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We are pleased to bring you the 13th edition of the Journal of the Osteopathic College of Dermatology. The journal has consistently been published on a quarterly basis, and we believe that the content continues to improve with every issue. In an effort to keep up this trend, there have been several recent and exciting changes in our journal.

We would like to introduce two new editors for the JAOCD: Jon Keeling, DO, and Andrew Racette, DO. Both recently completed their dermatology residency programs and have come on board with new ideas to improve and expand our journal. Jon Keeling trained at Wellington Regional Medical Center/LECOM, and has joined Advanced Dermatology in Brandon, FL. Andrew Racette trained at Midwestern University Phoenix Dermatology and has opened his own practice, Omni Dermatology in Phoenix, AZ.

The journal has recently made a critical move to using Editorial Manager, a program that is used by other respected peer reviewed journals across the country. Editorial Manager streamlines the editorial process, making it much easier for authors, reviewers, and editors to communicate throughout the publishing process.

The JAOCD has expanded the peer review process by establishing an editorial review committee. The committee consists of both D.O. and M.D. board-certified dermatologists from across the country. This committee will bring the JAOCD one step closer to achieving our goal of being a PubMed indexed journal.

We would like to thank the sponsors of the JAOCD: Global Pathology Laboratory, Medicis-The Dermatology Company, Stiefel Laboratory, Galderma, and our most recent sponsor, Ranbaxy Pharmaceuticals. These companies have shown their support for the AOCID, the JAOCD and the dermatology community through this educational resource. We also thank you for continuing to share your interesting cases with the JAOCD. To all readers, please consider joining us in our goals of expanding and improving our journal by submitting your manuscripts for publication in the JAOCD.

Sincerely,

Jay S. Gottlieb, DO
Jon Keeling, DO
Andrew Racette, DO
It is said that time passes quickly, and that certainly is true of this year being president of the AOCD. I want to acknowledge Dr. Jay Gottlieb and the editorial review board for their hard work on this journal. I also want to congratulate and thank both Dr. Jon Keeling and Dr. Andrew Racette for taking on the role of co-editors of the JAOCD. Compiling, editing and producing the JAOCD are truly labors of love. It requires time and dedication to publish such an outstanding journal. I applaud their efforts, and congratulate them on their commitment to publish the JAOCD on a quarterly basis, allowing it to be indexed with Medline. I do not know of any other osteopathic specialty or sub-specialty that has a journal like the JAOCD to represent its members.

As the newly elected President, I want to thank Jay for his hard work last year as President of the AOCD. I would like to continue what he started by opening up better communication between residents, members, and the organization. The AOCD is OUR organization, and it only gets better as our members become involved.

This year, I will strive to improve communication. I invite all members and resident members to contact me, other members of the Executive Committee or the AOCD office via email or phone with any questions or if you would like to serve on AOCD committees. Email is certainly a very efficient tool and allows us to communicate on a more rapid and concise basis. I am dedicated to serving you this year, and although I may not have the answers or the solutions to all issues immediately, I will work hard to resolve them.

I invite you to attend the midyear meeting in Steamboat Springs, Colorado. Dr. Glick has planned an outstanding meeting with a wide variety of speakers. Steamboat promises to be a great vacation site, so I encourage you to bring your family. Air transportation in and out of Steamboat is currently inexpensive and easily accessible. I encourage you to mark this event on your calendar.

I do look forward to a good year. I hope you and yours have a happy holiday and a blessed New Year.

Donald Tillman, DO, FAOCD

AOCD President, 2008-2009
FOLLICULAR MUCINOSIS: A CASE REPORT IN A TEENAGE GIRL

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ABSTRACT

Follicular mucinosis (FM) was first described by Pinkus in 1957,1 characterized histologically by the presence of mucin in the follicular epithelium and the sebaceous glands. Since then, three clinical types have been delineated. The first and most common type occurs as an idiopathic, benign condition typically seen in young patients. The second clinical type is a more chronic disorder affecting people 40 to 70 years of age. And the third type is secondary FM, or malignancy-associated FM, which usually occurs in the elderly and presents with widespread lesions. Despite the various studies conducted, recent reports have demonstrated no reliable clinical or histopathologic features that differentiate benign and malignancy-associated FM. We present a case of FM with unknown etiology presenting in a 14-year-old female.

Case Presentation

A 14-year-old white female presented with a two-month history of an asymptomatic red, scaly plaque on the right cheek that had enlarged in diameter. She denied contact with a new animal, and the family pets were free of skin disease. There was no history of photosensitivity, recent illness, recent travel or trauma. Review of systems was negative, and the patient was otherwise healthy. She had previously applied a topical steroid without improvement.

On physical examination, a 4cm, mildly indurated, erythematous plaque with fine scale was located on the mid-right cheek (Figure 1). Remainder of the skin exam was unremarkable. There was no lymphadenopathy.

Laboratory analysis including CBC, fungal culture and KOH were all negative.

A 3mm punch biopsy was performed, and a hematoxylin-eosin stain revealed extensive mucinous deposition within follicles and sebaceous glands. There was a perivascular lymphocytic infiltrate with occasional eosinophils. There was no lymphocytosis or other atypical lymphoid infiltrate (Figure 2, 3).

The diagnosis of follicular mucinosis prompted treatment with Tazorac (tazarotene) and intermittent topical steroids. The patient was sent for a chest X-ray and an abdominal ultrasound, which were both negative. Six months after the diagnosis was made, the lesion had a slight decrease in erythema but was still present.

When this condition affects hair-bearing skin, a non-scarring alopecia termed alopecia mucinosa can result.1 The exact pathogenesis is unknown, although the role of cell-mediated immunity and/or circulating immune complexes has been considered. Emmerson and Coskey further divided FM patients into three clinical types.2 The first and most common type occurs as an idiopathic, benign condition typically seen in young patients.1 It presents as a solitary, erythematous, indurated patch or plaque on the face, neck, or scalp. This type typically resolves spontaneously in two months to two years, although a study done by Brown et al. found this timeframe to be less reliable than once thought.2 In his series of seven young patients, early resolution was not demonstrated.2 The second clinical type is a more chronic disorder affecting people 40 to 70 years of age. These patients present with a widespread eruption that can persist indefinitely but is not associated with malignancy.2

The third type is secondary FM, or malignancy-associated FM, which usually occurs in the elderly and presents with widespread lesions. The most common malignancy associated with FM is cutaneous T-cell lymphoma. This occurs in approximately 15% to 30% of patients with FM.2 Cutaneous T-cell lymphoma can coincide with FM, precede FM, or develop months to years after FM. Other associated malignancies include leukemia, renal-cell carcinoma, Hodgkin’s disease, cutaneous B-cell lymphoma, and squamous-cell carcinoma of the tongue.1

The above three clinical types are not all inclusive and may give a false sense of security. Many patients do not fit the prototypical classifications stated above. In one study quoted by Brown et al.,2 a group of patients diagnosed with FM were followed for a period of 10 years. Sixty-two percent of the patients that were over the age of 40 did not develop a malignancy, while 23% of the patients aged 30 to 40 years did eventually develop mycosis fungoides. Another small study was done by Gibson et al.4 following nine children who were under the age of 21 at the time of diagnosis. Five patients had clearing of lesions, two did not have clearing of lesions, and two patients developed Hodgkin’s disease.

The unpredictability of FM has led to the use of molecular genetic analysis, targeting patients with a clonal T-cell receptor gene rearrangement. It has been suggested that patients with a clonal T-cell receptor rearrangement are at a higher risk for developing lymphoma.2 However, although the character of the lymphocytic infiltrate may be in question, there are numerous
reports of patients with and without this entity who have or have not progressed to a malignant state. A long-term follow-up study was conducted on seven patients with clonal T-cell gene rearrangement and were younger than 40 years old. This study concluded with no evidence of progression to CTCL in that population, and therefore clonality did not appear to predict the development of the disease.

The uncertain clinical course of the disease has also prompted histopathological reviews by Mereghan et al. and Cerroni et al. to try and ascertain features that would distinguish idiopathic FM from malignancy-associated FM. The former group performed a slide review of 33 cases of FM and proposed the absence of eosinophils may suggest the progression to mycosis fungoides. The latter group analyzed the histopathologic specimens of 44 patients with and without lymphoma, and found that in the group of lymphoma-associated FM, nine of the 28 patients showed histologic features that were more suggestive of benign FM. These findings included mild lymphocytic infiltrate, lack of epidermotropism and the presence of eosinophils. In fact, the initial diagnosis of these individuals was idiopathic FM, and it was not until repeated biopsies were analyzed over a period of time that the diagnosis of CTCL was made.

Despite the various studies conducted, recent reports have demonstrated no reliable clinical or histopathologic features that differentiate benign and malignancy-associated FM. Therefore, in cases of benign or idiopathic FM, long-term follow-up and multiple biopsies are recommended for a minimum period of five years.

Treatment has generally been ineffective, but it includes topical, intralesional, and systemic steroids. There has been little success with PUVA and isolated success with dapsone, indomethacin, and interferon. Other treatment options such as excision, localized radiation, and nitrogen mustard have also been tried. If FM is associated with a malignancy, the underlying malignancy should be treated.

References:
ERUPTIVE COLLAGENOMA IN A 50-YEAR-OLD WHITE FEMALE

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ABSTRACT

Eruptive collagenoma is a hamartomatous connective-tissue nevus primarily composed of dense, thickened collagen. It usually presents with the sudden appearance of several firm, white-to-flesh-colored papules symmetrically distributed on the trunk and lower extremities. Eruptive collagenoma is a rare disease for which definitive associations are not currently known. We present a case of a healthy 50-year-old white female with eruptive collagenomas of uncertain etiology.

Case Report

A 50-year-old healthy white female reported to the clinic with an approximate two-year history of multiple “bumps” gradually forming on her back. She was otherwise healthy and had no other complaints. ROS was negative, and there was no pertinent family history. Patient had never been pregnant, had no significant past medical history, was not taking any prescription or herbal medications, did not recall any illness before or during the onset of the eruption, and did not recall any of the lesions developing after an inflammatory cutaneous process.

Physical examination revealed over 50 flesh-colored firm cutaneous papules covering her back. No other similar lesions were noted on other body parts, and no other significant dermatologic findings were present on physical examination. Punch biopsy revealed hypocellular sclerosing process without identifiable mucin. Nodular dermal sclerosis with marked attenuation of the elastic fibers was present. The diagnosis was eruptive collagenoma based on of history, physical examination, and histology.

Discussion

Connective-tissue nevi of the skin are classified based on clinical, histopathologic and genetic features. Uitto et al. defined and classified connective-tissue nevi as those tumors formed by the proliferation of a single component of the extracellular matrix: collagen, elastin, or proteoglycan. Connective-tissue nevi are further categorized as either acquired or inherited, and the presence or absence of extracutaneous features distinguishes them further.7

Eruptive collagenoma (EC) is a hamartomatosus connective-tissue nevus primarily composed of dense, thickened collagen. Usually, this entity presents with the sudden appearance of several firm, white-to-flesh-colored papules and nodules of various sizes, usually less than 1 centimeter in diameter. Papules may coalesce to form large plaques.1-4 There are rarely epidermal changes, but occasionally lesions may have a peau de orange appearance.1 Lesions usually appear symmetrically on the lower trunk and extremities,1,2 but have been reported on the face as well as other body parts4,5 (see Table 1). Based on our literature review, the mean age for EC is 21, however other authors suggest that EC usually appears within the first two decades.1,5-7 There does not appear to be a predilection for a particular race. Histologic examination of the papules reveals an accumulation of thickened, homogenous collagen within the dermis with a diminished amount of elastin. A thorough and reliable family history must be obtained in order to differentiate EC from other collagenous connective-tissue nevi. Also, it is of importance to rule out other syndromes that have been associated with collagenomas or multiple connective-tissue nevi, such as multiple endocrine neoplasia type 1 (MEN-1), Buschke-Ollendorff syndrome, tuberous sclerosis, Hunters syndrome, Cowden syndrome and Proteus syndrome.1,5 Diagnosis of eruptive collagenoma is dependent on the appropriate clinical manifestations and histologic features, as well as a negative family history and absence of extracutaneous manifestations. The lesions of EC are benign. Pathogenesis is unknown, and no treatment option has been proven effective.

The differential diagnosis for the collagenous connective-tissue nevi includes familial cutaneous collagenoma (FCC), the shagreen patch of tuberous sclerosis, isolated collagenoma, and papular elastorrhexis.1,9

FCC may have a predilection for the upper two thirds of the back and proximal arms, while EC has been commonly reported on other body parts such as lower extremities, face and trunk.1,4,12 Based on the limited number of reports, though, this distribution pattern should not be used to differentiate between EC and FCC. The distinguishing feature between the two entities is the presence of an autosomal-dominant inheritance pattern in those with FCC.1 As McClung et al.2 discusses, this familial pattern has been demonstrated in previously. FCC appears within the first two decades of life and may be influenced by hormonal changes such as pregnancy and puberty. Extracutaneous manifestations such as cardiac abnormalities have been suggested by some authors to be associated with FCC.1,2 Because our patient denies any family history of similar lesions,
and any obvious extracutaneous manifestations are absent, we believe FCC is not a likely diagnosis.

The shagreen patch is a characteristic cutaneous finding in those with tuberous sclerosis (TS). Tuberous sclerosis is a rare genetic disease that affects multiple organs and manifests commonly as mental retardation and epilepsy along with other cutaneous and systemic abnormalities. Unlike FCC and EC, the collagenous shagreen patch most commonly appears within the first decade of life as one or several solitary plaque lesions which are asymmetrically distributed on the back, with an occasional pig-skin or pebbly appearance.1,2 Adenoma sebaceum, subungual fibroma and “ash leaf” macules are among the other cutaneous findings in TS. TS was ruled out in our patient based on the clinical appearance, distribution of hundreds of papules, and a lack of extracutaneous abnormalities. It is possible that hormonal mechanisms are not necessary for EC’s evolution.

Table 1

<table>
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<th>Resource</th>
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<th>race</th>
<th>Distribution</th>
<th>Size</th>
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<td>M</td>
<td>Indian</td>
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<td>M</td>
<td>?</td>
<td>trunk, ext</td>
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<td>M</td>
<td>C</td>
<td>neck, trunk, lower ext</td>
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<td>MEN4, Beckers nevus</td>
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References:

Case

A 45-year-old female presented with complaints of non-pruritic “bumps” to the posterior aspect of her upper arm and to her lateral neck. The lesions had developed while the patient was vacationing in Central America, spending time in both Costa Rica and on the west coast of Mexico. Although the lesions did not itch at any time and there was no recollection of an insect bite/sting, the patient initially dismissed the lesions as mosquito bites. When the lesions persisted after returning home and the passage of several weeks time, the patient decided to present for further investigation.

Physical examination of the patient revealed three 1.5 cm to 2 cm, edematous and erythematous nodules with crusted surfaces and violaceous borders on the posterior right upper arm (Fig. 1). There were also similar lesions on the right lateral neck. On palpation, numerous 2 mm to 3 mm subcutaneous nodules could be felt extending cephalad along lymphatic channels of the right upper arm. There was no palpable axillary or cervical lymphadenopathy.

A 4 mm punch biopsy was obtained from the periphery of one of the nodules on the right arm. Histologic examination revealed hyperkeratosis and pseudopapillomatous hyperplasia overlying a marked dermal infiltrate of chronic inflammatory cells (Fig. 2). Within the dermis, numerous histiocytes were present which contained intracellular, nonencapsulated organisms with a round nucleus and a smaller, rod-shaped paranucleus (Fig. 3). A diagnosis of cutaneous Leishmaniasis was made.

Introduction

Cutaneous Leishmaniasis is an infection caused by species of Leishmania, protozoa that are obligate intracellular parasites in the human host. Currently over 12 million individuals worldwide are affected by this disease, with a wide range of clinical outcomes and varying levels of morbidity. The infection occurs with a spectrum of clinical presentations, including localized cutaneous Leishmaniasis (LCL), diffuse cutaneous Leishmaniasis (DCL) and mucocutaneous Leishmaniasis (MCL). The variable clinical features are due to a complex interaction between the species of Leishmania involved, the particular vector, environmental factors and the immune status and response of the host.

We will review the most recent data on the epidemiology of this disease, the associated vectors and reservoirs, the clinical presentations, the current methods of diagnosis and the most common forms of treatment. Additionally, we will take a look at the increasing burden of disease in the United States due to the elevated numbers of U.S. military forces stationed in the Middle East and other areas endemic to this disease.

Epidemiology

Currently, cutaneous Leishmaniasis is endemic to more than 88 countries worldwide, with 90% of cases occurring in Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia and Syria. Each year more than 1.5 million individuals are infected with this parasite, contributing to an increasing burden of disease. In addition to those people who are native to endemic areas, infection also occurs in military personnel stationed in endemic areas, and in civilian workers and travelers who journey into endemic areas. Prior to the Gulf War in the early 1990s, there were only isolated reports within the United States of CL, usually occurring in travelers who had visited endemic areas. During the Gulf War, however, 12 cases of CL were diagnosed in U.S. troops who had been deployed to the region. Most recently and more staggering, at least 522 cases have been reported by the Department of Defense amongst military personnel serving in Southwest and Central Asia between 2002 and 2004 alone.

The majority of those persons were infected in urban areas of Iraq after a median...
period of deployment of only 60 days. Currently, it is believed that up to 1% of U.S. troops serving in Iraq and the Middle East may be infected by one of the species of Leishmania.

For those native to endemic areas, the prevalence of CL tends to increase with age up to the age of 15, and then the prevalence declines. This drop-off in prevalence is believed to be due to the acquisition of species-specific immunity. Disease risk factors in endemic areas have been found to be related to housing construction and design, presence of domestic animals, male sex and age.

Pathogenesis

There are 11 species of Leishmania that commonly cause cutaneous Leishmaniasis in humans, and the species varies based upon geographic region (Table 1). The protozoa are transmitted by the bite of the sandfly -- Phlebotomus spp in the Old World (Europe, North Africa, Middle East and Asia) and Lutzomyia spp in the New World (from southern Texas to northern Argentina). Although somewhat simplified, the ecological environment associated with Old World CL tends to be dry, semi-arid or desert conditions. New World CL is more associated with forest conditions. These environments have an impact on the species of sandfly and on the reservoirs that are involved. The arid habitats of the Old World translate into dogs, gerbils and desert rodents being the main reservoirs; whereas the forest habitats of the New World are more conducive to sloths, monkeys and forest rodents being the main reservoirs.

The lifecycle of the Leishmania organism begins as an extracellular promastigote in the gut of the sandfly. When the sandfly takes a blood-meal from either a human or a reservoir, the promastigote is released into the skin, where it phagocytizes by macrophages and transformed into amastigotes by binary fission. It is in this amastigote form that it is later taken up by another sandfly during feeding, allowing the cycle to start again. According to studies done by the CDC and Department of Defense, the infection rate in sandflies can vary from 0.06% to 2.78%.

Clinical Presentation

There are three main spectrums of clinical presentation: localized cutaneous Leishmaniasis (LCL), diffuse cutaneous Leishmaniasis (DCL) and mucocutaneous Leishmaniasis (MCL). The spectrum of disease seen is determined by the species involved and by host immunity. L. braziliensis is known to be a major cause of mucocutaneous disease, whereas L. amazonensis (New World) and L. aethiopica (Old World) are the major causes of DCL.

The localized form is the most common presentation, and clinically is made up of one to several lesions developing in locally contiguous areas. The diffuse form is the rarest and most severe manifestation of cutaneous disease. In this form, paramastigotes, non-ulcerated nodules disseminate both locally and hematogenously to other areas of the body, sometimes almost covering a patient's body surface. DCL presents an anergic response to infection, with a marked predominant Th2 lymphocyte response. Not only is this form cosmetically deforming, but it is also exceptionally difficult to treat, with some cases persisting indefinitely. The last form, mucocutaneous disease, has a distinctive late secondary phase in which metastatic lesions develop at mucocutaneous junctions days to years after the primary lesion(s).

The lesions heal slowly if at all, and secondary sepsis is a common occurrence. This type of Leishmaniasis is particularly resistant to treatment and may be fatal.

Regardless of the clinical spectrum, the most common initial presentation is a small, sometimes pruritic, erythematous papule, which appears anywhere from a few days to many months after the bite of the sandfly. Often the individual is not even aware of the initial sandfly bite, so a lack of recall regarding the bite probably has no clinical significance. As time passes, the papule may grow in size and ulcerate at the center, producing a “wet” sore common to New World species. Old World species are more likely to produce “dry” sores that become hyperkeratotic or smooth nodules. In all forms, the edge of the lesion takes on the characteristic thickened, often hyperplastic, violaceous border. More than 90% of lesions occur on exposed skin, correlating with the areas most susceptible to the bite of the sandfly.

Lesions may grow to be large (2.5 cm – 5 cm) but rarely grow beyond 10 cm in diameter. Even in LCL, satellite nodules may develop along draining lymphatic channels in a sporotrichoid fashion. The lesion(s) typically remains for a few months and then heals gradually with scarring. Healing is followed by species-specific immunity.

Diagnosis

When there is a history of obvious travel or past residence in an endemic area, a clinical diagnosis may be possible. However, there is a relatively extensive differential diagnosis for the clinical cutaneous presentation, including cutaneous tuberculosis, dermatophyte skin infections, myiasis, sporotrichosis, syphilis and sarcoidosis. Therefore, whenever feasible, a laboratory diagnosis should be made. Additionally, the identity of the implicated species should be sought so that appropriate treatment planning may occur. Skin punch biopsy is an ideal method of obtaining tissue for various diagnostic techniques, including histology, microscopy of smears, polymerase chain reaction (PCR) testing and culture. Demonstration of Leishmania in skin smears or biopsy specimens is highly sensitive; however, it does not allow for species identification. Leishmania species, especially those from the New World, are also notoriously difficult to culture, so having other options available is imperative. PCR is currently the diagnostic test of choice, as it is highly sensitive and allows for species identification. This is especially important when L. bразiliensis may be the etiologic agent, as prompt treatment may allow prevention of complications.

Another test to confirm a clinical diagnosis, which is mostly of historical significance, is the Montenegro skin test. It measures delayed hypersensitivity to the parasite and is useful after a granulomatous response has occurred, typically several months after inoculation. A suspension of antigen from the promastigote form is injected into the forearm, and a positive test occurs when a palpable nodule, 10 mm or more in diameter, is seen after 48 to 72 hours. The test is of diagnostic value only in patients who do not live in endemic areas, as it is unable to distinguish between past and present infection. It will also give false negative results in patients with diffuse anergic cutaneous Leishmaniaisis, as these patients do not develop a type IV immunologic response to the organism. The test is not species-specific and does not necessarily reflect immunity to Leishmania. It is, however, simple to use and highly sensitive and specific. Currently, it is no longer available in the United States and is used mostly for epidemiological surveys.

Pathology

In human tissue, the organisms are in the amastigote form and are small, round, non-flagellated forms 2.0 microns to 4.0 microns in diameter that usually stain with hematoxylin and eosin. They replicate within macrophages and are then released to infect other cells; therefore, they may be found within macrophages or free in the tissue. They typically have a large nucleus and a characteristic intracytoplasmic kinetoplast that may require accentuation with special stains such as Giemsa stain or Brown-Hopps gram stain. There tends to be hyperkeratosis, acanthosis and pseudoepitheliomatous hyperplasia overlying a marked dermal infiltrate of chronic inflammatory cells. Necrosis may develop and be visible within a biopsied lesion.
As immunity develops, parasite numbers decrease and a shift from a histiocytic reaction to a granulomatous reaction with lymphocytes, plasma cells, epithelioid cells, and Langerhans’ giant cells occur. Mucocutaneous lesions characteristically display a necrotizing granulomatous reaction with few organisms present.

**Treatment**

In the Old World version, most lesions will heal spontaneously and do not require systemic treatment. Typically, lesions will resolve within 12 months. Pharmacologic intervention, however, can be important and is indicated when lesions are large and/or potentially disfiguring, when there are multiple lesions present and when lesions occur in immunosuppressed patients.

The New World, the broad spectrum of clinical presentations, from benign to severe, makes species-specific treatment planning important. This is particularly important when infection with *L. braziliensis* is suspected, as 2% to 10% of untreated cases will progress to mucosal involvement, making systemic pharmacologic treatment mandatory.

Pentavalent antimonials remain the gold standard for the treatment of New World cutaneous leishmaniasis. The recommendation is for 10-20mg/kg/day of sodium stibogluconate (available through the Centers for Disease Control and Prevention within the United States) for a period of 20 to 30 days. The efficacy varies with the species involved, ranging from a 26% to 51% cure rate, regardless of other host variables. Unfortunately, administration can be difficult; it must be given either intravenously or intramuscularly as there is no oral form available. Additionally, there are numerous side effects and toxicities that must be monitored for, including EKG changes (T-wave abnormalities); abdominal pain; nausea and vomiting; fever; elevations of liver enzymes, amylase and lipase; leucopenia; and anemia. Fortunately, most abnormalities return to normal with only a short interruption of treatment and often remain normal even on reinstitution of the drug.

Other treatments that have been employed for LCL include intralesional injections of pentavalent antimony, paromomycin ointments, imiquimod, topical amphotericin B, cryotherapy, localized controlled heat therapy, carbon dioxide laser and photodynamic therapy. Additional systemic treatments for those in which systemic antimonials have either failed or are contraindicated include oral amphotericin B, azithromycin, miltefosine, and pentamidine. If systemic treatment is warranted, referral to an infectious disease expert or other specialist familiar with the systemic medications and their side effects is likely warranted.

**Conclusion**

Although cutaneous leishmaniasis is not endemic in the United States, with the exception of Southern Texas, it is more likely than ever that dermatologists may encounter a case in their own office. The increasing incidence in military personnel returning from the Middle East and the increasing ease of international travel mean that more U.S. citizens may be infected with this obligate intracellular parasite than ever before. It is important for each of us to have a good clinical understanding of the clinical presentations, the methods of diagnosis and the basics of effective treatment for this disease.

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**Table 1**

Most common *Leishmania* species causing cutaneous disease

<table>
<thead>
<tr>
<th>New World</th>
<th>L. mexicana</th>
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<tr>
<td>L. amazonensis</td>
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<td>L. venezuelensis</td>
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<td>L. bresiliensis</td>
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<td>L. peruviana</td>
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<td>L. colombiensis</td>
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<td>L. guyanensis</td>
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<td>LCL, DCL</td>
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<td>L. major</td>
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<td>L. tropica</td>
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<table>
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<tr>
<th>Old World</th>
<th>L. aethiopica</th>
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<tr>
<td>LCL, DCL</td>
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<tr>
<td>LCL</td>
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</table>

LCL = Localized Cutaneous Leishmaniasis, DCL = Diffuse Cutaneous Leishmaniasis, MCL= Mucocutaneous Leishmaniasis

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**References**

When the flares of dermatitis strike…

On target relief

KENALOG® SPRAY
Triamcinolone Acetonide Topical Aerosol USP

Precision application when treating hard to reach areas

- Indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

- Systemic absorption of topical corticosteroids has produced reversible, hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients. (See the Precautions section in Full Prescribing Information)

- Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio.

The Nozzle Makes the Difference!

For topical use only
Please see Brief Summary on reverse side.
KENALOG® SPRAY
Triamcinolone Acetonide
Topical Aerosol, USP

For dermatologic use only
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Brief Summary. Please see full prescribing information for complete product information.

DESCRIPTION
Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (30.3%), and isobutane propellant.

INDICATIONS AND USAGE
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS
Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifested by decreased adrenocorticotropic hormone (ACTH) stimulation tests, and in impairment of thermal homeostasis. If HPA axis suppression occurs, the patient should be evaluated periodically for evidence of HPA axis recovery after discontinuation of the drug. Occasionally, signs or symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Occasionally, a patient may develop a sensitivity reaction to a particular oclusive dressing material or adhesive and a substitute material may be necessary.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

Pediatric Use
Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing’s syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, aspergillosis, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and milia.

DOSAGE AND ADMINISTRATION
Directions for use of the spray can are provided on the label. The preparation may be applied to any area of the body, but when it is sprayed about the face, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided.

Three or four applications daily of Kenalog Spray (Triamcinolone Acetonide Topical Aerosol) are generally adequate.

Occlusive Dressing Technique
Occlusive dressings may be used for the management of pruritis or other recalcitrant conditions. Spray a small amount of preparation onto the lesion, cover with a pliable nonporous film or plastic film, and seal the edges. If needed, additional moisture may be provided by covering the lesion with a dampened clean cotton cloth before the nonporous film is applied or by briefly wetting the affected area with water immediately prior to applying the medication. The frequency of changing dressings is best determined on an individual basis. It may be convenient to apply the spray under an occlusive dressing in the evening and to remove the dressing in the morning (i.e., 12-hour occlusion). When utilizing the 12-hour occlusion regimen, additional spray should be applied, without occlusion, during the day. Reapplication is essential at each dressing change.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

Store at room temperature; avoid excessive heat.

Manufactured for Ranbaxy Laboratories Inc.
Jacksonville, FL 32237 USA

November 2007

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Kenalog® Spray triamcinolone acetonide spray
Exelderm® sulconazole nitrate 1.0% cream and solution
Eurax® crotamiton 10% cream and lotion
Lac-Hydrin® ammonium lactate 19% and 5% cream and lotion
Ultravate® halobetasol propionate 0.05% cream and ointment
Westcort® hydrocortisone valerate 0.2% cream and ointment

Desquam-X® benzoyl peroxide 5% and 10% wash
Lowila® care cleansing bar
PernoX® salicylic acid and sulfur cleanser
Sebulex® salicylic acid and sulfur shampoo
Balnetar® therapeutic tar bath
CASE REPORT AND REVIEW OF BEHCET’S DISEASE

*3rd-year resident, Saint Barnabas Hospital, Bronx, New York, USA
**Chief of Dermatology, Saint Barnabas Hospital, Dermatology Program, Bronx, New York, USA
***Program Director, Saint Barnabas Hospital, Dermatology Program, Bronx, New York, USA

ABSTRACT

Behcet’s disease (BD) is a multi-system inflammatory disorder characterized clinically by recurrent oral and genital ulcers, uveitis, and erythema nodosum. It runs a chronic course with unpredictable exacerbations and remissions. The disease can affect both genders, typically young adults, and has a worldwide distribution, although it is more prevalent in countries of the ancient Silk Route. The cause of Behcet’s disease remains unknown. The treatment of BD is symptomatic, but generally specific to the clinical features of each patient. The majority of affected individuals do not have life-threatening disease.

Case Report

History

A 26-year-old, Middle Eastern female presented with a five-day history of painful ulcers around her cheeks, tongue, palate and vulva. She stated that these lesions had recurred three times this year and four times in the past year. She also reported a history of erythema nodosum. Upon further questioning and the use of a translator, the patient reported a history of Behcet’s disease, diagnosed in Saudi Arabia when she was 18 years old. She reported no other past medical history. She had been previously treated with prednisone, colchicine, and topical and viscous lidocaine. To date she has had no eye findings, but did report a history of ulcers after blood draws. She also noticed she had lost a significant amount of weight in the last year.

Physical exam

Cutaneous examination revealed multiple 2 to 12 millimeter, discrete, painful, round, red-rimmed lesions on the mucosa of her cheeks, tongue, palate, and pharynx. She had similar lesions on her vulva.

Discussion

Introduction

Behcet’s disease (BD) is a chronic multi-system inflammatory disorder characterized clinically by recurrent oral and genital ulcers, uveitis, and erythema nodosum. BD was first described by the Turkish dermatologist Hulusi Behcet in 1937 as “recurrent oral aphthous ulcers, genital ulcers, and ‘hypopyon-uveitis.” The disease has a variable course with exacerbations being unpredictable. BD is a vasculitis, affecting vessels of different types, sizes, and locations. The diagnosis of Behcet’s disease is based on clinical criteria as established by O’Duffy and Goldstein and the International Study Group.

Diagnostic Criteria

The agreed diagnostic criteria for Behcet’s disease requires the presence of recurrent oral ulceration (three times in one year) plus two of the following in the absence of other systemic disease: recurrent genital ulceration, eye lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules), or a positive pathergy test (Table 1).

Epidemiology

Behcet’s disease is most common and more serious in people with Silk Road bloodlines. Silk Road countries include those in the Mediterranean basin, Middle East and Far East, where the incidence is around 1 in 10,000 people. Behcet’s disease is seen worldwide even in those with other ethnic heritage; in the United States, the incidence is reported to be 1 in 20,000.

In people with Silk Road ancestry, BD is more common in men than in women. However, the trend is reversed in people of other ethnic origins, with more women than men being affected. The disease can develop at any age, but mean age of onset ranges from the mid to late 20s to the fourth decade. It is relatively rare in children and the elderly. Behcet’s disease is also uncommon among black Africans, who tend to have more mucocutaneous features when affected.

Pathogenesis

The etiology of BD is unknown, but an autoimmune reaction triggered by an infectious or environmental agent in a genetically predisposed individual seems most likely. In the eastern Mediterranean and East Asia, HLA-B5 and HLA-B51 antigens have been associated with BD; however, in the United States and Europe, no consistent HLA association has been reported. The lesions could be the result of a combination of factors involving immune dysregulation, inflammatory mediators, and infectious agents such as herpes simplex virus and Streptococcus spp.

Table 1

<table>
<thead>
<tr>
<th>International Study Group Criteria for Behcet’s Disease (1990)</th>
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<tr>
<td><strong>Recurrent oral ulceration</strong></td>
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<td><strong>Plus 2 of the following criteria:</strong></td>
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<tr>
<td><strong>Recurrent genital ulceration</strong></td>
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<td><strong>Eye lesions</strong></td>
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<td><strong>Skin lesions</strong></td>
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<td><strong>Positive pathergy test</strong></td>
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OSHTORY, GROPPER, HOFFMAN 15
logical features of BD consist of increased T- and B-cell responses to heat-shock proteins, increased neutrophil activity, and alterations in cytokine levels, although the interrelationships between and among these features are not clear.1

Clinical Features

Behcet’s disease presents with a wide spectrum of clinical features characterized by unpredictable exacerbations and remissions (Table II). Oral and genital aphthae occur in all patients diagnosed with BD. Oral ulceration is the initial clinical feature in up to 86.5% of adults and children with BD.1 The most common sites of oral ulceration are the buccal mucosae, gums, tongue, lips, and pharynx. Oral ulcers in BD are typically painful, 1 to 3 cm in diameter, shallow or deep, and have a yellow fibrinous base. Patients may have single or multiple ulcers lasting one to four weeks that heal without scarring. Genital aphthae are usually found on the scrotum or vulva and have a similar appearance and clinical course as oral aphthae.7

Ocular manifestations in BD patients include panuveitis, anterior uveitis, posterior uveitis, bilateral swelling of the optic nerve head, retinal vasculitis, and bilateral lamellar macular holes. Ocular symptoms vary from gritty sensation and blurring of vision to severe pain and blindness. Ocular disease is the most common cause of significant morbidity in BD, since it may eventually lead to vision loss if not treated.3

A variety of cutaneous lesions have been observed in BD, including erythema-nodosum-like lesions, papulopustular eruptions, abscesses, pyoderma-gangrenosum-like lesions, palpable purpuric lesions of necrotizing vasculitis, and reactivity of skin to injections (pathergy).8

The neurologic complications of BD mainly involve the central nervous system. Neurologic features include headaches, meningoencephalitis, seizures, cerebral venous thrombosis, cranial nerve palsies, cerebellar ataxia, hemiplegia, and benign intracranial hypertension. These may occur from one to 10 years after initial presentation of BD.7

Musculoskeletal symptoms in BD usually manifest as arthralgias or arthritis, with mono-arthritides being the most frequent pattern of involvement. The knees and ankles are the most commonly affected joints.1

Gastrointestinal (GI) involvement in BD is characterized by ulceration along the GI tract including the esophagus and, most commonly, in the terminal ileum and cecum. Mucosal ulcers are the most common GI feature. Depending on the site of involvement, the ulceration can give rise to dysphagia, abdominal pain, diarrhea, intestinal perforation, and peri-anal fistula formation.1

Cardiac manifestations of Behcet’s disease include myocardial infarction, pericarditis, endocarditis, and valvular abnormalities including aortic and mitral regurgitation.9

Several renal disorders have been associated with BD and can be divided into five groups: (1) glomerulonephritis, (2) amyloidosis, (3) renal vascular involvement, (4) interstitial nephritis, and (5) other problems such as complications of drug therapy or genito-urinary system abnormalities.1

Management

Currently there is no cure for Behcet’s disease. The main goal is to treat and manage the symptoms so that complications do not develop. The treatment of BD is generally specific to the clinical features of each patient. Treatment is usually multi-disciplinary, and is challenging given the variable clinical course and lack of sufficient studies.1,5 Table III summarizes therapies for Behcet’s disease. Patients are initially treated with topical or intralesional corticosteroids and colchicine with the subsequent addition of dapsone. If conservative management fails, thalidomide, methotrexate, or oral prednisone tapers may be required.5

Prognosis

Behcet’s disease is a chronic disease in which the acute phases come and go with varying degrees of intensity. In the early stages of the disease, attacks may be frequent and last for several weeks. As time progresses, the intervals between attacks may become longer, and in some cases the attacks cease altogether. The disease is then considered to be in remission but may strike up again at any time. Death occurs

Table 2

<table>
<thead>
<tr>
<th>Clinical Features of Behcet’s Disease</th>
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<tr>
<td>Gastrointestinal</td>
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<td>Aphthous mouth ulcers</td>
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<td>Isolated multifocal ulcer</td>
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<tr>
<td>Commonly in ileocecal region</td>
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<tr>
<td>Urogenital</td>
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<tr>
<td>Scrotal and/or penile ulcers</td>
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<td>Vulval and/or vaginal ulcers</td>
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<td>Peri-anal ulcers</td>
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<tr>
<td>Epididymo-orchitis in men</td>
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<tr>
<td>Dermatologic</td>
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<td>Papules and pustules</td>
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<td>Erythema nodosum</td>
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<td>Ulcers</td>
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<td>Cutaneous pathergy response</td>
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<td>Ocular</td>
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<td>Anterior or posterior uveitis</td>
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<td>Retinal vasculitis</td>
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<td>Musculoskeletal</td>
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<td>Arthralgias</td>
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<td>Arthritis</td>
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<td>Fatigue</td>
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<td>Neural</td>
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<td>Headache</td>
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<td>Dural sinus thrombosis</td>
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<td>Parenchymal inflammatory lesions</td>
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<td>Meningo-encephalitis</td>
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<td>Cardiac</td>
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<td>Myocardial infarction</td>
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<td>Pericarditis</td>
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<td>Endocarditis</td>
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<td>Valvular abnormalities</td>
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Table 3

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<th>Therapies for Behcet’s Disease</th>
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<td>Topical corticosteroids</td>
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<td>Systemic corticosteroids</td>
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<tr>
<td>Corticosteroid-sparing immuno-suppressants:</td>
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<td>Colchicine</td>
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<td>Azathioprine</td>
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<td>Thalidomide</td>
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<td>Cyclosporine</td>
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<td>Tacrolimus</td>
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<td>Methotrexate</td>
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<tr>
<td>Interferon alpha-2a</td>
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<td>Anti-TNF alpha</td>
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Table II

| Ocular manifestations in BD patients associated with BD and can be divided into five groups: (1) glomerulonephritis, (2) amyloidosis, (3) renal vascular involvement, (4) interstitial nephritis, and (5) other problems such as complications of drug therapy or genito-urinary system abnormalities.

Management

Currently there is no cure for Behcet’s disease. The main goal is to treat and manage the symptoms so that complications do not develop. The treatment of BD is generally specific to the clinical features of each patient. Treatment is usually multi-disciplinary, and is challenging given the variable clinical course and lack of sufficient studies.1,5 Table III summarizes therapies for Behcet’s disease. Patients are initially treated with topical or intralesional corticosteroids and colchicine with the subsequent addition of dapsone. If conservative management fails, thalidomide, methotrexate, or oral prednisone tapers may be required.5

Prognosis

Behcet’s disease is a chronic disease in which the acute phases come and go with varying degrees of intensity. In the early stages of the disease, attacks may be frequent and last for several weeks. As time progresses, the intervals between attacks may become longer, and in some cases the attacks cease altogether. The disease is then considered to be in remission but may strike up again at any time. Death occurs...
in about 4% of Behcet’s cases. Causes of mortality are attributed to gastrointestinal perforation, central nervous system involvement and vascular aneurysms. Most Behcet’s patients live a full life, although they will most likely deal with some level of symptoms throughout this time.9

Conclusion

Behcet’s disease is a condition that remains difficult to diagnose and manage, having various clinical presentations and an unknown etiology. It therefore remains a significant challenge for clinicians of many specialties to manage and treat. Our patient was started on topical steroids and colchicine and improved with treatment. She was then lost to follow-up.

References

Case Report

A 16-week-old male presented to our clinic in the presence of both parents for evaluation of a progressive skin rash that reportedly began at eight weeks of age. The patient continued to develop new lesions despite twice daily application of triamcinolone 0.025 % cream. The patient’s mother reported an uneventful pregnancy and birth, and denied any recent illness in the patient. The patient’s immunizations were up to date, and he was growing and developing at an appropriate rate. The patient’s diet consisted only of breast milk, and the mother reported using allergy-free soap and unscented laundry detergent at home. The parents denied any family history of psoriasis, and the father admitted to a personal history of eczema. The patient’s physical exam revealed scattered, well circumscribed, polymorphic, erythematous, slightly atrophic macules, patches, and plaques, some with fine loose scale, on both the upper and lower extremities (Fig. 1, 2). Similar lesions were noted on the patient’s trunk (Fig. 3) and face, including distinct periorbital involvement (Fig. 4). Upon further questioning, the patient’s mother admitted to a personal history of SLE, a recent diagnosis just prior to her pregnancy. She reported that the patient had in fact had a normal EKG in the hospital, shortly after birth. The patient’s labs also demonstrated a mild anemia, mild hypoproteinemia, hypertriglyceridemia, and slight elevation of ALT (SGPT) liver enzyme. Given the patient’s clinical presentation and laboratory data, a diagnosis of neonatal lupus erythematosus was confirmed, and pediatric rheumatologic follow-up was recommended.

Discussion

The rash of NLE may be present at birth, but usually develops within the first six weeks of life and resolves by seven months of age.5,6 Tissue injury and resulting rash is presumed to be dependent on the transplacental passage of maternal IgG autoantibodies. The target antigens of these antibodies have been identified as two separate SSA/Ro proteins, 52 Kd and 60 Kd, as well as the 48 Kd SSB/La protein. These proteins are expressed on keratinocytes, red blood cells, and fetal cardiomyocytes, thus accounting for some of the clinical manifestations of NLE.5,6 Because the half-life of IgG antibodies is approximately 21-25 days, the resolution of the rash generally coincides with the disappearance of the transplacental acquired maternal autoantibodies.11
In a prospective study of infants born to mothers with anti-SSA/Ro antibodies, 16 percent of children demonstrated a skin rash characteristic of NLE. The study also noted that anti-SSB/La occurring with anti-SSA/Ro antibody seemed to increase the risk for development of cutaneous NLE, when compared to anti-SSA/Ro alone. Genetic factors in the infant are also believed to play a large role in the development of cutaneous lesions. In one study, the -308A allele, HLA-DRQB1*02, and HLA-DRB1*03 were detected in a majority of NLE infants with rash. Also, prominent tumor necrosis factor[alpha] staining was observed in the epidermis of lesional skin, thus supporting the notion that this inflammatory cytokine plays a role in the pathogenesis of cutaneous neonatal lupus, and providing evidence of a biologic link between NLE and subacute cutaneous lupus erythematosus (SCLE).

Treatment of the cutaneous lesions of NLE is usually not required given the self-limiting nature of the rash, and no significant difference in outcome between treated and untreated children has been observed. For those children whose rash was treated, only low-to-mid-potency topical steroids were used. Ultraviolet protection and avoidance should be stressed, as many patients’ rashes were reported as exacerbated after exposure to UV light. In one case report, delayed resolution of the cutaneous eruption was attributed to the high levels of IgA and IgG anti-nuclear and anti-Ro antibodies detected in the patient’s mother’s breast milk. In one retrospective review, by Neiman et al., of cutaneous-only NLE patients enrolled in a national registry, four of 57 affected children later developed signs or symptoms of autoimmune disease. Because the development of a rheumatic disease later in childhood or adolescence can occur, NLE patients warrant long-term follow-up. Mothers of children with cutaneous NLE should undergo serial echocardiographic monitoring of the fetus during subsequent pregnancies, as the crossover from rash to congenital heart block has been well documented.

References:
Case Presentation

An 82-year-old female living in Florida presented with redness and mild pain of her right thumb for two months duration. The patient denied trauma or history of similar symptoms. The other fingers were not affected. The patient had an X-ray of the right thumb that showed osteoarthritis and no foreign body. Past medical and family history was non-contributory.

Physical examination revealed a well-developed, well-nourished elderly female. Examination of the patient’s hands revealed a distal right thumb with erythema, edema, and induration that was mildly tender to palpation (Images 1, 2 and 3). There was no fluctuance or discharge present. During the exam, several of the patient’s fingertips turned white and then returned to their natural color.

Histopathology of a representative biopsy demonstrated focal interface dermatitis, intravascular thrombus and a very prominent superficial and deep infiltrate with chronic hidradenitis. There were areas of fibrin deposition and a thrombus in one of the superficial blood vessels. There were diffuse changes of venous vasculopathy. Acid-fast bacillus was negative. Findings were consistent with chilblains (chronic pernio).

The following laboratory studies were ordered and found to be within normal limits: Factor V Leiden, cryoglobulin, platelets, ESR, ANA, homocysteine, RPR, cryofibrinogen, factor IX, protein C, protein S, lupus anticoagulant, and PTT. The diagnosis of chronic chilblains associated with Raynaud’s phenomenon was determined.

Discussion

Chilblains are an abnormal inflammatory and vascular response to cold or damp conditions. It shows a genetic predisposition and has been described most often in temperate regions, where winters are occasionally cold and damp. It is more common in women, children, and people with a low body mass. Chilblains can be due to underlying myelomonocytic leukemia, dysproteinemias, anorexia nervosa, macroglobulinemia, cryoglobulinemia, cryofibrinogenemia, cold agglutinins, antiphospholipid antibody syndrome, Raynaud’s disease, and drug reactions. Sulindac-induced cases have been reported.

Pernio presents with single or multiple erythematous or violaceous papules or nodules. Blistering or ulceration may be present. The most common locations are the distal fingers and toes; less common locations are the nose, ears, and heels. Lesions may be accompanied by pruritus and a burning sensation. Purpuric lesions are not uncommon. Lesions will typically resolve in one to three weeks. In some, lesions may persist and become chronic, especially in the elderly with venous stasis.

This condition should be distinguished from other cold-induced syndromes, including chilblains lupus erythematosus and cold-sensitive blood dyscrasias. The latter can be assessed by laboratory evaluation: CBC to rule out hemolytic anemia and leukemia; cryoglobulin, cold agglutinin, and cryofibrinogen to rule out cold-sensitive dysproteinemia; and serum protein electrophoresis and quantitative immunoglobulins to rule out a monoclonal gammopathy causing an increase in serum viscosity. A false negative cryoprecipitate may occur, and therefore evaluating the patient for hepatitis C antibody or rheumatoid factor may be prudent in select cases.

Depending on the history and physical presentation, other differentials may include: septic or atheromatous embolism, erythrocytosis, erythromelalgia, erythema multiforme, granuloma annulare, acrocyanosis, polycythemia vera, hypersensitivity vasculitis, sarcoidosis, and cold panniculitis.

Chilblains have a nonspecific histology consisting of papillary dermal edema and a superficial or superficial and deep perivascular infiltrate comprised primarily of lymphocytes. Necrotic keratinocytes and lymphohcytic vasculitis have been noted.

Keeping affected areas warm and dry best prevents pernio. There is anecdotal evidence in the literature of treatment with systemic and topical steroids, vasodilators, IV calcium followed by IM vitamin K, and ultraviolet B radiation. The treatment of choice for symptomatic chilblains is nifedipine 10mg to 20mg three times daily for adults. Common side effects are headache, nausea, and facial flushing, which can
be troubling to some patients. In cases of crippling severity, thyrocalcitonin and hemodilution may be helpful.

In summary, our patient’s case exemplifies chronic chilblains due to abnormal microvascular disease as evidenced by Raynaud’s phenomenon, which presented itself on physical exam. A patient who resides in Florida, and is not exposed to damp, cold environments where this condition is most commonly seen, should arouse suspicion for other possible causal factors. In typical chilblains, the most important point in management is prophylaxis with adequate, loose, insulating clothing and appropriately warm housing and workplace.

References:

Allergic contact dermatitis (ACD) is a frequently encountered skin condition and is secondary to innumerable exogenous allergens. While the inciting allergen is not always revealed, some allergens demonstrate classic skin reactions, and pertinent patient history is often helpful to the clinician. Formaldehyde and formaldehyde-releasing preservatives (FRPs) are common, albeit under-diagnosed, causes of allergic contact dermatitis. We present a case of allergic contact dermatitis in a patient sensitive to her formaldehyde- and FRP-treated wrinkle-resistant clothing. Allergen avoidance resulted in complete resolution of her skin condition. We will discuss pertinent facts related to ACD secondary to formaldehyde and FRPs, specifically quaternium-15, as well as diagnosis and prevention of this skin condition.

Case Report

An 83-year-old female presented to the dermatology office complaining of pruritus of a three-month duration involving both her upper and lower extremities. Five years prior she was patch tested with the T.R.U.E. Test® due to an eczematous dermatitis of unknown duration, and she had positive reactions to formaldehyde and quatermerium-15. Allergen avoidance at that time yielded complete resolution of her condition. At her initial presentation to our office, a skin biopsy of the right forearm demonstrated a subacute spongiotic dermatitis (eczematous dermatitis) consistent with nummular/contact dermatitis. Pertinent history revealed she almost exclusively wore wrinkle-resistant clothing and cotton/polyester blends.

A standard patch-testing series revealed relevant positive reactions to formaldehyde and several formaldehyde-releasing preservatives (Figure 1). The patient had four positive reactions, to formaldehyde, quartenium-15, 5-chloro-2-methyl-4-isothiazolin-3-1, and 2-hydroxy-4-methoxybenzophenone. Additionally, this patch testing revealed pertinent positive reactions to other chemicals, including 2,5-diazolidinyl urea, DMDM hydantoin, ethylene urea melamine formaldehyde mix, dimethylol dihydroxy ethylene urea and triethanolamine. Patient education, along with allergen avoidance of specific textiles, once again resulted in complete resolution of her skin condition.

Discussion

Formaldehyde is easily soluble in polar solvents and also exists as a colorless gas. It is well known in its commercial form, formalin, which contains 37-50% formaldehyde by weight. Methanal, oxymetholone and p-Formaldehyde are other commonly encountered names for formaldehyde that may be seen on pack-
Formaldehyde-releasing preservatives are a common but often unrecognized entity. These chemicals are routinely found in both prescription and over-the-counter topical medications, as well as in cosmetics and household products. Formaldehyde- and FRP-treated fabrics can pose a problem in any sensitive patient, as in the case we presented. Pertinent clinical history, physical exam, appropriate patch testing and specific allergen avoidance are all crucial elements to diagnosing and preventing allergic contact dermatitis to formaldehyde and FRPs.

**REFERENCES:**

Case Report

A 10-year-old Hispanic male was referred to the emergency department by his pediatrician the evening of October 30, 2006, to rule out Stevens-Johnson syndrome. He presented with persistently high fever and a diffuse, generalized rash with bilateral involvement of palms and soles. The patient admitted to a burning sensation over affected areas with light touch. Past medical history was significant for obesity, reactive airway disease and fatty liver disease. The patient reported no allergies. Review of systems was otherwise unremarkable. Patient medications included Singulair and Advair. The only over-the-counter medication, ibuprofen, was given subsequent to commencement of the rash.

On physical examination, his vital signs showed: blood pressure 138/84 mmHg, HR 125 beats/min, RR 22 breaths/min, temperature 102.7°F. Physical findings were positive for non-purulent bilateral conjunctival hyperemia, mild pharyngeal erythema and exudates, an erythematous and edematous tongue, widely disseminated, blanchable targetoid lesions, and bilateral palmoplantar macules and papules. The patient had no cervical lymphadenopathy. Palms and soles were sensitive and tender to touch.

Laboratory data demonstrated elevated WBC 17,000 microliters with a predominance of neutrophils, slightly elevated prothrombin time 14.8 seconds, elevated total bilirubin 2.4, elevated AST 103 and ALT 145, and elevated ESR 9. Mycoplasma titers were negative. Rapid strep test was negative, ruling out Scarlet Fever. The patient was admitted with a presumptive diagnosis of viral exanthem vs. Kawasaki disease. Consults were ordered with cardiology, infectious disease and gastroenterology. A dermatology consult was not ordered. The patient was started on Azithromycin 900 mg IV and ibuprofen 600 mg every six hours.

The patient was hospitalized for six days. On day one, gallbladder and liver ultrasound were normal. On day two, fever persisted with a maximum temperature of 101.9°F, and the patient’s lips were beginning to peel. Azithromycin and ibuprofen were discontinued. The patient was started on oral aspirin 650 mg every six hours and IVIG therapy in titrated fashion. The patient received a total infusion of 170 mg every 10 to 12 hour period. On day four, status post IVIG infusion, the rash was beginning to clear and the patient was afebrile. The patient reported two episodes of emesis, one episode of diarrhea, epistaxis of the left nostril probably secondary to nose picking, and anorexia. Labs had improved, with CRP 15.93, ESR 13, WBC 11.4. Echocardiogram was negative for evidence of coronary artery disease. Aspirin was decreased to 325 mg, and discharge was postponed for 24 hours pending further observation. On day five, the patient remained afebrile with improvement in rash. The patient continued on aspirin 81 mg daily. On day six, he was discharged in the care of his parents and told to take the following oral medications daily: aspirin 81 mg, lansoprazole 30 mg, and loratadine 10 mg.

The patient was seen by his pediatrician 16 days post admission. His hands and feet were beginning to peel, but all other symptoms had improved. Labs showed improvement: AST 41, ALT 75, ESR 21, WBC 7.7, platelets 465, CRP 0.17. The patient was told to continue aspirin 81 mg daily for one more month. Upon follow-up, he had no symptoms.

Discussion

Kawasaki disease (KD), also referred to as mucocutaneous lymph node syndrome, is an acute systemic vasculitis that predominantly affects children. In 1967, Dr. Tomisaku Kawasaki first developed clinical diagnostic criteria, prior to which

ABSTRACT

Kawasaki disease (KD) is an uncommon syndrome characterized by polymorphous rash involving mucous membranes, high fever, and lymphadenopathy. Early recognition and treatment in the acute phase of this condition is essential to minimize risk of coronary sequelae. A 10-year-old Hispanic male was referred to the emergency department by his pediatrician for evaluation of a generalized rash including palms and soles to rule out suspected Stevens-Johnson syndrome. Complete medical work-up, including history, physical evaluation and laboratory data, resulted in the rendering of a diagnosis of Kawasaki’s Disease.

This article will encompass a detailed case report of KD and review of the literature including etiology, epidemiology, diagnostic criteria, differential diagnoses, therapy, prognosis and current outcome of the patient.
Systemic vasculitides tend to affect the elderly and the young. In the elderly, large-vessel disease will occur, as seen in giant-cell arteritis and primary systemic vasculitis, whereas in children there is a predilection for coronary vessels. These vasculitic changes subsequently lead to formation of coronary artery aneurysms and possibly myocardial infarction and death.

Acute symptoms of KD are considered self limited, but because of the aforementioned pathogenesis it is important to diagnose and treat patients early in the acute phase of the disease. KD has become the leading cause of acquired heart disease. Acute symptoms of KD usually subside within a few weeks or months; however, long-term outcomes in patients with coronary aneurysms are unknown. The mortality rate is lower than 1%.

Incidence of KD is highest in Japan, at >100/100,000 children less than five years of age. Reported incidence rates are lower in the USA at 9.2, in South Korea at >45, Australia at 3.7 and the UK at 3.4 per 100,000, according to a recent Australian Pediatric Surveillance Unit study. These rates do not include any atypical cases without cardiac complications. Prevalence is higher among boys than girls, with a ratio of 1.3-1.7:1. While children from all ethnic backgrounds can develop this condition, incidence remains highest among those of Asian descent.

The etiology of KD has not been elucidated; however, several sources suggest genetic predisposition, infectious causes or immunogenic causes. Postulated pathogens include staphylococci, streptococci, bacterial rickettsiae, Epstein-Barr virus, parvovirus, retrovirus, Candida albicans, herpes virus-6, and even mycoplasma pneumoniae, which has been cited in French literature. Review of the literature demonstrates no conclusive putative agent.

There has also been speculation of an association with house dust mites, detergents, or chemicals. An article published in the British Journal of Medical Science reported possible association between anionic detergents in carpet shampoo after the 1982 outbreak of KD in Colorado. It suggested that the anionic detergents in the shampoo provoked a hypersensitive reaction ultimately manifesting as KD. The other possibility was that this causative agent underwent aerosolization and subsequent inhalation upon the carpet cleaning process. A subsequent study published by Rogers et al. in 1985 was unable to establish a similar link, and thus these proposed theories remain in doubt. The same article [Lloyd, A.J. et al, Kawasaki Disease: is it caused by an infectious agent?, British Journal of Biomedical Science, 2001, 58:122-128.] also noted the house mite as a proposed allergen, suggesting it may be a vector for potentially infectious agents (e.g. Propionibacterium acnes) implicated in KD, although this too remains undetermined. The same was concluded for proposed links between chemicals in standing bodies of water and mercury poisoning. None of these associations has been irrefutably established in the literature.

One immune-mediated mechanism that has been examined is that of the superantigen theory. Strains of Staphylococcus aureus that express toxic shock syndrome toxin-1 (TSST-1) have been isolated in Kawasaki disease. These superantigens activate large numbers of T cells, specifically T-cell receptor V beta segments. These TCR V beta segments demonstrate T-cell expansion consistent with superantigen-driven T-cell proliferation. A case report of guttate psoriasis after Kawasaki disease reported in the British Journal of Dermatology is just one incidence that may corroborate this theory. Guttate psoriasis has been suggested partly to result from toxin-mediated T-cell activation.

Another interesting development has been the isolation of New Haven coronavirus (HCoV-NH) in respiratory secretions of KD patients. A study conducted by Esper et al. established a positive association between this virus and KD. This study suggested that patients with certain genetic backgrounds may be predisposed to such a viral infection and development of KD. More research is needed, however, to confirm the presence of the virus in Kawasaki disease.

The incidence of KD among siblings is high and thus suggests a genetic component.
that makes individuals susceptible to development of the condition. Atopic disease has also been studied because it shares immunoregulatory abnormalities with KD. The following studies reveal specific abnormalities associated with atopy: A study by Matsuoka et al. demonstrated that positive family history of allergy was more common in children with KD than in the control patients;17 Furukawa et al. demonstrated that there were increased levels of CD23+ B lymphocytes and serum IgE during the latter part of the acute stage of KD;18 a study by Tang et al. showed a correlation between an anti-Dermatophagoides pteronyssinus specific IgE19; and Matsubara et al. indicated a decrease in the number of interferon-gamma producing T cells but not the interleukin-4 producing cells in acute stages of KD.20

Kawasaki disease is typically a diagnosis of exclusion once differentials have been ruled out. This will often require a battery of tests to eliminate the possibility of Scarlet Fever, Staphylococcal scalded skin syndrome, Stevens-Johnson syndrome, toxic shock syndrome, measles, juvenile rheumatoid arthritis, and drug reactions.

Un-treated cases of KD or those treated with aspirin alone can lead to coronary lesions in as many as 20–40% of patients.21, 22, 23, 24 These percentages vary depending on the literature. Given this potential prognosis, it is paramount to treat patients early and possibly avoid the coronary sequelae. KD is treated with high-dose aspirin for its anti-inflammatory properties. Aspirin is administered at levels of 80–100 mg/kg/day, and subsequently reduced once fever has abated. Reduced levels of aspirin are given for its anti-platelet properties at levels of 3–5mg/kg/day once daily and continued for six to eight weeks until a follow-up echocardiogram is performed. Concurrent administration of intravenous immunoglobulin (IVIG) is given at 2g/kg infused over a 10-hour period. The role of IVIG is unclear, but it is suggested that it may provide passive immunity to the causative antigen(s) and have non-specific immunomodulatory effects.25 Opinions vary on response to therapeutic prevention of coronary artery aneurysms. Data reported in the current literature indicates that treatment usually reduces the formation of coronary artery aneurysms to 4–8%.21, 22, 23, 24

Corticosteroids have long been used to treat systemic vasculitides, yet their use in the treatment of KD remains a subject of debate. Use of corticosteroids as therapeutic agents in the management of KD compared to the management of other systemic vasculitides is controversial. Corticosteroids may adversely affect outcome by causing progression of coronary lesions. A case report in 2004 studied the use of pulse methylprednisolone (30mg/kg) in two refractory cases of KD patients (non-responsive to two IVIG infusions). Results were not in favor of this therapy, as one patient had a satisfactory outcome while the other developed giant coronary aneurysms and suffered a myocardial infarction two months after onset of illness. Studies were performed on 73 patients with mixed results, but still showed that corticosteroid therapy should be considered a feasible alternative in patients who have refractory KD and have failed two infusions of IVIG of 2g/kg.26

If a clinician has a high index of suspicion for Kawasaki disease, even in the absence of all the previously ascribed features of this condition (e.g. in the setting of a child with high fever, polymorphous rash, and elevated CRP and ESR levels), treatment should be instituted immediately. An initial echocardiogram should be performed and then redone at six to eight weeks at follow-up. It has also been recommended that the patients undergo annual echocardiogram at one and two years after initial onset of illness.27 Further information can be provided to the families of these patients via the Kawasaki Foundation on the Internet. The website is www.KDfoundation.org.

In summary, we have presented a patient manifesting the acute phase of KD, treated with intravenous immunoglobulin and high-dose aspirin, discharged from the hospital, and following up with his pediatrician. One year later he continues to do well. His labs to date have normalized, and his most recent echocardiogram has been negative for coronary artery aneurysm formation.

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Case Report

A 65-year-old Hispanic female presented with a seven-year history of having a large, erythematous plaque on her right leg measuring 4 cm in diameter. She denied any history of ulcers or any discharge. Her primary care physician previously treated her with antibiotics for cellulitis without improvement. As the plaque continued to expand, the erythema intensified to a wine-colored, slightly raised lesion that was tender, swollen, and warm to the touch. Imaging was done to rule out a DVT after her right leg was noted to be larger in circumference. Past medical history included hypertension, arthritis, and borderline diabetes. She was a retired window-factory worker who handled aluminum and other metals for 20 years. The patient had no significant family history of skin disease.

On physical examination, the patient was found to have an erythematous to violaceous, slightly elevated plaque with some nodularity measuring 16 cm x 10 cm on the right lower leg (Figure 1). She had +1 pitting edema on the right leg and minimal edema on the left leg. Her right leg was slightly tender to the touch.

A 3mm punch biopsy showed sections sparing the upper dermis; epithelioid tubercles incompletely surrounded by lymphocytes; and fibroplasias of the subcutis consistent with a granulomatous inflammation (Figure 2, 3). Acid-fast cultures, as well as fungal cultures, were negative. The patient was diagnosed with subcutaneous sarcoidosis.

Complete blood count, complete metabolic panel, and rheumatoid factor were within normal limits. Her cholesterol, triglycerides, antinuclear antibody (ANA) titer, angiotensin-converting enzyme (ACE) level and erythrocyte sedimentation rate (ESR) were slightly elevated.

Chest X-rays showed cardiomegaly but no acute pulmonary disease. CT of chest and abdomen were within normal limits. A Gallium scan performed on the whole body showed no focal abnormal activity. Two separate venous Doppler exams of the right lower extremity demonstrated no evidence of deep venous thrombosis. An ophthalmologic examination only showed early cataract and presbyopia.

Various therapies were instituted over several months including terbinafine, clobetasol 0.05 percent ointment, rifampin, doxycycline, minocycline, and injections of triamcinolone 5mg/cc to the subcutaneous nodules. The erythema on her right leg fluctuated in intensity, but never fully resolved. Because of her history of borderline diabetes, she was placed on plaquenil, which demonstrated significant improvement initially. Prednisone was then added at a low dose. The combination of Plaquenil and prednisone seem to keep the erythema, nodularity, and thickness of the plaque under relative control. The patient will continue to be monitored with serum ACE levels periodically.

Discussion

Sarcoidosis is a systemic granulomatous disease that affects the skin in approximately 25% of cases. Internal organs may be involved as well, including the lungs, mediastinal and peripheral lymph nodes, eyes, phalangeal bones, myocardium, central nervous system, kidneys, spleen, liver and parotid gland. Sarcoidosis occurs worldwide and affects both men and women. However, it seems to be most prevalent among African American women. A bimodal age distribution is seen, with peaks between ages 25-35 and 45-65 years. The exact etiology of sarcoidosis is unknown; however, the cell-mediated immune system appears to be involved. Genetics and environmental factors are also thought to contribute in the disease process. Since the cutaneous manifestations are so varied and it can have
almost any morphology, sarcoidosis is often known as the “great imitator.” Variants include subcutaneous, lupus pernio, and ulcerative.

Subcutaneous sarcoidosis was first described in 1906 by Darier-Roussy and is considered a rare, specific subtype of nodular cutaneous sarcoidosis. The nodules were often referred to as Darier-Roussy sarcoid, but the eponym is considered nonspecific because it was used to describe many subcutaneous inflammatory disorders. The lesions of subcutaneous sarcoidosis are typically non-tender, firm, mobile, flesh-colored or violaceous nodules that range in size from 0.5-2 cm in diameter, usually on the trunk or extremities. It represents sarcoidosis limited to the subcutaneous tissue, since it does not involve the epidermis. In order to make the diagnosis of subcutaneous sarcoidosis, a biopsy is required.

Histopathologically, subcutaneous sarcoidosis is demonstrated by epithelioid cell tubercles in the subcutaneous fat. The epithelioid granulomas have minimal or absent lymphocyte or plasma cells associated with them and are known as “naked” tubercles. Central caseation is usually absent, and multinucleated histiocytes are usually present. Biopsy specimens may need special stains to rule out infectious causes of granuloma formation, including mycobacterial and deep fungal infections.

The diagnosis of subcutaneous sarcoidosis is a diagnosis of exclusion, both clinically and histologically. In order to make the diagnosis, the clinical history should be supported by the presence of non-caseating granulomas in at least one organ system. Subcutaneous sarcoidosis usually indicates a form of sarcoidosis with non-severe systemic involvement and is not associated with chronic fibrotic disease. Recommended laboratory studies include complete blood count with differential, serum calcium and 24-hour urine calcium levels, serum ACE level, serum chemistries, ESR, and ANA titers. Imaging studies recommended include chest radiography, CT of thorax, and whole body gallium Ga 67 scanning. ACE level can be used to monitor the progression of the disease.

The differential diagnosis for sarcoidosis is extensive and includes multiple infectious causes that lead to granulomatous inflammation. Since sarcoidosis is a diagnosis of exclusion, other dermatologic conditions that need to be considered include: granuloma annulare, necrobiosis lipoidica, annular elastocytic giant-cell granuloma, rheumatoid nodules, Crohn’s disease, granulomatous mycosis fungoides, granulomatous rosacea, tuberculoid leprosy, and lupus vulgaris. Other histiologic mimics include foreign-body reactions to zirconium, beryllium, silica, and tattoo ink.

The mainstay of therapy is oral corticosteroids. Topical and intralesional corticosteroids can also be useful in treating cutaneous lesions. Therapy is guided by the severity of the disease and its progression. Hydroxychloroquine and chloroquine can be effective in controlling chronic disease. Other treatment options include: methotrexate, thalidomide, isotretinoin, minocycline, and allopurinol. Radiation has also been used to treat resistant cutaneous lesions. Since subcutaneous sarcoidosis is rare, many of the treatment options are based upon few reported cases. Consults from other specialists, such as an ophthalmologist, an internist, and a pulmonologist, are recommended to rule out and monitor other organ involvement.

REFERENCES:
PIGMENTED SQUAMOUS CELL CARCINOMA OF THE SKIN: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Pigmented squamous cell carcinoma is a rare neoplastic entity that is easy to confuse both clinically and histologically with malignant melanoma. Misdiagnosis as melanoma portends a more severe prognosis and leads to unnecessary treatment and work-up. We describe what appears to be the first case in the literature of a poorly differentiated, pigmented squamous cell carcinoma with basaloid features, as well as a review of the English literature. Recommendations are made for future characterization and understanding of why melanocytes colonize squamous cell carcinomas.

Case Report

A 78-year-old Caucasian male presented with a 30 mm erythematous and centrally ulcerated plaque to his left temple with an overlying dried hemorrhagic crust. The patient’s primary care physician had performed cryosurgery to the area “many times” prior to its evaluation by a dermatologist. A shave biopsy was performed, and upon lifting the lesion off the temple a black nodule was noted within the dermis. A punch biopsy was performed on the underlying black nodule.

Biopsy sections revealed a nodular and reticulated, sheet-like dermal proliferation of neoplastic cells with basaloid morphology, extracellular keratin formation and mucin production. Some of the tumor cells contained brown pigment within their cytoplasm, suggestive of melanin pigment. Scattered mitotic figures were seen as well as epidermal ulceration. Immunohistochemical staining was negative with S-100, ruling out melanoma. The findings were consistent with an invasive carcinoma with features of both basal and squamous cell carcinoma. Additional immunohistochemistries demonstrated focal positivity with BCL-2, cytokeratin 5/6 and Ber-EP4, and negative EMA. The added immunohistochemistries and the morphology are most consistent with a basal cell carcinoma.

The patient was referred for Mohs micrographic surgery, but was lost to follow-up for 59 days due to his having suffered a stroke. At the time of Mohs surgery, the lesion clinically resembled a malignant melanoma, and histologically demonstrated poorly differentiated malignant cells with basaloid and spindloid features. It was cleared by Mohs with a final postoperative defect of 61 mm. The defect was repaired with a full thickness skin graft.

The specimen was sent for repeat immunohistochemical analysis due to the lesion’s clinical appearance and the presence of plump dendritic melanocytes on histology. The specimen from the Mohs case demonstrated infiltrative and expansile nests and cords of atypical and poorly differentiated basal-squamoid cells with focal single cell necrosis and a background desmoplastic response. Numerous melanophages and pigmented dendritic melanocytes were associated with the proliferation. Sub-optimal fixation of the original biopsy was questioned, and the immunohistochemistries were repeated. Anti-S-100 and anti-MART-1 confirmed the presence of innumerable, focally enlarged dendritic melanocytes diffusely spread throughout the cellular proliferation. A few cords and nodules of the tumor cells show relative lack of proliferation of the dendritic melanocytes.

Similar to the initial biopsy, anti-pancytokeratin (AE1/AE3) did not reveal significant immunoreactivity within the tumor cells. Anti-cytokeratin 5/6 revealed focal cytoplasmic immunoreactivity within a few cords of malignant cells, scattered single cells and areas of keratinization. Anti-Ber-EP4 demonstrated a weak but relatively diffuse membranous immunoreactivity within the tumor cells. The immunohistochemistries support the diagnosis of a baso-squamous infiltrative and poorly-differentiated carcinoma with numerous intralesional dendritic melanocytes. No evidence of melanoma was present, and the final diagnosis was that of a pigmented squamous cell carcinoma with basaloid features. At the patient’s four-month follow-up, he was clinically disease free.

Discussion

Pigmented squamous cell carcinoma (PSCC) of the skin is a rare tumor. To date in the English literature, 21 cases exist in the non-English literature.5 The frequency range of pigmented squamous cell carcinoma commonly reported in the literature is 0.01% to 7%.6,11 Of the reported cases of PSCC of the skin, 89% involve the head.1,3-7,9-12 The other case reports involve the scrotum8 and chest;2 however, Becker’s series did not address the location of the lesions.13

The clinical differential diagnosis of pigmented skin lesions include melanoma, pigmented basal cell carcinoma, pigmented Bowen’s disease, capillary thrombosis,
Focally positive for S-100 and HMB-45, al. noted that some neoplastic cells stained antigen and negative for S-100.6,7 Jurado et al. cytokeratins and epithelial membrane positive for low and high molecular weight pigmented squamous cell carcinoma stain is 32 PIGMENTED SQUAMOUS CELL CARCINOMA OF THE SKIN: A CASE REPORT AND REVIEW OF THE LITERATURE. The histologic features. 4,6,7,11. Immunohistochemistry of melanocytes with benign cytologic atypia, mitotic figures and dyskeratosis and produces keratin horn pearls.6,7 Finally, PSCC is defined by intratumoral melanin pigment and colonization by dendritic melanocytes with benign cytologic features.4,5,11 Immunohistochemistry of pigmented squamous cell carcinoma stain is positive for low and high molecular weight cytokeratins and epithelial membrane antigen and negative for S-100.6,7 Jurado et al. noted that some neoplastic cells stained focally positive for S-100 and HMB-45, which was speculated to be due to antigenic transference or release of soluble protein from the cytoplasm of the dendritic melanocytes.3

Jauregui and Klintworth demonstrated that the squamous carcinoma cells phago-cytose melanin granules from the tips of dendritic melanocytes.15 (missing a verb here, and I don't know what it's supposed to be) Kuwabara et al. described the intimate relationship between the neoplasm and melanocytic dendritic processes as well as the presence of mature melanosomes in the carcinoma cells with very few premelanosomes.9 Speculation exists as to the mechanism of pigment induction within the neoplasm. The possibility of pigment induction due to collision with a lentigo or melanocytic nevus has been proposed.14 Other hypotheses include divergent deriva-tion of melanocytes from matrix stem cells and neoplastic production of a yet-to-be discovered factor inducing migration and proliferation of melanocytes.36 Satomura et al. demonstrated the increased production of stem cell factor and endothelin-1 in PSCC versus the nonpigmented SCC control.14 Dermoscopy is a useful tool to determine the characteristics of a pigmented skin lesion.37 Three of the PSCC case reports include results from dermoscopic analysis. Diffuse blue to grey-blue pigmentation is noted, either blue-grey granular or grey-brown to slate-blue nodular structures without peripheral pigment network, milia-like cysts, dots, globules, or truncated vessels.5,4,10 Ohnishi appreciated that the pigmented lesion was indistinguishable from a pigmented basal cell carcinoma by dermoscopy.1 The recommendation of Zalaudek et al. is to include PSCC in the differential diagnosis of pigmented skin lesions with homogenous blue pigmentation.2

Conclusion

We describe the case of a pigmented squamous cell carcinoma with basaloid features. This neoplasm appears to follow a similar course to classical SCC with no reported recurrences; however, the reported number of cases is quite small.3,5,6 Future research needs to focus on ultrastructural and immunohistochemical analysis of those squamous cell carcinomas with pigmentation to determine the stimulus for melanocytic colonization and pigmentary transfer to the neoplasm.

References

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Please see the brief summary of full prescribing information on adjacent page.
doxycycline. There have been reports of pseudotumor cerebri (benign intracranial hypertension) associated with
avoid contraceptive failure, females are advised to use a second form of contraceptive during treatment with
bismuth subsalicylate, proton pump inhibitors, antacids containing aluminum, calcium or magnesium and
iron-resistant bacteria to develop during the use of ORACEA, it should be used only as indicated.

Pseudotumor cerebri:
Some conditions disappeared when the drug was

Tissue Hyperpigmentation:

Photosensitivity:

As with other antibiotic preparations, use of ORACEA may result in overgrowth of non-susceptible micro-
organisms, particularly yeasts. If superinfection occurs, ORACEA should be discontinued and appropriate therapy
instituted. Although not observed in clinical trials with ORACEA, the use of tetracyclines may increase the
incidence of vaginal candidiasis.

ORACEA should be used with caution in patients with a history of or predisposition to candidiasis overgrowth.

Bacterial resistance to tetracyclines may develop in patients using ORACEA. Because of the potential for drug-
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Autoimmune Syndromes: Tetracyclines have been associated with the development of autoimmune syndromes. Symptoms may be manifested by fever, rash, arthropathy, and malaise. In symptomatic patients, liver function tests, ANA, CBC, and other appropriate tests should be performed to evaluate the patients. Use of all tetracycline-class drugs should be discontinued immediately.

Tissue Hyperpigmentation: Tetracycline-class antibiotics are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), skin and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administered, whereas other pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as over sites of scars or injury.

Pseudotumor cerebri: Pseudotumor cerebri occurs primarily in infants from doxycycline, ORACEA should not be used in mothers who breastfeed. (see WARNINGS section).

Nursing Mothers: ORACEA has not been studied in children of any age. Nurses should use contraceptives during treatment with ORACEA.
Case Presentation:

A 26-year-old African American female presented to the emergency room with a three-day history of progressively worsening fever, irritability, and malaise. The patient also complained of recent onset suprapubic pain and swelling with severe tenderness and redness along the abdomen at the site of longstanding hidradenitis suppurativa. She denied any recent medications and reported feeling well until the abrupt onset of the above symptoms.

The patient's past medical history was significant only for longstanding, refractory hidradenitis suppurativa of the axillae and suprapubic area. She had received numerous prolonged antibiotic courses in the past, but she denied any recent treatment for this disease. Family history was negative for any associated diseases or similar reactions. The patient had no known drug allergies, and although she admitted to multiple courses of antibiotics in the past, she denied any recent medications.

Within 24 hours of admission, a generalized eruption of flaccid bullae occurred with an abrupt onset of severe hemodynamic instability. The patient was transferred to ICU care and subsequently was intubated secondary to declining mentation and respiratory compromise. Empiric antibiotics were initiated, but dermatologic consultation was not obtained until generalized desquamation began on day three of hospital admission.

Physical examination upon dermatologic consultation revealed an obese, dark-skinned female who was being maintained with ventilator assistance. She was unresponsive to verbal or physical stimuli and was hemodynamically stabilized with pressor and fluid support. Cutaneously, there was diffuse erythema to the entire body with sparing only of the palms and soles, and there was scattered plate-like desquamation with a proclivity toward intertriginous areas. There were a few intact flaccid bullae present, and the epidermis of intact skin was able to be easily sheared with slight pressure (positive Nikolsky's sign). Minimal facial edema was present, with mild perioral crusting and fissuring, but no oral lesions were present. Examination of the lower abdomen and groin revealed several erythematous, eroded nodules with tracting and oozing of purulent material in the suprapubic area, medial buttocks, and gluteal fold.

Blood cultures obtained at the time of admission returned positive for methicillin-resistant *Staphylococcus aureus*. Cutaneous bacterial swab cultures taken at the time of admission to unspecified locations were negative. Empiric antibiotics were discontinued and replaced with intravenous vancomycin. Two separate 4mm punch biopsies were obtained from the right arm and buttocks area for histological analysis.

Cutaneous therapy with topical steroids and emollient-impregnated dressings was instituted, with continuation of hemodynamic and airway support.

Histological evaluation of the biopsies revealed a sharply demarcated zone of cleavage at the stratum granulosum. A few acantholytic keratinocytes were present with mild perioral crusting and fissuring, but no oral lesions were present. Examination of the lower abdomen and groin revealed several erythematous, eroded nodules with tracting and oozing of purulent material in the suprapubic area, medial buttocks, and gluteal fold.

Blood cultures obtained at the time of admission returned positive for methicillin-resistant *Staphylococcus aureus*. Cutaneous bacterial swab cultures taken at the time of admission to unspecified locations were negative. Empiric antibiotics were discontinued and replaced with intravenous vancomycin. Two separate 4mm punch biopsies were obtained from the right arm and buttocks area for histological analysis.

Cutaneous therapy with topical steroids and emollient-impregnated dressings was instituted, with continuation of hemodynamic and airway support.

Histological evaluation of the biopsies revealed a sharply demarcated zone of cleavage at the stratum granulosum. A few acantholytic keratinocytes were present with mild dermal edema. Additionally, there was a minimal inflammatory infiltrate with no epidermal necrosis present. The findings were consistent with the diagnosis of SSSS. No organisms were seen, and deep fungal cultures were also negative.

Viral swab cultures and repeated bacterial cultures of suprapubic, groin, and buttocks areas revealed negative findings.

Due to the above clinical, laboratory, and histological findings, a diagnosis of SSSS was given. The patient was continued on antibiotic and wound therapy as well
as ICU support. Her condition stabilized and then slowly began improving. She was eventually weaned off support systems and was discharged approximately two weeks after admission without obvious permanent sequelae.

**Discussion:**

SSSS was first described in 1956 and is part of a spectrum of infectious toxin-mediated disorders that also includes toxic shock syndrome and bullous impetigo. It is a rare disease that occurs primarily in infants and children less than six years of age, but can occur even more rarely in adults. Underlying chronic renal insufficiency and immunosuppression are predisposing factors.

SSSS is typically initiated by a localized infection of *Staphylococcus aureus*, most commonly at a remote site such as the nasopharynx or mucosal cavities. The cutaneous manifestations are incited by the release of exfoliative exotoxins and epidermolysins, which are produced by various strains of both methicillin-resistant and methicillin-sensitive *S. aureus* but mainly by strains from phage group II.

There are two human types of *S. aureus*-derived exfoliative toxins, ETA and ETB, and *S. aureus* uses these exfoliative toxins to proliferate by disrupting the epidermal barrier. Specifically, these exfoliative toxins bind directly with desmoglein-1, causing a conformational change that inspires a cleavage of the extracellular domain of desmoglein-1. This interaction results in the development of a split and sterile bullae formation at the granular layer of the epidermis.

Clinically, SSSS characteristically manifests as an acute, generalized exfoliative dermatitis. There may be an associated prodromal phase of fever, malaise, irritability or tenderness of the skin, as well as signs of a localized bacterial infection such as rhinorrhea, conjunctivitis, or abscess.

Erythema often first begins on the head and progresses to incorporate the entire body within 48 hours. The skin then takes on a wrinkled, sandpaper-like appearance with the development of flaccid bullae. The Nikolsky sign is positive, and within one to two days a sheet-like desquamation occurs, leaving behind areas of shallow denudation and thin crust. Facial edema and perioral crusting can occur, and although most pediatric patients do not appear severely ill, dehydration and hypothermia can ensue, and affected individuals (especially adults) can rapidly progress to the need for ICU supportive care. The mortality rate for pediatric patients is approximately 3% but approaches 50% for adults and can be much higher in patients with comorbid disease states.

Histologically, there is a sharply demarcated zone of intraepidermal cleavage at the granular layer. There is bullae formation but with the absence of inflammatory infiltrate. There is no occurrence of epidermal or keratinocyte necrosis or alteration, and no organisms are present.

Diagnosis is usually based on typical clinical-presentation characteristics supported by histopathological features consistent with SSSS. Bacterial cultures obtained from the bullae are negative but may be found positive if taken from the initiating infectious nidus. Hematologic infection does not usually occur in children, but blood cultures may be positive in adults. Diagnostic confirmation can be obtained through examination of frozen tissue sections or identification of serum exfoliative exotoxins through either slide latex agglutination or ELISA testing.

Management of patients with SSSS varies depending on the severity of the illness but typically requires hospitalization for supportive care, observation, and institution of oral or parenteral ß-lactamase-resistant antibiotics (or sensitive agents of MRSA). Mild pediatric cases can be successfully treated with admission to general pediatric units. More severe cases, though, and especially adult cases, should be maintained in an ICU or burn-unit environment where close supervision, intensive skin care, and ventilator as well as hemodynamic support can be offered.

Bland emollients should be applied to the denuded areas of the skin for lubrication and to decrease tenderness and pruritus. Affected newborns should be isolated from other neonates. Finally, it is important to identify *S. aureus* carriers so that treatment can be instituted.

**References:**

1. King, Randall W, et al. Staphylococcal Scalded Skin Syndrome. eMedicine from WebMD.
Case Report

A 54-year-old female presented to our clinic in July 2003 with a 25-year history of vulvar lichen sclerosus treated with betamethasone and testosterone ointments. She reported intermittent control and partial resolution of symptoms. While initially controlled, she had begun to experience an increase in pruritus, dysuria and vulvodynia in the three months preceding the initial office visit. Treatment options were discussed, but the patient declined any new therapies and was continued on topical betamethasone ointment.

She presented to the office six months later with continued symptoms. Treatment options were again discussed, and the patient opted for more aggressive therapy. She was started on hydroxychloroquine 200 mg daily with increase to twice daily dosing after two weeks of therapy. She was also given clotetasol 0.05% ointment, tacrolimus 0.1% ointment and testosterone 2% cream for topical use twice daily. At one month follow-up, the patient reported complete resolution of pruritus and dysesthesia. There were no objective signs of atrophy at that time. However, over the next nine months the patient experienced only one symptom-free month. She was subsequently lost to follow-up for 18 months.

She returned to the clinic in June 2007. Over time, the patient had experienced repeated, more frequent flares despite therapy with Plaquenil (hydroxychloroquine), class-I topical corticosteroids, topical testosterone and topical tacrolimus. Her symptoms of pruritus and burning were so severe that the patient had to file for short-term disability as she was only comfortable at home in recumbent position. She was placed on cyclosporine 100 mg daily and was slowly weaned off hydroxychloroquine. At two-week follow-up the patient reported some improvement in pruritus and dysesthesia, and atrophy was objectively improved. Cyclosporine was gradually increased to 100 mg three times daily over the following month. Symptoms were markedly decreased, and the patient remained stable for an additional two months, at which time cyclosporine was slowly tapered off. By February 2008, the patient reported complete resolution of symptoms and was completely weaned off cyclosporine, requiring only occasional use of topical corticosteroids. At the time of publication, the patient continued to remain symptom-free, reporting the only “true” resolution of her symptoms in 25 years and a return to activities she had long ago abandoned.

Discussion

Lichen sclerosus (LS) is a relatively uncommon, chronic, inflammatory mucocutaneous disorder of unknown etiology that can lead to vulvar atrophy and scarring. Various hormonal, infectious, autoimmune, genetic and cell-mediated immune responses have been associated with the disorder; however, the exact origin of LS is unknown.1,2,3,4,5,6 It is most commonly treated with topical corticosteroids and calcineurin inhibitors.7,8,9,10 There are few well-studied alternatives for those patients failing these treatment modalities. Baskan et al. reported five patients with refractory vulvar LS treated successfully with oral cyclosporine.1 To date, there has been no other similar study. We present a case that supports cyclosporine therapy in recalcitrant vulvar lichen sclerosus.

REFERENCES

5. Fujisawa H. et al. Detection of Borrelia burgdorferi DNA (B garinii or B afzelii) in morphea and lichen sclerosus et atrophicus tissues of German and Japanese but not from US patients. Archives of Dermatology 1997; 133(1): 41-44
CASE REPORT OF EXTRAGENITAL LICHEN SCLEROSIS ET ATROPHICUS IN AN ADOLESCENT FEMALE

2001;144(2): 387-392
Case Report

A 73-year-old Caucasian woman presented with a 20-year history of asymptomatic, violaceous nodules of the left periocular area and left chest that waxed and waned. These lesions were previously biopsied over 10 years ago, and were diagnosed as a low-grade follicular center cell lymphoma without evidence of systemic involvement. No chemotherapy was indicated at the time. Over the years, the lesions continued to wax and wane. She denied fever, night sweats, weight loss, or fatigue. Over the last few months, the lesions had gotten quickly larger. For the first time in 20 years, the patient presented with a 20-year history of asymptomatic, violaceous nodules of the left periocular area and left chest that waxed and waned. She denied fever, night sweats, weight loss, or fatigue. Over the years, the lesions continued to wax and wane. She denied fever, night sweats, weight loss, or fatigue. Over the last few months, the lesions had gotten quickly larger. For the first time in 20 years, the patient presented

Medical History

The patient had a history of fibrocystic breast disease, with bilateral mastectomy and breast implants. The patient also had a history of atrial fibrillation. She denied history of Lyme disease, cytomegalovirus, HIV, or Epstein-Barr virus. She had family history of breast cancer, but she denied family history of lymphoma.

Medications & Drug Allergies

The patient was on metoprolol for atrial fibrillation and she reported drug allergies to codeine, penicillin, and ibuprofen.

Examination

There were large, violaceous nodules and masses in the left periocular area (see Figure 1). There were similar lesions on the left anterior chest (see Figure 2) and right posterior flank (see Figure 3), which presented as plaques, papules, and patches. No ulcerations were present. No other bodily sites were involved. There was no fever, lymphadenopathy, or hepatosplenomegaly on exam.

Laboratory

Complete blood count (CBC) with differential and serum chemistries, including liver function tests (LFTs) and creatinine, were within normal limits. LDH was not performed. A peripheral blood smear was normal. Bone marrow aspirate and bone marrow biopsy were normal. Clonality studies revealed a restriction in lambda light chain. No lymph node biopsy was performed, as there was no lymphadenopathy on exam.

Imaging

A PET scan showed uptake in the left periorbital subcutaneous tissue, left upper anterior chest wall, and right axilla. These sites corresponded to cutaneous lesions.

Histopathology

The hematoxylin and eosin (H & E) biopsy showed expansion of the dermis by large, atypical lymphoid cells. A Grenz zone separated these lesional cells from the epidermis, which demonstrated an absence of epidermotropism. These cells had prominent nucleoli and mitotic figures, and were growing in a diffuse pattern. No follicular centers were noted (see Figure 4).

Immunophenotypical stains revealed positive lymphoid markers, such as LCA, and positive markers for B-cell, such as CD20 and CD79a (see Figure 5). T-cell markers, such as CD3 and CD5, were positive along the periphery and represented only reactive T lymphocytes to the lesional neoplastic cells. BCL-2 positivity was questionable. Negative immunophenotypical stains included: CD10, CD30, CD45RO, factor VIII, CK20, synaptophysin, and pancytokeratin.

Diagnosis

Diffuse large B-cell non-Hodgkin’s lymphoma, high grade.

Based on the patient’s workup, she had primary, cutaneous disease without evidence of systemic involvement.

Differential Diagnosis

A close differential diagnosis included high-grade diffuse follicular center cell lymphoma (FCC).


Staging

The patient was staged using the Ann Arbor staging system for non-Hodgkin’s lymphoma as stage IE, and her five-year survival rate was estimated to be between 51% and 73% (See Table 1).

Abbreviations Key

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CBCL</td>
<td>cutaneous B-cell lymphoma</td>
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<tr>
<td>CBCL-PI</td>
<td>cutaneous B-cell lymphoma prognostic index</td>
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<tr>
<td>CHOP</td>
<td>cyclophosphamide, doxorubicin, vincristine, prednisone</td>
</tr>
<tr>
<td>CHOP-R</td>
<td>cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>EORTC</td>
<td>European organization for research and treatment of cancer</td>
</tr>
<tr>
<td>FCC</td>
<td>follicular center cell lymphoma</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
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<tr>
<td>PCBL</td>
<td>primary cutaneous B-cell lymphoma</td>
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<tr>
<td>REAL</td>
<td>revised European American lymphoma classification</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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40 PRIMARY CUTANEOUS B-CELL LYMPHOMA

Course & Treatment

The patient underwent her first course of chemotherapy, which included the CHOP-R regimen consisting of cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab. After the first course of chemotherapy, the patient had dramatic improvement of her cutaneous lesions, with the large facial nodules flattening to patches. However, one week after starting chemotherapy, she suffered a cerebrovascular accident. She was hospitalized for three weeks and had motor and sensory deficits of the left leg and left hand, which improved with physical therapy. She was re-evaluated by her oncologist, who felt that the chemotherapy was not related to her stroke. Therefore, she was continued on chemotherapy, and subsequently suffered bilateral pulmonary emboli and a deep vein thrombosis. Her CHOP chemotherapy was then discontinued. Currently, she is undergoing radiation treatment and intravenous rituximab.

Discussion:

B-cell lymphoma and follicular center cell lymphoma transforming into diffuse large B-cell lymphoma

B-cell lymphomas are a type of non-Hodgkin’s lymphoma. The majority of primary cutaneous lymphomas are T-cell in origin, with B-cell lymphomas comprising a small minority. Primary cutaneous B-cell lymphomas (PCBL) are quite rare. There may be a slightly higher incidence of PCBL in Europe, associated with Borrelia burgdorferi infection. Previous cutaneous B-cell lymphomas were lumped with the systemic forms. They were not recognized as a distinct entity until the 1980s. Therefore, they likely occurred more frequently than previously believed.

The purpose of a staging workup is to calculate prognosis using the International Prognostic Index (IPI)2 (See Table 1). However, the Ann Arbor staging system that is currently used for systemic non-Hodgkin’s lymphomas is less appropriate to stage cutaneous lymphomas, as systemic lymphomas differ greatly in their prognosis compared to primary cutaneous lymphomas.3,4 Staging systems for cutaneous lymphomas have been proposed and include the Cutaneous B-cell Lymphoma Prognostic Index (CBCL-PI), which takes into account histology and bodily sites involved, and the International Society of Cutaneous Lymphoma & Task Force of the EORTC (European Organization for Research and Treatment of Cancer). No system has been universally accepted at this time, and staging systems for cutaneous lymphomas continue to develop.

Classification schemes for cutaneous lymphomas have been controversial and continue to be disputed. Multiple classification schemes have been proposed, and have led to confusion in terminology. The classifications that have been used in the past include the REAL (Revised European American Lymphoma) classification, the WHO (World Health Organization) classification, and the EORTC (European Organization for Research and Treatment of Cancer) classification. The latest classification scheme, the WHO-EORTC, arose from consensus meetings in 2003 and 2004 and lists the types of cutaneous B-cell lymphoma currently recognized (see Table 2).5 Gene studies have attempted to

Table 1

<table>
<thead>
<tr>
<th>Staging Classification</th>
<th>Areas involved</th>
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<tbody>
<tr>
<td>I</td>
<td>Single lymph node region involved (I).</td>
</tr>
<tr>
<td>II</td>
<td>2 lymph node regions involved on same side of diaphragm (II).</td>
</tr>
<tr>
<td>III</td>
<td>Lymph node regions on both sides of diaphragm involved (III).</td>
</tr>
<tr>
<td>IV</td>
<td>Multiple/disseminated involvement of extra-lymphatic organs.</td>
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</tbody>
</table>

<table>
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<tr>
<th>Prognostic factors</th>
<th>Risk</th>
<th>International Prognostic Index (IPI) score</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Low</td>
<td>0-1</td>
<td>73%</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>Low / intermediate</td>
<td>2</td>
<td>51%</td>
</tr>
<tr>
<td>&gt; 1 extranodal site</td>
<td>High / intermediate</td>
<td>3</td>
<td>43%</td>
</tr>
<tr>
<td>High LDH</td>
<td>High</td>
<td>&gt;4</td>
<td>26%</td>
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The Ann Arbor staging system for non-Hodgkin’s lymphoma and the International Prognostic Index (IPI) have been used to predict prognosis. Each factor is assigned one point, and cumulative points predict the five-year survival rate. This system is used in systemic lymphomas. Staging systems for cutaneous lymphomas are in development.
The purpose of a staging workup for cutaneous lymphoma is to evaluate for extracutanous involvement and to distinguish between primary and secondary disease. A workup includes history, physical exam, laboratory workup, and imaging.

A history should elicit the chronicity of lesions and their biological behavior. FCCs present as erythematous-to-violaceous nodules and masses on the head, neck, and upper trunk. Typically, there are no lesions of the extremities. These indolent lymphomas may wax and wane and be present for up to 20 years. Long-standing, chronic disease can transform over time to higher grade lymphomas. Aggressive forms of lymphoma, such as DLBCL, have a shorter course and exhibit more aggressive growth patterns.2,6 DLBCL of the leg arises on the legs of elderly women.2,7 Uncommon DLBCL that arises on the head or neck may be very difficult to distinguish from high-grade FCCs.6 Patients may complain of unexplained fever, weight loss, night sweats, and fatigue.4

Examination may reveal cutaneous erythematous-to-violaceous nodules, plaques or patches. The number and location of the lesions are helpful in determining the type of cutaneous lymphoma. A lesional skin biopsy should be performed. In addition to a cutaneous exam, the lymph nodes, liver, and spleen should be palpated to examine if these areas may be involved. A lymph node biopsy should be considered if lymphadenopathy is present on exam.

Laboratory workup should include a CBC with differential, serum chemistries to evaluate liver and renal function, and LDH. Further systemic evaluation may include a peripheral blood smear and bone marrow evaluation.9 Workup should also include imaging, such as computed tomography (CT) of the chest, abdomen, and pelvis or positron emission tomography (PET) scan, to rule out involvement of the lymph nodes and extracutanous organs, and help to exclude systemic disease.3 Clonality studies are not diagnostic of lymphoma, nor can they accurately predict progression towards lymphoma. However, they may help to lean the diagnosis towards malignancy if all other workup is unclear. If clonality studies show a restriction in either lambda light chain or kappa light chain, this may indicate a clonal population of cells, suspicious for malignancy.16 Table 3 shows a summary of staging workup for cutaneous lymphoma.

Differentiating between primary and secondary disease is important to direct treatment and predict mortality (see Table 4). Primary disease originates in the skin, and is limited to skin involvement only. Lymph nodes and organs are not involved. Typically, patients present with upper body lesions. Secondary disease originates in the lymph nodes, and then metastasizes to the skin. Patients usually present with widespread lesions. As expected, these patients have a worse prognosis.

Transformation

There have been reports of indolent low-grade lymphomas transforming into high-grade, more aggressive lymphomas. MALT and marginal zone B-cell lymphomas may transform to DLBCL, DLBCL of the anaplastic variant, Hodgkin's lymphoma, and high grade FCC. Mantle cell lymphomas may transform to a blastic variant of mantle cell lymphoma. Small lymphatic lymphoma/leukemia may transform to DLBCL, DLBCL of the anaplastic variant, and unclassifiable lymphoma resembling Burkitt's lymphoma or lymphoma with blastic morphology, or Hodgkin's lymphoma.2,8,9

Given the chronicity of our patient's lesions and the recent change in biological behavior, we believe that transformation occurred from a low-grade FCC to DLBCL. The risk of transforming to DLBCL can exceed 20% in five years and 30% in 20 years.7 Overall, transformation in cutaneous lymphoma can occur in up to 40%
of cases. Histological appearance and immunophenotypical stains may aid in diagnosing transformation, therefore any rapid change in lesion size or change in biological behavior should prompt re-biopsy to evaluate for transformation.

According to the WHO-EORTC classification scheme, diffuse-pattern FCCs are not classified as FCCs, but instead as DLBCL, and therefore we favor DLBCL as a final diagnosis. FCCs and DLBCL of the leg are two distinct entities that present very differently. There has been little discussion in the literature of the clinical appearance of patients who are transforming from indolent to aggressive lymphomas. This "transition zone" of clinical appearance, histology, etc. that exists can further muddle the clinical picture and can present a challenge to diagnosis (see figure 6). Our patient did not have leg lesions. But given the unclear clinical presentation of a transforming lymphoma, perhaps she does not have leg lesions yet.

**Histology**

Histologically, lymphoid cells are atypical with prominent nucleoli. If the lymphoma is aggressive, multiple mitoses may be easily seen. FCCs resemble the follicular center of a lymph node, and therefore have a nodular pattern of growth of small-to-medium-sized cells. Over time, this nodular pattern is lost, and FCCs take on a more diffuse pattern of growth. The cells also tend to get larger. Once this occurs, diffuse-pattern FCC may closely resemble DLBCL, and distinguishing between these two entities on histology may be impossible, even with immunophenotypical markers.

Immunophenotype will stain positively for lymphoid markers, such as LCA (CD45), and B lymphocyte markers, such as CD20 and CD79a.

The patient had a questionable BCL2-positivity, which may slightly lean the diagnosis towards DLBCL, particularly of the leg type. FCCs are typically BCL2 negative.

**Treatment**

Low-grade, indolent B-cell lymphomas do not require aggressive chemotherapy, and may be observed for malignant transformation. Localized lesions may benefit from radiation therapy. Generalized or multiple-site lesions may make radiation treatment more impractical. Rituximab, an anti-CD20 antibody that targets the CD20 receptor on B cells, is generally used for low- or high-grade B-cell lymphomas. Because aggressive, multi-agent chemotherapy does not improve patient survival or prevent relapse of disease, it is not indicated for indolent cutaneous B-cell lymphomas.

The standard treatment for aggressive, high-grade B-cell lymphomas includes multiple-agent chemotherapy. The agents that are typically employed are cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen). Chemotherapy is often combined with rituximab, which has shown to improve survival. This may be followed with radiation treatment. Other systemic treatments for aggressive cutaneous lymphoma include interferon alfa.

**Conclusion**

Primary cutaneous B-cell lymphomas are quite rare. Occasionally, and particularly in chronic lesions, they may transform into more aggressive forms of lymphoma. There has been little in the literature about how these transformed cutaneous lymphomas present clinically. We have presented a case of FCC that transformed to DLBCL. More attention should be directed towards how these transforming, cutaneous lymphomas present to recognize transformation, and to correctly diagnose and manage these patients.
Table 3

The workup for cutaneous lymphoma assesses possible systemic involvement. Referral to an oncologist may aid in the workup.

<table>
<thead>
<tr>
<th>Cutaneous lymphoma workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History (duration of lesions, biological activity of lesions, fever, weight loss, night sweats, fatigue)</td>
</tr>
<tr>
<td>- Exam (skin exam: number and location of lesions; palpate lymph nodes, liver, and spleen)</td>
</tr>
<tr>
<td>- Labs (CBC, LFTs, creatinine, LDH)</td>
</tr>
<tr>
<td>- Peripheral blood smear</td>
</tr>
<tr>
<td>- Skin biopsy</td>
</tr>
<tr>
<td>- Lymph node Bx (if lymphadenopathy on exam)</td>
</tr>
<tr>
<td>- CT scan of chest, abdomen, pelvis; or PET scan</td>
</tr>
<tr>
<td>- Bone marrow aspirate / bone marrow biopsy</td>
</tr>
<tr>
<td>- Clonality studies</td>
</tr>
</tbody>
</table>

Table 4

Differentiation between primary and secondary cutaneous B-cell lymphoma includes history, examination, labs, and imaging.

<table>
<thead>
<tr>
<th>Primary cutaneous B-cell lymphoma</th>
<th>Secondary cutaneous B-cell lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originates in the skin</td>
<td>Originates in the lymph nodes</td>
</tr>
<tr>
<td>Limited to skin involvement only</td>
<td>Metastasizes to the skin</td>
</tr>
<tr>
<td>No lymph node or distal organ involvement</td>
<td></td>
</tr>
<tr>
<td>Lesions typically above the waist</td>
<td>Widespread lesions</td>
</tr>
<tr>
<td>CBC, LFTs, and Cr normal</td>
<td>CBC, LFTs, or Cr abnormal and may show liver or kidney involvement</td>
</tr>
<tr>
<td>Peripheral blood smear normal</td>
<td>Peripheral blood smear abnormal, indicating circulating lymphoma cells</td>
</tr>
<tr>
<td>No lymphadenopathy</td>
<td>Lymphadenopathy may be present and lymph node Bx may show lymphoma</td>
</tr>
<tr>
<td>CT or PET scan normal</td>
<td>CT or PET scan shows extracutaneous involvement</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Symptomatic, such as unexplained fever, unexplained weight loss, night sweats, or fatigue</td>
</tr>
<tr>
<td>No hepatomegaly or splenomegaly</td>
<td>Hepatomegaly and/or splenomegaly present, which may represent involvement of these organs</td>
</tr>
<tr>
<td>Bone marrow aspirate / bone marrow biopsy normal</td>
<td>Bone marrow aspirate or bone marrow biopsy abnormal, indicating involvement</td>
</tr>
</tbody>
</table>
**ABSTRACT**

Androgenic alopecia (AGA) is an extremely common disorder affecting more than 90% of all men over the course of their lifetime. It is a progressive condition in which almost all patients will have onset prior to the age of 40. The progression of AGA is the gradual transformation of pigmented terminal hair to line, colorless, almost invisible vellus-like hair follicles. The roles of androgens have been identified in the pathogenesis of AGA. Thus, primary pharmacologic therapy has been aimed at targeting the formation of those androgens. Surgical treatment options are also available, but proper patient selection and surgical technique are critical in order to obtain a successful outcome. Recent advancements in the understanding of AGA have allowed physicians to provide patients with accurate counseling and effective treatments.

**Background**

Throughout history, hair has played an important role in human self expression and communication. Hair is a feature an individual can uniquely tailor according to style and/or religious or cultural beliefs. The loss of hair limits this self expression and can result in a poor self image, a loss of self confidence and a feeling of being older. Cultures have long recognized the psychological sequel of this condition and have worked to develop various treatments. In 2000 BC, the Egyptians recorded treatment recipes for hair loss. In the days of Aristotle (384-322 BC), scholars recognized and noted that eunuchs did not suffer from hair loss, nor did it occur in individuals prior to sexual development.1,2

In 1942, the modern understanding of male pattern hair loss or androgenic alopecia (AGA) was theorized by Hamilton. It was established that AGA is a physiologic process induced in genetically predisposed hair follicles and is influenced by androgens.3 It was noted that below the normal level of androgens, genetically determined individuals would manifest the clinical characteristics of AGA. In 1951, Hamilton developed the first grading scale for AGA. This scale was modeled after Caucasian men and women, with a range from type I to type VIII. Type I represents the prepubertal scalp, with terminal hair growth on the forehead and all over the scalp, and type VII and VIII represent progressive balding, with hair only present on the back and sides of the head. The classification system was later modified by Norwood to include variations of the middle grades. These were labeled IIIa, IVa, and Va, and they show a more prominent recession of the middle and frontal hairline.1,4

Figure 1 shows the Norwood-Hamilton classification. The Norwood-Hamilton scale is used for the assessment of efficiency of medication for hair restoration in clinical trials.

**Androgenic Alopecia**

AGA is far and away more common in Caucasian males. However, some sources have estimated the incidence of AGA to be greater than 80% in all races and as high as 96% in Caucasians. Sixty-two percent of Caucasian men aged 20 to 40 years have bitemporal recession, and 54% of Caucasian men over the age of 30 years are affected with AGA.4 In the mid 1990s, Savin designed a system of eight computer-engineered pictures of hair loss with progressive severity. The pictures were top views of the scalp with the hair parted down midline. By comparing the width of the patient’s part to one of the eight examples, the system could be adapted to clinical trials and serve as a method by which practitioners could quantify their patient’s hair loss and growth. The flaw in the Savin scale is that it does not depict the typical pattern of hair loss experienced by most patients, and it has not been widely accepted by hair-restoration surgeons.1,2,4

**Role of Androgens in Pattern Hair Loss**

The role of androgens in AGA was first identified in eunuchs who did not receive hormone replacement therapy. The androgen most closely associated with AGA is dihydrotestosterone (DHT). This was studied in a group of males from the Dominican Republic who genetically lacked Type II 5α-reductase (5AR), the enzyme required to convert testosterone to DHT, and who consequently never developed typical AGA. The medication finasteride targets the conversion of testosterone to DHT. It works by competitively inhibiting Type II 5AR and thus decreasing the levels of DHT, resulting in the effective treatment of AGA.4

Androgens affect the hair by a pathway of testicular and adrenal gland testosterone that diffuses passively into the skin cells. Once in the cells, it is converted to DHT by 5AR. Two types of 5AR exist in the cells. Type I is found on sebaceous glands and in the pilosebaceous unit, whereas Type II is found in the outer root sheath of the scalp hair follicles, prostate, and dermal papillae. A cytosol androgen receptor protein then forms a complex with DHT, allowing access into the cell nucleus. Once inside the nucleus, DHT causes conformational change to lead to the inactivation of the hair follicle.4

**Treatment Overview**

Only two classes of medications have been proved to be effective in the treatment of AGA. The first is a direct hypertrichotic...
agent, and the second affects the androgen pathway. In each of the two categories, only one medication has gained approval by the U.S. Food and Drug Administration (FDA) for the treatment of pattern alopecia. 

Minoxidil is a potassium channel opener and vasodilator, initially approved for use as an antihypertensive agent, with the notable side effect of hypertrichosis. The FDA originally approved a 2% topical solution and later a 5% topical solution, both of which were prescription products. It was first speculated that minoxidil produced hair growth by way of vasodilation, but this was found to be incorrect. Minoxidil enhances hair survival in tissue cultures even in the absence of a blood supply. Topical minoxidil is considered to be a nonspecific biologic modifier with an unknown mechanism of action in hair growth.

The second approved medication, finasteride, is a competitive inhibitor of Type II 5AR. Finasteride is administered as a pill taken orally at 1mg/day. Multiple studies have determined that finasteride has proven clinical efficacy over placebo alone. Because finasteride has been known to reduce serum prostate-specific antigen (PSA) levels by 30-50%, men over the age of 40 are advised to have their PSA levels doubled for interpretation; however, because this correction might not adjust PSA accurately, a potentially unnecessary or missed diagnostic procedure may occur.

Finasteride works best to prevent ongoing hair loss. Patients are therefore encouraged to begin treatment as soon as hair thinning is noted.

Diagnostics

The diagnosis of AGA in men is usually not difficult. The hair loss is non-scarring and shows a preservation of the follicular ostia. Basic qualitative tests, such as a hair-pull test, contrast paper, and dermoscopy, can easily be used as a tool during a hair consultation. A hair-pull test is usually used as a quick assessment of the activity of the telogen count in the involved area. A scalp biopsy allows a definitive diagnosis, as it provides information on histological features, the number of terminal and vellus hairs per area, and the number of anagen and telogen hairs; but for routine diagnostics, a scalp biopsy is usually not necessary.

Summary

AGA, or male pattern hair loss, affects approximately 50% of the male population. AGA is an androgen-related condition in genetically predisposed individuals. DHT has been identified as the unregulated mediator, but its exact mode of action on the dermal papilla is not fully understood. There is no treatment to completely reverse AGA in advanced stages, but with medical treatment, the progression can be arrested and partly reversed in the majority of patients who have mild to moderate AGA.

Despite many years of research and investigation into the pathogenesis of AGA, very little is actually known about the entirety of this condition. It is crucial for practitioners to fully understand the known elements of this process in order to recommend and prescribe appropriate therapeutic treatment options. In the past, few treatments, if any, were effective in the treatment of AGA. In the future, through continued scientific research, more effective and better-tolerated therapies may become available. Physicians who specialize in male health issues should be familiar with this common condition and all available approved treatment options.

References:
ABSTRACT

Perniosis is characterized by a localized, pruritic, sometimes painful, erythematous to violaceous rash with nodules (chilblains) that present in the acral skin as an abnormal response to repeated exposure to cold. A diagnosis of perniosis is made clinically and can be supported by dermatohistopathologic findings. This condition may be associated with systemic illnesses, and it can be difficult to distinguish idiopathic perniosis from secondary perniosis and similar cutaneous manifestations of lupus erythematosus. A review of literature supports an investigation and biopsy of lesions for confirmation of the underlying pathology.

Case Report #1

A 33-year-old Caucasian female presented to our clinic with a long-standing history of recurrent, eruptive, erythematous, tender papules on her toes. She reported having a similar outbreak yearly, coinciding with the first significant cold front of the fall season. This eruption had been occurring annually in October or November for more than 10 years.

Physical exam revealed multiple, tender, erythematous papules on all 10 digits dorsally. Mild edema was noted without purpura, ulceration or bullae formation.

Case Report #2

A 25-year-old Caucasian male presented to our dermatology clinic in mid-December with symptoms of recurrent, swollen, pruritic toes with subsequent sanguineous blister formation. Pruritus was always the initial symptom, followed by erythema at his distal toes, progressing to his mid-foot. This was followed by an eruption of multiple, painful, erythematous papules, which progressed to significant edema and pain of all 10 digits. Symptoms lasted five to seven days, but never completely resolved before another recurrence. No prior history of similar findings was reported.

Initial physical exam revealed blanching, erythematous and violaceous skin with marked edema confined exclusively to the digits. Areas of bullae formation were also evident. The toes were tender to palpation, with limited motion. Sensation and capillary refill remained intact.

The patient denied a personal history of coronary artery disease, diabetes, vasculitis, rheumatoid arthritis, systemic lupus erythematosus or autoimmune disease. He had been on no recent medications and denied use of tobacco, alcohol or other recreational drugs.

Diagnosis:

Punch biopsies were taken from both patients, exhibiting similar histology. Characteristically, they revealed: a dense, lichenoid, lymphocytic, inflammatory cell infiltrate within the superficial dermis, associated with scattered vacuolar keratinocytes; and a prominent superficial dermal edema with a tightly cuffed, moderate, perivascular, lymphocytic, inflammatory cell infiltrate in the mid-to-deep reticular dermis.

Based on the characteristic histopathology and negative clinical work-up, a diagnosis of perniosis (chilblains) was confidently rendered.

Pathology:

Perniosis is caused by exposure and inadequate protection in a cold (non-freezing), humid environment. Patients with perniosis typically present through the winter months, and it is more common in areas of moderate cold as opposed to areas of severe cold.1

In one study of a moderately cold area in Pakistan, the disease was found to have greater prevalence among outdoor workers and young adolescent.2 The annual incidence in the United States is not known, but it is reported as high as 10% in England.

Perniosis most commonly occurs in young women, but it has been known to occur among older individuals and even children. Some authors have noted an association with thin body habitus, BMI <25th percentile.3 A positive family history has been noted in approximately 20% of cases.4 Up to 67% of cases have been associated with outdoor workers.5

Lesions typically occur on the fingers and toes, but can also occur on the ears and the face.

Exceptional case reports have included horse riding enthusiasts wearing tight clothing in cold weather, and cases occurring on the thighs of individuals after wading across cold mountain rivers.6,7 There has been one case report linking celiac disease with perniosis.8

Physicians’ unfamiliarity with perniosis gives rise to unnecessary hospital admissions with expensive laboratory and radiologic evaluations and, at times, hazardous therapy.9

Pathogenesis:

The abnormal response to cold exposure is thought to induce vasospasm in the exposed tissue, producing a lymphocytic vascular reaction and lymphocytic infiltration and exudation of fluid into the tissue.5 Cold temperature has been described as a cause of arteriolar and venule constriction with subsequent edematous response.1

Acute perniosis may develop 12 to 24 hours after exposure to cold. Chronic perniosis, with the persistence of lesions, occurs with repeated exposure to cold.

Diagnosis:

Perniosis is generally a clinical diagnosis. A history of cold exposure with subsequent
development of localized pruritic or tender, erythematous to violaceous papules or nodules (chilblains) with associated edema is a classic presentation for perniosis.

There are several systemic diseases whose initial symptoms and dermatologic manifestations present similarly to that of perniosis. These include systemic lupus erythematosus, antiphospholipid antibody syndrome, viral hepatitis, rheumatoid arthritis, cryoglobulinemia, hypergammaglobulinemia, Crohn’s disease, Raynaud’s phenomenon, small joint arthralgias, positive ANA, acrocyanosis, emboli (septic or cholesterol), erythromelalgia, ischemia, polycythemia vera, and chronic myelogenous leukemia. Thus, in suspected cases, a baseline work-up has been recommended to include: CBC, ANA, antibodies to SSA (Ro), SSB (La), RF, cryoglobulins, cryofibrinogens and antiphospholipid, hepatitis screen and serum electrophoresis with quantitative immunoglobulins.4

Dermatohistopathology has also been helpful in distinguishing perniosis (idiopathic chilblains) from lesions that are similar in patients with lupus erythematosus. Perniosis exhibits findings of necrotic keratinocytes and spongiosis in the epidermis with perieccrine infiltrate, and edema of the dermis. These findings can be helpful to confirm a diagnosis of idiopathic perniosis.5

**Treatment:**

Treatment of perniosis should first be directed toward prevention of exposure to cold. Education focused on limiting exposure to cold and adequate rewarming can prevent initial onset or recurrence of symptoms.

The patient’s symptoms are self-limited, and relief can be hastened using nifedipine 10 mg TID or 20 mg BID-TID. Upon resolution, the patient can be maintained on a sustained-release preparation of nifedipine 20 mg BID.6 This has been shown in limited clinical trials to significantly reduce the time to clearance of existing lesions and to prevent the development of new chilblains. Nifedipine also reduced the pain, soreness and irritation of the lesions.6

Nifedipine is a calcium channel blocker that induces vasodilation, causing increased blood flow, and has antiplatelet effects. These qualities perhaps explain the resolution of signs and symptoms generally occurring between eight to 28 days for lesions on the hands, thighs and feet.6,12

Aside from the above noted study, which is frequently cited throughout the published literature on treatment for perniosis, it should be noted that strong evidence with placebo-controlled trials for the use of nifedipine is lacking.

Other treatment options that have been suggested include: topical and systemic steroids, nicotinamide, hexyl nicotinate, amlodipine, and UVB. These suggestions are based primarily on anecdotal reports.
Perniosis is a cold-induced abnormal response of the skin primarily in the acral areas. A diagnosis can be made clinically and can be supported by histopathology. It is recommended to complete a baseline work-up in patients with suspected perniosis (idiopathic chilblains) to identify possible systemic illnesses, particularly connective-tissue disorders. The mainstay of treatment is prevention. Nifedipine has been shown to reduce the duration of symptoms and is the most supported pharmacologic intervention. Increasing awareness in patients and physicians may prove to prevent future cases, unnecessary treatments and recurrence.

REFERENCES:
Dermatopathologists integrating your unique concerns
Providing superior diagnostic medical care for your practice and patients

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www.globalpathlab.com
GR AFT-VERSUS-HOST DISEASE IN A LIVER TRANSPLANT PATIENT WITH GRAFT DYSFUNCTION

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Case Report

A 56-year-old, Caucasian, female liver transplant patient was admitted into the hospital for elevated liver function tests (LFTs) and neutropenia. The patient had undergone an orthotopic liver transplant for Laennec’s cirrhosis approximately three months prior to admission, without complications. She was noted to have an increasing trend in liver function tests at routine follow-up in outpatient clinic and was sent for hospital admission. The patient had a past medical history of hepatitis C, alcoholic liver cirrhosis, hypertension, diabetes mellitus, mitral valve prolapse, and bipolar disorder. The patient had a history of alcohol abuse but had been sober for over a year. Once admitted, the patient was started on aggressive immunosuppressant therapy with Solu-Medrol®, mycophenolate mofetil (CellCept®), and tacrolimus (Prograf®). An endoscopic retrograde cholangiopancreatography (ERCP) revealed a stricture of the common bile duct at the anastomosis site. The patient underwent a sphincterotomy, and a stent was placed. The patient continued to have elevated LFTs and started complaining of epigastric pain. A repeat ERCP revealed continued blockage, and a stent revision was performed. The patient continued to have fluctuating LFTs and elevated bilirubin. A liver biopsy revealed nonspecific inflammation. The patient then underwent an exploratory laparotomy with hepatic jejunostomy and Roux-en-Y reconstruction. Approximately 10 days post-op, the bilirubin levels remained elevated and the LFTs fluctuated. Another liver biopsy revealed central venous congestion and micro-hemorrhage. The patient also started to develop a blanchable, erythematous maculopapular rash, predominantly over the bilateral upper and lower extremities involving the palms and soles. There were no ulcerations, vesicles or bullae present (Fig. 1). The patient was also noted to be very jaundiced.

Skin biopsies performed revealed superficial lymphohistiocytic dermatitis with focal satellite cell necrosis consistent with GVHD early stage (Fig. 2, A and B). Gram and PAS stains were negative for pathogenic organisms. Tissue cultures were negative for CMV and Epstein-Barr virus. Approximately 10 days later, the skin eruption progressed to become more generalized, involving the trunk and extremities. There were also noted to be some areas of white hypopigmentation. Repeat skin biopsies revealed acute GVHD with a histological grade of II (Fig. 2, A and B). Triamcinolone 0.1% cream and hydroxyzine were added to the patient’s treatment regimen. The patient’s LFTs continued to be elevated, and there was no improvement in her overall status. The patient underwent another liver biopsy, which revealed central venous congestion and micro-hemorrhage. The patient was then placed on the transplant list. Approximately two weeks later, the patient underwent transplant of another liver. Post-recovery was unremarkable. The GVHD cutaneous findings resolved at the time of discharge, 10 days status post second liver transplant.

Discussion

Acute GVHD is a rare complication of liver transplantation that affects 1-2% of patients and has high morbidity and mortality.1-21 GVHD is more frequently seen as a complication of allogeneic bone-marrow transplantation and was only recently first described by Burdick et al. in 1988 as a complication of liver transplantation.1-21 The inciting event of GVHD is thought to be immunologically active T lymphocytes from the donor liver that engraft and mount an immune response against the recipient tissues.1-21 The devastating effects are multisystemic, involving the skin, gastrointestinal tract and bone marrow.1-21

Patients affected by GVHD typically present two to six weeks after transplantation with fever or skin rash that is maculopapular, starting distally on the palms and soles and then spreading centrally to become generalized.1-21 Vesicles or bullae may form as the eruption progresses.1-21 The patient may experience diarrhea as a result of donor lymphocytic infiltration and destruction of intestinal mucosa.1-21 Marked pancytopenia may present, leading to life-threatening infection and hemorrhage.1-21 Unlike classic GVHD in bone-marrow transplantation, the liver is not involved and LFTs are normal.1-21 This is because the source of the activated lymphocytes is the donor liver, and thus they do not affect the liver epithelium.1-21 However, this case is unique in that the patient had elevated LFTs and bilirubin due to graph dysfunction from a common bile duct stricture. The GVHD skin rash developed after the initiation of aggressive immunosuppressant therapy.

Consideration of GVHD requires a high clinical suspicion correlated with skin biopsy for evaluation of any patients presenting with an erythematous maculopapular rash and history of transplantation. Other considerations should include drug eruptions, viral infections and graft rejection.1-21

The histological picture of acute GVHD involves a superficial perivascular lympho-
of epidermis. The histopathology must be correlated with the clinical picture. The most severe, with bullae formation and necrolysis. Thus, current studies have been focused on alternative diagnostic tools that may aid in the diagnosis of GVHD after liver transplantation by fluorescent in situ hybridization. Such therapy may lead to graft rejection or worsening of GVHD by lifting any restraining effects of immunosuppression on donor lymphocytes. Even though withdrawal of immunosuppressant therapy is not recommended, our patient presented in this case was noted to have developed signs and symptoms of GVHD after initiation of aggressive immunosuppression. Thus, there is still much to elucidate about the role of immunosuppressant therapy, medical management should be directed toward the prevention of infection. Broad-spectrum antibiotics and antifungal prophylaxis is recommended. CMV prophylaxis should also be considered. Patients with severe neutropenia or pancytopenia may benefit from administration of granulocyte colony stimulating factor.

In conclusion, GVHD after liver transplantation is an uncommon complication and requires a high clinical suspicion. The most common presenting signs include fever and rash. Typically, the transplanted liver is not affected. However, in this case the graft was dysfunctional secondary to a CBD stricture. Most patients succumb to death by infection and hemorrhage. The use of in situ hybridization for the detection of donor lymphocytes in skin biopsies may aid in making the diagnosis. Current therapy for GVHD in liver transplant patients is largely empirical and based on management of GVHD after bone marrow transplantation. It includes immunosuppressant therapy and control of infection.

References

AXILLARY GRANULAR PARAKERATOSIS - A CASE REPORT

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ABSTRACT

A 52-year-old woman developed a pruritic, erythematous eruption in the axilla on her right side. Histopathologic examination showed orthokeratosis, parakeratosis and hypergranulosis, which is consistent with the diagnosis of axillary granular parakeratosis, also known as granular parakeratosis.

Granular parakeratosis is a benign, idiopathic disorder of the intertriginous areas that manifests as red or brown, scaly or hyperkeratotic papules or plaques. Histopathology is characterized by parakeratosis with retention of keratohyaline granules. The cause is thought to be a defect in the conversion of profilaggrin to filaggrin and hence a defect in the keratinization process. Treatment with corticosteroids, retinoids, Vitamin D analogs, and cryotherapy have been employed but still need more evidence-based data.

Case Report

A 52-year-old woman presented with a two-week history of unilateral, pruritic, erythematous rash in the right axilla. Other intertriginous areas were not involved. The patient’s past medical history was consistent with right-sided breast cancer that was treated successfully five years prior, with no evidence of recurrence.

Histological examination showed orthokeratosis, parakeratosis, hypergranulosis and mild acanthosis. A periodic-Schiff exam was negative for fungi. A diagnosis of axillary granular parakeratosis was made. The patient was treated with 2.0% hydrocortisone and 1.0% iodoquinol cream (Alcortin) and was advised to avoid deodorant. The eruption cleared up in a few weeks, and there was no recurrence three months later.

Discussion

Axillary granular parakeratosis is a rare, benign, acquired dermatitis of intertriginous skin first described by Northcutt, Nelson, and TechNet in 1991 in four patients with a maxillary eruption similar to Hailey-Hailey.1 Metze and Rutten1 suggested the term granular parakeratosis since the eruption can occur in other intertriginous areas besides the axilla.2 Granular parakeratosis can occur in either sex, but it is more common in women in their fifth or sixth decade. It presents as erythematous or hyperpigmented papules and plaques in the axilla or other intertriginous areas,2,6-8 unilaterally or bilaterally. Secondary lesions with crusts and scales can be present. Patients can have associated pruritus and burning.

The etiology of granular parakeratosis is unknown. Northcutt et al.1 first proposed the hypothesis that a defect in the cornification process, specifically in the processing of profilaggrin to filaggrin and retention of keratohyaline granules, is the cause. This hypothesis of retention hyperkeratosis is supported by Metze and Rutten1 and Webster et al.3 Also, reports of cases with response to retinoids4,5 suggest that granular parakeratosis is a disorder of keratinization. Even though the primary triggers for this condition are unknown, antiperspirant and deodorants1 have been suggested as a causative agent. However, other intertriginous areas besides the axilla, where these products are not applied, have been involved.2,6-8 Occlusion and maceration has been suggested as the cause. Microbiologic cultures have not found a known pathogen, but the role of unrecovered microorganisms cannot be excluded.10 There has been no association with any systemic diseases, but in 2002, Rodriguez reported three cases in obese women.11

The optimal treatment of granular parakeratosis is not known. In various reports, patients have shown response to topical corticosteroids, oral and topical retinoids, topical antifungals and antibiotics and vitamin D analogues. Physical destruction with cryotherapy has been reported, as well as spontaneous resolution.2 In our case, the patient responded to 2.0% hydrocortisone and 1.0% iodoquinol (Alcortin).

In conclusion, granular parakeratosis is a rare, benign disorder of the intertriginous areas most likely caused by a defect in the keratinization process.

References

Merkel cell carcinoma (MCC) is an uncommon but aggressive tumor usually occurring in sun-exposed areas of elderly men. The clinical presentations of this tumor are varied. We present an 81-year-old man with a rapidly growing cyst, treated locally without resolution. Subsequent biopsy revealed MCC, and the patient was treated with Mohs surgery and radiation. A review of the literature for diagnosis and management of MCC is also discussed. Clinicians should have a high clinical suspicion when evaluating a cyst in sun-exposed areas of the elderly.

Case Report

An 81-year-old white male with Parkinson’s disease and nonmelanoma skin carcinoma presented to the dermatology clinic with a 1 cm, firm but freely movable cyst on his right mandibular angle. The patient returned to the clinic two months later, and the cyst had doubled in size (Figure 1). Incision and drainage of the cyst was attempted, but no contents were expressed; because of this, a 3 mm punch biopsy was performed. There was no appreciable lymphadenopathy or oral lesions. Histopathology revealed Merkel cell carcinoma (Figures 2,3). Confirmatory immunohistochemical stains were positive for cytokeratin 20 (Figure 4), chromogranin, and synaptophysin. Stains were negative for cytokeratin 7, thyroid transcription factor 1 (TTF-1), leukocyte common antigen (CD45), S100, and HMB45. He was sent for CT scans of head, neck, and thorax. CT of the head was normal. CT of the neck revealed a 1.9 x 2.1 cm right upper neck lesion infiltrating the skin and subcutaneous fat with questionable infiltration to the parotid gland, and an enlarged 1.1 cm left supraclavicular lymph node. A 6 x 6 mm speculated lesion was found at the anterior aspect of the left upper lobe, suggesting primary versus metastatic lesion. PET scan was normal. The patient was scheduled for Mohs surgery, followed by plastic surgery one week later (Figure 5). He subsequently received radiation therapy for six weeks. In addition to dermatology, the patient was followed by hematology/oncology. A repeat PET scan to assess therapy was done six months later. It revealed numerous confluent focal areas of intensely increased tracer uptake in liver, ribs, spine, pelvis, proximal femur and left gluteal muscles. Diffuse metastatic disease was seen on MRI of the spine. Patient was admitted to the hospital for lethargy, and soon after expired.

Discussion

The median age of MCC is 69 years, but it may occur earlier in immunocompromised patients. It predominantly affects elderly Caucasian men. Synonyms include trabecular cell carcinoma, neuroendocrine or primary small cell carcinoma of the skin, and anaplastic cell carcinoma. MCC is most commonly seen in sun-exposed areas, especially the head and neck, although there are cases on genitalia and perianal locations.1

Overall incidence of MCC has increased from 0.15 to 0.44 cases per 100,000 population between 1986 and 2001, according to the Surveillance Epidemiology and End Results data.2 While there are no definitive causes of MCC, there may be possible associations with ultraviolet radiation, immunosuppression (renal cell transplantation, HIV, CLL) and chronic arsenic exposure.2,3 There are no clear cytogenetic abnormalities, but some reports indicate structural abnormalities in chromosomes 1, 11 and 13 and mutations in tumor suppressor genes p73 and p53.4,5 There are also ongoing debates as to whether MCC is derived from Merkel cells, mecanoreceptors in the basal layer, or from pluripotent dermal stem cells.3 Although not confirmed, a recent research study suggests an association between polyomavirus and MCC.6

Merkel cell carcinoma is most commonly found on the head and neck region, followed by extremities, trunk, and genitalia. The typical presentation is a rapidly growing firm, nontender, shiny, pink-red to violaceous, dome-shaped solitary nodule. At the time of diagnosis, there were few reports describing MCC mimicking a cyst as seen in this case report. Recently, however, in a study of 195 patients, a cyst or acneiform lesion was the most common presumptive diagnosis. Other tumor characteristics in that report include: 88% asymptomatic, 63% were rapidly growing (≤ 3 months), 56% were pink or red, 56% were presumed benign, and mean tumor diameter was 1.8 cm.1 There are other reports of Merkel cell carcinoma presenting as or within a cyst. Two cases discuss Merkel cell tumors associated with trichilemmal cysts.7,8 One report describes a 58-year-old man with Merkel cell carcini-
The most commonly used staging system is from Memorial Sloan-Kettering Cancer Center (MSKCC):

- **Stage I (T1, N0, M0, primary tumor <2cm)**
- **Stage II (T2 N0 M0, primary tumor >2 cm)**
- **Stage III (any T, N1, M0)**
- **Stage IV (any T, any N, M1)**

Five-year mortality data is:

- **Stage I - 81%**
- **Stage II - 67%**
- **Stage III - 52%**
- **Stage IV - 11%**

Visceral metastasis occurs in liver, bone, lung, and skin. Work-up may include chest X-ray (to exclude small cell lung carcinoma), CT chest, abdomen and pelvis, PET, and CT head. Sentinel node lymph node biopsy is helpful in establishing staging and prognosis; however, more studies need to be done to assess benefit in survival.2

Treatment is varied due to the lack of defined guidelines for this rare tumor. Surgery remains the hallmark of treatment of MCC. Wide local surgical excision has been the mainstay of treatment, with recommended margins of 1-3 cm. Recent studies have shown that Mohs micrographic surgery is at least comparable to wide local excision especially in head, neck and distal extremities.13,14,15 One study showed 4% marginal recurrence and 16% overall recurrence (marginal recurrence plus in-transit metastases) in small stage I disease.16

MCC is considered to be radiosensitive, but there are no strict guidelines on when to use adjuvant radiation therapy (RT), or when to radiate only the primary site, or to include the lymph node basin. A recent review of the literature showed that surgery plus local adjuvant irradiation was associated with significantly lower rates of local and regional recurrence of MCC than surgery alone.17 However, treatments did not vary significantly in a study comparing Mohs with or without adjuvant radiation, and the authors suggested radiation for patients unable to have complete excision or for large or recurrent tumors. Additional studies are needed to determine if this affects overall survival. Radiation may be beneficial for larger primary tumors, close or positive surgical margins, or inoperable patients.

Controversy exists as to the management of micrometastatic disease found with sentinel lymph node biopsy. Limited data suggests that complete lymph node dissection (CLND) is the first line of treatment.2 RT to the lymph node basin may be another option or an addition to CLND in patients with extensive lymph node disease. In patients who have not had a sentinel lymph node biopsy, adjuvant nodal therapy may be warranted.11

Chemotherapy is the least studied treatment, and the optimal regimen is unknown. It is generally not recommended for node negative MCC with good prognosis considering the lack of survival benefit and side effects. It may be considered for distant metastases or advanced local or regional disease in a palliative manner.

Favorable prognostic factors are: small size of the primary lesion, initial localized disease, primary tumor in head and neck, female sex, age less than 65 year old, and absence of nodal disease. In one report, 43% of patients with local or regional disease developed recurrence, and the median time was nine months. Recurrence typically occurred at the draining lymph node basin. Eight percent of patients with a margin-negative excision developed local recurrence.12 Although a time period has not been established, frequent follow-ups with physical examination and chest radiograph to rule out recurrences or metastases are recommended. CT scans of chest, abdomen and head may also be performed, especially in symptomatic patients.

In conclusion, this case report emphasizes the need for the clinician to have a high index of suspicion when evaluating a cyst, especially in a patient who describes a cyst with a rapid increase in size or who has risk factors including elderly age, immunosuppression and cyst location in sun-exposed areas.

**References**

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Verrucous psoriasis is a rare, clinico-histopathological variant of psoriasis that may clinically and histopathologically resemble verruca vulgaris. This variant of psoriasis is thought to result from repeated trauma or irritation to pre-existing psoriatic lesions. We present a case of verrucous psoriasis occurring in a 47-year-old African American male with no history of psoriasis.

Introduction

Psoriasis is a common, chronic, immune-mediated disorder of the skin that has various clinical features. There are several clinico-histopathological variants that include classic psoriasis vulgaris, erythrodermic, guttate and pustular. A rare, under-recognized variant given the name verrucous or hypertrophic psoriasis produces lesions that may clinically and histopathologically resemble verruca vulgaris. The lesions typically occur in patients with a history of psoriasis and present as wart-like growths on the extremities. Histopathologically, the lesions have overlapping features of both psoriasis and verruca vulgaris. We report a case of new-onset verrucous psoriasis developing in a patient with no history of psoriasis.

Case

A 47-year-old African American male presented to the office with a five-month history of an asymptomatic rash, which started on his abdomen. Initially, he was treated with a three-month course of terbinafine by his primary care physician, who suspected a fungal infection as well as onychomycosis of several toenails. His toenails and several skin lesions cleared; however, a few lesions persisted. The eruption then worsened. The lesions spread to involve the head, neck and extremities and became thicker and more wart-like in appearance. The patient had no history of psoriasis or joint pain, and his past medical history included hypertension, which was controlled by valsartan. He had a six-year history of an asymptomatic rash, which was thought to favor the dorsal hands and extensor surfaces of the extremities. He had a history of chronic hepatitis C. Current treatment options specific for this variant of psoriasis are not well reviewed in the literature. Treatment with topical corticosteroids, coal tar, PUVA and cryotherapy have been reported in the literature. Kuan et al. reported a patient with multiple verrucous carcinomas who was successfully treated with acitretin.

Histopathologically, psoriasis typically shows parakeratosis, Munro’s microabscesses, regular elongation of the rete ridges, decreased or absent granular layer, suprapapillary thinning, dermal vascular dilatation and perivascular lymphocytic infiltrate. In addition, histopathologic features of verruca vulgaris are common, including epidermal papillomatosis, creating finger-like projections and bowing of the peripheral rete ridges toward the center of the lesion (buttressing). Hypergranulosis and koilocytic changes observed in verruca vulgaris are not present.

Treatment options specific for this variant of psoriasis are not well reviewed in the literature. Treatment with topical corticosteroids, coal tar, PUVA and cryotherapy have been reported in the literature. The authors believed the patient actually had verrucous psoriasis, which would explain the rapid response to acitretin.

Conclusion

Verrucous psoriasis is a distinct, clinico-histopathologic variant of psoriasis that may clinically and histopathologically resemble verruca vulgaris. The lesions are thought to be a cutaneous response to repeated trauma in patients with pre-existing psoriasis. Clinically, the lesions are reminiscent of verruca vulgaris and tend to occur on the dorsal extremities, sites with a higher predilection for trauma. Histopathologically, epidermal papillomatosis and epidermal buttressing seen in these lesions is suggestive of verruca vulgaris.
Our patient is unique because he developed a majority of his lesions on the head, neck and trunk and has no history of pre-existing psoriasis.

References:
ABSTRACT

X-linked recessive ichthyosis is an inherited disorder of keratinization that affects approximately one in 6,000 boys and men. It is due to steroid sulfatase deficiency, and most cases are caused by deletions of the steroid sulfatase (STS) gene found on the distal portion of the short arm of the X chromosome (Xp22.3). Two first-degree siblings presented with a lifelong history of diffuse, brown, thickened scales that mostly covered their extensor surfaces of the extremities, trunk and face. They reported having biopsy-proven X-linked recessive ichthyosis diagnosed while in the Dominican Republic. This case report outlines the details of their clinical presentation and medical management, and reviews publications of similar findings.

Case Presentation

Two brothers, F.A. and A.A., aged 13 and 14 years, respectively, presented to our office with a lifelong history of very dry skin with thick scales and some itching. The boys were accompanied by their grandmother, who reported a biopsy being done in the Dominican Republic six years prior to this visit. She reported that they were given the diagnosis of X-linked recessive ichthyosis. They were treated with multiple topical medications, including tazarotene, ammonium lactate 12% lotion, and urea lotion, with marked improvement. They also reported taking acitretin with significant improvement. The dosage and length of time were unknown. Our patients reported not being on any medication for several months due to medical insurance issues, and presented for treatment for exacerbation of their skin rash.

F.A. and A.A. denied any other complaints at that time, including no eye difficulties, smelling problems, or any abnormalities with the testicles. There was no report of intellectual impairment or other problems with their health. They did report recently having blood work and an ophthalmologic examination ordered by their primary care physician. The grandmother denied any known family history of similar skin conditions in male or female members.

On physical examination of both patients, there was generalized symmetrical, thickened, hyperpigmented and translucent scaling of the face, neck, extremities and trunk. Both the extensor and flexor surfaces were affected, and large areas of desquamation were noted as well. There were no significant differences in severity or location on the two brothers. No signs of secondary infection were noted. Otherwise, both patients were pleasant, well nourished, well developed and in general good health. No gross eye, ear, nose or testicular abnormalities were found.

F.A. and A.A. were placed on acitretin 25mg orally starting every other day, tazarotene cream 0.1% to the hands at bedtime, and ammonium lactate 12% lotion twice daily to the rest of the body. In addition, general instructions regarding treatment for xerosis were advised, including mild soaps and the liberal use of moisturizers. Copies of their most recent blood work were ordered, and both patients were sent for a testicular ultrasound and ophthalmologic examination if warranted. A copy of the biopsy performed in the Dominican Republic could not be obtained.

The two first-degree siblings returned for a follow-up approximately one month later, with minimal improvement. They were only using the 12% ammonium lactate because of difficulties obtaining the other medications through their insurance. Again, they reported no other symptoms or problems at that time. Blood work results were reviewed, and were all within normal limits. Eye exams showed mild ectropion of both lower lids in F.A., and mild everted with concomitant scarring in A.A. Testicular ultrasound in A.A. revealed a small left hydrocele and no testicular masses. The report on F.A. was still pending at that time.

The patients were continued on the 12% ammonium lactate lotion twice daily, and prior authorization for the acitretin and tazarotene were initiated. Again, both patients were advised to continue with general dry skin care. Yearly eye exams and self testicular exams with periodic testicular ultrasounds were also recommended. No biopsies or genetic testing were performed, and the patients were due for follow-up at the time of this documentation.

Discussion

X-linked recessive ichthyosis, also known as steroid sulfatase (STS) deficiency, has been reported to occur after complete gene deletion on the Xp22.32 location in 90% of patients and inactivating mutations in others. A prenatal diagnosis can be made with chorionic villus sampling (CVS) by a steroid sulfatase assay and by increased dehydroepiandrosterone sulfate (DHEAS) levels. The worldwide birth incidence ranges between 1 in 2,000 to 1 in 9,500 males, and the age of presentation is from two to six weeks old.

An STS gene deletion leads to decreased steroid sulfatase activity in the stratum corneum. This leads to increased cholesterol sulfate and DHEAS with subsequent accumulation of cholesterol-3-sulfate in the epidermis. This process is believed to play a role in retention hyperkeratosis. Failure of labor to begin or progress in a mother carrying an affected fetus occurs because of decreased placental sulfatase and estrogen, as well as increased fetal DHEAS. This leads to insufficient dilation of the cervix. This can be partially overcome by oxytocin administration, but often requires

Figure 1

Figure 2
The key features of X-linked recessive ichthyosis are the brown, firmly adherent, large polygonal scales predominantly on the extensors, posterior neck and trunk, with relative sparing of the flexures. Sparing of the palms, soles and face is common, with the exception of the preauricular area. This last finding is thought to be pathognomonic by some clinicians. Other findings include asymptomatic, comma-shaped corneal opacities occurring in 50% of adult males and some female carriers. There also is cryptorchidism in approximately 20% of affected males, with an increased risk of testicular cancer.

The cutaneous involvement waxes and wanes throughout the patient’s life, with seasonal variation. It does not significantly subside with age, in contrast to ichthyosis vulgaris.

The histopathologic findings include hyperkeratosis or parakeratosis overlying a normal or slightly thickened granular layer. Follicular hyperkeratosis may also be present. On electron microscopy there are an increased number and size of keratohyalin granules. In the stratum corneum, the cells contain a large number of melanosomes, and the desmosomes are retained.

Clinically, ichthyosis vulgaris is distinguished from X-linked recessive ichthyosis by sparing of the flexural areas, especially the neck, and an association with hyperlinear palms and soles as well as keratosis pilaris. Other conditions to be considered in the differential diagnosis of STS deficiency are Kallmann syndrome and Rud syndrome.

It is important to maintain good hydration in these patients, and multiple medications improve the scaling. Emollients, in particular propylene glycol, topical keratolytics and retinoids, are effective alone or in combination. The administration of systemic retinoids is rarely necessary.

REFERENCES:
**Case Report of Extragénatal Lichen Sclerósis Et Atrophióca in an Adolescént Female**

Derrick H. Adams, DO,* and Michael Mahon, DO, FAOCD**

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ABSTRACT

Lichen sclerosis et atrophicus (LSetA) is an uncommon cutaneous disease of unknown cause that manifests itself as white plaques with epidermal atrophy. Extragénatal LSetA is quite rare in children, with the majority of cases favoring females.1 We describe a case of a 6-year-old female with LSetA involving her abdomen, and we discuss the available literature regarding the emerging pathophysiology and treatment of extragenital LSetA.

Case Report

A 6-year-old white female in a usual state of good health was referred to the dermatology clinic for “white patches” on her abdomen of four-month duration. She had been previously treated by her family physician with over-the-counter moisturizers without any benefit. On exam, two atrophic, well-demarcated hypopigmented patches with “cigarette-paper” appearance were noted on her right lower abdomen. The remainder of her exam was unremarkable. The patient had no systemic symptoms and no family history of autoimmune diseases. There were no other family members with LSetA. Desoximetasone cream 0.25% was prescribed twice daily, and the benign nature and course of LSetA was discussed with the parents. On follow-up a month later, the father stated the size of the patches was slightly improving, but they were still present. The desoximetasone was tapered to daily application during the week and twice daily on weekends. The patient continues to do well, is monitored with monthly appointments, and remains free of corticosteroid-induced side effects. Close follow-up with the patient and parents is maintained to ensure treatment utilization is consistent with their understanding and expectations.

Discussion

LSetA is a benign, but chronic inflammatory cutaneous disease of unknown cause that appears as hypopigmented patches with epidermal atrophy, rendering a classical “cigarette paper” or parchment-like appearance. LSetA of the vulva and penis in children is more common, and females are usually afflicted more than males, at ratios as high as 10:1.2 There have been numerous case reports discussing LSetA having been mistaken for child abuse by practitioners unfamiliar with this entity.

While the majority of cases described have been seen on both female and male genitalia, approximately 15%-20% of cases do not involve the genitals. On the non-genital skin, the disease may manifest itself as atrophic, porcelain-white patches and can appear as discrete plugs inside the orifices of follicles or sweat glands. Atrophy of the skin also commonly occurs. Typical extragenital distribution is seen in the body folds, inframammary areas, shoulders and neck. While rare, oral cases have been reported. Extragénital cases are typically asymptomatic except for pruritis and associated cosmetic concerns. Both genital and extragenital cases are characterized by cycles of remission and exacerbations, often independent of treatment efforts.

While the exact cause of LSetA is still unknown, several autoimmune mechanisms have recently been elucidated. Inflammation and altered fibroblast activity results in fibrosis in the upper dermis. Associations in the abnormal ratios of interleukin-1 (IL-1) and interleukin-1 receptor antagonist (IL-1ra) have been observed.3 IL-1ra is a naturally occurring cytokine that inhibits interleukin-1 (IL-1) by binding to IL-1 receptors, halting intracellular signal transduction; thus, IL-1ra acts as a powerful endogenous anti-inflammatory molecule. A genetic repeat resulting in the decreased production of IL-1ra has been isolated in patients with LSetA, cutaneous lupus, and inflammatory bowel diseases3 and has been hypothesized to play a partial role in this disease state.

Other recent investigations have centered on the development of ELISA methods to quantitatively measure circulating autoantibodies to the glycoprotein extracellular matrix protein 1 (ECM1) in patients with LSetA. Higher anti-ECM1 titers correlated with more longstanding and refractory lesions and cases complicated by squamous-cell carcinoma.4 Demonstration of passive transfer, with anti-ECM1 IgG inducing histopathologic changes of LSetA in the murine model, has also been achieved.4 These two previous examples support the numerous observational reports of familial cases of LSetA.5 Additionally, it has been observed that the condition is likely to spontaneously resolve during puberty, leading to the hypothesis that unknown developmental factors may be implicated.6 The Koebner phenomenon has also been reported in areas of repeated trauma, sunburn, and old surgical scars. Extragénital LSetA along the distribution of Blaschkó’s lines has also been described.1

Except for the occasional associated pruritis, extragenital LSetA rarely requires any therapeutic intervention. High-potency topical steroids are the most accepted treatment, but they have been associated with a greater than 50% relapse rate at 16 months in one study.7 Therefore, it must be stressed that any potential cosmetic benefits of treatment must be carefully weighed against development of steroid-induced complications or contact dermatitis. Pimecolimus cream 1%, topical retinoids, metronidazole (250mg three times a day), and erythromycin (250mg a day) have been successfully utilized in genital LSetA and would likely be well-tolerated in our patient; however, no literature supporting the effectiveness of these treatments could be located specifically in regard to extragenital cases.8,9 There have been sporadic reports in the literature of vulvar LSetA progressing to squamous-cell carcinoma, but the precise risk and...
which cofactors are involved remain under investigation.\textsuperscript{1} While there is a paucity of data regarding the malignant transformation potential of extragenital lesions, that potential is widely believed to be low.\textsuperscript{10}

In summary, we describe a case of extragenital LSetA and briefly review the pathophysiology and treatments of this uncommon inflammatory entity.

References:
\textsuperscript{8} Shelley W, Shelley E. Lichen sclerosus et atrophicus. Advanced Dermatologic Therapy. 2001; 647-49
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Case Report:

A 44-year-old Hispanic woman presents with pain in her hands and feet for the past six months. The patient states both her hands and feet are pruritic and swollen. She also complains of cold hands for which she needs to wear gloves despite the warm temperature. This is her first occurrence. She denies any history of dermatological disorders. Her past medical history is significant for carpal tunnel syndrome. She denies a family history of skin or rheumatologic disease. She does not take any medications. On review of systems, she complains of dysphagia, chest pain, frequent urination, xerostomia, arthralgia, and diffuse pruritus. On physical examination, there is skin tightness along with induration of both her dorsal hands and feet. There is a salt-and-pepper appearance to the skin, with areas of hyperpigmentation alternating with hypopigmentation (Figures 1 and 2). Areas of her skin appear shiny with loss of hair, mostly on the forearms. The fingertips appear well perfused. There are no telangiectasias on the face, hands, or chest. There is no perioral or facial involvement. She has atrophic plaques on both knees with tenderness (Figure 3). Examination of the heart, lungs, and abdomen are unremarkable. There are no neurologic deficits.

The laboratory values were assessed at this time. Her complete blood count, comprehensive metabolic panel, and thyroid function test were within normal limits. Sjogren’s anti-SS A and B were within normal limits. RNP antibodies, anti-myeloperoxidase antibodies, and anti-proteinase 3 were negative. C-ANCA and P-ANCA had normal titers. C-reactive protein was high at 6.2. ANA was positive with a ratio of 1:80. ACE, RF, and ESR were normal. Antiscleroderma-70 antibodies were negative. Due to the limited outside clinical facility, the patient did not have a skin biopsy done. She did not follow-up in our hospital clinic for a skin biopsy.

She was started on Claritin 10mg daily, Kenalog cream 0.1% twice a day, and over-the-counter moisturizers for her pruritus. She was given prednisone 5mg twice a day and Cuprimine 250mg three times a day by her rheumatologist. She was also prescribed Flexeril 10mg at bedtime as needed. The patient was encouraged to wear double gloves for her hands to keep them warm and well circulated. She was instructed to avoid skin trauma and cold exposure. Physical therapy of the hands and feet were recommended to prevent contractures. She was instructed to follow-up with cardiology, rheumatology, gastroenterology, and nephrology.

Discussion:

Scleroderma is derived from the Greek word “sklerosis,” meaning hardness of the skin. The group of diseases called scleroderma fall into two main classes: localized scleroderma and systemic sclerosis. Localized scleroderma can be further categorized into morphea and linear scleroderma. Systemic sclerosis is divided into limited cutaneous and diffuse cutaneous.

Limited cutaneous scleroderma typically comes on gradually and affects the skin only in certain areas: the fingers, hands, face, lower arms, and legs. Most people with limited disease have Raynaud’s phenomenon for years before skin thickening starts. Telangiectasias and calcinosis often follow. People with limited disease often have all or some of the symptoms called CREST, which includes calcinosis, Raynaud’s phenomena, esophageal dysfunction, sclerodactyly, and telangiectasias.

Systemic sclerosis is an autoimmune disorder of the connective tissue and is characterized by skin induration and thickening. This condition typically comes on suddenly. Skin thickening begins in the hands and spreads quickly over much of the body in a symmetrical fashion. Skin changes can cause the skin to become edematous, shiny, tight and pruritic. Other associated cutaneous symptoms include Raynaud’s phenomena, healed pitting ulcers in the fingertips, and cutaneous and mucosal telangiectasis. The skin of the face becomes masklike and expressionless, with loss of the normal facial lines and then thinnning of the lips and constriction of the opening of the mouth (microstomia).
Radial furrowing around the mouth is seen. There may also be a small, sharp appearance to the nose.

Systemic sclerosis is also accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs. People with diffuse disease often are lethargic, lose weight, and have joint swelling and/or pain. Patients can have gastrointestinal reflux, dyspepsia, constipation, chest pain, and dyspnea. They may also suffer from arthralgia, loss of joint range of motion, and palpable tendon friction rubs. Sclerodactyly causes the fingers to become tapered. Trigeminal neuralgia and carpal tunnel symptoms may result from peripheral entrapment neuropathies. Cardiac manifestations may include palpitations, conduction abnormalities, congestive heart failure, pericardial effusion, and myocardial fibrosis. Patients may develop erectile dysfunction, dyspareunia, hypothyroidism, hypertension, renal crisis, or chronic renal insufficiency. Xerostomia and xerophthalmia may be part of the examination findings. The patient may also have poor dentition. Oropharyngeal and esophageal cancers can occur.

The American College of Rheumatology (ACR) criteria for the classification of systemic sclerosis require one major criterion or two minor criteria, as follows. Major criteria include proximal scleroderma characterized by symmetric thickening, tightening, and induration of the skin and other organs. A skin biopsy is not usually necessary but characteristically shows a squared-off biopsy with fibrosis, edema, and sclerosis in the dermis. Lymphoplasmacytic inflammatory infiltrates separate collagen strands, surround eccrine coils in the deep dermis, and are associated with loss of adipocytes around the eccrine apparatus.

Specific circulating antibodies are useful in establishing the diagnosis. Antinuclear antibodies can be detected. Centromere antibody is common with limited disease and CREST. A nucleolar pattern, although less common, is more specific for systemic sclerosis. Topoisomerase I antibodies (formerly Scl-70) are present in approximately 30%-40% of patients with diffuse disease (absent in limited disease) and are associated with pulmonary fibrosis. Other studies include ESR and hypergammaglobulinemia. Imaging studies can include CT scan, chest X-ray, echocardiography, and esophagography. Pulmonary function testing, 24-hr Holter monitoring, and bronchoscopy may be necessary as well.

There is no cure for systemic sclerosis, and treatment is aimed at controlling symptoms and preventing complications. Corticosteroids, emollients, and PUVA are used for pruritus. Avoidance of cold temperatures and the use of gloves and socks to prevent Raynaud’s phenomena should be encouraged. Calcinoic is treated with calcium channel blockers, intravenous steroids, or anticoagulants. Hydroxychloroquine sulfate 200mg twice a day is considered for patients who show active inflammatory stage. In patients with kidney involvement, ACE inhibitor therapy is indicated. Blood pressure monitoring should be routinely performed. Calcium-channel blockers, prostaglandins, and cyclophosphamide have been used to treat pulmonary issues. Proton pump inhibitors and H2 blockers can help control gastroesophageal reflux symptoms. Surgery for esophageal strictures can be utilized. Antifibrotic treatment options include D-penicillamine, interferon alpha and gamma, corticosteroids, methotrexate, thalidomide, and cyclophosphamide. Early and continuous physical therapy is crucial to maintain joint mobility. Smoking cessation should be encouraged to decrease the morbidity associated with Raynaud’s phenomena.

In this case report, we describe a middle-aged Hispanic woman with systemic sclerosis. Our patient has the major criteria of sudden onset of skin thickening and induration of her hands and feet. She has also developed dysphagia, dyspnea, Raynaud’s phenomena, and arthralgia. D-penicillamine (Cuprimine) has been recently discontinued and azathioprine (Imuran) has been substituted. She is currently stable and able to function at work. To date, our patient is undergoing a multi-specialty approach to her condition.

References:
AN INTERESTING CASE OF LEUKODERMA ASSOCIATED WITH SYSTEMIC DISEASE

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Case Report:

A 40-year-old woman presented with a two-year history of diffuse spotty hypopigmentation. The patient stated that her hypopigmentation gradually progressed over two years to its current state. She denied any repigmentation of her lesions. She stated that the lesions had not changed for many months. The patient denied any medications or any medical issues except that her primary care physician had recently told her she might have lupus based on a series of blood tests that she could not recall. Upon further review of systems, our patient admitted to shortness of breath, stating that she often found it difficult to catch her breath even at rest. She also noted that her fingertips had often become blue and cold at room temperature.

Physical exam revealed patches of hypopigmentation with areas of retained pigment around the follicular orifices (Figures 1-2). These lesions covered her face, chest, back, upper extremities, and upper thighs. In addition to these skin findings, the patient’s exam revealed signs of resolving finger tip ulceraions and mild digital clubbing (Figures 3-4).

Recent outside labs included an ANA titer of 1:640 and an ESR of 23. Complete blood count, serum chemistry, and liver function tests were all within normal limits.

Histopathology:

A biopsy of the right upper extremity revealed a square punch biopsy on low power (Figure 5). On high power, the dermal collagen bundles appeared thickened, and there was a relative lack of skin appendages within the reticular dermis. The dermis appeared hypocellular, with few vessels. MART-1 (Melan-A) stain was performed on the sample, and it was found that the part of the basal layer of the epidermis corresponding to the leukodermic skin did not stain, while the pigmented portion stained positively (Figure 6). These findings were consistent with scleroderma superimposed on vitiligo.

Background:

Systemic scleroderma is commonly categorized into two disease states: progressive systemic sclerosis (PSS) and Thibierge-Weissenbach syndrome (also referred to as CREST syndrome). As the name implies, PSS is a progressive multi-organ disease. It is characterized by thickening and fibrosis of the skin. Systemically, this disease can involve many internal organs including the heart, lungs, kidney, and gastrointestinal tract. Extensive disease can lead to death as a result of complications with these organ systems. Classic criteria for PSS are proximal sclerosis or two or more of the following: sclerodactyly, digital pitting scars, and bilateral pulmonary fibrosis. The earliest sign of disease in the majority of patients is Raynaud’s phenomenon.

CREST syndrome (calcinosis cutis, Raynaud’s phenomenon, esophageal dismotility, sclerodactyly, and telangiectasias) is considered a limited form of systemic sclerosis. CREST syndrome rarely progresses to involve the lungs or kidneys and portends a more favorable prognosis when compared to PSS. The anticientromere antibody is relatively sensitive and specific for CREST syndrome, while Scl-70 and ANA correlate to PSS.

Limited cutaneous scleroderma is referred to as morphea, which is characterized by circumscribed ivory, leather-appearing patches or lesions. Morphea seldom progresses to systemic disease.

Initial skin findings in systemic scleroderma are usually acral and facial, with swelling and induration of the hands, digits and around facial orifices. The effect on the face is that the skin becomes drawn tight and expressionless, while the lips are pursed and the nose appears pinched. The hands become contracted and claw-like, ultimately impairing function. Additionally, pterygium inversum unguis (fusion of the hyponychium to the undersurface of the distal nail plate) can occur, as well as hypopigmentation of the skin. This might exist in a large patch or with perifollicular pigment retention, mimicking the pattern of perifollicular pigmentation that one sees when a patch of vitiligo undergoes repigmentation.

Vitiligo is characterized by stark, white, depigmented patches of skin with well-defined borders that histologically correlates with the epidermal loss of melanocytes. Though vitiligo is believed to be an autoimmune disorder, little is known about the pathogenesis. However, it is not uncommonly associated with other autoimmune disorders such as thyroid disease and diabetes mellitus.

Strong evidence that vitiligo is an autoimmune disorder derives from several factors. One example is Vogt-Koyanagi-Harada syndrome, wherein aseptic meningitis triggers an autoimmune reaction causing the disease to manifest in the tissue derived from neural crest origin. This is characterized by vitiligo, iritis, retinitis, and central nervous system manifestations.1 Vitiligo has been seen in association with multiple autoimmune syndrome (MAS), defined as three or more concurrent auto-
immune diseases in the same patient. Also, multiple sources describe similar inflammatory infiltrates of T-lymphocytes in the early lesions of vitiligo, scleroderma, and other autoimmune disorders. While specific autoantibody associations in vitiligo are not defined as in scleroderma, evidence is strong for an auto-self etiology.

Discussion:

While the association of systemic scleroderma and vitiligo is very rare, some case reports describe leukodermia or “vitiligo-like macules” in association with either limited or systemic scleroderma. Cases describing both morphea and linear scleroderma have been reported to be associated with vitiligo. These reports include cases with overlap of onset as well as distribution of the lesions. There are several case reports that describe scleroderma along with “vitiligo-like macules,” “pseudo-vitiligo” or “salt and pepper depigmentation.” One case details a patient presenting with systemic sclerosis and vitiligo but lacking the characteristic skin findings of scleroderma.

Scleroderma and vitiligo have not only been observed together, but they have also been experimentally induced. In the process of attempting to devise a therapy for malignant melanoma, Lacour et al. extracted lymphocytes from a melanoma lesion of a patient. These lymphocytes were irradiated and injected back into the same patient. The result was the development of limited lesions of both scleroderma and vitiligo. Sanchez has argued that, while the hypopigmentation associated with some cases of scleroderma has many overlapping characteristics with vitiligo, they are not the same entity. However, our patient’s pathologic specimen clearly showed the characteristics of both vitiligo and scleroderma in the same pathology specimen. This provides evidence that vitiligo not only occurs with scleroderma but also that the underlying pathologic disease mechanism may overlap. This could also explain the limited efficacy of common therapies used to treat both conditions. Likewise, potential for new treatments of both conditions have recently become realized in the form of T-cell-directed anti tumor necrosis factor alpha biologics.

Increasing case reports of patients having improvement of scleroderma and vitiligo while receiving biologic therapy for other diseases have recently made their way into the literature. One such report involves a patient being treated for ankylosing spondylitis with infliximab, a biologic. While infliximab helped resolve the patient’s ankylosing spondylitis, resolution of long-standing vitiligo lesions was also observed.

In scleroderma, the evidence of efficacy of biologics is even stronger. Regopoulos conducted a study that described the successful treatment of vitiligo with etanercept. In a randomized trial, bleomycin was used to induce sclerodermatous lesions in mice. The experimental group was given etanercept to clear the lesions, while the control group was given a placebo. The result was a more extensive and persistent disease burden to the control group that did not receive treatment with etanercept.

A study analyzed a large series of patients having both collagen vascular disease and pulmonary fibrosis in respect to progression of pulmonary fibrosis while treated with infliximab. A percentage of these patients had progressive systemic sclerosis. It was found that in treated patients, disease remained more stable than in patients not treated with biologics.

Conclusion:

It is evident that scleroderma and vitiligo not only occur concurrently in the same patients, but also have overlapping lesions. Moreover, both types of lesions have been induced in laboratory animals by similar methods. Both types of lesions may occur secondarily to similar insults in predisposed humans, and both diseases respond to the same standard therapies. It is therefore intuitive that we begin to explore the possibility that these diseases are different manifestations of the same pathologic mechanism at work. This could entail the reconsideration of common auto-antibodies and their predictive factor on these diseases. Additionally, as more patients with diverse diseases are treated with biologics, and as a result of direct clinical trials, the role these medications will have for these diseases will become clear.

References:

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### 2. General Registration

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

<table>
<thead>
<tr>
<th>Before 12/31</th>
<th>After 12/31</th>
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<tbody>
<tr>
<td>Physician Registration</td>
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</tr>
<tr>
<td>ARNP's, PA's and Medical Staff</td>
<td>$995</td>
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<tr>
<td>Administrative Office Staff</td>
<td>$499</td>
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<tr>
<td>Dermatology Resident</td>
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**Registration Total**

| $____ | $____ |

### 3. Guests & Social Events

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