 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 demonstrative HPA-axis suppression in 2 patients (12% and 20% BSA) where the HPA suppression for a corticosteroid is shown in a similar manner.

**PRECAUTIONS: General**

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

*PROTEIN NUTRITION*,

It is not known whether systemic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether any patient receiving topical corticosteroids should breast-feed.

**Pregnancy Category C**

Corticosteroids have been shown to be teratogenic to laboratory animals when administered systemically at relatively low doses. 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 adverse 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 any patient receiving topical corticosteroids should breast-feed.

**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.

**OVERDOSAGE**

Overdosage of topical corticosteroids is usually localized to the skin area to which they are applied. The potential systemic absorption of these agents can be minimized by avoiding occlusive dressings or the use of high potency corticosteroids. The use of occlusive dressings or the use of high potency corticosteroids results in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether any patient receiving topical corticosteroids should breast-feed.

**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% of body surface area involved at baseline had one or more areas of 10% or less of body surface area with VANOS™ Cream, 0.1% twice daily 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 the end of treatment.

**Table 1**: Plaque-Type Psoriasis in Adults

<table>
<thead>
<tr>
<th>Site Reaction</th>
<th>0 (0)</th>
<th>0 (0)</th>
<th>0 (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients cleared</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patients achieving treatment success</td>
<td>10 (19%)</td>
<td>4 (7%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Patients achieving treatment success</td>
<td>6 (12%)</td>
<td>58 (57%)</td>
<td>10 (19%)</td>
</tr>
</tbody>
</table>

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

**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 and older (see PRECAUTIONS: Pediatric Use).

**CONTRAINDICATIONS**

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

**General**

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency if used on more than 20% of the body surface area day after day. More frequent and/or prolonged use, higher potency corticosteroids, and the use of occlusive dressings increase the potential for HPA-axis suppression.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin-to-surface body mass ratios.

If irititation 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 evaluation of the site reaction should be done in all cases of allergic contact dermatitis.

If concurrent skin infections are present or develop, an appropriate antimicrobial or antifungal 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.

**CLINICAL STUDIES**

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 demonstrative HPA-axis suppression in 2 patients (12% and 20% BSA) where the HPA suppression for a corticosteroid is shown in a similar manner. 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 demonstrative HPA-axis suppression in 2 patients (12% and 20% BSA) where the HPA suppression for a corticosteroid is shown in a similar manner.