This is the 12th issue of the JAOCD. Each successive journal improves and shows signs that our residents are being exposed to more and more variety and pathology in their residency programs. We are entering the third quarter of 2008. The Olympics are now behind us, and our country did very well. Records were set and new world champions arose from Beijing.

So much effort goes into becoming great. It is not about perfection, it is about persistence! Never stop because you are not as good as somebody else. Never stop trying harder to become better. All of this practice and all of this effort leads to greatness.

There was a televised golf tournament about 30 years ago. Arnold Palmer made a hole-in-one shot on a long par 3 hole. He was interviewed and you could see his excitement. The person conducting the interview said, “Well, you must feel just so lucky?” You could see the smile leave Arnold Palmer’s face as he said, “Well, it seems the more I practice, the luckier I keep getting.”

How well said? Nothing great comes without persistence and a lot of effort. The same is true of our organization and the JAOCD. But it doesn’t have to take a lot of effort on the part of a few, it can take a very little amount of effort on the part of many. That is how greatness occurs.

We encourage all of our membership to contribute a small amount to the AOCD and to the JAOCD. This will assure that our organization and the journal representing our organization continue to improve and cast a great reflection upon all of us.

As in every issue, we thank our corporate sponsors for making the JAOCD possible. Global Pathology Laboratory, Medicis-The Dermatology Company, Stiefel Laboratory and Galderma all have come forward and given their support to the JAOCD. They continue their commitment to the dermatology profession and support the AOCD in all of its endeavors.

Jay S. Gottlieb, DO, FAOCD, FOCOO (Editor)
Stanley E. Skopit, DO, FAOCD (Editor)
LETTER FROM THE PRESIDENT
OF THE AOCD

JAY GOTTLIEB, D.O.,
F.A.O.C.D., F.O.C.O.O., PRESIDENT

Decisions and Transitions!

It is said that time passes quickly, and that certainly is true of this year being president of the AOCD. I must say that it has been smooth sailing and I appreciate all of the help that I have received from others within the AOCD. I feel like I just wrote my first letter stating my goals of being president and now I am writing my last letter as the outgoing president.

So what have I learned this year? I have realized that we have a great organization. We must always strive to make it better and never be content with the way things are. I have learned to be more tolerant of others and realize that everybody is doing the best they can, from where they are, with what they have.

Last October Dr. Peter Ajluni, the incoming president of the AOA, talked about ‘life is what happens when we are busy making other plans”. He challenged everybody present at that meeting to ‘get fit for life, and on that day I made my decision. If I am to accomplish all that I wish to accomplish in my lifetime, I must be ‘fit for life’. I took on this challenge and a by-product of this is that I feel great, I accomplish more on a daily basis and I look pretty darn good!

Making a decision is cutting off any other possibility other then that outcome. From these decisions come transitions. Moving on to do more and better things with what we have. It takes us to new levels where we can do even better and reach further then we ever thought possible.

I have come to realize how little time it really takes to make a difference in an organization and in others’ lives. The best part of taking action and getting involved, is the self-satisfaction and personal growth that I have experienced.

I encourage all of the members of the AOCD to take part, play a role, and make a difference in the AOCD. There are so many ongoing issues, and new ones popping up all of the time, that require our efforts. That is what keeps us “green and growing” and from becoming “ripe and rotten.”

It has been fun and an honor serving as your president during the 2007-2008 year. I thank my friends and mentors who have helped me have the life that I have today. I want to recognize my friend and mentor, Dr. Stan Skopit, for all that he has done for me. Jere Mammino is always in the background and always “the wind beneath my wings.” Drs. Ed Yob, Lloyd Cleaver, and Jim DelRosso have done so much to help me, and continue to work for you and the AOCD. Becky and Rick Mansfield and Marsha Wise run our organization efficiently and professionally. I wish to thank my partner, Dr. Sandy Goldman and my Physician Assistant Daughter Amy Gottlieb for picking up the slack this year when I was tied up doing other things. I thank my oldest daughter Lori for always being there on the phone to keep me smiling and laughing.

These acknowledgements would not be complete with thanking my wife Shirley, our AOCD Coordinator of Corporate Development, for putting up with me on a daily and a minute-to-minute basis. I know that this is no easy task

Remember “thoughts become things,” so choose good ones. Thank you for allowing me to serve as your president.

Sincerely,

Jay Gottlieb, DO, FAOCD, FOCOO
AOCD President, 2007-2008
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This is a free service for all active members of the AOCD. A 3" column black and white ad will be provided in the journal as a free service. If members wish to use a larger space, they may do so. The cost for this advertising is:

Black and White - 1/4 page-$125,
1/2 page-$200, full page-$350

Full 4 color ad - 1/4 page-$275,
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Resident members may run a 3" column black and white ad stating their desired professional position.

These ads must be submitted as an e-mail attachment and sent to jaocd@aol.com. Any photos to be included in an active member's ad, must be in a .pdf format.
Seborrheic dermatitis (SD) includes inflammation of the scalp consisting of redness, pruritus, and powdery scales. Patients with seborrhea may later get seborrheic dermatitis. It appears the main culprit is a yeast-like fungus in the Malassezia family, with immunity and individual susceptibility playing secondary roles.

The pathogenesis of SD results from an overgrowth of Pityrosporum ovale (Malassezia furfur) in the sebum. Sebum is composed of triglycerides and esters, as well as fatty acids, cholesterol and squalene. As the triglycerides and esters are broken down on secretion, individual free fatty acids accumulate. Recent research has shown Malassezia to thrive in a free fatty acid medium. Malassezia fungi contain lipases that break down triglycerides and esters in a non-specific manner and create such an environment. They degrade sebum, free fatty acids from triglycerides, consume specific saturated fatty acids, and leave behind the unsaturates. Penetration of the modified sebaceous secretions results in inflammation, irritation, and scalp flaking.

Skin cells die and are subsequently replaced by new skin cells in a never-ending cycle. In normal people, this cycle takes about one month, and is usually not noticeable. On scalps where Malassezia thrives, the whole process can take less than half that time. Seborrheic dermatitis typically affects areas of the skin where sebaceous glands appear in high frequency and are most active. The sebum secretion rate increases throughout the teens, remains steady through the 20s and 30s, then lessens with age. In males, the rate remains higher longer, into the 50s and 60s, but in females, the secretion rate drops quickly after menopause.

Human sebaceous glands (SG) are found over the entire skin surface (except the palms of the hands and soles of the feet), but sebum secretion is highest on the scalp, face, chest, and back. The distribution is classically symmetric, and common sites of involvement are the hairy areas of the head, including the scalp and scalp margin, eyebrows, eyelashes, mustache and beard. Other common sites are the forehead, the nasolabial folds, the external ear canals, and the postauricular creases. One of the characteristics of SD is dandruff; patients may complain of the scalp itching with dandruff, and because they think that the scale arises from dry skin, they decrease the frequency of shampooing, which allows further scale accumulation resulting in greater inflammation and worsening symptoms. This article attempts to relate SD as a common clinical finding in patients with neurological disease and immunodeficiency; immobility plays a significant role in generating conditions for disease pathogenesis. Neurological disease often results in a decrease in neuronal activity to areas where sebaceous glands exist in abundance, causing pooling of the sebum and thereby fostering conditions suitable for SD. Patients with immunodeficiency are also more prone to SD due to unopposed growth of Malassezia. However, immobility may also be present in these patients due to a decrease in activity, further encouraging sebum collection and inflammation.

Dermatologists should recognize the relationship between immobility caused by neurologic or immunologic disease to SD. Patients with histories of epilepsy, Down syndrome and immunodeficiency are presented as cases here, demonstrating the role of immobility in facilitating the pathogenesis of SD.

Case I
A 29-year-old African American male presented with a history of epilepsy and a five-year history of SD. The patient stated that SD outbreaks occur during stressful situations and during changes in weather. Findings began typically, with dry red patches around the nose, beard, and scalp area with some flaking of skin around the eyebrows. At a follow-up visit, he still complained of scaling, itchiness and erythema in the same areas with no relief using OTC creams and lotions. He was then prescribed Naftin cream and Ketoconazole shampoo to use for three weeks, until the next follow-up.

He recently had a vagal stimulator put in to help control his seizures. He is currently taking the following medicines: Topamax, Resipridol, Zonegran, and Depakote.

Case II
A 36-year-old male with Down syndrome presented with a two-year history of SD. He was seen at follow-up with redness around his lips and cheek bones and complaints of itchiness and scaling around the scalp. He has been on MetroGel since the last visit, three weeks ago, with little to no relief.

Case III
A 14-year-old girl presented with a history of an IRAK-4 immunodeficiency disorder and a mild neurological deficit. Interleukin-1 receptor-associated kinase (IRAK)-4 deficiency is a rare primary immunodeficiency disorder particularly characterized by severe, invasive infections with S. pneumonia. She presented with itchiness and redness around the nasolabial folds and eyebrows. She also complained of itchiness and scaling of the scalp.

Conclusion
As stated previously, the pathogenesis of SD has been linked to lipid metabolism of the Malassezia family. The above cases have been submitted to demonstrate specifically how immobility creates conditions that increase one’s susceptibility to SD, whether the immobility is the result of a neurological deficit, immunodeficiency or a combination of both. The patient discussed in Case I is limited to few activities because of his neurologic problems and therefore is less mobile than his peers. The patient’s immobility can be seen as a decrease in movement and in facial expression. Furthermore, the patient is unable to groom himself. Without proper assistance in personal hygiene, the environment becomes a suitable medium for growth. This could cause increased pooling of the sebaceous glands, thereby predisposing him to SD. Furthermore, the decreased neuronal activity could also play a role in disrupting the natural balance of the immune system’s ability to control the population of Malassezia species. Similarly, the patient in Case II requires special care each day because of his mental limitations. He spends most of his time indoors and is limited in his activities. The combination of his neuronal impairment and lack of activity both predispose him to SD.

Case III provides a combination of both immunodeficiency and neurological deficit. Due to her immunodeficiency, the patient is hindered from participating in many activities, and as a result is less active on a daily basis. The limited activity, especially during the ages surrounding menarch, can...
lead to increased pooling of the sebaceous glands, as they are very active during this period and can provide a substantial food supply for the fungus.

Treatment options for SD vary depending on region. The head and scalp areas can be treated with OTC shampoos containing salicylic acid (Scalpicin) or selenium sulfide (Selsun Blue, Exsel). If these are ineffective, ketoconazole or a coal tar shampoo (DHS Tar, Neutrogena T/Gel, Polytar) may be used. Other areas of the body may also be treated with the antifungal ketoconazole (Nizoral), ciclopirox (Loprox) and naftifine HCl (Naftin) in addition to steroids (hydrocortisone) used to treat inflammation. Isotretinoin (Accutane) has been used in severe cases.

References:
TREATMENT OF TEN WITH IVIG – A CASE REPORT


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ABSTRACT

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are acute, rare, life-threatening mucocutaneous diseases that are almost always drug related. Massive apoptosis of keratinocytes, mediated by the interaction of the death receptor-ligand pair Fas-FasL and the perforin/granzyme pathways, leads to rapid extensive necrosis of the epidermis and separation of the skin at the dermal epidermal junction. 2 Mucous membrane involvement is common, and mucositis generally precedes skin lesions by a few days. 1 Features of TEN include an abrupt onset of fever, generalized rash, extreme skin pain, purulent conjunctivitis and asthenia. All organs may be involved, and sepsis is the most important complication, leading to death. Toxic epidermal necrolysis is associated with a mortality rate of 30%. 1 Elderly and immunosuppressed patients have a higher mortality rate.

Optimal treatment remains to be clarified. Discontinuation of the offending agent and care in a burn unit is agreed upon by most authorities. IVIG has been shown to be beneficial in the treatment of SJS/TEN, to varying levels. A case of SJS/TEN rapidly progressing to TEN and treated with IVIG is presented here. Despite the patient’s multiple co-morbid conditions, including AIDS and end-stage renal disease, treatment with IVIG resulted in an arrest of progression of TEN and re-epithelialization in two weeks.

Case Report

A 29-year-old male with a past medical history significant for AIDS, renal failure and pulmonary embolism presented to the emergency room with a five-day history of a rapidly progressing rash and constitutional symptoms. The patient stated that the rash initially started on his trunk and spread to the face and extremities. The patient had been started on phenytoin one week prior to the onset of the rash. He did admit to being non-compliant with his HIV medications. The patient recalled experiencing a burning sensation in his eyes combined with painful swallowing prior to the onset of the rash. There were no known allergies up to this point.

Physical exam revealed an ill-appearing male with widespread erythematous, dusky, atypical targetoid and purpuric macules on extremities, trunk and face, covering more than 30% of body surface area (BSA) (Figure 1). Flaccid bullae were present on the skin as well (Figure 2). Nikolsky’s sign was positive. The detachment of skin was roughly 10%-15% on admission. Affected areas of the skin resembled wet cigarette paper. The patient had bilateral conjunctival injection with hemorrhagic crusts and erosions on the labial and gingival mucosa. The skin lesions were very tender.

Based on the history and clinical presentation, a diagnosis of SJS/TEN overlap due to Phenytoin therapy was made. SCORTEN4 severity-of-illness score was determined to be 3. Punch biopsies (Figure 3, 4) were performed for definitive diagnosis. Histopathology revealed confluent necrosis of the epidermis and a sparse perivascular infiltrate of lymphocytes.

The patient rapidly developed TEN within hours of initial evaluation while awaiting transfer to a burn unit. The patient was admitted to the ICU with wound care, hydration and nutritional support. Phenytoin was immediately withdrawn, and IVIG therapy was initiated at 1g/kg/day for four days. The patient was aggressively managed with wound care and nutritional support. A cessation of skin and mucosal detachment was seen within three days of starting IVIG therapy, and re-epithelialization of the skin was noted within two weeks of therapy. The patient eventually attained near normalization of skin. However, he developed pulmonary and renal complications due to his multiple co-morbid conditions and was transferred to hospice.

Discussion

First described by Lyell in 1956, TEN is one of the most formidable conditions faced by dermatologists. It is a life-threatening cutaneous drug reaction that appears to be mediated by cytotoxic T lymphocytes. 3 TEN/SJS is rare, with an annual incidence of two per million people. TEN occurs in all age groups including infants, children and adults. Patient groups particularly at risk are immunocompromised patients (HIV infection, lymphoma), patients undergoing radiation therapy for brain tumors and concomitantly receiving phenytoin. 5-7 Patients treated with aromatic anticonvulsants, slow acetylator types and slow metabolizer genotypes. HIV patients have reduced levels of detoxifying chemicals such as glutathione and cysteine and have a much higher risk of developing TEN as compared to the general population. Our patient had several risk factors that could have contributed to developing TEN, including HIV positivity, end-stage renal disease and anticonvulsant therapy.

The overwhelming majority of cases of SJS/TEN are caused by drugs, especially the anticonvulsants phenytoin, phenobarbital and carbamazepine. The risk of TEN is highest in the first two months of therapy. More than a hundred drugs have been identified as being linked to SJS/TEN.
and include anticonvulsants, antibiotics (particularly sulfonamides), NSAIDs, nevirapine and allopurinol. Non-drug-related causes include exposure to industrial chemicals, vaccinations and certain Asian herbal products.8-11

The pathophysiology of TEN remains only partially understood. TEN is considered a T-cell-mediated disorder. Viard et al.12 demonstrated that massive keratinocyte apoptosis is mediated through upregulation and activation of specialized cell membrane receptors such as Fas. Fas ligand (FasL) expression is upregulated on the cell surface of keratinocytes in TEN, and upon contact with Fas, FasL induces polymerization and triggering of the caspase cascade. This leads to keratinocyte apoptosis. Increased levels of certain cytokines such as tumor necrosis factor- (TNF-) and interleukin 6 (IL-6) are also present in the lesional skin of TEN patients. Perforin/granzyme pathways have also been implicated in the pathogenesis of TEN. It has been shown that IVIG inhibits keratinocyte cell death by inhibiting Fas-FasL interaction. Other proposed mechanisms of IVIG therapy include regulation of cellular immune responses and elimination of active complexes.12

Initial symptoms of SJS/TEN include malaise, fever, odynophagia and a stinging sensation in the eyes. Skin lesions tend to favor the trunk, spreading centrifugally. Widespread, purpuric macules and dusky, atypical targetoid lesions are seen, including bullae. Involvement of the ocular, genital and buccal mucosa is seen in more than 90% of patients. The involved skin acquires a gray hue as the epidermal involvement progresses and eventually leads to detachment of the dermis from the epidermis. Nikolsky’s sign is usually positive and is elicited by the epidermis being displaced laterally upon slight pressure from the thumb. Involvement of the GI tract and respiratory tract can occur due to the release of large amounts of proinflammatory cytokines in the epidermis.14 Complications include sepsis, multiorgan failure, pulmonary embolism and gastrointestinal hemorrhage.15 Vulvar adenosis of the labia minora has been reported following SJS/TEN.16-18 With the proper treatment and care, the skin starts to re-epithelialize in a few days. Skin sequelae include scarring, hypopigmentation or hyperpigmentation, vulvovaginal stenosis and phimosis. Ophthalmologic sequelae are the most serious and include corneal ulcers, photophobia, xerophthalmia and foreign-body sensation.19

SJS and TEN lie at the two ends of a spectrum of reactive disorders. The extent of skin detachment divides the spectrum into one of three major groups:

1. SJS: epidermal detachment of <10% of the body surface area.
2. SJS/TEN overlap: epidermal detachment of 10%-30% of the body surface area with widespread atypical purpuric and targetoid lesions.
3. TEN: epidermal detachment involving >30% of the body surface area. This is further divided into two categories:
   a. TEN with spots: large areas of epidermal detachment involving >30% of the body surface area, with widespread, flat, atypical targetoid or purpuric lesions.
   b. TEN without spots: large areas of epidermal detachment involving >10% of the body surface area, without targetoid or purpuric lesions.

In 2000, a severity of illness score for TEN (SCORTEN) was proposed to assess illness severity and predict mortality. SCORTEN is a sum of seven measurable clinical variables, each with equal weight. The variables are: (1) age ≥ 40 years; (2) heart rate ≥ 120 beats per minute; (3) epidermal detachment involving >10% body surface area; (4) presence of cancer or hematologic malignancy; (5) glucose >252mg/dL (14mmol/L); (6) blood urea nitrogen >28 mg/dL (10mmol/L); and bicarb ≥20mEq/L. Each variable is allotted one point, and the mortality increases with each additional point (Table 1).4

The clinical presentation and patient history are usually enough to make the diagnosis of TEN. However, other diagnoses to be considered include Staphylococcal scalded skin syndrome (SSSS), paraneoplastic pemphigus (PNP), drug-induced pemphigus, acute generalized exanamnetic pustulosis (AGEP) and linear IgA dermatosis.

Histologically, early lesions of TEN reveal apoptotic keratinocytes in the basal and suprabasal layers of the epidermis. Late-stage lesions reveal full thickness epidermal necrosis with subepidermal blisters.20 There is usually a sparse dermal mononuclear cell infiltrate seen in the dermis. However, Quinn et al. have demonstrated a range of mononuclear cell infiltrates, from sparse to dense.21

Due to the high mortality rate associated with TEN, early diagnosis and specific therapy is imperative. Most authorities agree that the patient should be admitted to a unit that is equipped to handle patients with burns and extensive cutaneous injuries.22-24 Daily wound care, nutritional support, hydration and pain relief is essential. Patients’ skin manipulation should be minimized, and special attention should be paid to the eyes, respiratory tract and electrolyte balance. Debridement of necrotic epidermis and use of artificial membranes, porcine xenograft or human skin allograft may be required.

Adjuvant treatments, including plasmapheresis, cyclosporin, corticosteroids, TNF-alpha inhibitors and IVIG, have been tried with variable results. Adjuvant treatments remain complementary to supportive care in a unit capable of handling burn patients.

The patient presented here was treated with supportive care in addition to receiving IVIG therapy. IVIG is derived from pooled plasma of human donors and consists mainly of the IgG class of immunoglobulins. IVIG contains anti-Fas IgG, which blocks Fas-FasL interaction, thus

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<th>SCORTEN (sum of individual scores)</th>
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interfering with keratinocyte apoptosis in TEN. A number of studies have been conducted with varying levels of evidence for the efficacy of IVIG therapy versus other treatments. 

Toxic side effects were determined to be 88%. In another study, out of 16 patients with TEN treated with IVIG (1g/kg/day), 15 patients survived. The efficacy of IVIG therapy in TEN is also well established in the pediatric literature.

Some studies have shown minimal or no benefit from IVIG therapy due to its toxic side effects. The lack of uniformity in IVIG therapy in TEN calls for multi-center, controlled, randomized studies to test the effectiveness of IVIG therapy versus other modalities.

Acknowledgements:

The authors wish to thank Angelos Poulos, M.D., Director, Global Pathology Laboratory Services, and Kristen Aloupis, D.O., 2nd-year resident at NSU-COM/BGMC, for their help in this case.

References:

Background

Originally, sinus histiocytosis with massive lymphadenopathy was reported in African children in 1965 by Destombes.¹ It was not until Rosai and Dorfman described it in 1969 that the disease acquired the eponym Rosai-Dorfman disease (RDD).² RDD is considered a self-limited, reactive histiocytosis of unknown etiology. RDD is typically classified into two forms: 1. sinus histiocytosis with mass lymphadenopathy or RDD; and 2. cutaneous histiocytosis or cutaneous RDD. Herein, we report a case of purely cutaneous RDD that showed no signs of systemic involvement.

Case Report

A 69-year-old Caucasian male presented for a routine skin examination. His medical and surgical history included a stroke with ventricular peritoneal shunt placement 20 years prior, coronary artery bypass grafting, hypertension, hypercholesterolemia and osteoarthritis. He reported no known drug allergies and denied any new medications. His medications included phenytoin, metoprolol, clopidogrel, simvastatin and a multivitamin. A review of systems was negative.

On physical exam, there were two 1.2-cm pink-purple nodules, one on his right posterior shoulder and one on his right lateral back (Picture 1). The initial clinical impression was that of a basal-cell carcinoma.

Histopathologic examination showed a nodular infiltrate of foamy histiocytes surrounded by a margin or rim of lymphocytes. This high-magnification appearance has sometimes been likened to a “lymph node in the skin” (Picture 2). Intact lymphocytes with rare plasma cells and erythrocytes were seen within the cytoplasm of histiocytes, a phenomenon known as emperipolesis (Picture 3). Immunohistochemical staining revealed that the histiocytic cells stain CD 68 +, S-100 +, CD1a −, and factor XIIIa +. These findings are consistent with a histopathologic diagnosis of RDD.

Upon further questioning, the patient revealed to have had a biopsy of a “cyst” on his left forearm over a year ago. The histopathologic diagnosis of that lesion was reported as Rosai-Dorfman disease.

There were no abnormalities noted on a CBC with differential and comprehensive metabolic panel. A CT scan of the chest/abdomen/pelvis revealed no lymphadenopathy.

Discussion

Classic RDD presents with massive, painless cervical lymphadenopathy, fever, leukocytosis, anemia, elevated ESR, and a polyclonal gammopathy.³ It is more commonly seen in black males during the first to second decade of life. The cervical lymph nodes are affected in the majority of cases, and extranodal involvement occurs in 30-40% of cases.³ The most common site of extranodal involvement is in the skin.² Other sites of involvement include but are not limited to bone marrow,⁴ salivary gland,⁵ CNS,⁶-⁹ genitourinary tract,⁸,¹⁰ respiratory tract,¹¹ liver and gastrointestinal tract,¹² and breast.¹³

Associations reported with classic RDD include infection,¹⁴ hematological malignancy,¹⁵,¹⁶ and autoimmune diseases.¹⁷,¹⁸ Although the condition is considered to be benign, the course can be unpredictable. It may be characterized by a prolonged clinical course with exacerbation and spontaneous remission phases. It rarely may be complicated by organ compression, immune dysfunction and unusual infections. There are some reports of death associated with complicated cases of classic RDD.¹⁹

Treatment is often not necessary because of the self-limited nature of the illness. However, corticosteroid therapy,¹⁰ radiation,¹¹ chemotherapy,¹² surgery¹³ and interferon-α therapy²⁰ have all been tried.

Cutaneous RDD is a rare variant of RDD with localized involvement of the skin. Usually, there are no systemic symptoms; but rarely, fatigue and weight loss have
been reported. It is more commonly seen in white females in the fifth to seventh decade of life.25

The clinical presentation of cutaneous RDD is variable, and any body region can be involved. There may be solitary or multiple, yellow-red-brown papules/nodules; or it may localize to the soft tissue, mimicking a tumor26-28 or panniculitis;29 or it may present clinically as a vasculitis.29

The histopathologic features of cutaneous RDD and extranodal RDD are the same. They are characterized by a nodular or diffuse infiltrate of foamy histiocytes whose overall silhouette is that of a “lymph node in the skin.” The diagnostic feature is intact lymphocytes and, on occasion, plasma cells or erythrocytes in the cytoplasm of histiocytes. This phenomenon is known as emperipolesis.30

Immunohistochemical staining of the histiocytes in RDD shows that they are S100+, CD1a-, and CD 68+, a phenotype that has been described as indeterminate and may represent a form of active macrophage.31

Cutaneous RDD recapitulates the histopathological characteristics of RDD but has a more favorable clinical behavior than its systemic counterpart. There are no reported cases of cutaneous RDD developing into systemic disease. Cutaneous RDD tends to be spontaneously regressed, but it may persist for years32 or recur after excision.33 There are rare reports of localized Langerhans-cell histiocytosis coexisting with cutaneous RDD.33,34

The pathophysiology of RDD is not known, but a viral etiology like HHV-6 or EBV has long been postulated. However, no specific virus has been fully confirmed.35

There is one case where monocyte-colony stimulating factor (M-CSF) played a role in recurrent RDD. In cell culture, M-CSF can stimulate macrophages to engulf lymphocytes in a process similar to emperipolesis.36

Treatment of purely cutaneous RDD is not necessary. It may be treated for cosmetic purposes or symptomatic relief. Modalities that have been tried include radiotherapy, crotetherapy,37 excision, topical/oral or intralesional corticosteroids,38 dapsone,39 thalidomide,40 and acitretin.41

The clinical and histopathologic appearances of the cutaneous lesions in the two forms of RDD are indistinguishable. However, the epidemiology is quite different, with cutaneous RDD having on older age at onset and a reversed male-to-female ratio. Cutaneous RDD remains localized to the skin even with long-term follow up, and no significant systemic, extracutaneous, or serologic manifestations have been described. Hence, some authors believe that cutaneous RDD is in fact its own, distinct clinical entity.42,43

It is important to remember that cutaneous RDD has an overall benign course, resolves spontaneously and shows no signs of systemic involvement. It tends to occur in older, white females and likely represents a reactive process to a not-yet-identified antigen.

Special thanks to Peter Motel, M.D.

References
12. Lauwers GY, et al. Rosai-Dorfman disease presenting as a peripheral mononeuropathy and clinically mimicking a tumor26,27 or panniculitis; 28 or nodules; or it may localize to the soft tissue, mimicking a tumor26,27 or panniculitis;29 or it may present clinically as a vasculitis.29

38. Chan CC, et al. Dapsone as a potential treatment for cutaneous Rosai-Dorfman disease with neutrophilic pre-
**Case Presentation**

A 14-year-old male presented with a three-year history of patches on the trunk. They were asymptomatic, but would come in waves with increasing numbers at times. The patient had a history of asthma but no other cutaneous or serious medical illness. There was no history of Lyme disease.

**Exam**

There were 2mm-to-5mm macules scattered over the entire integument. The macules were somewhat atrophic and had a "step-off" configuration (Figures 1, 2).

**Histopathology**

The superficial dermis showed a few telangiectatic vessels. The dermis showed the adnexal structures to be intact. Sweat coils were seen in the dermis. The subcutaneous fat included was unremarkable. Acid-Orcein-Giemsa showed elastic fibers to be intact. There was reduced dermal thickness (Figure 3).

**Diagnosis**

Atrophoderma of Pasini and Pierini

**Differential Diagnosis**

- Morphea
- Anetoderma

**Discussion**

Idiopathic atrophoderma of Pasini and Pierini (IAPP) is a form of dermal atrophy that presents as one or several sharply demarcated, depressed patches. The patches usually appear on the backs of adolescents or young adults. Whether atrophoderma is an atypical, primarily atrophic form of morphea or a distinct entity is still debated. The disorder is more frequently encountered in women than in men, with a ratio of 6:1 in adults. Whether atrophoderma is an atypical, primarily atrophic form of morphea or a distinct entity is still debated. The disorder is more frequently encountered in women than in men, with a ratio of 6:1 in adults. Whether atrophoderma is an atypical, primarily atrophic form of morphea or a distinct entity is still debated. The disorder is more frequently encountered in women than in men, with a ratio of 6:1 in adults. Whether atrophoderma is an atypical, primarily atrophic form of morphea or a distinct entity is still debated. 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not diagnostic, so diagnosis is primarily a clinical one. The epidermis is usually normal or slightly atrophic. Basal-cell pigmentation may be increased. A perivascular infiltrate consisting of T-cells and histiocytes may be seen. Dermal thickness is eventually reduced when compared with adjacent normal skin.3

The course of the benign disease is progressive, and lesions can continue to appear for decades before reaching a standstill. Transformation to generalized morphea has not been observed. The natural course of the disease is often protracted (10 to 20 years), making the evaluation of therapy difficult.5 No treatment has been proven effective. IAPP has no known effect on the patient’s overall health. Penicillin has been used to treat atrophodera of Pasini and Pierini because of case reports of an underlying Borrelia burgdorferi infection.7 Pсорalen and UVA (PUVA), potassium benzoic acid and oral antibiotics may be helpful to some patients if Borrelia burgdorferi antibodies are elevated.10 However, the results have been inconclusive.9 Excessive sun exposure may cause the more deeply pigmented lesional skin to become darker, resulting in further uneven discoloration of the skin. In some cases, the Q-switched alexandrite laser was effective in diminishing the hyperpigmentation by 50 percent.1

References:
Report of a Case:

An 18-year-old male presented to the office with his mother and siblings and complained of a rash that covered his body. Multiple, honey-crusted papules and pustules that were erythematous, inflamed and excoriated were noted. He reported the rash started on the back of the neck and spread over the entire body. He stated that it was very itchy and uncomfortable. There were several places on his neck where he had scratched so hard that it left red finger markings. The rash extended into his nostril, and he reported purulent drainage on occasion. His genital area was swollen and erythematous.

The patient’s mother stated that he had poor hygiene, which was evident along with the body odor that emanated from him. The mother stated that her son did not sleep much. The patient laughed inappropriately and stated that he didn’t think it was necessary to take a bath every day. The patient did state that a few days earlier he was outside moving plants around the house. He also stated that he did not wear clean clothing and spent hours in front of a computer playing computer games. The patient stated that he dropped out of high school last year.

The mother also stated that the patient would threaten to touch them if he didn’t get his way. She’d taken the patient to the hospital a few days earlier because of her concern with his rash. His lack of understanding of the importance of personal hygiene combined with the inappropriate laughter led to a suspicion of possible altered mental status along with his poor hygiene habits. The patient had developed impetigo with cellulitis. He was referred to counseling and told to bathe regularly. The patient was treated with oral cephalosporin.

A streptococcus bacteria. Impetigo is a highly contagious infection that presents with the symptoms of pruritus, burning, and lymphadenopathy. The infection can appear either as a primary infection that occurs in superficial breaks in the epidermis, or as a secondary infection due to a preexisting dermatological problem.

The initial lesion presents as a small, erythematous macule that changes into fluid-filled vesicles. When the vesicles burst, the exudate forms a honey-colored crust over the vesicles. The yellow, honey-crusted exudate is often seen in impetigo, but it is not pathognomonic.

Bullous impetigo presents as lesions that are tense, clear bullae containing yellow, slightly turbid fluid arising on normal-appearing skin. It is commonly distributed in areas of the body where there is skin-on-skin contact. There is also nonbullaous impetigo, which is characterized by small vesicles which, when ruptured, result in erosions that become covered in the yellow crust. The lesions are scattered and may become confluent without treatment.

Satellite lesions can appear due to auto-inoculation by the patient. If left untreated, impetigo can cause glomerulonephritis, although it will not cause rheumatic fever. Ecthyma is a variant of impetigo that is more common on distal extremities and causes punched-out, ulcerated lesions.

Treatment of both ecthyma and impetigo involves the debridement of adherent, crusted areas. The removal of the crusted exudate allows better penetration of topical antibiotics, such as mupirocin. Mupirocin is a highly effective topical antibiotic used against the gram-positive bacteria S. aureus and group A streptococcus, which are the causative agents of ecthyma and impetigo. Mupirocin inhibits the protein synthesis of the bacteria by specifically binding to isoleucyl-tRNA synthase. This inhibits the incorporation of isoleucine into bacterial proteins. Mupirocin is applied three times a day for seven to 10 days.

Cellulitis is a skin condition caused by the same bacteria, S. aureus and group A streptococcus. Cellulitis affects the dermis and subcutaneous tissues. The lesions lie flat against the skin and are extremely painful. The epidermis undergoes epidermal sloughing and superficial erosion. There is no crustling, oozing, or weeping because the infection is limited beneath the dermal-epidermal junction. Treatment for cellulitis is oral and topical therapy. If no improvement is noticed or if the patient becomes septic, intravenous therapy is recommended. Ciprofloxacin and cephalosporin are recommended antibiotics. If there is purulent discharge, cultures should be taken and appropriate therapy provided.

Differential Diagnosis:

Scabies, herpetic ulcers, allergic contact dermatitis

Resources:

Dermatopathologists
ingrating
your unique
concerns
Providing superior diagnostic medical care for your practice and patients.

Global Pathology Laboratory Services
Phone Direct: 305.825.4422 • Toll Free: 1.866.825.4422
16250 N.W. 59th Avenue • Suite 201 • Miami Lakes, Florida 33014
www.globalpathlab.com
Case Presentation:

A 40-year-old Caucasian female presented to the office with complaints of a one-month history of an off-white to yellow plaque on her frontal scalp with accompanying hair loss. The lesion was occasionally pruritic, tender-to-touch, and accompanied by a pulling sensation on the left side of her forehead and scalp. Several visits later she noted expansion of the lesion inferiorly with the development of a depression in her forehead (Figure 1). She did not recall having been bitten by a tick, had no family history of connective-tissue disease, and had no pain in her joints. She denied headaches, seizures, and visual changes. Medical history is significant only for hypothyroidism.

Physical examination during the initial visit revealed a healthy, well-appearing middle-aged female. A hypopigmented to yellow sclerotic plaque was present on the left frontal scalp, with overlying alopecia and tenderness to palpation. Several appointments later after workup was commenced, the plaque began to extend superiorly into the mid scalp and inferiorly onto the left paramedian forehead with a linear depression (Figure 1). Otherwise, the face was normal and symmetric.

Laboratory analysis showed a positive ANA screen, with an ANA titer of 1:640 nucleolar and 1:160 homogenous pattern. The antibodies to ssDNA were also positive. This is typically associated with more extensive involvement of skin and underlying tissue. All other lab findings, including a CBC, CMP, TSH, anti-dsDNA, anti-Smith, and SSA/SSB, were normal.

A punch biopsy measuring 3 mm was taken from the scalp during the office visit. It was described as having diminished hair-follicle population with catagen predominance. There were thickened collagen bundles in the dermis with sclerotic dermal fibrosis surrounding remnant hair follicles. The pathology report also showed a moderate deep perivascular infiltrate of lymphocytes and plasma cells. The scarring process is highlighted by diminished van Gieson elastic-fiber staining in the deep reticular dermis.

Treatment consisted initially of intral- esional glucocorticoid injections of triamcinolone acetonide 2.5 to 5.0 mg/ml into the plaque on the forehead/scalp, along with Olux foam (clobetasol propionate) topically. When the diagnosis was rendered and the acuity noted, oral prednisone was instituted in an attempt to halt the progression and sclerosis. She was then placed on Methotrexate as a steroid-sparing agent, 15 mg every week, and is being maintained on this regimen to date. She also continues to receive intralesional triamcinolone acetonide injections every three to four weeks.

The condition has remained stable without progression of the sclerosis or worsening of the clinical appearance of the depression on her forehead. This case is unique in demonstrating how the diagnosis of scleroderma en coup de sabre was made very early on in the progression of the disease. The disease process was halted due to early aggressive treatment. The patient is very pleased, and we will continue to follow and monitor her.

Discussion

En coup de sabre is a type of linear scleroderma and is characterized by linear bands of atrophy and a furrowing of the skin. The extent of atrophy can be extensive, including not only skin and subcu- taneous tissue, but also muscle and bone. It is normally unilateral and typically extends paramedially from the forehead into the frontal scalp. Although infrequent, multiple lesions of en coup de sabre may be found on a single patient. There is a female preponderance of 3:1, with a higher incidence around menarche, pregnancy, and menopause.1 Onset is usually during the first two decades of life.

A retrospective analysis of patients who developed morphea between 1960 and 1993 in Olmstead County, Minnesota, showed the incidence of en coup de sabre to be 0.13 cases per 100,000 population.2 Of the 82 cases of morphea identified in the study, 16 patients had linear scleroderma, including four with en coup de sabre and two with Parry-Romberg syndrome. None of these patients developed systemic sclerosis. Progression of linear scleroderma to systemic scleroderma has been reported in rare cases. Skin softening or disease resolution occurred in eight of 16 patients within five years of diagnosis. Unlike skin in localized morphea, skin in linear sclero- derma may be fixed to underlying tissue. Calcinosi may rarely occur. Cutaneous changes accompanying the facial hemiatrophy asso ciated with the Parry-Romberg syndrome may be similar to those found in en coup de sabre. Unlike the gradual spontaneous remissions seen in morphea, linear scleroderma tends to have a longer and occasionally progressive course. Some authors suggest scleroderma en coup de sabre occurs along Blaschko’s lines, which suggests that it may arise in a mosaic clone of susceptible cells.3

As with other forms of scleroderma, the exact etiology of localized scleroderma is unknown. Hypotheses include microchimerism, which leads to a chronic low-grade graft-vs.-host-like disease, or an alteration
in antigens caused by ischemic damage.\textsuperscript{4} Other suggested contributors to the pathogenesis of the disease are environmental exposures, trauma, and Borrelia burgdorferi infection.\textsuperscript{5} The vast majority of cases are sporadic. However, a small number of familial localized (linear) scleroderma cases have been reported. No clear HLA associations with localized scleroderma have been established. Many consider localized scleroderma to be an immunologic disorder, since it is often accompanied by the presence of autoantibodies. Linear morphea is more frequently associated with high ANA titers, in up to 40-80\% of patients. Also, single-stranded DNA antibodies are particularly common and specific to linear morphea, and are uncommon with plaque-type morphea. Additional serologic abnormalities include a positive rheumatoid factor. Eosinophilia may be present, particularly during early active phases, and may correlate with disease activity. A polyclonal IgG and IgM hypergammaglobulinemia may also be present and is found more often with severe cases and with clinical progression.\textsuperscript{6}

Various modalities have proven effective in the treatment of localized scleroderma. Many of them have yet to be proven in controlled trials. These include topical/intralesional/systemic glucocorticoids, antimalarials, etretinate, penicillin, D-penicillamine, phenytoin, vitamin E, griseofulvin, retinoids, interferon, calcitriol, and methotrexate. Surgical excision of stable plaques is also an option. Ultraviolet A (UVA) phototherapy, with and without psoralens, and NB-UVB have both been shown effective in treating localized scleroderma, including cases of en coup de sabre.\textsuperscript{7}

We have presented a case of en coup de sabre that was successfully halted. The treatment of this disease was simple and efficacious when recognized and initiated early.

References:
Case Report: Granular Parakeratosis


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ABSTRACT

Granular parakeratosis is a rare disorder characterized by hyperpigmented and hyperkeratotic plaques usually located in cutaneous folds. It is thought to be exacerbated by overuse of topical preparations as well as over-cleaning. We present a 52-year-old black female with axillary granular parakeratosis, along with the condition's clinical manifestations.

Introduction

Northcutt et al. first described granular parakeratosis in 1991 as the presence of reddish-brown, hyperkeratotic papillae and plaques, with a size ranging from 3 to 4 millimeters, located in intertriginous areas. The etiology of this condition is unknown; however, Northcutt postulated that a basic defect existed in the processing of profilaggrin to filaggrin. Filaggrin’s role in the skin is to maintain the keratohyaline granules in the stratum corneum during cornification. Metze and Rutten later defended this hypothesis. The Ackerman Institute of Dermatopathology in New York, over a five-year period, processed 363,343 slides total, of which 18 were granular parakeratosis. This condition is said to be extremely rare. We are presenting a patient with axillary granular parakeratosis seen in our Wilmington, NC, office.

Case Report

In January 2008, a 52-year-old black female presented complaining of a lesion in the left axilla. She claimed the area had been present for one and a half months. The patient had no major deformities, was well developed, well groomed, and was in no apparent distress. She denied both excessive use of antiperspirants and excessive cleaning. She denied any allergies as well as any irritation with the rash. Upon physical examination, a linear hyperkeratotic area was seen underneath the left arm extending three-quarters of the axilla. This area was a scaly, raised plaque with a bluish-brown discoloration (Fig. 1). No abnormalities of hair, nails, or teeth were observed. The differential diagnosis included acanthosis nigricans, linear epidermal nevus, and a verruca.

A biopsy was taken, and the remaining lesion was curetted off. The biopsy revealed a thickened and parakeratotic corneum with abundant purplish granules. The underlying epidermis showed no significant atypia. These features indicated a diagnosis of granular parakeratosis.

Discussion

Axillary granular parakeratosis (AGP) appears as erythematous, hyperpigmented, and hyperkeratotic plaques usually located in the cutaneous folds. It is occasionally associated with pruritis and has been associated with excessive use of topical preparations including antiperspirants and deodorants. This condition has also been found in individuals who have not used such products, as well as those with an occlusive environment. Researchers have tried to link granular parakeratosis to obese individuals, but there have been cases seen in slim patients as well. Due to the abundant postulated causes of AGP, the cause of this skin lesion remains unknown. There have been approximately 40 case reports of this condition in the United States, and it has no sexual or racial association. Even though axillary granular parakeratosis has been reported in children, the majority of cases have been reported in adults aged 40 to 50 years.

From a histopathological point of view, AGP demonstrates psoriasiform hyperplasia, a thickened stratum corneum with retention of keratohyalin granules, and parakeratosis. Most pathologists report a well-developed granular layer and a sparse lymphohistiocytic inflammatory infiltrate. The retained granular layer sometimes demonstrates focal vacuolization. A granular parakeratosis confined to the follicle and a dermatophyte-related granular parakeratosis have also been described.

A KOH preparation can be performed in order to distinguish this condition from a fungal infection. A skin biopsy with correlation from the history and physical is sufficient to diagnose AGP.

The treatment regimen of this rare condition consists of topical and/or oral retinoids, as well as topical corticosteroids.

Conclusions

We have presented a case of axillary granular parakeratosis arising in a 52-year-old black female. We have reviewed the literature with regard to history, physical characteristics, and pathology. This condition is considered to be rare; however, we feel it is more common than sited in the literature as we have had eight biopsy-proven cases here in Wilmington, a town of fewer than 100,000 people. The patient was advised to limit use of topical preparations.
and excessive cleaning to the axilla. No topical preparations were used at this time, as the lesion was removed in its entirety by curettage.

References:
Report of a Case:

A 71-year-old Caucasian male presented to the office with a complaint of dry, scaly areas on the palm of his left hand and back of his right hand. Both of his legs were covered in scattered and coalesced brown macules along with a dry, scaly rash that continued from just below the knee all the way to his toes. He said that his skin-color changes were not itchy, but made him feel self-conscious, and he had decided not to wear shorts. He reported that the scaly rash on his legs did itch.

The patient stated that the rash started out as a number of bumps along the mid-calf. The bumps then spread together and down his legs to include the feet and toes. He also said that he had recently noticed the rash spreading up toward his knees. The patient stated that he’d had a heart attack several years ago and later noticed the beginnings of this brown color change.

What distinguishes this case from stasis dermatitis, and did his heart attack play a role in the development and exacerbation of the disease?

Diagnosis:

Schamberg’s Disease

Discussion:

Schamberg’s disease (progressive pigmented purpura, or PPP) is a slow, progressive, purpuric dermatosis that is characterized by flat, petechial hemorrhages. This disease is seen in children and on the lower legs of older men. Schamberg’s disease presents as lesions that are irregular patches, red and brown in color, with superimposed, pinpoint cayenne-pepper macules. The discoloration is due to the leakage of blood from small blood vessels near the skin surface. The red lesions are newer hemorrhages, and the older lesions are brown in color. The brown color is due to the hemosiderin deposits from the degradation of the extravascular erythrocytes. There are typically no symptoms, although some people can experience itching and discomfort.

There are three other types of pigmented purpuric dermatoses that are similar to Schamberg’s disease. Majocchi’s disease is an annular from of Schamberg’s disease that has telangiectasias. Gougerot-Blum disease has lesions of Schamberg’s disease along with lichenoid papules, plaques, and macules. The last pigmented purpuric dermatosis is Lichen aureus. It has few patches that are rust colored, purple, or golden, which arise from the extremities or from the trunk.

Stasis dermatitis, on the other hand, is a chronic venous insufficiency disease that results when venous blood fails to return to the heart. It occurs over a long period of time due to venous incompetence of the lower extremities. The changes that occur are edema, hyperpigmentation, fibrosis of the skin and subcutaneous tissue, along with ulceration. Stasis dermatitis occurs around the lower leg and ankles, with scaling and weeping patches. There are inflammatory papules present with scaly and crusty erosions. The prevention of progression of hyperpigmentation of the lower extremities is accomplished by elevation of the legs, the use of support hose, and mild topical cortisone creams. This patient’s heart attack likely contributed to the addition of stasis dermatitis to his Schamberg’s disease.

Differential Diagnosis: Stasis dermatitis, parapsoriasis, primary amyloidosis, senile purpura, lichen aureus, Gougerot-Blum disease, Majocchi’s disease.

Resources:

**MULTIPLE TRICHOEPITHELIOMAS, CYLINDROMAS, AND SPIRADENOMAS IN BROOKE-SPIEGLER SYNDROME: A UNIQUE CASE OF MALIGNANT TRANSFORMATION AND REVIEW**

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**ABSTRACT**

Brooke-Spiegler syndrome (BSS) is an autosomal dominantly inherited genodermatosis characterized by the concomitance of multiple trichoepitheliomas, cylindromas, and, rarely, spiradenomas.1 We present a rare case of BSS that demonstrates malignant transformation of trichoepitheliomas into basal-cell carcinomas, and review the theory set forth by Ackerman about the relationship between basal-cell carcinomas and trichoepitheliomas. A novel approach to treatment is presented also, and includes a discussion of genetic counseling, psychological therapy, and routine full-body skin examinations.

**Report of a Case**

A 69-year-old Caucasian female initially presented with a long-standing history of multiple, painless lesions on her face. She reported that the lesions had developed during adolescence and, subsequently, had increased in size and number. She could not recall other family members who were similarly affected, nor did she have any children. Her past medical history was significant for chronic stable angina, currently treated with nifedipine. No significant family history or social history was reported, though she did have a drug allergy to bacitracin. A review of systems was negative for preceding illness, recent weight loss or constitutional symptoms.

Physical examination revealed a well-appearing patient with multiple flesh-colored, smooth, round, papules on the mid face, ranging in size from 0.5cm to 1.5cm. Multiple lesions were grouped around the nose and the nasolabial folds, and several were present on the ears and eyebrows, bilaterally. The papules were non-tender and firm. The remainder of the exam was essentially normal. There was no cervical lymphadenopathy. A clinical diagnosis of trichoepitheliomas was made at that time.

Over a span of 10 years, the patient continued visiting our office for annual total-body skin exams. Twenty-one facial lesions suspicious for skin cancers were removed and sent for biopsy during this timeframe. The histopathologic results of these biopsies are tabulated in Figure 1.

Several lesions were consistent with basal-cell carcinoma and were removed with Mohs' micrographic surgery, but benign tumors were not treated. The combined results of the pathologic examinations, coupled with the constellation of clinical features, supported a diagnosis of BSS. It is interesting to note that our patient presented with two special features: The lesions were confined to her face, and she developed malignant degeneration of two trichoepitheliomas (Figs. 2 and 3), which are rare findings.

**Discussion**

BSS is an autosomal dominantly inherited genodermatosis characterized by the concomitance of multiple trichoepitheliomas, cylindromas, and, rarely, spiradenomas.1 Mutations affecting the CYLD gene on chromosome 16q12-q13 cause BSS. A unique feature of BSS is phenotypic variability,2 and therefore any or all of these lesions may be apparent at presentation, though the literature highlights a broad clinical spectrum. For instance, the presence of spiradenocylindromas,3,4 trichoblastomas,8 basal-cell carcinomas,9,10 follicular cysts,5-7 organoid nevi,1,2 psoriasis,11 and malignant degeneration of pre-existing tumors has been observed.3,5-8,12-20 Several forms of malignant parotid and salivary gland tumors,10,11 as well as one case of invasive ductal breast carcinoma,2 have also been described as rare associations.

A number of reports have defined the clinical picture of BSS, ultimately shaping our view of the entity as we see it today. The inherited occurrence of cylindromas and trichoepitheliomas was recognized in the 1800s. Ancell in 1842 first described a family with inherited multiple scalp tumors,21 later reviewed by Spiegler in 1897.22 Ancell-Spiegler cylindromas became the eponym of these tumors, and currently they are called cylindromas. In 1892, Brooke described the features of inherited trichoepitheliomas.23 Case reports postdating these initial findings noted the combination of trichoepitheliomas and cylindromas in a series of patients, which suggested the occurrence of the tumors within a single genetic entity, namely BSS.

BSS presents most commonly during the first and second decades of life.1,2,24-27 and demonstrates a female predominance (2:1).3 To date, there appears to be no epigenetic modifying factors, such as ethnic background or race, contributing to the disease. Although BSS is often a benign disorder, it may have an unpredictable course. Occasionally, de novo malignancies or malignant transformations of existing lesions occur. While there have been no fatalities reported in the literature, the development of any type of malignancy can be a potentially life-threatening complication. Subsequently, an annual full-body skin examination should be completed, including inspection of the salivary and parotid glands. In females, the gynecologist should be aware of the disease, as a case report of invasive ductal breast carcinoma has been indentified2 (however, no other cases of breast cancer have been reported in association with BSS). Furthermore, the size and number of lesions in those affected by BSS increase with aging. Over time, the lesions can become progressively disfiguring and cause extreme discomfort. In fact, many reports document extensive development of cylindromas on the scalp, coalescing to form unsightly turban tumours.5,20,28,29 Severe facial alterations have also been documented.2 Infection, anemia secondary to chronic bleeding, and a malodorous smell can also occur.21

Trichoepitheliomas, cylindromas, and spiradenomas are the primary lesions seen in patients with BSS. These skin appendage tumors are clinically similar, and therefore a histological diagnosis is necessary. Both clinical and histological descriptions of the lesions are provided here.
Trichoepitheliomas are rounded, flesh-colored papules or nodules that are mainly located on the nasolabial folds, nose, forehead, upper lip, and scalp. Histologically, these lesions characteristically reveal a cribiform pattern of multiple nodules composed of uniform, basaloid cells, frequently with central, keratin-filled lumina. The lobules contain eosinophilic globules and are surrounded by eosinophilic membranes. These lobules lie closely together, often resembling pieces of a jigsaw puzzle. Cytologic examination shows two different populations of epithelial cells: smaller ones with little cytoplasm and a dark-staining nucleus mostly at the periphery of the lobule, and larger ones with a lighter-staining nucleus in the center. Cutaneous lesions are solitary, firm, rubbery nodules with pink, red, or sometimes blue coloring. Cylindromas are typically found on the head and neck, but can also be seen spread diffusely over the body. The size of lesions is highly variable, and numerous masses can bunch on, or completely encompass, the scalp (turban tumors).

Preferentially, spiradenomas involve the trunk and extremities, but can develop at other anatomic sites, as was the case with our patient, whose tumor appeared on the nasal tip. Spiradenomas are usually gray, pink, purple, red, or blue nodules of about 1 centimeter diameter and seem to have apocrine and trichoepitheliomatous differentiation. Spiradenomas consist of one or more large, sharply delineated, basophilic nodules in the dermis, resembling cannon balls or big blue balls. The nodules are unattached at the epidermis, can sometimes extend into the subcutis, and are formed by cords, islands, and/or sheets of cells. Small, dark, basaloid cells with hyperchromatic nuclei and cells with large, pale, vesicular and ovoid nuclei are amongst the two types of cells in the nodules. Strands of cells are positive for cytokeratin and carcinoembryonic antigen.

One focus of discussion in the literature surrounds the potential for malignant transformation of these lesions. Spiradenomas progress to malignancy most commonly, with more than 32 cases reported. About 12 cases of cancerous cylindromas have been noted in the literature, along with four cases of undifferentiated carcinomas and one case of spiradenocarcinoma. Finally, malignant parotid gland tumors and breast masses infrequently transform.

One school of thought exists about the possible follicular origins of basal-cell carcinomas. Ackerman et al. postulated that basal-cell carcinomas show follicular differentiation and therefore are related to trichoblastomas. Furthermore, Ackerman uses the term trichoblastoma liberally in referencing any benign tumor derived from hair germ epithelium. The trichoepitheliomas of BSS would therefore be considered trichoblastomas. Rarely, trichoepitheliomas have been transformed into malignant basal-cell carcinomas in BSS. To our knowledge, there are four cases in the literature, along with four cases of cancerous cylindromas and one case of spiradenocarcinoma. Our patient underwent degeneration of two trichoepitheliomas into basal-cell carcinomas, but also had nine basal-cell carcinomas in close proximity to the malignant trichoepitheliomas. The transformations themselves and the close anatomical positioning of the transformed malignancies to the basal-cell carcinomas may provide evidence in support of Ackerman’s postulation.

Given the clinical heterogeneity of cutaneous lesions seen in BSS, the differential diagnosis may initially appear vast. For instance, facial adenoma sebaceum, basal-cell carcinomas, sarcoidosis, microcytic...
adnexal carcinomas, tricho adenomas, infundibulomas, and basaloid follicular hamartomas should be in a differential for trichoepitheliomas. However, the existence of numerous lesions presenting simultaneously should raise suspicion for a genodermatosis or syndrome. With this notion in mind, multiple trichoepitheliomas may be seen in Rombo syndrome and Bazex syndrome. Furthermore, other genodermatoses present with multiple skin appendage tumors including familial cylindromatosis (FC) and multiple familial trichoepithelioma (MFT). These diseases may clinically resemble BSS. Cylindromas are the only tumors that define FC, and trichoepitheliomas are the only tumors that define MFT. In contrast, any or all of these lesions may be simultaneously apparent in BSS, which makes the diagnosis difficult. In our patient, the diagnosis was clear because she did in fact present with all three lesion types. It should be stressed that if patients present with one type of tumor, it is difficult to discern these genodermatoses initially.

Although all of the factors underlying tumorigenesis in genodermatoses of skin appendages have yet to be completely elucidated, recent decades have yielded tremendous gains in our understanding of the genetic underpinnings of these syndromes. In fact, the most recent studies suggest that BSS, FC, and MFT, all of which demonstrate mutations in the CYLD gene, may represent distinct entities with different clinical presentations.2,47,51

The role of mutations to the CYLD gene in producing such diverse phenotypes is still not completely understood; however, it has been established that CYLD negatively regulates nuclear factor κB (NF-κB) through its interaction with tumor necrosis factor receptor associated factor-2 (TRAF-2). TRAF interacting protein (TRIP), Iκ kinase in the NF-κB signaling pathway. While NF-κB activation has been linked to a variety of neoplasms, the precise role it plays in adnexal tumorigenesis is still unclear.57

There is no established treatment protocol for BSS. Although some lesions do not require treatment, therapy may be desired to alleviate discomfort/bleeding and for cosmesis. Treatments include surgical removal, electrocoagulation, dermabrasion, cryotherapy, trichloroacetic acid, CO2 laser, and erbium:YAG laser.26,29,39,45 One review article claims that the best treatment is surgical removal because of low recurrence rates, though currently metastases of basal-cell carcinomas arising in trichoepitheliomas has been shown in two cases.

Aside from surgical or pharmacological interventions, genetic counseling and psychological therapy may be discussed with patients. Little attention has been given to these holistic treatment concepts in the literature, despite their clear importance. The cosmetic repercussions of BSS are great, as are the potential psychological sequela. Thus, involvement of proband family members in genetic counseling and screening for depression are strong recommendations. While we are on the cusp of more promising treatments, there still remains a dearth of well-tested options for patients with BSS.

Finally, the metastatic possibility of transformed trichoepitheliomas has been previously mentioned herein. Normally, basal-cell carcinomas do not have a high rate of metastases, though currently metastases of basal-cell carcinomas arising in trichoepitheliomas has been shown in two out of five cases. To date, reports have not used this knowledge in shaping a treatment plan. Thus, it is our recommendation that yearly full-body skin exams be an integral component in the care of patients with BSS.

References:
Case Report

A 59-year-old, African American female presented with a changing nodule on her left upper arm. The patient was previously evaluated by a plastic surgeon and refused excision at that time. She was then evaluated by a dermatologist, and two punch biopsies (4mm and 5mm) were performed. Routine histology revealed a markedly atypical neoplasm with features of a malignant adnexal tumor (Figures 1, 2, 3). The differential diagnosis included seroma and spiradenoma.

Histology

Immunohistochemistry was performed, revealing positive expression for cytokeratin 7 throughout the neoplasm and focal positivity for epithelial membrane antigen (Figures 4, 5). Studies with S-100 protein showed aggregates of cells expressing the antigen, a feature that is typical of spiradenoma (Figure 6). A proliferation marker, Ki-67, was also used and revealed areas of high labeling index, usually not evident in spiradenomas (Figure 7).

Patient follow-up: Unfortunately, the patient refused any further work-up or treatment despite being counseled on the dangerous nature of her diagnosis and was lost to follow-up.

Discussion

Spiradenocarcinoma is a rare, aggressive adnexal tumor that often arises from a pre-existing spiradenoma. Less than 30 cases have been documented in the literature, and the earliest reported case was published by Dabaska in 1972. It is an aggressive, often fatal tumor that frequently presents with metastasis at the time of diagnosis. This is a case of a 59-year-old female with a changing nodule on the upper extremity.

Histologically, the tumor displays a carcinomatous area in combination with benign features of spiradenoma. Spiradenomas exhibit two cell populations, which are often lost with malignant transformation. Other distinguishing features of malignancy include hyperchromasia, an increase in nuclear to cytoplasmic (N:C) ratio, and increased mitotic activity (Ki-67). This tumor stains with epithelial markers and may show positivity with S-100. This case did show S-100 positivity, a typical feature of spiradenoma; however, the tumor also showed positive staining with epithelial membrane antigen (EMA), which stains adenoscarcinomas. There are some reports that the p53 suppressor oncogene is expressed by the malignant portion of the tumor, and p53 immunostaining may be useful in distinguishing the carcinomatous component of the tumor.

The pathology in this case did not require further studies with p53 immunostaining, as other markers were positive.

Summary

In summary, spiradenocarcinoma is a rare, aggressive tumor often evolving from a pre-existing benign lesion. The prognosis may be poor, as discovery of the tumor occurs late. The trunk and extremities are the most commonly involved sites; however, other sites have also been reported. Follow-up requires excision of the lesion and possible sentinel lymph node biopsy.
References:
A CASE REPORT: OSLER-WEBER-RENDU DISEASE

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ABSTRACT

Osler-Weber-Rendu disease, also referred to as hereditary hemorrhagic telangiectasia (HHT), is an autosomal-dominant disorder characterized by telangiectasia, aneurysms, and arteriovenous malformations. The reported prevalence of this disorder is one to two cases per 100,000 people. The patient’s skin, mucosa, and blood vessels of the lung, liver, and central nervous system can be affected. We describe a 62-year-old man who presented with multiple pin-point, non-pulsatile telangiectases on his face, lips, oral cavity, palms and soles. His family history is significant for premature death of his father due to cerebral hemorrhage; his father also suffered recurrent nosebleeds throughout his life. Although our patient was never diagnosed with HHT, based on diagnostic criteria we strongly believe he carries a diagnosis of Osler-Weber-Rendu disease, also known as HHT.

Case Report:

A 62-year-old Caucasian man presented with a complaint of “multiple red dots” on his face (Fig. 1), tongue (Fig. 2), palms (Fig. 3) and soles for over 30 years. On further questioning, he admitted having frequent nose bleeds, more than six times a year. His father also suffered from recurrent nose bleeds, and he died of a cerebral hemorrhage at the age of 58 years. On physical exam, he was found to have multiple pin-point, non-pulsatile telangiectases on his face (Fig. 1), lips, oral cavity (Fig. 2), palms (Fig. 3) and soles. Laboratory examination results included: hemoglobin 12.8 g/dl and hematocrit 34%; white-blood-cell count, platelet count, sedimentation, serum electrolyte levels, liver function and coagulation tests were within normal levels, and a hematocrit panel was negative. Upper gastrointestinal endoscopy, pulmonary bronchoscopy, abdominal ultrasonography as well as brain CT and MRI revealed normal findings.

Discussion:

Osler-Weber-Rendu disease was first recognized in the 19th century with abnormal vascular structures causing bleeding from the nose and gastrointestinal tract. Rendu, Osler, Weber and Hanes later described it, and Hanes suggested the name hereditary hemorrhagic telangiectasia (HHT). Abnormal vessels, particularly arteriovenous malformations (AVMs) of the pulmonary, hepatic and cerebral circulations, were described with HHT in the 1940s.

Hereditary hemorrhagic telangiectasia is comprised of epistaxis, gastrointestinal bleeding and iron-deficiency anemia associated with characteristic telangiectases of the lips, oral mucosa and fingertips. Symptoms typically present by the third decade of life, with recurrent epistaxis developing prior to the second decade. HHT may be diagnosed within the first year of life if associated with congenital pulmonary arteriovenous malformations. It has a wide range of prevalence, as many as one to two cases in per 100,000 people in the United States, with an increased incidence of one in 16,500 in Vermont, one in 5,000 in Europe, one in 8,000 in Japan, and one in 1,330 in Afro-Caribbean residents of Curacao and Bonaire.

The diagnosis of HHT is based on the following four criteria, with three criteria making a definite diagnosis and two criteria a possible diagnosis. The criteria include: spontaneous or recurrent nosebleeds; multiple telangiectases on the lips, oral cavity, fingers and nose; presence of internal lesions such as pulmonary, hepatic, spinal or cerebral AVMs or gastrointestinal telangiectasia; and a first-degree relative with HHT according to these criteria.

Epistaxis is the most common manifestation and occurs in 90% of affected patients, with blood transfusions required in 10-30% of patients. Recurrent, painless gastrointestinal bleeding occurs in 40-40% of patients in the fourth or fifth decade of life. Telangiectases occur throughout the gastrointestinal tract, more commonly in the stomach or duodenum than the colon. Telangiectasia of the skin and buccal mucosa occurs in 75% of patients after the age of 20 and increases in number and size with age. Telangiectases often occur one year after the first episode of epistaxis and are rarely seen before puberty.

Pulmonary AVMs are present in 15-20% of patients with HHT. They are thin-walled, abnormal vessels that provide a direct communication between the venous and arterial circulation, leading to right-to-left shunts, hypoxemia, and secondary polycythemia. Dyspnea is a common complaint in those with pulmonary AVM and may be due to high-output heart failure. Other symptoms of pulmonary AVM include hemoptysis from telangiectasia of the trachea or bronchi, which may occur in the third or fourth decade, and migraine headaches.

Eight to 12% of patients have neurological involvement with cerebral or spinal-cord telangiectases, cerebral AVMs, aneurysms or cavernous angiomas.
can lead to headache, seizure, and ischemia. Untreated patients have a 2% risk of stroke and a 1% risk of brain abscess. 

Hepatic involvement occurs in up to 30% of patients, with portal hypertension, biliary disease, right upper-quadrant pain, and cirrhosis.

Physical examination is characteristic for telangiectases on the skin, oral and nasal mucosa, conjunctiva, trunk, forearms, hands and fingers. Skin lesions begin as punctate, non-pulsatile vascular papules or dark red lines. Rarely, skin lesions are pulsatile, star-shaped and 1-3 mm in diameter. All of the mucus membranes are invariably involved. Recurrent epistaxis leads to fatigue and anemia, while pulmonary AVM leads to fistulae, dyspnea, cyanosis and clubbing of the fingers.

HHT subtype 1 (HHT1) is caused by a mutation on chromosome 9, endoglin; HHT2 is caused by a chromosome 12, activin receptor-like kinase 1 (ALK-1) mutation.

Endoglin and ALK-1 encode proteins that are expressed on vascular endothelial cells. ALK-1 is a transforming growth factor (TGF) beta type 1 receptor, and endoglin associates with different signaling receptors and can modify TGF-1 beta signaling. Abnormal vessels in HHT develop because of aberrant TGF-beta signaling during some stage in vascular development.

There are no widely available lab studies to confirm the diagnosis, but there are a few that suggest the diagnosis of HHT. Complete blood count may show decreased hemoglobin with an iron-deficiency anemia, thrombocytopenia and polycythemia due to chronic hypoxemia. Urine and stool should be evaluated for hematuria and melena. An arterial blood gas (ABG) will show a low PO2 if there is a right-to-left shunt. The hyperoxic test with the ABG confirms the diagnosis of a pulmonary AVM. In another test, the patient is put on 100% oxygen and the arterial partial pressure of oxygen is measured. Normally, with 100% oxygen, the partial pressure should rise significantly, but in the presence of a shunt it only rises minimally.

MRI is the best noninvasive imaging study to view the extent of pulmonary and central nervous system AVMs. Chest radiography may show a peripheral, non-calcified coin lesion attached by vascular strands to the hilus. Colonoscopy shows telangiectases as small, well-defined lesions surrounded by an anemic halo. Although the diagnosis is made on clinical findings, a skin punch biopsy may be helpful in the diagnosis. Dilated capillaries and new vessel formation in the dermal upper horizontal plexus are the classic features.

One-third of cases of HHT are mild, one-third moderate, and one-third severe. Mild cases may need no treatment. Cauterization may damage the nasal mucosa, leading to vascular re-growth, so that is generally avoided. Treatment for epistaxis is generally reserved for those patients experiencing massive hemorrhages or having daily episodes of epistaxis. Treatments include arterial ligation, septodermoplasty and, in severe cases, unilateral or bilateral surgical closure of the nostril or nasal-septum using skin grafts from the lower trunk.

Treatment of telangiectasic skin lesions includes laser ablation by pulse dye laser.

Short-term control of gastrointestinal bleeding may include the use of endoscopic ablation of lesions, although results are not as good as in the non-HHT population. Iron-deficiency anemia is treated with oral iron supplementation. Pulmonary AVMs should be treated with embolotherapy, while cerebral AVMs should be treated with embolotherapy, surgical removal or stereotactic radiotherapy. Liver transplantation is the treatment of choice if medical treatment fails for hepatic AVMs.

Hormonal therapy, including the use of estrogen, tamoxifen, danazol, octreotide, desmopressin, aminocaproic acid and tranexamic acid, has been shown to be beneficial in the treatment of recurrent bleeding secondary to gastrointestinal and nasopharyngeal AV malformations. Oral contraceptives have been shown to be more effective than estrogen alone for mucosal bleeding.

Pregnancy has an associated risk potential in women with HHT, but the majority of pregnancies are uneventful. Many anesthetists will not perform an epidural analgesia in women with HHT since 1-2% of patients with HHT have spinal AVMs. Some studies have also shown that epistaxis and telangiectases may worsen throughout pregnancy. Pulmonary AVMs will enlarge during pregnancy, so women with HHT should be screened for pulmonary AVM before pregnancy. Any hemotysis during pregnancy is considered a medical emergency and requires prompt hospitalization.

Most patients with HHT have a favorable prognosis, with the prognosis depending on the degree of systemic involvement. Only 10% of patients die from complications. Patients with HHT should be carefully monitored by their physician and specialists according to the organ system involved.

In summary, since our patient meets three out of four criteria to make a diagnosis of HHT, which includes recurrent nosebleeds; multiple telangiectasias on the lips, oral cavity, face and palms; and a first-degree relative with possible diagnosis of HHT, in our experience he carries the definite diagnosis of HHT.

References:
TREATMENT OF LICHEN AMYLOIDOSIS WITH THALIDOMIDE – A CASE REPORT

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ABSTRACT

Amyloidosis is caused by the deposition of amyloid, a proteinaceous fibril material. Lichen amyloidosis is the most common presentation of primary cutaneous amyloidosis. Clinical presentation involves discrete red-brown pruritic papules, sometimes with keratotic scale, that coalesce into reticulated plaques.

We present a case of 75-year-old woman with a 10-year history of a pruritic rash on her trunk and extensor surfaces of her extremities. Examination showed hyperpigmented papules coalescing into plaques covering her trunk, and reticulated plaques along her extremities. Biopsy demonstrated eosinophilic aggregates of amorphous material, and crystal violet stained focally positive for amyloid.

After failing other regimens, the patient was started on thalidomide in addition to triamcinolone cream. After three months of treatment, the patient reported less pruritus, and examination showed a less extensive area of involvement.

Thalidomide may have promise in the treatment of cutaneous amyloidosis. In our patient, treatment was well tolerated, and there was improvement in cutaneous findings.

Introduction

Amyloidosis is a deposition disorder, classified as a systemic or cutaneous disease, and is caused by the deposition of amyloid, a proteinaceous fibril material. The primary cutaneous forms are subdivided into macular amyloidosis, lichen amyloidosis (papular) and nodular amyloidosis.1 Lichen amyloidosis is the most common presentation of primary cutaneous amyloidosis (PCA), comprising 67% of the diagnosed cases.2 Clinical presentation involves discrete red-brown pruritic papules, sometimes with keratotic scale, that coalesce into reticulated plaques, mostly presenting on the extensor surfaces of the lower legs and arms.2-5 This condition is most prevalent in middle-aged people of Chinese descent and with skin phototypes III and IV.6-13 While in most cases it is idiopathic, the condition has been associated with numerous connective-tissue diseases.6-13 It is also more common in females than in males.14 Other associations with primary cutaneous amyloidosis include: pachyonychia congenital, dyskeratosis congenital, familial palmoplantar keratoderma, scleroderma, SLE, dermatomyositis, primary biliary cirrhosis, and Sipple syndrome (MEN 2a).

The differential diagnosis for lichen amyloidosis includes hypertrophic lichen planus, lichen simplex chronicus, and papular mucinosis, making diagnosis challenging for healthcare providers. The exact etiology of amyloid deposition is unknown, but the favored theory is that epidermal trauma induced by chronic scratching and rubbing results in keratinocyte degradation and formation of amyloid.15 Cutaneous amyloid deposits are thought to be derived from degenerated keratin peptides of apoptotic keratinocytes, transformed into amyloid fibrils by dermal macrophages and fibroblast.5,16-17 Treatment is primarily symptomatic, with a target goal of controlling pruritus. Overall, treatment of lichen amyloidosis is challenging and often unsatisfactory.

Typical histology shows acanthosis, hyperkeratosis, and amyloid deposits in the papillary dermis that may displace the elongated rete ridges laterally. Pigment incontinence within melanophages and a sparse perivascular lymphohistiocytic infiltrate are seen as a reticulated pattern. On hematoxylin and eosin stained sections, homogenous, hyaline, and eosinophilic deposits are seen. Special stains such as crystal violet and Congo red have been shown to stain best for lichen amyloidosis.

Case Report

A 75-year-old woman of Indian descent presented with a 10-year history of a pruritic rash on her trunk and extensor surfaces of her extremities. She had an initial biopsy that was uninformative. She was treated unsuccessfully in the past with topical steroids and UVB.

The treatment of cutaneous amyloidosis is challenging and often unsatisfactory. Reducing skin friction -- breaking the rubbing/scratching cycle -- is paramount.15 Occlusion plays a role in penetration for topical treatments and in blocking trauma. Though the bulk of evidence and treatment experience is unsatisfactory.

After three months of treatment, the patient reported less pruritus, and examination showed the area of involvement to be less extensive (Figure 2). The patient’s thalidomide was decreased to 50mg daily, but the patient was subsequently lost to follow-up.

Upon further contact, months following her previous visit, the patient reported discontinuing the thalidomide and, within days, a worsening of her cutaneous findings and pruritus. She returned and was restarted on therapy. At the time of her return, the lichenoid component was less evident, with flattening of the lesions (Figure 2).

Discussion

The treatment of cutaneous amyloidosis is often challenging. Reducing skin friction -- breaking the rubbing/scratching cycle -- is paramount.15 Occlusion plays a role in penetration for topical treatments and in blocking trauma. Though the bulk of evidence and treatment experience is unsatisfactory.
ment and topical 0.1% tacrolimus have been found to be equally effective in small trials. Other reported treatments include topical DMSO, UVB, PUVA, dermabrasion, double frequency Nd:YAG laser, surgical debridement, oral retinoids, keratinolytics, and cyclophosphamide. Unfortunately, these treatments are partially effective at best.

Thalidomide was introduced into Western Europe in the late 1950s as a “sleeping agent” with negligible adverse effects. However, this drug never obtained popular appeal in the United States and was never FDA approved in the American market due to reports of its association with fetal limb defects (phocomelia) and other internal fetal deformities. In 1961, the drug was rapidly withdrawn from the world market due to its teratogenicity.

However, thalidomide’s exile was short-lived. In 1965, thalidomide’s resurgence as the treatment of choice for erythema nodosum leprosum (ENL) brought this drug back on the market as a therapeutic alternative. In 1997, the FDA granted thalidomide “approvable” status for the treatment of ENL, opening the door to its off-label indication for other diseases (Table 1). The United States instituted a program called the System for Thalidomide Education Prescribing Safety (S.T.E.P.S) to prevent adverse events like teratogenicity.

In dermatology, thalidomide treatment has been used successfully in conditions like sarcoidosis, lupus erythematosus profundus, porphyria cutanea tarda and pemphigoid, to name a few. It should be noted that not all inflammatory cutaneous diseases improve with the use of thalidomide. A clinical trial evaluating the use of thalidomide in the treatment of toxic epidermal necrolysis (TEN) found thalidomide to be more harmful than placebo and was shown to increase mortality compared with the placebo group.

The exact mechanisms of action of thalidomide are unknown; however, it is thought to be a sedative and have anti-inflammatory and anti-malignancy effects. The sedative effects have been demonstrated in activation of the sleep center of the brain. Thalidomide’s anti-inflammatory effects include decreasing the T-helper/T-suppressor ratio, inhibiting polymorphonuclear leukocyte chemotaxis and decreasing TNF-α production.

Improvement was seen in two case reports of systemic amyloidosis with cardiac involvement. In both cases, the patients were treated with thalidomide and dexamethasone at doses of 100mg daily, subsequently increased to 200–300mg daily, with clinical improvement and few side effects.

Thalidomide may have promise in the treatment of cutaneous amyloidosis. In our patient, treatment was well tolerated with no reported side effects; however, further studies are warranted to evaluate the effectiveness and side-effect profile of thalidomide in treating cutaneous forms of amyloidosis.

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Case Presentation

A 17-year-old Hispanic male was referred to our clinic, by the Florida Department of Juvenile Justice, with an eight-month history of a generalized "rash." The patient stated it had started on his abdomen and spread to his back and face. He had associated symptoms of pruritus and numbness within the skin lesions. The patient had been treated with one course of Medrol Dosepak eight months prior and had started on prednisone 10 mg/day two weeks prior to our evaluation, with no changes in his symptoms. He denied any recent illnesses or travel outside the United States. He was up to date on all of his immunizations.

On physical exam, the patient had numerous indurated, annular, polycyclic, erythematous plaques and patches with central clearing on his face, back and abdomen (Fig. 1, 2, 3). He had associated symptoms of numbness and decreased sensation to light touch within the lesions. Differential diagnosis included leprosy or Hansen’s disease, granuloma annulare, sarcoidosis, SCLE, plaque psoriasis, syphilis and leishmaniasis. Punch biopsies of lesions on the abdomen and mid-back were obtained and sent for H&E, Fite, PAS, Giemsa and Steiner stains. Biopsies revealed nodular, pandermal, histiocytic-rich granulomatous dermatitis involving neurovascular bundles (Fig 4). Fite stains showed bacilli in red in only one section (Fig 5, marked by arrow). PAS, Giemsa and Steiner stains were negative for fungi, parasites and spirochetes. The working diagnosis of leprosy, borderline tuberculoid type, was made based on clinical history and biopsy results.

Introduction

Leprosy is an ancient disease, dating back to 600 B.C. In 1873, Hansen identified Mycobacterium leprae as the causative agent of leprosy, hence it is also known as Hansen's disease. Leprosy is a chronic infection that primarily affects the skin, peripheral nerves and nasal mucosa. M. leprae, a gram positive, intracellular acid-fast bacillus, has an incubation period of five years for paucibacillary and 20 years for multibacillary cases before signs of overt disease.7 The main mode of disease transmission is via nasal secretions.8

Epidemiology

In 1991, the World Health Organization passed a resolution to eliminate leprosy as a public health problem by 2000. The WHO’s definition of elimination is a prevalence rate of less than one case per 10,000 persons in all endemic countries. Brazil, India, Madagascar, Mozambique and Nepal are the five countries in which elimination still has not been achieved. In 2006, there were approximately 259,000 new cases; when leprosy was at its peak in 1998, there were 804,000 cases.1,2 Approximately 85% of new cases in the United States are among immigrants, and the rest are from exposure to infected armadillos, overseas travel or close contact with an infected patient.

Classification

Leprosy has a broad spectrum of clinical presentations. The Ridley and Jopling system helps to classify leprosy based on clinical, histologic, and bacterial presentations (see Table 1). The classifications are: Tuberculoid (TT), Borderline tuberculoid (BT), Borderline borderline (BB), Borderline lepromatous (BL), Lepromatous (LL), and Indeterminate (I). Borderline disease is unstable and may move from the TT→LL pole during the course of the disease.2 Cell-mediated immunity is highest in tuberculoid form and lowest in lepromatous form.

Tuberculoid Leprosy (TT)

Tuberculoid lesions are either solitary or few in number (often fewer than five). The typical lesions are large, sharply defined, dry, scaly, hairless, reddish-brownish plaques with elevated borders and flattened atrophic centers. They are asymmetrically distributed on the trunk or limbs. Patients afflicted with the tuberculoid type have a high cell-mediated immunity, which is reflected clinically as the paucibacillary form of leprosy.9 The lesions are characteristically anhidrotic and either anesthetic or hypesthetic, and the surrounding superficial, peripheral nerves are enlarged, tender or form giant nerve "abscesses."9 Nerve involvement is asymmetric, localized to the skin lesions, and leads to changes in the muscle groups served, such as atrophy and wasting, early in the course of the disease.9

Borderline Leprosy

Borderline tuberculoid (BT) – BT lesions are similar to TT except they are smaller in size and increased in number. Small satellite lesions around larger macules are common, and nerves are less enlarged than in TT.9

Borderline borderline (BB) – BB cutaneous lesions are made up of numerous, erythematous, irregular plaques surrounded by satellite lesions. Anesthesia within lesions is moderate. Lesions may
remain in this stage, improve or worsen in the course of the disease.8

Borderline lepromatous (BL) – BL lesions are similar to LL and consist of numerous, symmetrically distributed macules, papules and nodules. Anesthesia is often absent within the lesions.8

Lepromatous Leprosy (LL)

Lepromatous lesions are generalized macules, papules, plaques or nodules that are symmetrically distributed. There is little or no loss of sensation, and there are no signs of anhidrosis. These patients have poor cell-mediated immunity and therefore have a multibacillary type of leprosy. Nerve involvement occurs later in the disease in the form of neuropathy that causes skin wounds, clawing and contractures of digits, and blindness, which lead to physical disabilities. Lepromatous lesions include madarosis or loss of eyebrows and diffuse infiltration of the face, giving a leonine appearance.9

Histopathology

Punch biopsies should be performed of most active lesions and should include subcutaneous tissue. M. leprae is best seen by using Fite-Faraco stain; however, immunofluorescent techniques or PCR can also be used.7

Tuberculoid lesions consist of non-caseating granulomas, which are made of epithelioid cells, Langhans giant cells, and lymphocytes. They may extend into the epidermis, leaving no Grenz zone, and into the peripheral nerves. Dermal nerves demonstrate edema and fibrosis that can be visualized with S100 stain. Bacilli are few in number and mostly found in nerves, subepidermal zone and arrector pili muscles.6

Lepromatous granulomas are composed of lipid- and bacilli-laden histiocytes called lepra or Virchow cells. Lesions are localized in the dermis, and a Grenz zone may be visualized. There are abundant bacilli visualized on Fite stains.

Leprosy Reactions

There are two major types of leprosy reactions, and they may be triggered by multiple drug treatment of the disease, vaccinations, pregnancy and stress. However, treatment should not be stopped in the presence of either reaction.11

Type 1 reaction occurs in borderline disease as a result of interaction between patients’ cell-mediated immunity and M. leprae antigen, a type of delayed hypersensitivity reaction. Clinical signs include edema, ulceration and nerve damage. It is usually managed with bed rest and NSAIDs. If there are signs of nerve damage, then oral prednisone is initiated and then tapered once symptoms resolve.11

Type 2 reaction, also known as erythema nodosum leprosum (ENL), is an immune-
complex-mediated disease that occurs in borderline or lepromatous disease. Unlike type 1 reaction, where there are no systemic signs of illness, type 2 reaction presents with fever, myalgias and arthralgias. Patients have multiorgan disease with conjunctivitis, synovitis, nephritis and orchitis, accompanied by tender erythematous nodules on extremities. Thalidomide is the treatment of choice for ENL.11

Treatment

Early detection and treatment with multi-drug therapy (MDT) are the most important steps in preventing deformity and disability associated with leprosy. The treatment protocols for leprosy are based on the number of skin lesions and bacilli present. The paucibacillary treatment is given to those who have five or fewer skin lesions without detectable bacilli, whereas the multibacillary treatment is given to those who have six or more skin lesions and may have detectable bacilli. The first, FDA-approved treatment protocol includes dapsone 100 mg PO daily and rifampin 600 mg PO once a month (observed) for six months for paucibacillary disease, and dapsone 100 mg PO daily, rifampin 600 mg PO daily and clofazimine 50 mg PO monthly under supervision for two years for multibacillary (see Tables 2 and 3).

Resistance to MDT has not yet been established, but there are relapses. The relapse rate varies based on paucibacillary or multibacillary type, just over 1% and just under 1% respectively.19 If relapses occur, it is recommended that the prior treatment is reinitiated unless the form has changed. For those patients with the multibacillary form who relapse, in addition to the two-year regimen it is also recommended to consider dapsone indefinitely to prevent further relapses.

Outcome

Our patient was immediately started on prednisone 20 mg a day, rifampin 300 mg twice a day and triamcinolone 0.1% cream twice a day pending biopsy results. The patient followed up in two weeks with marked improvement of his lesions and symptom of numbness. The patient was started on standard multi-drug therapy for paucibacillary leprosy, which included rifampin 600 mg PO monthly and dapsone 100 mg PO daily. The patient was moving to a new city and was scheduled to follow up at National Hansen’s Disease clinic in his area. He has yet to experience any leprosy reactions.

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A NEW TREATMENT FOR EYE LID LAXITY

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We have no affiliation with Ellman or any of the other products listed here.

ABSTRACT

Baggy eye lids and skin laxity of the eye lids are common complaints that we encounter in the dermatology office. For 10 years we have used treatment by electric cautery to tighten the skin and allow patients to avoid blepharoplasty surgery. This treatment does not replace blepharoplasty in patients with significant infra-orbital fat pads, but it is an excellent option for many patients.

Introduction

Many patients complain about wrinkled, sagging skin or bags under the eyes. We are presenting a non-invasive technique to tighten the skin under the eyes. We have been utilizing this technique, which involves using an electric cautery to tighten skin, for more than 10 years. In this case we used an Ellman Surgitron FFPF. We also perform treatments with a Bovie AARON 900 high-frequency desiccator and a Con Med hyfrecator. The cautery is applied at low intensity, usually at a setting between 1 and 2. We use a “hemo” or “cut and coag” setting on the Ellman. On other cautery units, we always stay away from straight “cut” settings.

We do not use any anesthetic. The electrode is lightly touched to multiple spots on the eyelid, treating approximately 20 to 30 spots per lower eyelid. See example with red dots representing where we would touch the electrode for a brief instant (with actual patients we do not mark the spots). We watch to see just a slight skin discoloration, contracture, or skin sloughing in the spot touched. Following the procedure, polysporin is applied under the eyes bilaterally. This treatment is performed bi-weekly for a total of eight to 10 treatments.

Case Report

A 53-year-old Caucasian female presented complaining of bags under the eyes. She previously had used topical over-the-counter cosmetic products. Upon physical examination, under-eye bagginess, laxity, and rhytides were noted. The area underneath the eyes also appeared slightly hyper-pigmented, with no scarring or deformities. We discussed possible treatment options including topical retinoid eye creams, applying the electric cautery for skin tightening, and bilateral lower blepharoplasty. We explained that the results of electro cautery would not be equal to surgical procedures but would offer some lifting and tightening of the under-eye skin.

The patient elected to use the Ellman electrocautery to tighten her eyelids. We treated the lower lids every two weeks for a series of 10 treatments. The patient commented on her fourth treatment that she felt her lower eyelids were close to 100 percent improved. By the sixth treatment, patient stated she was “extremely happy,” and by the last treatment she commented that her eyelids “looked fabulous.”

Discussion

It is postulated that the radio frequency heats the collagen and causes tightening. In addition to heat, cauterizing may result in micro scarring, which potentially could play a role in skin tightening. The heating of the collagen below the epidermis causes contracting of the collagen fibrils. The ablative cutaneous injury induces a healing response, resulting in the deposition of a new skin matrix with improved characteristics. During this healing process, skin rejuvenation probably occurs by a proliferation of fibroblast activity, the action of inflammatory mediators, and a deposition of new collagen and other dermal-matrix proteins. In short, heating results in collagen remodeling and a subdermal injury, leading to an inflammatory process and remodeling.

Conclusion

The Ellman Surgitron offers a great option for non-invasive treatment of under-eye laxity. Results will vary from patient to patient, but we tell our patients...
to expect around 30 percent improvement. During and for three months after the treatment, the patient is advised to avoid sun exposure. There may be some scabbing and redness of the under-eye area for a week or so after each treatment. Applying polysporin twice a day for seven days will help prevent infection and assist with healing. This is a great treatment option for patients who are looking to avoid blepharoplasty surgery and still obtain significant improvement.

Reference:
Neutrophilic eccrine hidradenitis (NEH) is a self-limited inflammatory dermatosis usually associated with chemotherapeutic agents, manifesting as erythematous eruptions on the trunk and extremities. Since its first description in 1982, a form of NEH referred to as idiopathic palmoplantar hidradenitis (IPH) has been reported in healthy children and is identified for its specific location on the body. More recently, a subset of cases associated with microorganisms and viral illness has been identified in literature. NEH without underlying malignancy or palmoplantar distribution is exceedingly rare. We describe a child with neutrophilic eccrine hidradenitis who presented with erythematous plaques that developed on the upper extremities in the second week after new onset of generalized seizures. Histopathologic findings show characteristic features of neutrophilic eccrine hidradenitis as well as squamous syringometaplasia occurring without associated chemotherapy or microorganism. A review of the literature, highlighting unusual case presentations of NEH, is further discussed.

**Introduction**

Neutrophilic eccrine hidradenitis (NEH) is a neutrophilic dermatosis affecting the eccrine glands and was initially described in patients with acute myelogenous leukemia (AML) receiving chemotherapy. The condition is usually self-limited, resolving in 1-3 weeks with no scarring following discontinuation of the offending agent. NEH manifests clinically as nonspecific cutaneous lesions on the extremities which are typically tender, erythematous or purpuric macules, papules, nodules, or plaques. Fever can often accompany NEH although many patients are neutropenic. Anatomical locations besides the distal extremities are distinctly unusual and have included the face, trunk, or proximal extremities. Rarely, NEH presents in a generalized distribution. A diagnosis of NEH can be confirmed with a skin biopsy showing characteristic pathologic changes, specifically neutrophils infiltrating eccrine glands. With prolonged lesions, squamous syringometaplasia may supervene atop the inflammatory changes.

NEH falls under a broad category of dermatological diseases referred to as neutrophilic dermatoses. Bolognaia et al., describes neutrophilic dermatoses as a heterogeneous set of cutaneous diseases with similar histopathology and therapeutic options. Neutrophilic infiltrate without associated infectious disease is the histopathologic finding. Neutrophilic dermatoses are further grouped as having epidermal involvement or dermal involvement with or without vasculitis. The epidermal category includes conditions such as pustular psoriasis and keratoderma blennorrhagicum. Sweet’s syndrome, Behcet disease, pyoderma gangrenosum and neutrophilic eccrine hidradenitis fall under the subcategory of dermal type without vasculitis. Finally, small vessel vasculitis and erythema elevatum et diutum are examples of the third subcategory, dermal type with vasculitis.

NEH is one of the least common of all the known neutrophilic dermatoses. A total of 79 cases of NEH have been reported in literature since 1982. Of these cases, only 13 have been reported in healthy patients. NEH in a child without underlying malignancy or palmoplantar distribution is exceedingly rare. Unusual presentations of this rare disease raise questions about causality and may result in unnecessary tests and delayed resolution. Further evaluation of unusual presentations of NEH may lead to a better understanding of the etiology and pathology of disease. We present an unusual case of NEH in a 14 year old girl with new onset seizures.

**Case Report**

A 14 year-old girl with no significant prior medical history presented to the hospital emergency department with new onset of generalized seizures and altered mental status with a week-long history of myalgia and headaches. Her vital signs were normal. No focal neurological problem was identified. The patient experienced between 5 and 13 seizures a day for the first week of hospitalization which were controlled with Valproate, Dilantin, and Levetiracetam. Her altered mental status persisted until hospital day 12 when she began following commands. Electroencephalogram showed severe generalized encephalopathy with nonspecific findings. Cerebrospinal fluid analysis was unremarkable. Serology for anti-double stranded DNA and Herpes Simplex Virus PCR were negative. Nasopharyngeal swab cultures and stool cultures were negative. Titers of Anti –EBV antibodies were reported as IgG= 1:160 (reference range:<1:10) and IgM <1:20 (reference range:<1:20). Computerized tomography scanning and magnetic resonance imaging of the head revealed no significant abnormalities, including no evidence of multiple sclerosis. On hospital day 14 she developed umbilicated pink papules on her bilateral wrists, right forearm, and mid lower back ranging in size from 3 mm to 6 mm. The lesions appeared in various stages of healing, some with crusts (Fig1). At that time, there were no other skin findings.

4 mm punch biopsy of the skin revealed features of neutrophilic eccrine hidradenitis (Fig 2), with a dense neutrophilic infiltrate within and around the eccrine coils, with associated necrosis of the sweat coils and squamous syringometaplasia. No vasculitis was observed. No microorganisms were noted with special stains including PAS, Gomori-Methenamine silver, tissue Gram stain, and Ziehl-Nielsen stain for AFB. Tissue cultures of lesion...
for Varicella-Zoster virus and fungus were negative. An immunohistochemical stain with EBV LMP1 (Latent membrane protein 1) antigen was negative. The lesions resolved spontaneously after 2 weeks and the patient remained free of any seizures.

**Literature Review**

Using Pubmed, a systematic review of the literature utilizing the search terms neutrophilic eccrine hidradenitis and eccrine hidradenitis, from 1982 to 2007, was conducted. In total, 79 cases of NEH were identified from the PubMed search. Idiopathic palmoplantar hidradenitis and plantar hidradenitis were also searched to further include all types of NEH. A total of 65 cases of IPH were identified in the literature since the first case was published in 1948.

**Discussion**

The discovery of NEH in patients undergoing chemotherapeutic treatment for acute myelogenous leukemia (AML) lead investigators to first hypothesize that the condition develops from a toxic drug reaction in the sweat glands. Since the first published cases of NEH, multiple types of malignancies and chemotherapeutic agents have been reported with this condition (Table 1). The association of NEH with malignant hemopathies remains strong although it is not an exclusive feature of the disease. Non-chemotherapeutic medications such as acetaminophen and Granulocyte Colony Stimulating Factor (GCSF), as well as medical conditions such as Behcets and lupus erythematosus have subsequently been reported with NEH. A list of the various medical conditions and medications reported in association with NEH are listed in Table 1.

Although the clinical picture of NEH continues to expand over time, the pathogenesis of the disease remains elusive. Multiple hypotheses exist in order to account for the range of clinical scenarios associated with NEH. What remains consistent in all of the hypotheses is that NEH represents an altered inflammatory reaction to nonspecific stimuli or chemotherapeutic agents requiring both a triggering agent and an altered immune response. The most common theory suggests that NEH represents direct damage and inflammation to the eccrine duct from the drug agent. Others suggest that NEH is a paraneoplastic syndrome, or that it develops from leukemic precursors which differentiate following chemotherapy.

Supporting the theory that an offending agent induces an inflammatory reaction within the eccrine ducts is the propensity for NEH to spontaneously resolve when the medication is discontinued. The recurrence of disease can be seen when the same chemotherapeutic agent is once again administered. Contributing to the theory that chemotherapy incites the lesions is a study by Templeton et al, in which injections of bleomycin into the skin of healthy volunteers led to the development of NEH and syringosquamous metaplasia (SSM) within 24 hours.

Although most lesions resolve spontaneously, reports demonstrating the need for a short trial of dapsone or colchicine have also been described in literature. These treatments are particularly useful in NEH diagnosed late, in cases of comorbid disease including Behcet's, or in patients who must continue chemotherapy. Occasionally, corticosteroids or NSAIDS have been used, usually for the treatment of concurrent pain or fever, and seem to shorten the course of the lesions. Fortunately, once the lesions have resolved there are enough dermal eccrine remnants to regenerate without scarring.

The presumed target of NEH is the eccrine duct, a thermoregulatory sweat gland that responds to increased body temperature by secretion of water on the skin surface. The eccrine duct also excretes waste products, which although minor compared to the thermoregulatory role, is an important factor in the etiology of some forms of NEH. There are approximately two to four million eccrine glands on every person and are found almost universally throughout the skin but concentrated in various areas. For example, the palms and soles have the greatest number of eccrine glands, followed by the head, trunk and then extremities in decreasing order. This pattern of density corresponds to the most common locations for NEH lesions, that is, the extremities, the face, and the trunk. Normal physiological processes occurring in the eccrine ducts include the concentration and excretion of certain drugs. As reviewed by Wenzel and Horn (2000), drugs including ethanol, amphetamines, cocaine, nicotine, and ciprofloxacin have been studied, while many others have been attributed to eccrine disorders such as NEH.

**Other diseases associated with NEH**

A variety of medical conditions, in addition to malignant hemopathies, have been identified in patients diagnosed with NEH. The most commonly reported condition is Behcets disease (BD). A neutrophilic dermatosis characterized by systemic inflammation and mucocutaneous lesions. In one case, NEH was thought to represent a form of neutrophil mediated cutaneous lesions in BD. In another case, the patient was found to have oral aphthosis, anterior uveitis and a positive pathergy test in addition to pruritic papules on her arms and legs confirmed to be NEH. She responded well to 100mg dapsone daily and had no recurrence over 9 months. Other diseases reported in association with NEH include a patient with systemic lupus erythematosus (SLE) undergoing cyclophosphamide therapy and a patient being treated with methotrexate for actinic reticuloid syndrome. The etiologic association with NEH is unclear.

Patients with malignant hemopathies but without concurrent chemotherpay...
have also been reported with NEH. In these cases, NEH has been proposed to represent a paraneoplastic syndrome. In five patients, NEH was reported as the heralding symptom prior to the development of AML or CML; none of the patients had recently undergone chemotherapy. In one case, the patient was previously diagnosed with chronic myelogenous leukemia and developed NEH six months after his final round of chemotherapy, just prior to a relapse of CML. Lesions associated with chemotherapy have been reported to begin on average 10 days after initiation of the agent; if chemotherapy was the inciting agent, this case would represent a delayed response.

The other four cases describe NEH as the first indication of new onset leukemia; after the onset of NEH, three patients subsequently developed AML and one patient developed CML. All of the patients’ symptoms resolved spontaneously after approximately 3 weeks. A paraneoplastic syndrome is defined by a symptom or disease caused by the presence of cancer in the body. These symptoms are thought to be the result of cytokines or hormones released from tumor cells rather than originating directly from cancer cells. These reports of paraneoplastic syndrome, in addition to the known association between NEH and malignancies, lend further support to continually evaluate patients for signs of malignancy.

Other medications associated with NEH

NEH has also been reported in association with other medications, including G-CSF and acetaminophen. G-CSF is a hematopoietic growth factor which stimulates the differentiation of neutrophils in bone marrow, and is often used in patients with bone marrow toxicity following chemotherapy. A 40 year old male with leukemia was given two treatments with G-CSF over a period of months; following the second course he developed a purple plaque on his leg. Biopsy evaluation identified the lesion as NEH. After discontinuation of the G-CSF the lesion disappeared in two weeks. G-CSF is proposed to cause NEH by stimulation of neutrophilic precursors and accumulation of neutrophils in the dermis through chemotaxis. Interestingly, G-CSF has also been reported to cause other neutrophilic dermatoses including Sweet’s syndrome and pyoderma gangrenosum.

Two reports indicate acetaminophen in the development of NEH. In one case the patient developed NEH while taking only acetaminophen. The patient had no other underlying disease or malignancy. Another case of NEH is described in a 68 year old female with untreated CLL. Administration of acetaminophen was the causative link upon retrospective review of her medical file. Within 30 minutes of taking acetaminophen periorbital, violaceous patches appeared and were confirmed to be NEH. The patient was treated with methyprednisolone 80mg/day and the lesions resolved within 1 week. The latter case represents both, an unusual presentation and causative agent; the presence of CLL adds evidence to the theory that an underlying immune dysfunction may contribute to NEH without regard to the type of systemic medication.

Infectious agents associated with NEH

Eccrine ducts have been described as resistant to microbes but the mechanism by which the sweat glands protect the body from invading organisms is not well known. Research suggests that there are high levels of IgA in the sweat glands and that these immunoglobulins are inhibitory to bacterial growth. Recently, an anti-microbial peptide called “cathelicidin” has been found to be secreted by sweat glands, perhaps contributing to its innate defense against microbes. Despite the aforementioned defense mechanisms, adding to the spectrum of NEH are reported cases associated with microorganisms including Streptococcus, Nocardia, Enterobacter, Staphylococcus, gram positive cocci, Rocky Mountain Spotted Fever (RMSF) and coagulase negative staphylococcus.

In one case of NEH, skin biopsy cultures revealed Serratia marcescens and the patient had multiple recurrences of disease. With each recurrence the patient’s symptoms resolved with a short course of antibiotics. In a recent case series of 10 children with NEH, biopsies from two infants with classic symptoms of NEH grew coagulase negative staphylococcus. The patient’s symptoms consisted of multiple papules and nodules of the limbs which resolved within three weeks. One case of NEH was reported in a 15 year old boy with Rocky Mountain Spotted Fever (RMSF); the boy’s skin lesions showed signs of both NEH and leukocytoclastic vasculitis.

Table 1
Adapted from Bachmeyer and Aractingi (2000)

<table>
<thead>
<tr>
<th>Chemotherapeutic agents</th>
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<td>5-Fluorouracil</td>
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<td>6-Thioguanine</td>
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<td>Chlorambucil</td>
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<td>Cyclophosphamide</td>
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<td>Cytarabine</td>
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<td>Daunorubicine</td>
<td>Non Hodgkin’s Lymphoma</td>
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<td>Decarbazine</td>
<td>Wilms’ Tumor</td>
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<td>Etoposide</td>
<td>Lung Cancer</td>
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<td>Imatinib mesylate</td>
<td>Breast Cancer</td>
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<td>Lomustine</td>
<td>Osteosarcoma</td>
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<td>Methotrexate</td>
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<td>Mitoxantrone</td>
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<td>Vinblastine</td>
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<td>Vincristine</td>
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<td>Zidovudine</td>
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<th>Other Medications</th>
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<td>G-CSF</td>
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<td>Acetaminophen</td>
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<th>Microorganisms</th>
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<td>Staphylococcus</td>
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<td>Nocardia</td>
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<td>Rocky Mountain Spotted Fever</td>
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<th>Viral infections</th>
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<th>Other conditions</th>
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<tr>
<td>Actinic Reticuloid Syndrome</td>
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<td>Behcet’s</td>
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<td>Bullous Pemphigoid</td>
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<td>Lupus</td>
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Acetaminophen was identified as the causative agent of two cases of NEH. In one case of NEH, skin biopsy cultures revealed Serratia marcescens and the patient had multiple recurrences of disease. With each recurrence the patient’s symptoms resolved with a short course of antibiotics. In a recent case series of 10 children with NEH, biopsies from two infants with classic symptoms of NEH grew coagulase negative staphylococcus. The patient’s symptoms consisted of multiple papules and nodules of the limbs which resolved within three weeks. One case of NEH was reported in a 15 year old boy with Rocky Mountain Spotted Fever (RMSF); the boy’s skin lesions showed signs of both NEH and leukocytoclastic vasculitis. In each of the reported cases of infectious NEH,
the microorganism is either cultured from a skin biopsy\textsuperscript{14, 48} or directly observed in the inflamed eccrine ducts.\textsuperscript{49} Additionally, a short course of antibiotics successfully resolves the cutaneous rash whereas in aseptic cases of NEH the lesions generally resolve spontaneously over time.

NEH has also been described in patients with viral infections including HIV\textsuperscript{50-63}, HSV\textsuperscript{4}, and hepatitis C\textsuperscript{54}. One HIV patient with NEH was being treated with stavudine, a reverse transcriptase inhibitor\textsuperscript{52}; a second HIV patient was being treated for non-Hodgkin’s lymphoma and subsequently developed NEH\textsuperscript{54}; and a third HIV patient was taking no medications.\textsuperscript{55} NEUTROPHILIC ECCrine HIDRADENITIS: EXPANDING THE CLINICAL SPECTRUM IN NON-CHEMOTHERAPY PATIENTS

Cases of NEH with no associated chemotherapy, or chemotherapy.\textsuperscript{56-58} An increased density of neutrophils leading to the development of the tender lesions.\textsuperscript{49} After rest or avoidance of wet footwear, the lesions resolve spontaneously. Only a few cases reported the use of steroids and NSAIDs as treatment, leading to a resolution of disease in 1 – 2 weeks.\textsuperscript{62} NEH has also been described in association with non-Hodgkin’s lymphoma and subseque ntly been reported the use of steroids and NSAIDs as treatment, leading to a resolution of disease in 1 – 2 weeks.\textsuperscript{62} Appar ently children, the avoidance of unnecessary diagnostic tests, antibiotics or steroid treatments may be significant.

NEH in healthy adults or in children without a palmoplantar distribution is extremely rare. A handful of NEH cases in healthy adults have been reported\textsuperscript{37, 59-61}, including the two cases suggesting the role of acamprosate in the etiology of disease.\textsuperscript{62} In a case series of 10 children, 8 of the children are described as having NEH with no associated chemotherapy, malignancy, or microorganism. The lesions in these cases were distributed primarily over the lower limbs and resolved spontaneously after three weeks.\textsuperscript{63} Another case of NEH was described in a neonate also suffering with neonatal onset multi-organ inflammatory disease (NOMID).\textsuperscript{64} Examining the etiology in the current patient presents a challenge to clinicians and highlights the necessity to evaluate nuances in unusual cases as the search for the pathogenesis of disease continues. Syringosquamous metaplasia

Eccrine syringosquamous metaplasia (ESSM) is a distinct dermatologic condition considered to fall within histopathologic spectrum of NEH. Squamous metaplasia is the defining histopathologic feature of ESSM and is also a feature described in the later stages of NEH. Eccrine syringo- metaplasia is similar to NEH in both its etiology and histology. Similar to NEH, it is often found in patients undergoing chemotherapy for malignancies\textsuperscript{65, 66} and has been described in association with viral illnesses such as CMV and HIV.\textsuperscript{52, 67} ESSM is characterized by squamous metaplasia of the epithelial cells lining the sweat ducts and it can mimic squamous cell carcinoma because of the presence of islands of squamous epithelium as well as necrosis of the ductal epithelium.\textsuperscript{68} ESSM is distinct from NEH in its sparsity of neutrophilic infiltrates. Additionally, the cutaneous eruption of ESSM is more likely to be found centrally on the body (trunk, abdomen, neck) rather than on the extremities as in NEH. Investigators have suggested that NEH represents the inflammatory stage of the disease while ESSM represents the noninflammatory or late stage of disease.\textsuperscript{52, 69} Alternatively, the lack of inflammatory infiltrate, i.e. neutrophils, in ESSM may implicate a direct toxic effect of the chemotherapeutic agent or viral infection on the sweat gland.\textsuperscript{70, 71} The current patient presents with features of both NEH and ESSM including central and peripheral clinical lesions, as well as histological evidence of a neutrophilic infiltrate in addition to syringosquamous metaplasia. The question remains why some patients develop neutrophilic eccrine hidradenitis with squamous metaplasia and others develop eccrine syringosquamous metaplasia. Given the similarities between the two conditions, further evaluation of ESSM may help to elucidate the pathological mechanism of disease in NEH.

Other unusual presentations of NEH

There has been one case report of IPH presenting in pustular form.\textsuperscript{72} Annullar plaque presentations of NEH have been reported on multiple occasions\textsuperscript{73-75}; one case of annular NEH was reported on a patient’s hands.\textsuperscript{76} NEH appearing as facial plaques has also been identified\textsuperscript{77-80}, one of which presented as bilaterally swollen ears.\textsuperscript{81} NEH mimicking other diseases has also been reported including facial cellulitis\textsuperscript{82} and orbital cellulitis.\textsuperscript{83} Finally, a serpentine supraventricular eruption was reported at the chemotherapy injection site on the arm of a child being treated for a malignancy.\textsuperscript{74}

Summary

Our case is distinctly unusual, occurring in an immunocompetent patient with no history of an underlying blood dyscrasia or chemotherapy. Furthermore, the wrists, arms, and back are unusual locations for NEH to manifest. The patient’s altered mental status and elevated viral titers to Epstein-Barr virus suggest a possible viral etiology for these clinical and histopathologic changes. Although an immunohistochemical stain to Epstein-Barr virus LMP1 was negative in our patient, this does not exclude the possibility that the virus may have facilitated an inflammatory cytotoxic response. New onset seizures requiring a daily dose of multiple anti-epileptic medications, which preceded symptom onset by two weeks, suggests a possible medication etiology. However, this etiology is unlikely since the signs and symptoms resolved while the anti-seizure medications were still administered. Further research is needed to investigate the underlying mechanisms to explain
these histopathologic changes. In conclusion, this case report and review examines the expanding clinical profile of NEH. Avoidance of unnecessary tests and treatments in patients with NEH is critical as most cases resolve spontaneously upon removal of the offending agent or after treatment for a specific infectious organism. Various anatomical locations and medications continue to broaden the clinical picture associated with NEH. A characteristic histopathologic finding in an unusual clinical setting should alert the clinician to consider NEH in the clinical differential diagnosis.

References:
Introduction

Pseudomonas folliculitis (PF) has been well documented and reported in random outbreaks since the early 1970s. Although generally associated with recreational use of hot tubs and whirlpools, outbreaks have been reported after exposure to saunas, swimming pools, bathing facilities, water slides and diving suits, and there has been at least one reported outbreak after industrial exposure to water used in a cardboard manufacturing plant.1 Pseudomonas aeruginosa has a ubiquitous distribution in soil and water and is not considered normal skin flora. PF outbreaks have been reported in the United States, Canada, Europe and Japan. P. aeruginosa serotype O:11 is most commonly associated with folliculitis outbreaks, but other serotypes have been reported.2 Since 1971, the Centers for Disease Control and Prevention (CDC) and the U.S. Environmental Protection Agency have surveilled and reported on waterborne diseases and outbreaks associated with recreational water use (natural and treated).1 To our knowledge, this is the first reported case of PF associated with swimming in a freshwater pond.

The skin manifestations of PF include an erythematous, papulopustular rash that is often pruritic and/or painful. Lesions appear 24 to 48 hours after exposure to contaminated water. The rash can have a generalized distribution but is most concentrated around areas of tight-fitting clothing. Associated symptoms may be present and include fever, muscle aches, fatigue and earache. Most cases are mild and self-limiting, with symptoms resolving spontaneously over seven to 15 days.

Case Report

An 11-year-old Caucasian female from North Texas presented to the Dermatology Institute in August complaining of a rash of two days duration that first began one day after swimming in a pond behind her house. She first noticed the “bumps” around her waist and buttocks. The bumps were extremely itchy, “felt like a bad sun burn,” and prevented her from being able to sleep. She also reported having a low-grade fever and generalized achiness. She was current on her immunizations. No one else in her family had any lesions, and they all denied any recent travel or hot tub/whirlpool use.

The patient’s past medical and surgical history was unremarkable, and she had no known drug allergies. Her review of systems was negative except for the presenting complaint.

On physical exam, she had hundreds of 1 to 3mm erythematous papules and pustules distributed most densely in areas along where the elastic bands from her bathing suit had been, specifically her waist line, panty line, and bra line (Images 1,2). Some of the papules were also scattered on her back, abdomen and proximal extremities. Most of the lesions were centered on a follicle. No lymphadenopathy was appreciated.

A presumptive diagnosis of swimmer’s itch (cercarial dermatitis) was made based on the history of swimming in a fresh water pond. The physical exam was not entirely consistent with this diagnosis since she had a heavy concentration of lesions in areas that had been covered by her swimsuit. We ordered a Gram stain from a scraping of one of the lesions; however, the specimen was mishandled so we did not get these results. We decided to treat the patient symptomatically, and reserve biopsy for a future visit if she did not respond adequately.

To investigate the possibility of a bacterial folliculitis, a bacterial culture was obtained from a pustule on the patient’s back. Also, because she was having systemic symptoms of fatigue and low-grade fevers, we obtained a complete blood count with differential.

Since the patient had been vaccinated against measles and chicken pox, we did not believe these were the etiology of her rash; but to rule out an atypical presentation of a herpes virus, a Tzanck smear was made from the scraping of a pustule. We elected to treat her severe itching with a short course of tapering oral steroid, since the rash was affecting her and her parents’ sleep. We prescribed an oral antihistamine, hydroxyzine, as needed for itching. She was given a sample of a topical...
later, the patient stated she was feeling much better and had less itching. She had only needed a few of the “itch pills.” Upon inspection, most of the papules had cleared, and she just had some residual post-inflammatory hyperpigmentation (Images 3-5). No pustules or open areas could be found. The bacterial culture that was taken four days earlier showed a heavy growth of *Pseudomonas aeruginosa*. Her CBC was within normal limits, and the Tzanck smear was non-diagnostic. A diagnosis of *Pseudomonas* folliculitis was made.

Based on the fact that there were no signs of a persistent, active infection, and a review of the literature, we decided not to start antibiotic therapy. The patient was instructed to finish her oral steroids and only use the topical steroid and oral antihistamine if needed for itching. She was to return to the clinic in two weeks.

Eight days after her initial visit, the patient’s mother called, stating the patient had “a few new bumps” on her waist line. She was prescribed Silvadene (silver sulfadiazine) cream and told to come back into the office if fever developed or the rash spread. Otherwise, she was to keep her next follow-up appointment in 10 days. Over the next few days, we were informed that the pruritis had resolved and she had no new papules or pustules.

**Discussion**

In the United States from 1971 to 2000, a total of 259 outbreaks of waterborne disease involving over 21,000 cases were reported in association with recreational water use. *Pseudomonas* was responsible for 31% of cases from treated water, as compared to less than 1% from untreated water. The reported illnesses included dermatitis, otitis externa and conjunctivitis. *Pseudomonas* folliculitis was associated most frequently with whirlpool baths, hot tubs and swimming pools. The most commonly cited reason for *Pseudomonas* outbreaks was improper maintenance of pH and chlorination in pool water, with heavy swimmer burden and contamination as contributing factors.

*Pseudomonas aeruginosa* is a ubiquitous, gram-negative, motile bacillus. Its thermophilic properties allow it to survive the warm temperatures of hot tubs and whirlpools. Its pathogenesis in dermatitis is thought to occur, in part, from superhydration of the stratum corneum, promoting colonization and follicular invasion. This is supported by observations that frequent and extended use of whirlpools may be risk factors. Occlusion likely promotes invasion as well. The rash is typically most dense under areas occluded by bathing suits or diving suits. Showering after swimming does not seem to be protective. In a clinically distinct but related syndrome, *pseudomonas* hot hand-foot syndrome, *pseudomonas* infection of the palms and soles is attributed to skin abrasions secondary to gritty, abrasive linings of pools and wet decks. These cases present with painful, erythematous palmar and plantar nodules. Other cases of *pseudomonas* folliculitis have been documented after wax epilation.

Our original diagnosis of cercarial dermatitis in this patient was clinically based on history, her presenting symptoms of tender, pruritic papules, and the strong association of cercarial dermatitis with swimming in warm, shallow, freshwater ponds and lakes. While the rashes may be similar in appearance and share identical symptoms, the distribution of the rash may help distinguish between the two. Cercarial dermatitis usually affects areas of skin not covered by clothing, whereas *pseudomonas* folliculitis most commonly affects areas that are covered. As is the case with many conditions, there may be overlap between the two. We believe this case demonstrates that *pseudomonas* folliculitis is not limited to hot tubs and pools, and that history of swimming in a freshwater pond should not discourage a diagnosis of *pseudomonas* folliculitis when considering a diagnosis of cercarial dermatitis.

**Clinical Features**

The rash of *pseudomonas* folliculitis will appear, on average, 48 hours after exposure to contaminated water, with a range of eight hours to five days. It begins as a pruritic, erythematous, follicular and papular dermatitis with a characteristic distribution. It quickly progresses to a tender and pruritic, papulopustular rash. The rash will be worst on areas of skin occluded by tight-fitting swimming suits. The head and face are usually spared, with the waist, buttocks, back and axilla being most commonly affected. Although this distribution is characteristic, it is not unique to *pseudomonas* folliculitis.

Other symptoms are uncommon but include fever, lymphadenopathy, malaise, otalgia, conjunctivitis, pharyngitis and myalgias. These symptoms do not necessarily indicate bacteremia or systemic spread. The eruption clears usually within seven to 15 days, but some patients may experience recurrent crops of lesions for up to three months. It is unlikely that the infection is spread from person to person; however, multiple members within a family may develop folliculitis concomitantly if the source of infection is within the home.

Diagnosis is generally made by history of hot tub or whirlpool exposure and supported by physical exam. Under Wood’s lamp, a pale, green fluorescence may be appreciated. It is not uncommon for bacterial cultures from pustules to be negative. The CBC may show an elevated white
blood cell count with a rise in neutrophils. Histopathology demonstrates perifollicular, perivascular and pericorneal neutrophil infiltration with edema of the interfollicular papillary dermis.\(^4\)\(^,\)\(^10\)

**Differential Diagnosis**

The differential diagnosis for PF includes staphylococcal infection, cercarial dermatitis, seabather’s eruption, scabies, and insect bites.\(^1\)\(^,\)\(^8\) Furthermore, the rash has been confused with herpes simplex, chicken pox and contact dermatitis.\(^2\)\(^,\)\(^7\) In at least one outbreak of pseudomonas hot hand-foot syndrome, the palmoplantar lesions led physicians to consider meningococemia, Rocky Mountain spotted fever and idiopathic palmoplantar hidradenitis.\(^8\) Swimmer’s itch, or cercarial dermatitis, may occur on exposure to fresh or salt water. It is very pruritic and tends to cause erythematous papules on body parts that were exposed to the water. Bacterial folliculitis can present as follicularly centered papules and pustules with varying degrees of pruritis. Potential causes of bacterial folliculitis include *Staphylococcus*, *Streptococcus* and *Pseudomonas*, as well as many others. Seabather’s eruption usually begins after bathing in the Atlantic Ocean; it is caused by larvae that become trapped under the bathing suit and release their toxin because of external pressure. These lesions tend to affect the buttocks, waist and bra area. Viral exanthems can present as widespread erythematous papules, most specifically varicella or measles.

**Management**

The infection of PF is generally mild and self-limited, demonstrating spontaneous involution without medical therapy. However, a 5% acetic acid wet compress applied for 20 minutes two to four times per day and/or silver sulfadiazine cream may be helpful.\(^1\)\(^,\)\(^2\) In patients who fail topical treatment, have severe or prolonged cases, or have fever and constitutional symptoms, a third generation oral cephalosporin or a fluoroquinolone may be used.\(^5\)\(^,\)\(^10\) A more aggressive approach would be necessary in immunosuppressed patients, including those with AIDS. In the immunosuppressed patient, PF can progress to cellulitis, panniculitis and/or ecthyma gangrenosum.\(^1\)\(^,\)\(^4\)\(^,\)\(^15\)

**Conclusion**

We described an isolated case of PF associated with swimming in a North Texas pond. While PF is generally associated with swimming in pools and hot tubs or other chemically treated waters, we do not believe a history of only non-treated water exposure should discourage this diagnosis. We also believe that a bacterial culture and sensitivity should be obtained anytime a patient presents with pustules. Although PF is usually mild and self-limited, prompt recognition can help guide appropriate management.

**References:**

Safety Considerations
In clinical trials, the most common adverse events reported were gastrointestinal upsets, nasopharyngitis/pain and nasal congestion/sinusitis. Oracea should not be used to treat microbial infections, and should be used only as indicated. This drug is contraindicated in people who have shown hypersensitivity to any of the tetracyclines, and, like other tetracycline drugs, may cause fetal harm when administered to a pregnant woman. Oracea should not be used during pregnancy, by nursing mothers or during tooth development (up to age of 8 years). Although photosensitivity was not observed in clinical trials, Oracea patients should minimize or avoid exposure to natural or artificial sunlight. All contraindications, warnings and precautions associated with tetracyclines must be considered before prescribing Oracea. The safety of Oracea treatment beyond 9 months has not been established.

Please see the brief summary of full prescribing information on adjacent page.
INDICATIONS AND USAGE
ORACEA is indicated for the treatment of cutaneous infections caused by susceptible organisms. If the causative organism is not known, a broad-spectrum agent should be selected for the initial treatment of the infection. The efficacy of ORACEA has been demonstrated in the treatment of bacterial infections caused by susceptible strains of the following organisms:

- Acne vulgaris
- Mild to moderate inflammatory papulopustular acne
- Furunculosis
- Erysipelas
- Cellulitis
- Perianal abscess
- Pemphigus foliaceus

WARNINGS
- Tetracycline resistance is increasing in many areas. If an infection is suspected to be resistant to ORACEA, alternative therapy should be used.
- Doxycycline may cause reversible bone and tooth discoloration in infants and young children. Excessive tooth deitement is the primary reason for the suspension of doxycycline in children and infants.
- Doxycycline may cause photosensitivity and increase the risk of skin cancer in children and infants.
- Doxycycline may cause irreversible bone changes in infants and young children.
- Doxycycline may cause harm to the fetus and should not be used during pregnancy.
- Doxycycline may cause adverse effects in the newborn.
- Doxycycline may cause harm to the mother and child.

PRECAUTIONS
- Pregnancy: Teratogenic Effects:
- Doxycycline, like other tetracycline-class antibiotics, can cause fetal harm when administered to a pregnant woman. If tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be informed of the potential hazard to the fetus and treatment stopped immediately.
- ORACEA should not be used during pregnancy (see PRECAUTIONS: Pregnancy).
- Labor and Delivery: Doxycycline crosses the placenta and is found in fetal tissues.

ADVERSE REACTIONS
- The following adverse reactions have been observed in patients receiving ORACEA:
**Varicella-Zoster Vasculitis Presenting As Ecthymatous Ulcers**

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**ABSTRACT**

Uncommon presentations of varicella zoster virus (VZV) are difficult to recognize and are often misdiagnosed. Herein, we describe a 71-year-old, immuno-competent male who presented with three circumscribed papules with central eschar and surrounding erythema. Upon histological examination, pronounced infiltrate of neutrophils and accompanying fibrin thrombi were visualized. Positive staining for VZV in-situ was localized to the vascular endothelia nuclei. A diagnosis of necrotizing leukocytoclastic vasculitis was rendered secondary to VZV. This report underscores the importance of clinico-pathologic correlation and should alert the reader to the varied clinical and pathologic presentations potentially encountered in VZV.

**Introduction**

Cutaneous eruptions caused by Varicella-zoster virus (VZV) are relatively common, and in the average patient population, characteristic clinical findings can lead to a correct diagnosis. Varicella zoster, a member of the herpes virus family, is a common eruption conventionally characterized by painful macules and papules that progress to vesicles and then to ulcers. These lesions manifest themselves in specific dermatomes.1 A prodromal period often occurs, presenting as severe pain, paraesthesia or pruritus. Less commonly, the vesicular stage is circumvented, instead initially manifesting as a papular eruption, bullae, or hyperkeratotic lesions. Herein, we report a case of a previously documented presentation of VZV as an ecthymatous eruption with histologic features of leukocytoclastic vasculitis.

**Presentation of Case:**

A 71-year-old, previously healthy male presented with complaints of a “rash” on his right leg that developed precipitously two weeks prior. The patient denied any insect bites, itching, burning or oozing from the affected areas. Physical exam revealed three ulcers located on the right anterior thigh ranging from 3-6mm in size. The well-circumscribed papules consisted of a central black eschar with surrounding erythema (Figure 1). A punch biopsy and the following serologies were performed: complete blood count, complete metabolic panel, C-reactive protein and herpesvirus 1 and 2, along with Varicella-zoster virus and mycoplasma pneumonia antibody titers, rheumatoid factor, anti-nuclear antibody, anti-phospholipid antibodies, Sjogren syndrome antigen A/Sjogren syndrome B, complement studies, rapid plasma reagin, hepatitis panel and serum protein electrophoresis. The Varicella-zoster IgG and IgM (1:1200) titers were positive. All of the remaining titers, including herpes simplex virus 1 and 2 and other lab work, were normal.

Microscopic examination revealed epidermal ulceration (Figure 1) with superficial dermal coagulative necrosis (Figure 2). The dermal vessels contained a pronounced infiltrate of neutrophils, both intact and fragmented, with accompanying fibrin thrombi (Figure 2-3). VZV in-situ hybridization showed positive staining localized to the vascular endothelia nuclei. A diagnosis of VZV with leukocytoclastic vasculitis was rendered.

**Discussion**

Immunosuppressed patients (particularly HIV+ patients or individuals with hematologic disease) are most likely to present with atypical clinical findings in cutaneous VZV.2-4 Unusual presentations may mimic a cutaneous lymphoma, pseudolymphoma,2,5,4 or in one of several guises of cutaneous vasculitis. The most common histologic types include leukocytoclastic, lymphocytic or granulomatous vasculitis. Leukocytoclastic vasculitis may be primary (i.e. caused by the herpes virus itself) or represent a reactive process.2 Erhard et al6 described the only other similar clinical presentation of a painless skin eruption consisting of ecthymatous nodules that failed to form vesicles throughout the disease process. The patient was immunosuppressed, receiving treatment with systemic chemotherapeutic agents for Stage IV cutaneous T-cell lymphoma. Biopsies in this case similarly revealed a lack of epidermal involvement, with endothelial changes of vasculitis and viral cytopathic effects confirmed by polymerase chain reaction (PCR) testing. Erhard et al. hypothesized that upon re-activation with VZV, epidermal invasion and/or follicular involvement was circumvented by the close proximity of dermal nerves to blood vessels. Although endothelial involvement is a routine accompaniment of cytomegalovirus infection, it is exceptional for such changes to appear in conjunction with the other herpes virus agents, including HSV or VZV infection.

Lymphocytic vasculitis may be seen in conjunction with reactivation of the virus. Less commonly, granulomatous vasculitis may be seen with lymphocytic vasculitis.7,8 The granulomatous inflammation may be seen within the blood vessels or the surrounding dermis, and rarely may produce an interstitial pattern reminiscent of granuloma annulare.7 Cerebral vasculitis, although rare, has been described in association with VZV, detectable by polymerase chain reaction in the affected vessels as well as concomitant clinical findings such as a classic herpes zoster elsewhere on the body.9,10

In cases of ecthymatous eruption with histologic features of leukocytoclastic vasculitis, VZV should be suspected, particularly among the immunosuppressed, where VZV can present in a variety of guises. Although our patient was not immunosuppressed...
pressed, the serologic studies and nuclear hybridization results aided in the correct diagnosis, establishing the importance of such studies in confirming a diagnosis.

References:
WAARDENBURG SYNDROME: A CASE PRESENTATION

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ABSTRACT

Waardenburg syndrome (WS) is a rare, inherited disorder of neural crest cell development that was first described in 1947 by Dr. Petrus Johannes Waardenburg, a Dutch ophthalmologist. It is an auditory-pigmentary syndrome caused by a defect in neural crest cell migration and melanin synthesis. WS is the most common form of inherited congenital deafness worldwide. In this paper, a case report of WS will be presented. Also, we will discuss the prevalence, clinical findings, diagnostic criteria, inheritance patterns, pathophysiology, and prognosis of WS in order to raise awareness and provide a better understanding of this rare genodermatosis.

Case Presentation

History

A 53-year-old Caucasian male with a past medical history significant for hypertension, hypertriglyceridemia, and piebaldism presented with the complaint of non-healing, red, scaly patches of skin on his arms and face for several months duration. His medications included amlodipine, gemfibrozil, and aspirin. He had no known medication allergies. His family history was significant for a son, mother, and aunt with white forelocks of hair resembling his own (Figure 1), a sister with a white forelock and deafness since birth, and his maternal grandmother with a white forelock and hearing loss.

Physical Exam

On physical exam, erythematous, scaly papules were found scattered on the face and forearms. These were clinically diagnosed as actinic keratoses, and subsequently treated with liquid nitrogen cryotherapy.

More interestingly, our patient was noted to have a white forelock of hair on the frontal scalp, present since birth according to the patient, as well as pigmentary incongruity of many terminal hairs on his arms, legs, and abdomen, with underlying leukoderma. He was previously diagnosed in childhood with piebaldism based on these findings. However, in addition to the above, he also had bilateral segmental heterochromia irides, a broad nasal root with mild synophrys, and extensive leukoderma of his arms, legs, and abdomen, giving an overall “dappled” appearance to his skin (see Figures 1-4).

Due to the additional physical findings and abnormalities, the previous diagnosis of piebaldism was questioned. Subsequently, we diagnosed our patient with Waardenburg syndrome (WS), autosomal-dominant type 1, established by his family pedigree (Figure 5) and the clinical findings and criteria set forth for WS as discussed below (Table 1).

Discussion

Background

WS is a rare, inherited disorder of neural crest cell development with almost complete penetrance but variable expressivity.1 It is characterized by deafness in association with pigmentary anomalies of the skin, hair, and eyes, as well as sometimes other neural-crest-derived tissue defects. It has also been referred to as Van der Hoeve-Halbertsma-Gualdi syndrome, Ptosis-Epicanthus syndrome, and Mende syndrome.

The first documented description of WS was in 1947 by Dr. Petrus Johannes Waardenburg, a Dutch ophthalmologist. He reported a patient having hearing loss, dystopia canthorum, and retinal pigmentary differences. In 1951, the syndrome was formally named after Dr. Waardenburg subsequent to him identifying many other patients with similar signs and symptoms, as well as describing six characteristic features.

The six characteristic features first described by Dr. Waardenburg include: 1) dystopia canthorum – lateral displacement of the medial canthi in addition to dystopia of the lacrimal puncta; 2) broad and high nasal root; 3) synophrys – hypertrichosis of the medial part of the eyebrows; 4) partial or total heterochromia iridis; 5) white forelock; and 6) congenital sensorineural hearing loss.2 Today, these findings are most closely associated with WS type 1.

Epidemiology

The prevalence of WS is estimated to be one in 42,000 worldwide, with men and women being equally affected. WS is responsible for 2-5% of all cases of congenital deafness.2 Today, there are four known subtypes of WS, classified by phenotype and clinical findings, mode of inheritance, and gene mutations (Table 2). The most common forms of WS include types 1 and 2, while types 3 and 4 are rare.

WS can be inherited in an autosomal-dominant (AD) or autosomal-recessive (AR) fashion, with the latter being less common. It is frequently apparent at birth and is the most common form of inherited congenital deafness worldwide.3 Affected individuals have a higher risk for neural-tube defects, cleft lip and palate, limb abnormalities, and Hirschsprung disease, also known as congenital aganglionic megacolon.

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Diagnosis

In 1992, the Waardenburg Syndrome Consortium proposed diagnostic criteria for WS type 1 based on specific clinical findings. Individuals with two major, or one major plus two minor criteria are considered to be affected with WS type 1 (Table 1). In 1995, Liu et al. defined WS type 2 as those individuals having two major criteria without dystopia canthorum.

WS types 3 and 4 are diagnosed using the criteria for WS type 1 in addition to other neural-crest defects specific for each type. WS type 3, also known as Klein-Waardenburg syndrome, has musculoskeletal defects, such as upper limb hypoplasia, as its distinct feature. And WS type 4, also known as Shah-Waardenburg syndrome, has Hirschsprung disease as its distinct feature.

Clinical Findings

Clinical findings in WS include pigmented disturbances of the iris that include complete heterochromia iridis, partial or segmental heterochromia iridis, or hypoplastic blue iridis. A white forelock and a broad and high nasal root are also commonly seen in those affected with WS. Dystopia canthorum is found in WS types 1, 3, and 4, and is present when the calculated W index exceeds 1.95 in the formula W index = X + Y + a/b (Figure 6).

Other clinical findings in WS include: multiple nevi, eyebrow anomalies, cleft lip and palate, receding chin, Sprengel’s shoulder (congenital upward scapular displacement), spina bifida, syndactyly (WS type 3), hypoplasia or contractures of the limbs (WS type 3), and Hirschsprung disease (WS type 4).

Differential Diagnosis

Because WS consists of auditory and pigmentary abnormalities, the differential diagnosis varies widely and includes any syndrome with either auditory or pigmentary abnormalities, or both. The differential diagnosis includes diseases such as: Tietz syndrome, Ziprkowski-Margolis syndrome, Woolf’s syndrome, Fisch’s syndrome, Rozycki’s syndrome, ocular albinism with sensorineural deafness, piebaldism, and nonsyndromic sensorineural hearing loss (Table 3).

Pathophysiology

WS is an auditory-pigmentary syndrome caused by a defect in neural crest cell migration, melanocyte differentiation, and melanin synthesis. The physical absence of melanocytes from the skin, hair and eyes and stria vascularis of the cochlea is responsible for the expressed phenotype of WS. To date, there are six known gene mutations in WS, all of which are critical for the development and migration of neural crest cells, in particular melanocytes (Table 2).

Microphthalmia transcription factor (MITF) is a leucine zipper transcription factor that transactivates the gene tyrosinase, a key enzyme for melanogenesis. MITF is critically involved in melanocyte differentiation. Defects in MITF lead to absence of melanocytes affecting pigmentation of the hair, skin and eyes and stria vascularis of the cochlea.8 MITF gene mutations are seen in WS type 2, where there is a higher incidence of hearing loss as compared to WS type 1 due to the stria vascularis being affected (Table 2).9

Paired box gene 3 (PAX3) encodes for DNA-binding transcription factors and is defined by a paired homeodomain transcription factor. PAX3 transactivates the MITF promoter, thereby indirectly regulating MITF. PAX3 defects result in craniofacial and skeletal malformations.10 Mutations in PAX3 result in WS types 1 and 3.

SRY-related HMG-box gene 10 (SOX10) belongs to the high-mobility group (HMG)
box super-family of DNA-binding proteins. SOX10 is expressed in the formation of the peripheral nervous system, and can be detected in the enteric ganglia. SOX10 works in synergy with PAX3 to activate MITF[11] SOX10 gene mutations result in WS type 4, where Hirschsprung disease is seen.

Snail homolog 2 (SNAI2 or SLUG) is a zinc finger transcription factor that is a downstream target of MITF and a marker for neural crest cells. SLUG gene mutations result in WS type 2, where dystopia canthorum is absent.

Endothelin 3 (EDN3) and endothelin receptor type B (EDNREB) are endothelium-derived vasoactive peptides that interact together and are essential for development of neural-crest-derived cell lineages such as melanocytes and enteric neurons. Mutations in EDN3 and EDNREB result in WS type 4, where Hirschsprung disease is seen.

**Figure 6**

W index = X + Y + a/b
where X = (2a – 0.2119c – 3.909)/c
where Y = (2a – 0.2479b – 3.909)/c
a = inner canthal distance in millimeters
b = interpupillary distance in millimeters
c = outer canthal distance in millimeters

**References:**

**Conclusion**

WS is a rare, inherited disorder of neural crest cell development characterized by deafness in conjunction with pigmentary abnormalities, and sometimes other neural-crest-derived tissue defects. Though penetrance is nearly 100%, there is a wide degree of expressivity among those individuals affected. However, WS remains the most common form of inherited congenital deafness worldwide.

This case presentation serves as a reminder that diagnoses, just as disease processes, can be dynamic and ever changing with increasing knowledge. Our patient was originally diagnosed with piebaldism, but later was found to meet the criteria for WS based on family history and subtle but pertinent clinical findings. This case presentation serves to bring greater awareness and a better understanding of WS, a rare genodermatosis, in order to aid in accurate diagnosis, appropriate genetic counseling and testing, and early intervention strategies.
A 48-year-old African American male with HIV/AIDS presented to the clinic for evaluation and treatment of a rapidly progressing lesion on his right tricep. He stated that it began as a very small lesion but got progressively larger over the course of a two-month period. He reported continued, serous drainage, which had increased in the past week. The patient stated the triamcinolone cream prescribed by his primary care physician worsened his condition. In addition, over the past few weeks he noticed two similar, smaller lesions both on his right buttocks and perirectally.

Past medical history was remarkable for a diagnosis of HIV 10 years prior (CD4 45, viral load undetectable), as well as depression. His antiretroviral regimen consisted of Videx, Kaletra, and Truvada. His other medications included Dapsone 50mg daily and acyclovir 800mg twice daily, which he admitted to taking only sporadically over a one-year period secondary to financial difficulties. His drug-allergy history was negative. Family history was noncontributory.

Physical exam of the posterior aspect of the right distal arm revealed an ulcerated, vegetating 4.5 x 5cm plaque with yellow exudates and hemorrhagic crusting.

At the time of presentation, a shave biopsy was performed, and the patient was treated empirically with Ciprofloxacin and Bactroban ointment. The patient returned for follow-up one week later with clinical improvement. A lesional skin biopsy was performed, and the patient was started prophylactic acyclovir. The incidence of acyclovir-resistant infection in HIV-positive patients is approximately 5%. Acyclovir resistance has made treating HSV infections in HIV patients significantly more challenging for physicians. Higher doses may be required, susceptibility testing may be necessary, and there may be a need to make use of second- and third-line antiviral drugs. If the HSV lesion does not respond to acyclovir in five to 10 days, then resistance can be suspected. Intravenous Foscarnet is the most effective drug used for treating acyclovir-resistant herpes simplex lesions, but it is limited by its substantial, renal-toxic side effects.

Further, atypical presentations of the herpes simplex virus seem to be more common in patients who have already started prophylactic acyclovir. The incidence of acyclovir-resistant infection in HIV-positive patients is approximately 5%. Acyclovir resistance has made treating HSV infections in HIV patients significantly more challenging for physicians. Higher doses may be required, susceptibility testing may be necessary, and there may be a need to make use of second- and third-line antiviral drugs. If the HSV lesion does not respond to acyclovir in five to 10 days, then resistance can be suspected. Intravenous Foscarnet is the most effective drug used for treating acyclovir-resistant herpes simplex lesions, but it is limited by its substantial, renal-toxic side effects.

Summary

Taking into consideration the variability of presentations of HSV lesions, the chronic nature of this disease in HIV patients and the increasing resistance to acyclovir, it is necessary for the physician to be thorough in the diagnostic workup of this disease. Physicians must be aware that multiple biopsies and cultures may be necessary to come to a final diagnosis. Sensitivity testing and a more aggressive approach to medical and surgical therapy may be necessary to assist in care and treatment of this disease.
CLASSIC PRESENTATION OF NEVOID BASAL CELL CARCINOMA SYNDROME IN A 49-YEAR-OLD FEMALE: A CASE PRESENTATION AND REVIEW

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ABSTRACT
We present a 49-year-old patient who demonstrated plantar-palmar pitting as well as widespread basal-cell carcinoma lesions classically seen in nevoid basal-cell carcinoma syndrome (NBCCS). We present clinical findings and her response to trichloroacetic acid, and we review current literature for other physical manifestations of the disease as well as comparisons of various treatments. These treatments include Mohs surgery, INF/immunoglobulins, curettage with and without electrodessication, CO₂ laser resurfacing, cryosurgery, and both trichloroacetic acid and 5% fluorouracil topical applications.

Introduction
Since the skin is the organ most commonly affected by neoplasms, it stands to reason that key cutaneous disorders and diseases be paid special attention and periodically reviewed, especially those with classic and easily recognizable presentations. The following article serves as a review for the condition known as nevoid basal-cell carcinoma syndrome (NBCCS). It has been well documented that NBCCS, also known as Gorlin-Goltz syndrome and basal-cell nevus syndrome, is a disorder characterized by an autosomal-dominant pattern of inheritance. The classic manifestation consists of keratocystic odontogenic tumors (KCOT), multiple basal-cell carcinomas (BCC) arising throughout the skin, and a multitude of consistently documented musculoskeletal abnormalities (Table 1). The BCCs resulting from the disease are common in areas unexposed to the sun, and they most commonly affect the face, neck, back, thorax, abdomen and extremities, in that order.

The genetic mutations or deletions leading to NBCCS are located on chromosome 9q22.3, which codes for the PTCH gene, a gene that interacts with the hedgehog set of genes involved in the segmentation and development of the limbs and other anatomical structures. Regardless of the initial origin of BCCs, sporadic or hereditary, the histologic presentation and pathologic course are indistinguishable. The incidence of NBCCS is approximately one per 56,000.

Case Presentation
Our patient is a 49-year-old Caucasian female with a familial history of NBCCS. She was first diagnosed with NBCCS at the age of 11. Both her mother and maternal grandmother were known NBCCS patients. The patient's grandmother was the first known family member to have the disease. The grandmother reportedly manifested multiple and recurrent KCOTs, with subsequent extreme craniofacial disfigurement, as well as the characteristic cutaneous BCCs on the body and palmar-plantar pitting as seen in Figures 1 through 4. The patient's mother, however, was affected only by the cutaneous neoplasms. Our patient has two sisters, one 42 years old and the other 46, both of whom are also NBCCS patients. The younger sister has a history of a solitary KCOT and recurrent history of BCCs. The older sister has a history of multiple and recurrent keratocystic odontogenic tumors with only occasional BCCs. Generally speaking, patients are affected primarily by either the cutaneous manifestation of NBCCS or the oral manifestations, as opposed to both. Our patient has a son in his mid-twenties who was first diagnosed with NBCCS at the age of six. He reportedly was affected exclusively by KCOTs, which necessitated a string of invasive oral procedures. The KCOTs present in the son displaced at least one tooth into the child's orbit, though with removal of the cyst and with braces it was brought back into the oropharynx proper. Much like the cases previously reported, the occurrence of new KCOTs subsided as he approached the end of his third decade. This family holds true to the generalization that complications within NBCCS families are relatively similar throughout generations.

Our patient, much like her mother, was affected only by the cutaneous manifestations of the disease, demonstrating the classic palmar-plantar pitting seen in anywhere from half to three-quarters of patients (Figures 1-4). She also had multiple BCCs over her body surface, classically in areas unexposed to the sun (Figures 3-10). Interestingly, these palmar-plantar pits, as well as the KCOTs that commonly develop in these patients, are unlikely to transform into malignant lesions.

Initially, the patient was treated with 0.1% Differin cream at night along with the systemic retinoid acitretin. Over time, the patient felt Differin cream was ineffective at preventing recurrent BCC lesions. Acitretin was discontinued primarily due to the patient's complaint of xerostomia, a known side effect of retinoids. Other treatments attempted before reaching
Table 1
Musculoskeletal and other physical malformations associated with NBCCS.

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<th>Musculoskeletal Malformations</th>
<th>Abnormal Cutaneous Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal/temporal bossing</td>
<td>Facial milia</td>
</tr>
<tr>
<td>Prognathism</td>
<td>Comedonal lesions</td>
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<tr>
<td>Cardiac fibroma</td>
<td>Epidermal cysts</td>
</tr>
<tr>
<td>Keratocystic odontogenic tumors</td>
<td>Fibromas</td>
</tr>
<tr>
<td>Bifid/splayed ribs</td>
<td>Lipomas</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>Café au lait spots</td>
</tr>
<tr>
<td>Cervical/thoracic vertebral anomalies</td>
<td>Numerous pigmented nevi</td>
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<tr>
<td>Spina bifida</td>
<td>Hypertrophic ectopic calcification</td>
</tr>
<tr>
<td>Marfanoid syndrome</td>
<td>Palmar/plantar pits</td>
</tr>
<tr>
<td>Pectus excavatum</td>
<td>Misc. Other Manifestations</td>
</tr>
<tr>
<td>Pectus carinatum</td>
<td>Ovarian fibromas</td>
</tr>
<tr>
<td>Shortened 4th metacarpals</td>
<td>Hypogonadism</td>
</tr>
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</table>

Table 2

<table>
<thead>
<tr>
<th>Neurologic/Brain Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental retardation</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>EEC abnormalities</td>
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<tr>
<td>Corpus callosum agenesis</td>
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<td>Dural/falx/tentorial calcification</td>
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<td>Congenital hydrocephalus</td>
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<tr>
<td>Nerve deafness</td>
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<td>Medulloblastoma</td>
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</table>

Discussion

As previously stated, there can be numerous findings in NBCCS patients, the most recognizable of which are widespread BCCs and KCOTs. The triad of BCCs, KCOTs, and dural calcifications were concomitantly found in the majority of patients (70.6%) in one 2007 study, making these findings together highly suggestive of NBCCS. Ocular abnormalities present in more than one-quarter of patients, and ovarian fibromas/calcifications present in almost one-quarter of female patients with NBCCS. Recurrent BCCs, with or without palmar-plantar pitting, is highly suggestive of NBCCS.

A patient presenting to a dermatology office may not be innately inclined to report elements of his or her oral and craniofacial medical history. Should there be any question of NBCCS or a history of recurrent BCCs, questioning the patient directly about his or her dental health could prove pertinent. The high incidence of patients with NBCCS presenting with KCOTs (up to 90.5%), and the fact that in one study, 8% of all 83 patients presenting with any number of KCOTs were found to have NBCCS, highlights the need for close monitoring of patients with these oral lesions. Consultation with the patient’s primary dentist is also warranted, as oftentimes a dentist or other oral health care professional is first to discover the signs of NBCCS. In one 2007 study, 24 percent of patients were diagnosed with NBCCS as an incidental finding upon presentation to an oral health clinic. For those patients who presented to a dental clinic in this same study, approximately 75% of patients reported the vague symptoms of swelling, pain, or discharge of the oropharynx. Patients with recurrent KCOTs may find some solace in the fact that the incidence of KCOTs drops off after puberty, though any patient with NBCCS has an increasing risk for the development of an initial KCOT as he or she ages. Patients can be assured that while the oral neoplasms have potential to be disfiguring if not treated early, there is little or no concern for malignant transformation of the cysts. Any patient who
patients with medulloblastomas, suggesting this group has a predilection for developing mental retardation. Any NBCCS patient has a 5% lifetime risk for developing a medulloblastoma.\(^3\)

As with any inheritable genetic disorder, genetic counseling should be discussed with NBCCS patients. The primary focus should center on the fact that a child with one parent known to have NBCCS has a 50% chance of developing NBCCS in his or her lifetime, and the complications of NBCCS tend to be similar within families, as already discussed.\(^3\) Patients who ultimately choose to have children should be reminded of the importance of regular checkups and sun protection.

**Treatment and Prevention**

In the review of current literature, it is apparent there are many approaches for the long-term treatment and management of NBCCS, though there seem to be few reports of trichloroacetic acid used prophylactically. The treatment regime chosen for any particular patient will be highly dependent upon physician knowledge, skill and comfort, available options, cost and insurance coverage of specific treatment options, and the individual desires of the patient. Treatment will be lifelong; therefore, any treatment should have the patient’s full support so that compliance is not an issue.

If we look at the treatment etiology of NBCCS as no different than the treatment etiology of spontaneous BCCs unrelated to NBCCS, as their histologic appearance and pathologic progression are essentially the same,\(^4,11\) then differing therapies can be assessed. Recurrence at a site of a previous BCC is considered to result from incomplete removal of the initial neoplasm. In the case of sporadic BCCs, methods that produce lower recurrence rates are considered more successful at fully excising or otherwise completely resolving the neoplasms. In comparing these therapies, however, it is important to remember that recurrent BCCs are to be expected in NBCCS regardless of the chosen therapy.

In treating BCCs curettage alone has reportedly been similarly effective to curettage with electrosiccation,\(^2\) with curettage alone having the advantage of being less likely to cause hypertrophic scarring (see Table 2). In the non-randomized clinical trial of 204 patients in the paper by Rodriguez-Vigil et al., a recurrence rate as low as 1.2% at five years for patients treated with curettage and electrodesiccation was reported. It is important to note, though, that in this achievement of such a low recurrence rate, all patients studied were treated by the same physician, who had over 30 years experience.\(^15\)

Mohs surgery achieved recurrence rates as low as 1.4% at five years for primary BCCs in a study of over 1,800 Australian patients.\(^4\) Mohs surgery has also proven highly effective in the treatment of patients with established histories of recurring BCCs, with subsequent recurrence rates of 4% after surgery (patients numbered 1,484).\(^13\) Regardless of whether the lesions were primary or recurrent, Mohs surgery had an overall recurrence rate of less than 3% in an Australian study of more than 3,000 patients.\(^14\) Surgical procedures on any NBCCS patient should be limited, as these patients will be treated for recurrent BCCs throughout their lives (for an example of a primarily surgical approach to the initial treatment of NBCCS in a 32-year-old female, read the article by Doctoroff et al.).\(^15\)

Intravenous interferon and immunoglobulin agents may also be used off-label in the management of BCCs, with complete responses commonly greater than 60% and reportedly as high as 100% (see Smith et al. for more detailed information and summary of multiple studies).\(^16\) And, of course, imiquimod 5% cream may also be used open-label in the treatment of BCC, with similar success to the topical interferon agents.\(^15,17,18\) A 64% confirmed histopathological clearance of BCCs was reported in one 2007 study utilizing 5% imiquimod cream.\(^19\) One case study reported successful prophylactic treatment of a 25-month-old with the combination treatment of 5% 5-FU cream and 0.1% topical tretinoin cream.\(^19\)

Anatomic location is always an important factor in choosing any form of dermatological treatment, and this is no different for patients with NBCCS. The literature on the specific use of trichloroacetic acid chemical peels for the prophylactic treatment specifically of BCC is sparse. However, one randomized, prospective five-year study comparing the incidence of non-melanoma skin cancers (NMSC) between controls and three different treatment modalities, including topical 5-FU, 30% topical trichloroacetic acid, and CO\(_2\) laser resurfacing, determined all three were equally effective, but the application of 30% trichloroacetic acid once a month had the lowest NMSC incidence per patient years as compared to the other two modalities\(^16\) (see Table 2). The authors also reported patients preferring chemical peels to 5% 5-FU due to the once-a-month application, reduced cutaneous irritation, and rapid recovery times.\(^20\) Both the trichloroacetic acid group and the 5% 5-FU group had only a single incidence of squamous-cell carcinoma (SCC), and neither group had any incidents of primary BCC.\(^20\) The CO\(_2\) laser group, however, developed three primary BCCs in three different patients.\(^20\)

Doctoroff et al. chose to use combination therapy in a 32-year-old female NBCCS patient presenting with approximately 45 BCC lesions on her face.\(^13\) Full-face CO\(_2\) laser resurfacing was chosen as her primary...
treatment modality for these lesions.15 While she had complete facial re-epithelization at one month, at two months two BCCs developed on her face (subsequently treated with Mohs surgery), and four additional BCC neoplasms developed at 10 months (also subsequently treated with Mohs surgery).15 In another paper by Iyer et al. in 2004, 23 patients treated with multiple-pass UltraPulse CO\textsubscript{2} laser resurfacing had a BCC recurrence rate of 3.2% (two patients) within 36 months.21 Additional studies question the effectiveness and utility of CO\textsubscript{2} laser resurfacing in the treatment of BCCs,22 some reporting rapid development of NMSC after laser resurfacing,15,22,23 while still others are inconclusive or supportive.15,22,23 It should be noted that most of the studies discussing laser resurfacing hold little or no discussion of sunscreen utilization by the patients after the procedure, excluding Fulton et al., which does state a moisturizer with SPF-34 was used post-resurfacing.5,22-24 Fulton et al. theorized the ineffectiveness of laser resurfacing may be attributable in part to its precise nature of penetration, which does not penetrate any deeper at pre-malignant sites, which generally have greater depth than surrounding tissue.23 Cryosurgery can also be highly effective in the treatment of BCCs, provided proper selection of candidates and adequate procedures are undertaken. In the treatment of one series of 552 BCC lesions, Kuflick had a recurrence rate as low as 1.2% at five years.25 In the treatment of over 4,400 NMSC lesions, of which nearly 4,000 were BCCs, Kuflick reported a total cure rate of 98.6%.25 The success of his treatments is likely due to his strict implementation of technique.

Photodynamic therapy uses topically applied chemicals that are activated by light to kill superficial tissues. Its success in the treatment of BCCs has been variable, and there is a trend toward more effective treatments for superficial lesions.26-29 The cosmetic outcome with the use of photodynamic therapy has generally been described as good to excellent.26-29 Though not referenced here, both topical and systemic retinoids may be used in the management of NBCCS patients.30 The side effects of retinoids should, of course, be discussed with patients ahead of time. They commonly include: cheilitis, dry mucosa, xerosis, retinoid-induced dermatitis, enhanced granulation tissue, body stiffness, and hyperlipidemia. Retinoids are not generally considered to be a primary treatment for NBCCS, but they may have significant adjunctive benefits.30-33 In one twin study from 1989, with one twin on...
Table 2 summarizes the benefits and consequences, in very general terms, of the different treatments discussed in regard to managing BCC lesions. Some of these studies address the management of BCCs in NBCCS patients, while others only address the treatment of BCCs from non-hereditary causes. We are allowed to compare these two different BCC etiologies only because their histopathologic progression and description is indistinguishable from one another. We were unable to find any large-scale comparative studies specifically addressing the use of trichloroacetic acid chemical peels in managing BCC lesions in NBCCS patients. The only other discussion we found concerning trichloroacetic acid chemical peels specifically in the management of BCC lesions in NBCCS patients was a case reporting of a 76-year-old woman by the Japanese authors Kaminaka et al., from the Department of Dermatology of Wakayama Medical University in Japan. 

This patient presented to the authors with multiple BCC lesions ranging from 3-50 mm in diameter. She was treated three times in one month using a combination of 60% trichloroacetic acid and phenol chemical peels. She was followed up at one-year with complete resolution. At two years, additional biopsies from previous BCC sites demonstrated no recurrence. However, as promising as these results might sound, the diagnosis of NBCCS in this patient was based on skin biopsies and the concomitant presence of dural calcifications confirmed by X-ray only. There was no family history with this patient, which is rarely the case with NBCCS as it is a genetically inheritable disorder, and the authors failed to report when the BCC lesions first began to arise.

The fact that there were no new BCC lesions reported in the two-year interim without continued therapy makes it highly doubtable that this patient suffered from NBCCS. Her age alone can easily account for both the multiple BCC lesions and dural calcification, both of which are much more common in the elderly. We would like to have more data supporting the use of trichloroacetic acid chemical peels for both treatment and prophylaxis of BCCs in NBCCS, but studies and case reports on the subject are sparse.

Compared to the raw data presented in Table 2, trichloroacetic acid has the lowest recurrence rate for the treatment of BCCs; however, the largest limitation is the small number of patients, just 10, treated in this manner. The benefits of choosing a regime of trichloroacetic acid is its easy application, infrequent application (in our case, every six to eight weeks), little to no scarring, as result of treatment, and compliance outside the office visit is not an issue. The drawbacks to trichloroacetic acid chemical peels as treatments for BCC are cost, which may not be covered by insurance; and while there are limited studies proving trichloroacetic acid as highly effective in treating primary BCCs, there are no large-scale studies supporting its use in BCC caused by NBCCS.

Curettage with electrodessication (ED) and cryosurgery have recurrence rates as low as 1% in the treatment of BCC lesions at five years. Both are inexpensive and easy to administer and generally cause minimal or no scarring. Studies proving the effectiveness of using cryosurgery alone as treatment for BCC lesions are limited. Both treatments can be considered in treating NBCCS patients, but it must be remembered that any NBCCS patient will have recurrent BCC lesions throughout his or her lifetime, and as such even a small potential for scarring can have significant cosmetic consequences over time. Curettage with or without ED can have recurrence rates as little as 3.0% or as high as almost 20%, with a mean of approximately 8.0% at five years.

The data used to generate this information comes from a review of literature over the course of several decades from 10 different studies in which the skill level of the physicians involved is highly variable. As such it is difficult to accurately interpret whether curettage alone should be the sole treatment choice as there is a high degree of variability in outcomes.

Five percent 5-FU cream, double-pass CO2 laser resurfacing, and INF/immunoglobulins may also be used as treatment options. Both 5-FU cream and CO2 laser resurfacing have recurrence rates of less than 0.21%, but the small number of patients treated with these methods in this review does not allow these two treatments to be considered conclusively effective. 5-FU has the benefit of being easy to administer and results in essentially no scarring. While CO2 laser resurfacing seemingly has a low recurrence rate, it is also a much more invasive and expensive modality that some studies suggest may actually increase the recurrence rate of BCCs. INF and immunoglobulins may be easy to administer and result in little scarring, but their clinical outcome is also highly variable, and the medication is expensive. While INF and immunoglobulins are not ruled out in the treatment of BCCs in NBCCS, it is questionable to use them as a first-line treatment when compared to the alternatives.

Mohs surgery has a great deal of data supporting it as an effective treatment with low recurrence rates of primary BCCs. However, due to the nature of continued BCC lesions expected in NBCCS, relying solely on Mohs surgery for long-term treatment seems a poor choice despite good expected cosmetic outcomes for single surgeries. Additionally, Mohs surgery is not readily available in many areas and is much more expensive than other treatment choices that have good results. What Mohs surgery has over most of the other treatment modalities is large-scale studies proving its effectiveness in the treatment of primary BCCs.

### Conclusion

More data is needed before trichloroacetic acid and other topically applied medical treatments can be conclusively determined to be beneficial in the treatment of BCCs in NBCCS. However, there is enough evidence to support the use of some of these treatments in the management of NBCCS. Which modality is chosen will be determined by the clinician’s experience and skill, the patient’s insurance coverage, local availability, and the patient’s acceptance of various cosmetic outcomes. It was our decision to treat our patient with a once-a-month, topical treatment of trichloroacetic acid. In our case the concentration used to treat our patient was considerably higher than in previous studies already mentioned. The patient was started at a lower concentration of trichloroacetic acid and gradually titrated up to higher concentrations (50-70%) as tolerated. Given our success in the prophylactic prevention of hereditary BCCs and the apparent success of other authors in the treatment of primary BCC lesions using the application of trichloroacetic acid once a month, or every six to eight weeks, we suggest this trichloroacetic acid peel be considered in the management of all NBCCS patients afflicted with the cutaneous manifestations of the disease.

62 CLASSIC PRESENTATION OF NEVOID BASAL CELL CARCINOMA SYNDROME IN A 49-YEAR-OLD FEMALE
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A 58-YEAR-OLD FEMALE WITH A HISTORY OF RENAL TRANSPLANT AND MULTIPLE NON-MELANOMA SKIN CANCERS, RECENTLY DIAGNOSED WITH MERKEL-CELL CARCINOMA

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* Second-year Resident, Genesys Regional Medical Center, Grand Blanc, MI, Michigan State University Statewide Campus System
**Program Director, Genesys Regional Medical Center, Grand Blanc, MI, Michigan State University Statewide Campus System

ABSTRACT

Solid-organ transplant recipients comprise a growing population at high risk for cutaneous neoplasms resulting in significant morbidity and mortality. Non-melanoma skin cancer accounts for 90% of all skin cancer in transplant patients, with squamous-cell carcinoma being the most common by far, occurring 65 times more frequently than basal cell and 10 times more frequently than in the general population. Other types of skin cancers such as Merkel cell, AFX, angiosarcoma, venous carcinoma, and CTCL are thought to have a higher incidence as well, although the actual numbers are not known because the data is based solely on anecdotal reports. These skin cancers are more aggressive in transplant patients, with a higher frequency of local recurrence, metastasis, and mortality. We present a case of a 58-year-old female with a history of multiple SCCs and a recent diagnosis of Merkel-cell carcinoma as well as a literature review of squamous-cell carcinoma in transplant patients.

History and Clinical Presentation:

We present the case of a 58-year-old female who first presented to our office two years ago with multiple actinic keratoses on her extremities, some of them thickened with cutaneous horns, and some lesions suspicious for Bowen’s disease. She has a history of renal transplant in 2000 for focal segmental glomerulosclerosis, and her medications include cyclosporine150mg qd, mycophenolate mofetil 500mg bid, and prednisone 5mg qd. She has blond hair, blue eyes, and a prior history of sun exposure but no previous diagnosis of skin cancer. She has been in good health otherwise, and her past medical history includes controlled hypertension and hyperparathyroidism. Her graft status has been excellent, with a stable creatine and transplant surgeon.

The patient follows up on a regular basis with our office, every two to three months, for surveillance and treatment and has done so for the past two years, often with a clinical presentation similar to the one described above. Recently she presented with a different-appearing lesion involving the dorsal web space of the right hand, which is described in greater detail below.

Physical Exam:

There are multiple erythematous, hyperkeratotic lesions involving the sun-exposed surfaces of her extremities, some of which have cutaneous horns (Figure 1). There is a field effect of sun damaged skin involving the sun-exposed surfaces of her integument. She also has multiple well-healed surgical scars from previous excisions.

The nodule of her right hand measures 1.6cm and involves the dorsal web space of the 2nd and 3rd metacarpal. It is freely movable and does not appear fixed to any underlying structures (Figure 2).

Lymphatic exam failed to reveal any adenopathy.

Dermatohistopathology:

Many biopsies of her extremities have been performed over the two years we have been following her, and they have revealed numerous occurrences of squamous-cell carcinoma in situ. She did have one incidence of a well-differentiated, invasive squamous-cell carcinoma as well.

The lesion from her hand shows irregular sheets and cords of hyperchromatic cells within the dermis. The cells have relatively uniform size, round to ovoid in shape, with scant cytoplasm and fine dusky chromatin. Mitotic figures are quite abundant. Immunohistochemical stains are positive for pancytokeratin and synaptophysin, and show perinuclear, globular-appearing dot-like positivity with Cytokeratin 20. This is consistent with Merkel-cell carcinoma (Figures 3, 4, 5, 6).

Therapy and Course:

The patient’s therapy for her actinic keratoses, squamous-cell carcinoma in situ, and invasive SCC has been largely surgical, with electrodestruction and curettage, excision, and cryosurgery (for AKs). In total, she has had approximately 40 cancerous and pre-cancerous lesions removed by our office. She had been on topical 5-FU prior to her presentation to our office, and the large surface area of damaged skin limited the tolerability. We will likely proceed with long-term systemic retinoid therapy pending approval from her nephrologist.

Upon the diagnosis of the Merkel cell, she was sent to the Merkel-cell clinic at University of Michigan, where she underwent successful, wide local excision of the lesion with split-thickness skin-graft coverage. The sentinel lymph node study was negative, and she is continuing to progress in her recovery.

Discussion:

Solid-organ transplant recipients (OTRs) comprise a growing population at high risk for cutaneous neoplasms resulting in significant morbidity and mortality. There were 25,000 solid-organ transplantations performed in the United States in 2003,1 and this number continues to increase as techniques are refined and postoperative management improves. Non-melanoma
skin cancer (NMSC) accounts for 90% of all skin cancer in transplant recipients. There is an inversion of the normal basal-cell carcinoma (BCC) to squamous-cell carcinoma (SCC) ratio, which is four to one in non-immunosuppressed patients. In transplant recipients, SCC occurs 65 times as frequently as in the general population, and BCC is increased by a factor of 10. The cumulative incidence increases with number of years post-transplantation, from 7% after one year of immunosuppression, to 45% after 11 years, to 70% after 20 years as shown in an Australian study. These squamous-cell carcinomas are more aggressive, with a high frequency of local recurrence (13.4%) during the first six months after excision, and lymph node metastasis (7%) during the second year after excision. SCC is a significant source of mortality, with 5.2% of OTRs in one series dying from skin cancer, 63% of which were SCC. There is also a suspected role for HPV, specifically types 5 and 8, in the development of SCC in transplant recipients as it is found at a higher frequency in this population.

Risk factors associated with the development of NMSC in transplant recipients include increased age, exposure to ultraviolet radiation, increased amount of immunosuppression, Fitzpatrick skin types I-III, prior history of AKs, NMSC, or melanoma, and HPV infection. Heart transplants have the highest risk of NMSC, followed by kidney and then liver.

Other types of skin cancer are also at an increased risk. There is a 3.8- to 5-fold increased incidence of de novo melanoma after transplantation. Kaposis sarcoma has been shown to have an 84-fold increased incidence in OTRs. Merkel-cell carcinoma also appears to be more common, as well as atypical fibroxanthoma, angiosarcoma, verrucous carcinoma, leiomyosarcoma, and cutaneous T-cell lymphoma. No large-scale studies have been performed on these diseases, thus the actual incidence is unknown because the data is based solely on anecdotal reports.

The most important elements in the preventive management of skin cancer in transplant patients are patient education, rigorous sun protection, and a multidisciplinary approach to patient care.

Application of prophylactic topical retinoids or episodic 5-FU may be warranted in patients who develop multiple AKs or NMSC. Five percent imiquimod cream appears safe on skin surfaces up to 60cm2 in renal transplant patients, and a small study of 14 patients suggested a possible reduction in SCC. Other potential chemopreventative agents include difluoromethylornithine (DFMO) and cyclo-oxygenase-2 (COX-2) inhibitors, although controlled clinical-trial data is lacking. The medications 5-fluorouracil, cisplatin, bleomycin, doxorubicin, and methotrexate all show activity against NMSC, but data on their use has been limited to treatment of existing aggressive or metastatic disease rather than for prophylaxis in OTRs. Resveratrol, perillyl alcohol, green and black tea polyphenols, and black tea theaflavins have been suggested to have chemopreventative activities, but there is little in vivo data on their use in prevention or management of NMSC.

Merkel-cell carcinoma is a rare skin neoplasm originally described by Toker in 1972. It is an aggressive tumor characterized by frequent relapse and an overall mortality rate of 35%. There have been between 500 and 1,000 reported cases in the literature, and it is thought that transplant patients are at increased risk because of immunosuppression. A study of Merkel cell in 41 transplant patients showed that compared to non-immunosuppressed patients, many were younger (29% < age 50), 68% had nodal disease present at diag-
nosis (30% in non-immunosuppressed), and consequently 60% died of their disease (35% in non-immunosuppressed). Treatment in transplant patients is no different than in the general population and depends on the stage of the disease. This includes wide surgical excision, MOHS surgery, sentinel lymph node biopsy, radical lymph node dissection, radiation therapy, and chemotherapy.

In summary, there is a large and ever-increasing population of solid-organ transplant patients who are on chronic immunosuppression. Skin cancer, especially squamous-cell carcinoma, is more frequent, more aggressive, and has higher rates of metastasis in this population. There should be a low threshold for biopsy of suspicious lesions. Early and aggressive surveillance and treatment is needed, as is vigorous sun protection and patient education. This can be optimized using a multidisciplinary approach utilizing dermatologists, dermasurgeons, transplant teams, nephrology, cardiology, and hepatology.

References:
One less battle in the fight against acne
Answer irritation with hydration —Duac® Care System (CS)

Irritating acne treatments can discourage compliance

- Increasing irritation correlates with increasing transepidermal water loss (TEWL)
- Poor compliance has been reported to be the most common cause of nonresponse to acne medication

Duac® CS is designed to minimize irritation

- Duac® Topical Gel is unique acne medication because it contains 1% dimethicone and 4% glycerin
- With its unique hydrating vehicle, Duac® Topical Gel significantly reduces TEWL ($P = .0193$)

Patients agree, Duac® Topical Gel delivers impressive results

- Significant improvement in acne grade began as early as week 1 ($P = .013$) and continued throughout the study ($P = .038$)
- At 12 weeks, ~90% of patients using Duac® Topical Gel ($n=65$) agreed with physician assessment that their acne was improved

DUAC Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Important Safety Information

DUAC Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops.

Side effects may include erythema, peeling, burning, and dryness.

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

References:


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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

For Dermatological Use Only. Not for Ophthalmic Use. Rx Only

**INDICATIONS AND USAGE**

Duac® Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

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

**CONTRAINDICATIONS**

Duac® Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to clindamycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

**WARNINGS**

**Oral and Parenteral Administration of 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. Patients with a history of pseudomembranous colitis, or antibiotic-associated colitis, should have the diagnosis of colitis confirmed before using Duac® Topical Gel. Stool culture for Cl. difficile will confirm the diagnosis.

**Pregnancy**

There are no adequate and well-controlled studies in pregnant women. Use in pregnancy should be reserved for those in whom, in the opinion of the physician, the potential benefit justifies the possible risk to the fetus.

**Lactation**

It is not known whether Duac® Topical Gel is secreted into human milk after topical application. Because many drugs are excreted in human milk, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in this product in pediatric patients below the age of 12 have not been established.

**ADVERSE REACTIONS**

During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on a 5-point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

<table>
<thead>
<tr>
<th>Local reactions with use of Duac® Topical Gel</th>
<th>% of patients using Duac® Topical Gel with symptom present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment (Baseline)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Erythema</td>
<td>28%</td>
</tr>
<tr>
<td>Peeling</td>
<td>6%</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Percents derived by # subjects with symptom scored enrolled Duac® Topical Gel subjects, n = 397).

**NASAL LOOPS**, as well as allergic reactions leading to hospitalization, has been reported in post-marketing use with Duac® Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate a causal relationship to drug exposure.

**HOW SUPPLIED**

Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in:

- 4 gram tube
- 4 gram tube
- 4 gram tube
- 4 gram tube
- 4 gram tube

**Care System Kit** includes Duac® Topical Gel (clindamycin, 1% - benzoyl peroxide, 5%) 4 gram and SFC®rolen 106 ml (93 FL Oz)

Prior to Dispensing: Store in a cold place, preferably, in a refrigerator, between 5°C and 8°C (41°F and 46°F). Do not freeze.

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

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

U.S. Patent No. 5,665,446

Patent Pending

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**STIEFEL**

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01135 Rev. July 2008

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Morphea is the term used to describe the clinical entity that presents as an erythematous-to-violaceous patch or plaque that evolves into a firm, indurated lesion. Histologically, morphea can closely mimic lesions of systemic sclerosis (scleroderma), but can be differentiated by certain features upon examination. The presence of Raynaud’s phenomenon, digital sclerosis and internal organ involvement, namely pulmonary or GI tract, in systemic sclerosis helps to make the clinical differentiation from morphea. In addition to the classical plaque-type morphea, other variations exist. Some of these variations include linear, guttate, generalized, deep or subcutaneous, superficial, keloidal, bullous and sclerodermaid inflammatory disorders. In this paper, we describe a case of unilateral generalized morphea in a healthy Caucasian adolescent.

Case Report

An 11-year-old Caucasian female presented to the outpatient resident dermatology clinic with her mother for a chief complaint of purple spots on her body. She stated that the spots had been present for approximately five years and had been previously diagnosed as “bruises” and “birthmarks.” She denied any symptoms of pain or pruritus in the lesions, but revealed that new lesions were still appearing over recent months. Her past medical history was only significant for recently (within the previous year) diagnosed hyperlipidemia, which she has been on lovastatin for three months, and multiple upper respiratory infections as a young child requiring a tonsil and adenoidectomy and placement of tympanostomy tubes. She denied any symptoms of dysphagia, Raynaud’s phenomenon or restriction of motion (she plays softball in a league without any limitations).

Physical exam revealed a healthy appearing, mildly overweight young female in no distress. Numerous violaceous patches and plaques with very slightly erythematous borders were noted on her right upper extremity, right chest and abdomen, right lower extremity, right groin and right lower back and buttock. Her face, scalp, palms and soles and left side of her body were spared. There was a sharp cutoff at the midline between involved skin and non-involved skin (Figs. 1-3). Scattered plaques on her right abdomen and right volar forearm showed moderate induration; the other areas were atrophic. No incidence of telangiectasia, dilated nail fold capillary loops, digital sclerosis or Raynaud’s phenomenon was noted. Full range of motion of all extremities without discomfort was demonstrated.

A 4 mm punch biopsy was taken from an indurated area on her right abdomen. Histological examination revealed a deep perivascular and interstitial mixed-cell infiltrate of lymphocytes and plasma cells concentrated in the lower two-thirds of the dermis and subcutaneous fat. Dermal edema was noted, as well as a subtle alteration in collagen bundles (Figs. 4-5). A Verhoeff van Gieson stain showed preservation of elastic fibers and accentuated the subtle sclerosis of the lower dermal collagen bundles (Fig 6).

Laboratory workup revealed normal chemistries and normal hematology. Calcium level was 10.7 mg/dl (range: 9.0-10.6), and lipid levels were moderately elevated: total cholesterol 231 mg/dl (range: 0-199), LDL 155 mg/dl (range: 0-99), triglycerides 204 mg/dl (range: 40-149) and HDL 36 mg/dl (range: 40-59). Antinuclear antibody (ANA) was negative (<1:40), as was the Scl-70 antibody. Erythrocyte sedimentation rate was 13 mm/hr (range: 0-20).

Treatment with super-high potency corticosteroid ointment was started on the most indurated lesions. This treatment was gradually reduced to a mid-potency corticosteroid ointment and finally to a combination of tacrolimus 0.1% ointment at bedtime and calcipotriene 0.005% cream in the morning. Due to the mostly symp-
asymptomatic nature of the problem, systemic options such as prednisolone, PUVA and methotrexate were withheld at the time. Since being on topical therapy, the patient has not seen any new lesions, and her previous lesions have become much less indurated. She is being followed by her pediatrician for her hyperlipidemia.

Discussion

Morphea is a relatively uncommon condition, affecting approximately 27 per million persons annually, with women representing the majority of cases (almost 3:1 over men).1 Children under the age of 18 are commonly affected, with the localized plaque and linear types being the most common variants reported.2 Generalized morphea, especially in a unilateral distribution, is a rarely reported entity. Naga1 et al. reported the first case of unilateral generalized morphea in a 6-year-old Japanese boy in 2002.3 Their patient showed involvement of the right side of his body with indurated plaques, but no evidence of systemic involvement. Laboratory evaluation was positive for a mildly elevated ANA titer (1:320) and a positive anti-SS DNA; all other labs were within normal limits. Topical steroid therapy was initiated, and softening of the lesions was noted over a period of 10 months.

Appelhans et al. published a case series of four patients with unilateral generalized morphea.4 In their article, they detail four cases, all women between the ages of 14 and 38 with a history of long-standing disease. In each case, lesions had been present for more than five years; in one patient, lesions began at the age of four. Key characteristics of each case included: right-side only involvement in three of four cases (the other case showed left-side involvement), significant elevation of ANA titers in all patients, and varying degrees of sclerosis and contractures affecting range of motion. As treatment for these more severely affected patients, the authors used a combination of pulsed dose IV prednisolone, low-dose methotrexate and UVA1.

The etiology of the unilateral nature of these lesions is still undetermined. Current theories include: a developmental anomaly showing a Blaschkoid distribution, or inflammatory involvement along a nerve segment.5,4 Serum tests that are commonly elevated in generalized morphea include ANA and anti-SS DNA, with the latter being more indicative of severe disease.5

Treatment of generalized morphea is dependent on the severity of symptoms. Asymptomatic, non-disabling lesions can be treated conservatively: topical corticosteroids, calcipotriene cream/ointment,6 calcineurin inhibitors,7 PUVA/UVA1/ NB-UVB light therapy,8,9 or simple “active non-intervention,” as many cases are known to resolve spontaneously. When lesions are symptomatic, impair motor function or involve areas that are important for everyday functioning, systemic treatment is warranted. Current systemic treatments that have showed promise include: methotrexate,10 pulsed dose IV prednisolone,4 UVA phototherapy, penicillin antibiotics/ penicillamine11 and physical therapy.

In summary, we have presented a case of unilateral generalized morphea in a child as an unusual variant of localized scleroderma. Due to the relatively asymptomatic nature of our patient’s disease, local topical therapy was initiated with acceptable results. The finding of hypertriglyceridemia and hypercholesterolemia has not been previously reported as a co-existing morbidity with generalized morphea as was seen in our patient. Whether or not this is simply a coincidence or a marker of an increased systemic inflammatory response needs to be determined, and further investigation is warranted.

References:
Urticaria in Eastern Saudi Arabia

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ABSTRACT

Objective: To study the pattern of urticaria in Eastern Saudi Arabia

Method: The data of patients clinically diagnosed as urticaria seen in the Dermatology Clinic, King Fahd Hospital of the University (KFHU), Al-Khobar, between January and December 2005, was analyzed using SPSS package program.

Results: 51 patients (28 males, 23 females; ages between 3 and 60 years) were seen with an occurrence rate of 43%. The male-female ratio was 1.2:1. The clinical pattern of urticaria was as follows: chronic idiopathic 16 (31.4%), chronic with identifiable/detectable causes 10 (19.6%), physical 12 (23.5%), acute with detectable cause 8 (15.7%), acute idiopathic 4 (7.8%), other urticaria disorders 21 (41.2%) patients.

Conclusion: Urticaria is not uncommon in Saudi Arabia. A high consanguinity rate among parents may account for the increased frequency of allergic disease in our patients. A possible etiology was identified in 35.3% of our cases and suggests thorough history and physical examination supported by investigation for causes of chronic urticaria.

Key words: Urticaria, Saudi Arabia, angioedema, consanguinity, investigation

Introduction

Urticaria is a cutaneous vascular reaction characterized clinically by the appearance of evanescent itching wheals. It presents as erythematous, elevated, edematous plaques surrounded by flares. Each new lesion usually lasts for a few hours, but not more than 24 hours. It may be replaced by new crops of similar eruptions recurring for a few days, weeks, months and even years. Subcutaneous and mucosal swelling, particularly involving the lips, eyelids, hands and feet, may accompany the cutaneous findings. In severe urticaria, the affected person may complain of abdominal pain and respiratory distress due to the involvement of mucous membranes of the gastrointestinal and respiratory tract.1,2

Urticaria has diverse clinical presentations and causes, and it can be broadly classified as spontaneous urticaria and physical urticaria. Spontaneous urticaria may present as acute, where the wheals recur daily for a few days or weeks but not more than six weeks, or as chronic when the wheals persist beyond six weeks. Physical urticaria may be due to exposure to cold, heat or sun, or due to trauma (delayed pressure, vibrations and dermographism). There may be other unclassified variants like aquagenic urticaria, contact urticaria, cholinergic urticaria and exercise-induced urticaria.3,4

Regarding the pathophysiology, urticaria may be mediated by type-I allergy reactions, IgE reactions, and type-III allergic reactions, where immune complexes (IgG, IgM and antigens) are deposited into blood vessel walls. The triggering factors for such allergic reactions may be food, food additives, drugs, infections, etc. Sometimes urticaria may not be related to allergy, but rather to a direct effect of the agents, causing release of histamine from the mast cells, e.g. plants (nettles and strawberries), animals (caterpillars, jellyfish and lobsters), chemicals (cinnamic aldehyde, dimethylsulfoxide [DMSO]) and medications (aspirin, morphine, codeine, polymyxin, etc.).3,4 Urticaria may also appear as an associated or a preceding symptom of a systemic disease, including autoimmune diseases (Hashimoto’s thyroiditis, systemic lupus erythematosus, scleroderma, dermatomyositis and rheumatoid arthritis), thyroid disease, malignancies (reticuloses and lymphomas) and some rare urticarial syndromes (Muckle-Wells syndrome and Schnitzler syndrome).3,4

The aim of this study is to document the pattern of urticaria in Eastern Saudi Arabia.

Methods

All patients with the diagnosis of urticaria and/or angioedema who attended the outpatient department of Dermatology Clinic at King Fahd Hospital of the University (KFHU), Al-Khobar, between January and December 2005, were included. The clinical types of urticaria were diagnosed based on history alone.

The obtained data was collected in a data entry form and statistically evaluated using the Statistical Package for Social Sciences (SPSS), version 11.5.

Results

Of 1,188 new patients seen in the Dermatology Clinic of the KFHU, Al-Khobar, during the study period, 51 had a confirmed diagnosis of one of the clinical types of urticaria, giving an occurrence rate of 43% in new dermatology patients in one year.

Twenty-eight (54.9%) were males and 23 (45.1%) females, giving a male to female ratio of 1.2:1. Forty (78.4%) were Saudi nationals, and 11 were non-Saudis (21.6%). The age at onset ranged between 3 and 60 years, with an average age of 27.3 years at onset. Consanguinity among the parents of the patients was observed in 20 (39.20%). None of 51 patients (17.6%) had a positive family history of atopic dermatitis or other allergic diseases (Table 1). These findings were based on detailed history and physical examination supported by laboratory investigations when needed. Of the acute urticaria with identified causes, in five patients history alone was enough to identify the cause, while in three patients, laboratory investigations were needed. Only three patients with chronic urticaria were diagnosed based on history alone.

The clinical types of urticaria are shown in Table 2; chronic idiopathic urticaria was found in 16 patients (31.4%). Repeated investigations did not reveal any obvious cause or specific allergen. Acute idiopathic
urticaria was found in four patients (7.8%). Detailed history, physical exam and investigations did not reveal any obvious cause or specific allergens. Chronic urticaria with a detectable cause was found in 10 patients (19.6%). The details of the causes were as follows: three due to food allergens; one with Hashimoto’s thyroiditis; one due to inspired airborne allergens; two due to intestinal parasites (positive stools for ova and parasites); one with internal malignancy; and two with chronic peptic ulcer disease with positive Helicobacter pylori.

Acute urticaria with a detectable cause was found in eight patients (15.7%), with details as follows: three due to drugs (Penicillin 1 and Nonsteroidal anti-inflammatory drugs (NSAIDs) 2); two due to food allergens (one to nuts, one to eggs); two due to viral infections (hepatitis B and acute respiratory viral infection); and one due to bacterial infection (β-hemolytic streptococcal tonsillitis). Angioedema was found in 17 patients (33.3%). In most of the cases, 18 out of 21, angioedema presented as an associated symptom of urticaria, while in three out of 21, angioedema occurred as an isolated finding. Other urticaria disorders were found in 21 patients (41.2%), with the following clinical types: physical urticaria in the form of dermographism in 17 (33.3%), with 11 of those on top of urticaria and six as isolated findings; cholinergic urticaria in two patients; and aquagenic urticaria in two patients.

Besides the classical features of urticaria, the following findings were encountered: co-existing allergic diseases were present in 16 patients (31.4%), including: bronchial asthma in three patients, allergic rhinitis in 10, atopic dermatitis in two, and hay fever in one. There was elevated IgE in 19 patients (37.2%), dyspnea and wheezing in five (9.8%), and arthralgia and/or joint swelling in five (9.8%).

A majority of the treated patients (25, 49%) responded well to H1-antihistamines alone or in combination with H2-blockers. Those who did not respond well even to combination therapy (15 patients, 29.4%) needed various alternative therapies, such as systemic steroids and immunosuppressants. Eleven patients did not receive any treatment.

**Discussion**

Although urticaria is a very common dermatosis that can affect 15%-20% of the population at some time in life, to the best of author’s knowledge there are very few reported studies in the literature from the Middle East. In this study, there was a slight male preponderance (1:2:1). However, in some studies, a significantly higher prevalence of urticaria has been reported in females. This might be related to the male/female proportion in the general population. In Saudi Arabia, there are quite a few male expatriates without their families, which might have influenced the ratio.

In this study, chronic urticaria is more frequent (26, 51%) than acute urticaria (12, 23.5%). In comparison, reports in the literature range from 16%-84%. This is probably because patients with hives of acute urticaria not associated with anaphylaxis may not go to the physician, as has been suggested by Beltrani.22

The causative factors of acute urticaria were found in 15.7% of patients, including: acute viral infections (hepatitis B and respiratory viral infection), hypersensitivity to drugs (penicillin and NSAIDs), food allergy (eggs and nuts), and acute bacterial infection (β-hemolytic streptococcal tonsillitis). These possible causative agents have been reported among causes of acute urticaria.21 Beltran22 found that the cause of acute urticaria is identified by history in the majority of patients. In one study, 63% of patients were suspected to have food etiology, but with thorough investigation, food was found to be the causative agent for acute urticaria in only one out of 109.14

Chronic urticaria with detectable causes was found in 10 patients (19.6%) (three based on history and seven based on investigations). This is in agreement with other studies, which concluded that success of detecting a causative factor for chronic urticaria does not exceed 5%-20%, even with the performance of repeated episodes of sophisticated investigations.17 However, because of patients’ and physicians’ fears, extensive and costly investigations are still recommended by some investigators.19–24 Kozel25 found that in 86% of chronic urticaria, the cause was identified by taking a history. Pseudoallergic reactions to food and food additives have also been reported in the literature: Zuberbier et al.26 reported reactions to food additives in 19% of patients; Pigatto and Valsecchi27 found reactions to food additives in 37%; and another study by Zuberbier et al.26 confirmed the role of aromatic compounds of food as an eliciting factor of pseudoallergic reactions in chronic urticaria. Parasitic infestation was detected in 3.9% of our patients. Parasitic infestation is a relatively rare cause of urticaria in developed countries, e.g. in Northern European countries.19–24 The role of Helicobacter pylori as a possible cause of chronic urticaria has been confirmed in some studies.29–31 The association of thyroid autoantibodies with chronic urticaria has also been documented by some investigators.32–34

Idiopathic urticaria may be due to some unknown abnormality, which can be modified by numerous other factors including allergy.24 The relevance of anti-Fc-εRI-α autoantibodies in the pathophysiology of some urticaria cases has been studied.35–37 These antibodies could be found in idiopathic chronic urticaria patients as well as in patients with pseudoallergy to food whose symptoms cleared on elimination of the causative diet. These autoantibodies have been shown to cross-link the unoccupied IgE-receptors.38,39 Possible explanations for these findings have been suggested by Zuberbier and Maurer.2 First, the Fc-εRI-α autoantibodies are not of pathophysiological relevance in all patients with urticaria, and second, anergy between the autoantibodies and the eliciting stimuli, e.g. food, is necessary for the appearance of clinical symptoms in some patients.3 Histamine-releasing IgG autoantibodies to a subunit of IgE receptors may be found in the circulation of some patients with chronic idiopathic urticaria.2,4 About 30%-40% of patients with idiopathic chronic urticaria have clinically relevant functional autoantibodies to the high-affinity IgE receptor (Fc-εRI-α) on basophils and mast cells; less commonly (about 10%), patients have anti-IgE.40 This subgroup of chronic urticaria is known as autoimmune urticaria. These patients present with highly symptomatic, severe, continuous urticaria associated with systemic symptoms, but without any known cause or physical triggers.

Physical urticaria in the form of dermographism was found in 17 patients (33.3%). Of these, six (11.8%) patients had dermographism as an isolated finding, corresponding to reports in the literature of about 6.2%-10.7%.30,31 Co-existing allergic disease in the form of atopy were found in

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**Table 1**

<table>
<thead>
<tr>
<th>Demographic features of urticaria in Eastern Saudi Arabia</th>
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</thead>
<tbody>
<tr>
<td>SEX</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Number of Patients</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
</tbody>
</table>

(54.0%) | (45.1%) | (78.4%) | (21.6%) | (31.4%) | (7.8%) | (60.8%) | (17.6%) | (82.4%) |
16 patients (31.4%). Buss et al found 23% of his patients with history of atopy, which corresponds to the prevalence of atopic disease in general population. Elevated IgE was found in 19 patients (37.25%) and most of them had acute urticaria. This is less than what has been reported by others. The high consanguineous rate (39.2%) and family history of allergic diseases might have contributed to high rate of coexisting atopic diseases (31.4%).

In all guidelines, intense and costly general-screening programs for urticaria are discouraged. It has been reported that acute urticaria is significantly associated with atopic/allergic disease, and that these patients have a higher incidence of developing one type of urticaria than do normal persons.

In one retrospective study of urticaria and angioedema, 49% of patients had both conditions at the same time, while 40% had urticaria alone and 11% had angioedema alone. Regarding guidelines for the diagnosis of chronic urticaria, angioedema and physical urticaria, a system review by Kozel et al concluded that 10 studies emphasized the importance of history in the diagnosis, 13 studies stated that routine laboratory tests are of little value, and seven studies stated that laboratory tests are only useful if based on history. Five studies stated that routine laboratory screening could be useful.

Conclusion

This study shows that urticaria in not uncommon in Saudi Arabia and has a marginal male preponderance. The high consanguinity among the parents of our patients may account for an increased frequency of allergic diseases in our patients. A possible cause of urticaria was found in 35.3% of our patients. This suggests that the search for a cause of urticaria may be beneficial after detailed history and physical examination. However, it is unnecessary to do costly and invasive investigations for every patient with acute urticaria, unless it is associated with serious systemic manifestations.

References:

Case Report

A healthy 18-month-old African American female with a past medical history for sickle-cell trait presented with a 1.5 cm x 1.0 cm, light brown patch located on her left lower back. Her parents noticed the lesion at birth, and report that it has increased in size. The baby appeared to have no discomfort associated with the lesion. The parents reported seeing a recurrent clear fluid over the lesion that would reappear after being wiped dry. A 4 mm punch biopsy of the lesion was performed and submitted for pathology with a clinical differential diagnosis of benign adnexal tumor vs. plexiform neurofibroma. Histology of the lesion showed hyperplastic ducts.7

Recently, a variant of eccrine nevus was described by Romar and Taira (1994).8 They described a tender, erythematous nodule 1 cm in diameter on the right lower extremity of a 47-year-old female. They described the variant "mucinous eccrine nevus" (MEN).8 Since then, four other reports of MEN have been published. In 2003, Llombert et al. described two brown nodules, 1 cm in diameter, on the buttoc of a two-year-old female. They first occurred at three months of age.9 The lesions were without associated pain or hyperhidrosis.9 In 2004, Park et al. described a firm, tender, erythematous, 2.5 cm x 1.5 cm patch on the dorsum of the left fourth toe of a 46-year-old man, which had been present for one month.10 This lesion was without hyperhidrosis.10 In 2006, Espana et al. described several brown, irregular, 1 cm to 1.5 cm nodules following the lines of Blaschko on the left buttock and on the leg of a 32-year-old female, present since age 12.11 These lesions increased in size and number from their original presentation, and were noted to be pruritic with increased areas of hyperhidrosis.11 Also in 2006, Man et al. reported the latest case of MEN, in an 18-year-old female in whom it had been present for 17 years. The lesion was a 4 cm x 3 cm, well-demarcated plaque on the distal left foot associated with hyperhidrosis.12 See Table 1 for a summary of these cases.

Treatment

Treatment options are varied and should be tailored to a patient’s symptoms. In most reports of eccrine nevus, pain is rarely present, and hyperhidrosis is variable.2 Instances in which treatment for these symptoms was requested, total excision of the lesion was the most common successful therapy.13 Other reported therapies for hyperhidrosis include: topical aluminum chloride or anticholinergics, injections of botulinum toxin (BOTOX), systemic treatment with antidepressants containing anticholinergic properties, as well as clonazepam and clonidine.2,14,15,16

ABSTRACT

Eccrine nevus is a rare lesion, with the mucinous variant only being reported in five previous individuals. The mucinous variant has shown a female predominance (4:1) and various ages of onset, from infancy (3 mo) to middle age (46 yr). Four of the lesions were reported on extremities, while the other was on the buttock. We report a case of mucinous eccrine nevus that occurred on the left lower trunk in an 18-month-old African American female. Of the five previous cases of mucinous eccrine nevus reported, two were associated with hyperhidrosis. We report the third case of mucinous eccrine nevus that presented with hyperhidrosis.
To date, there are no reports of malignant transformation of eccrine nevi. Recently, a report of eccrine angiomatous hamartoma was reported to have spontaneous regression.¹⁷ Due to its benign nature, patients may elect conservative treatment of their lesions unless symptomatic. The parents of our patient plan to have the lesion excised due to the complications of hyperhidrosis.

References:


Table 1

<table>
<thead>
<tr>
<th>Age of onset, Sex</th>
<th>Location/# lesions</th>
<th>Pain</th>
<th>Hyperhidrosis</th>
<th>Treatment</th>
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</thead>
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<td>no</td>
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</tr>
<tr>
<td>3 mo, F</td>
<td>Buttock / 2</td>
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<td>no</td>
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</tr>
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<td>46 yo, M</td>
<td>L 4th toe / 1</td>
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<td>no</td>
<td>none</td>
</tr>
<tr>
<td>12 yo, F</td>
<td>L buttock, leg / multiple</td>
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<td>yes</td>
<td>unknown</td>
</tr>
<tr>
<td>1 yo, F</td>
<td>L distal Foot / 1</td>
<td>no</td>
<td>yes</td>
<td>excision w/ medical therapy</td>
</tr>
<tr>
<td>Birth, F</td>
<td>L lower back / 1</td>
<td>no</td>
<td>yes</td>
<td>excision</td>
</tr>
</tbody>
</table>

*Right lower extremity
CASE REPORT: MILIARIA CRYSTALLINA TREATED WITH BOTOX® BOTULISM TOXIN TYPE A

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ABSTRACT
Miliaria is a unique skin condition brought on by occlusions of eccrine ducts. It is divided into three categories depending on the level of obstruction. These three subtypes are discussed below: We are presenting a case report of a 32-year-old man with miliaria on both cheeks. This condition was exacerbated when he perspired. His formation of miliaria was so frequent and severe that he was ready to move to Alaska from Wilmington, N.C., so as to stay in a cool environment.

Introduction
There are three types of miliaria: miliaria rubra, crystallina, and profunda. The etiology of this rash is an obstruction of the eccrine duct, triggered by environments of high heat and humidity. The three subtypes of this condition differ on where the obstruction occurs at the level of the eccrine duct. Miliaria rubra, referred to as a “heat rash,” produces extremely pruritic, erythematous papules and is occluded at the level of the intraepidermal eccrine duct. This produces leakage of sweat around the duct and the release of local inflammatory mediators. Miliaria profunda appears as subtle, asymptomatic, flesh-colored papules and is due to an occlusion at the dermal-epidermal junction. The crystallina subtype is a result of a more superficial occlusion and appears as clear vesicles. This condition is usually present in newborn infants but can also present in adults. We are reporting miliaria crystallina in an adult male.

Case Report
A 32-year-old Caucasian male presented complaining of “bumps” that occur when he sweats a lot or is out in the sun, present for a year and a half. He explained they have been getting worse. At his job, when he works in the operating room, the mask and O.R. lights seem to cause the rash to flare up. The patient stated he can even jog in place and numerous of these “bumps” show up on his cheeks. He found this to be a huge blow to his self esteem. He found that people were often staring at him. He had no shortness of breath and was alert and oriented. Vesicular areas were noted upon the cheek bilaterally (Figure 1 and Figure 2). A 3 mm punch biopsy was taken of the right cheek. While waiting for the biopsy results we advised the patient to avoid hot tubs and saunas, and to try to stay cool at night. The patient was prescribed Differin gel to apply every night and Azelex cream to use every morning. This topical treatment did not help. The pathology report demonstrated some obstruction of the parracrine duct with little lymphocytic infiltrate in the dermis and epidermis. These results led us to the diagnosis of miliaria crystallina. The absolute cure for this skin condition is to cease sweating. We therefore decided to begin injections with Botox®. Using a dilution of 2.2 cc of normal saline per 100 unit vial, we began injecting Botox® intradermal about his cheeks and forehead. We used two units per site and spaced the sites at about 1 cm intervals. This relieved the miliaria, and he now does very well with injecting Botox® every six months.

Discussion
Miliaria crystallina is very common in newborn babies who are “bundled” up a large part of the time or who live in warm environments. The conditions of high heat and humidity lead to occlusion of the eccrine ducts. Occlusion of the skin due to clothing and bandages can also lead to miliaria. Miliaria crystallina is a blockage at the superficial level of the duct, the stratum corneum. At this superficial point, few inflammatory mediators are present, and the rash can be asymptomatic but still unsightly to the patient. In contrast, in miliaria rubra, the leakage of sweat into the subcorneal layers produces spongiotic vesicles, along with a chronic periductal, inflammatory cell infiltrate in the papillary dermis and lower epidermis; and miliaria profunda results in sweat escaping into the papillary dermis, generating a substantial, periductal lymphocytic infiltrate and spongiosis of the intra-epidermal duct.

Normal skin flora such as Staph epidermidis and Staph aureus are thought to play a role in the pathogenesis of the condition. It has been shown that people with miliaria have three times as many bacteria per unit of skin versus normal subjects.1 A hyperkeratotic plug can be found upon biopsy, occluding an eccrine duct. This is thought to be a late change in the disorder, not the causing agent. Miliaria crystallina is mostly found in neonates but, as in the above case, can be found in adults as well. Worldwide, miliaria is most common in tropical environments, especially among people who recently moved to such environments from more temperate zones. Miliaria has been a significant problem for American and European military personnel who serve in Southeast Asia and the Pacific. This skin condition occurs in individuals of all races, and no sex preference is seen.

Upon physical exam, miliaria crystallina appears as clear, superficial lesions 1 to 2 millimeters in diameter. These lesions occur in clusters and usually do not possess any surrounding erythema.

In infants, lesions tend to occur on the head, neck, and upper part of the trunk. In adults, they usually occur on the trunk. Lesions rupture easily and resolve with superficial branzy desquamation. This skin condition is thought to primarily occur in neonates due to their immature eccrine glands, which easily rupture. The rupture leads to the occlusion of the duct and the appearance of miliaria. Pseudohypoaldosteronism has also been linked to miliaria due to the mineralocorticoid resistance. This resistance leads to excess salt loss through the sweat ducts and is associated with repeat bouts of miliaria.
Candidiasis, herpes simplex, and folliculitis are all in the possible differential. History and physical examination are sufficient for diagnosing miliaria, but a biopsy can confirm the diagnosis, especially in an adult case.

Conclusion

We have presented an unusual case of miliaria crystallina arising on the face of a 32-year-old Caucasian male. We have reviewed the literature with regard to history and physical and pathological traits. Treatment is usually not needed due to the fact that this condition is asymptomatic and self limiting. However, we treated our patient with Botox® injections, as we would with a hyperhidrosis patient. After his first treatment, the patient reported an 80 percent improvement in symptoms. Therefore, we have continued to manage this patient with Botox® to limit his sweating and thus limit miliaria crystalline.

References:
The South Beach Clinical Dermatology Symposium will host the world’s top medical and surgical dermatology faculty to cover topics ranging from advances in clinical and therapeutic dermatology, photodynamic therapy, immune response modifiers, biologic therapies for psoriasis, wound care management, acne, rosacea, psoriasis and much more.

The South Beach Aesthetic Symposium will present new innovations in aesthetic procedures and technologies and feature the world leaders in cosmetic and aesthetic dermatology. It will offer multiple live patient demonstration and certification workshops on new fillers and new filler applications, botulinum toxin-type A, demonstrations of new laser, light and radiofrequency devices.

The South Beach Practice Management Symposium will include an interactive session on how patients view dermatologists, financial benchmarks, elements to improve both clinical and cosmetic practice, EMR and imaging solutions and risk management strategies.

More than 40 hours of AMA & AAD Category 1 CME Credit offered!

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Hosted by the Florida Society of Dermatology and Dermatologic Surgery
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# 2009 South Beach Symposium™ Registration

**February 12–16, 2009 • Loews Miami Beach Hotel, Miami, FL**

## General Registration

Please check your appropriate fee. Registration fees include all lectures, course materials, and two tickets to all meeting events.*

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<tr>
<td>Physician Registration</td>
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<td>ARNP's, PA's and Medical Staff</td>
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**Registration Total**

$____ $____

## Guests & Social Events

* One guest badge included in registration fee. Please enter your complimentary guest’s name below, plus any additional tickets needed for the South Beach Gala.

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**Social Events and Guest Total**

$____

**Combined Total Sections 2 & 3**

$____

## Meeting Registration Payment

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<td>Make checks payable to: SBS Medical Education</td>
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**NO** reservation will be confirmed without a deposit.

## HOTEL INFORMATION

Hotel reservations are on a first come, first serve basis. Book your rooms early and guarantee your spot in the HOST Hotel! Hotels are based on availability on the date the request form is received. Should the host hotel be sold out for the dates requested, your room reservations will automatically be confirmed in the next available hotel.

### DEADLINE DATE

**January 9, 2009** - Any reservation received after this date cannot be assured of hotel availability or the group rate and will be accepted on a space-available basis.

### HOST HOTEL—Loews Miami Beach Hotel

- Room Rate—$339 single/Double
- 1601 Collins Avenue • Miami Beach, Florida 33139

### OVERFLOW HOTEL—Royal Palm Hotel

- Room Rate—$359/single, $389/double plus a $19/night resort fee
- 1545 Collins Avenue • Miami Beach, Florida 33139

**Room Type (indicate quantity needed)**

- single (1 Bed) $____
- double (2 Beds) $____

**Arrival Date:**_______________    **Departure Date:**_______________

**No. of Adults in Room:**______      **No. of Children:**______

**Special Needs/Requests:**_____________________________________

### HOTEL DEPOSIT

A credit card guarantee of one night’s room and tax is required as deposit. The deposit is refundable if cancellation is received 72 hours prior to arrival. A fee of $50 will be charged in the event of an early departure.

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**Credit Card #**

**Exp Date**

**Security Code**

**Signature**

**Name on Card**

**NOTE:** All changes and cancellations must be done in writing to SBS.

### CHANGE POLICY

Any changes made to a reservation after the initial confirmation is subject to a $25 administrative fee.

### ADA Compliance

Attendees who need additional reasonable accommodations or who have special needs should contact the SBS at 904-309-6262.

### Registration:

Registration and payment must be received no later than January 9, 2009. After this date a syllabus and name badge cannot be guaranteed—so register TODAY!

### Cancellation:

A written notice of cancellation must be received no later than January 9, 2009 and a $250 cancellation fee will apply. No refunds will be given after this date.

### Three Convenient Ways To Register:

- **Fax:** 904-998-0855
- **Mail:** South Beach Symposium
  - 6816 Southpoint Pkwy., Suite 1000
  - Jacksonville, FL 32216
- **Website:** www.southbeachsymposium.org

Any questions regarding this meeting please call 904-309-6262.