Letter from the JAOCDD Editors ........................................................................................................................................4
Letter from the President ..........................................................................................................................................................7
Pedal presentation of nodular localized primary cutaneous amyloidosis: An atypical presentation of an unusual condition ........8
Darier’s Disease: A Case Report ................................................................................................................................................11
The 308-nm Excimer Laser and the Treatment of Plaque Psoriasis: A Review ..............................................................................13
  Dawn Sammons, D.O., John Hibler, D.O.
Cutaneous Larva Migrans: A Case Report and Current Treatment Options ....................................................................................17
  Payal Patel, Elaine Miller, D.O., Bill W. Way, D.O.
Malignant Fibrous Histiocytoma: A Case Presentation and Discussion ...............................................................................................20
  Tony Nakhla D.O., Navid Nami D.O., Michael T. Borenstein M.D., Ph.D.
An Update on Sunscreens ................................................................................................................................................................23
  Aren Skolnick, BA, Rao N. Saladi, M.D., Joshua L. Fox, M.D.
White Piedra Mistaken for Head Lice: A Case Report and Brief Review ...........................................................................................30
A Case of Rapidly Progressive Benign Lymphangioendothelioma .................................................................................................32
A Quick Safety Reference for Systemic Medications Used in Dermatology .......................................................................................34
  Andrew J. Racette, D.O., David Stoike, B.S., Stephen Kessler, D.O.
Closure of a Large Scalp Defect After Mohs Surgery with Galeotony Assistance: A Case Report ..........................................................38
  William Kirby, D.O., Francisca Kartono, BS, Mark Horowitz, D.O., Robert M. Schwartz, M.D., David Horowitz, D.O.,
  Tony Nakhla, D.O., Tejas Desai, D.O.
Gartner’s Duct Cyst ......................................................................................................................................................................43
  Robert A. Norman, D.O., MPH, Melissa Maust, OMS III L.E.C.O.M.
Fixed Drug Eruption and Other Cutaneous Manifestations Secondary to Long-term Hydroxyurea Therapy: A Case Report and Review of the Literature ..................................................................................................................46
  Holley A. Bermel, D.O., Jennifer R. Lloyd, D.O.
Classification of Cutaneous Lymphomas Case Reports and Review ..................................................................................................46
Acquired Perforating Dermatosis: A Case Report ............................................................................................................................53
Case Study - Steroid Atrophy and Tinea Incognito ..........................................................................................................................56
  Robert A. Norman, D.O., MPH, FAAIM, Allison Evans, MS III
Paederus Dermatitis: An Outbreak on a Medical Mission Boat in the Amazon .....................................................................................57
  Jere J. Mammino, D.O., F.A.O.C.D.
Cutaneous Lymphoma as presenting sign of Richter’s syndrome ....................................................................................................61
  Joseph Schneider, D.O., Michael Mahon, D.O.
An Update and Review of Vitiligo Treatment Options ....................................................................................................................64
Calciphylaxis: Case Report and Review of the Literature ................................................................................................................66
  Leah M. Schammel, Jennifer R. Lloyd, D.O.
The Treatment of Lower Leg Ulcers with Topical Etanercept ..........................................................................................................68
After much consideration and deliberation, it has been decided that this journal should continue to represent our College, its members and its resident members. Expanding this journal to the dermatology world in general, has not proven to be of any benefit to the AOCD. Therefore, this journal will continue as the JAOCD-The Journal of the American Osteopathic College of Dermatology. The JAOCD will continue to be a journal for the members of the AOCD.

The support of our Sponsors continues to be strong and unwavering. Our Sponsors have committed to the resident physicians in our dermatology training programs. We owe gratitude and thanks to Allergan Skin Care, Global Pathology Laboratory, Medicis-The Dermatology Company and Stiefel Laboratory. They are all committed to the dermatology profession and support the AOCD in all of its endeavors.

As the editors of the JAOCD, we extend our deepest heart-felt sympathy and condolences to our president Dr. Bill Way and his family on the untimely passing of his beautiful and kind wife Sondra. She will missed by her family and all of us in the American Osteopathic College of Dermatology.

Julia Layton of Freelance Proofreading and Editing continues to help improve the JAOCD in every way possible.

The Education and Evaluating Committee encourages every program director to work with their residents to assure that their papers being submitted for consideration for publication are of the highest possible quality.

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

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

John A. Strosnider, D.O.

110th AOA President
October 29, 1947 - June 21, 2007

Dean, Pikeville College School of Osteopathic Medicine

Osteopathic Physician, Husband, Father, Friend
Sondra Darlene Way, the beautiful and wonderful wife of Dr. Bill Way, unexpectedly died on her birthday, May 27, 2007. They had been married for 21 years. Two children, Julie and Chris, and three grandchildren, Taylor, Levi, and Nathan. Her life was her husband, children, and grandchildren. She loved her horses and Yorkie dogs. Darlene was active in local and Texas DO organizations. She was an inspiration and wonderful women to know and love. She loved dermatology and was the woman behind the successful life of Dr. Way. She will be greatly missed by Dr. Way, her family, and all who knew her, for truly, she was a wonderful lady. Donations and contributions may be sent to the Foundation of the American Osteopathic College of Dermatology in her memory.
Dear Fellow & Resident AOCD members,

This year has been a very busy year for me and various committees of the AOCD. The executive committee and committee chairman have done an outstanding job in getting members to participate. I encourage all Fellow members and resident members to get active in the AOCD.

In February, I represented the AOCD at the AAD presidential reception. I felt welcomed and well received by the members of the AAD. I will continue to work with the AAD leadership in helping our two great dermatology organizations work more closely together.

In March, we had a great midyear meeting in Santa Fe, New Mexico. I wish to thank Dr. Marc Epstein and our AOCD staff for a most enjoyable and successful meeting. I have worked with the ASDS and reestablished our DO dermsurgeons membership status for our Fellows and new membership category for our AOCD residents. In May, many AOCD members across the country participated in the AAD annual skin cancer screening program.

The resident in-training examination has been restructured. All AOCD program directors and all AOCD residents will submit questions for the next AOCD resident in-training examination. This new format will be both challenging and educational for our residents. As our AOCD residency programs continue to grow and increase in numbers of residents, we must continue to set the highest standards for our residency programs.

Plans are in place for the AOCD annual convention. Dr. Jay Gottlieb, our president-elect, has put together a program schedule that will be both educational and inspirational. At this annual convention, the residency program directors will hold a very important meeting that will help shape the direction of AOCD residency training. The Presidential Reception and Awards ceremony in its new format should be entertaining. Mark your calendars now and plan to take your family and come to the AOCD annual convention in San Diego, September 30th – October 4th, 2007.

During this year, I have tried to lead our great dermatology college into the future, but it is up to each of you to become more active in the AOCD. Together we will continue to improve and make the AOCD a more interactive and educational college which stands for “Excellence in Dermatology.”

Bill V. Way, DO, FAOCD
Pedal Presentation of Nodular Localized Primary Cutaneous Amyloidosis: An Atypical Presentation of an Unusual Condition

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ABSTRACT

Amyloidosis is the extracellular deposition of proteins in a specific organ or throughout the body, leading to a change in tissue structure and function of the target organ.1-3

Nodular localized primary cutaneous amyloidosis is one of three forms of cutaneous amyloidosis. The three types of cutaneous amyloidosis are nodular (also referred to as tumefactive), lichen and macular. We report a case of nodular localized primary cutaneous amyloidosis (NLPCA) localized to the feet bilaterally. The unique findings of this case will be presented. A review of the literature regarding classification, epidemiology, etiology, clinical criteria, histopathological criteria and treatment are discussed.

Case Report

History

A 72-year-old Caucasian male presented to the clinic with a complaint of a “rough texture” on the bottom of his feet, present for more than six months. He denied pruritus, pain or drainage, but he did report intermittent periods of tenderness over the plantar aspects of his feet. Past medical history was significant for actinic keratosis, hypertension, hypercholesterolemia, bronchitis, asthma, and osteoarthritis. He also reported childhood-associated measles, mumps and varicella. Past surgical history was noncontributory. Family history was negative for genetic disorders, structural protein mutations or amyloidosis. Current medications included aspirin, olmesartan, piroxicam, and a multivitamin. His drug-allergy history was negative. He is retired, denied illicit drug use and tobacco use and reported drinking two beers per day.

Physical Exam

The cutaneous examination revealed multiple, firm, reddish-orange-to-violaceous, amorphous, dermal papules and bullous-like plaques on the plantar and medioplantar aspects bilaterally, with the right plantar surface more severely affected than the left (Fig. 1a and 1b). There were no other similar cutaneous lesions noted on the body.

Histopathology

A 0.3-cm punch biopsy of the right lateral heel was sectioned and stained with hematoxylin and eosin, revealing nodular amyloid deposition of the superficial and deep dermis (Fig. 2). Adjacent telangiectasia and red cell extravasation were also noted. These findings were confirmed by crystal violet (Fig. 3) and Congo red stains (Fig. 4).

Results and Management

Nodular cutaneous amyloidosis may follow a benign course, or it may progress to systemic amyloidosis with an underlying paraproteinemia.4 Primary systemic amyloidosis can affect the heart, kidney, liver, gastrointestinal tract, nervous system and skin.5 For this reason, when cutaneous nodular amyloid lesions are diagnosed, an assessment for systemic pathological disease needs to be completed. Evaluation for systemic amyloid involvement included a complete blood count with differential, complete metabolic profile, urinalysis, serum protein electrophoresis, urine protein electrophoresis, 24-hour urine protein, ANA, SS-A antibodies, SS-B antibodies, chest roentgenograph, EKG, abdominal ultrasound, echocardiogram and a complete radiographic bone survey.

The patient was referred to an oncologist for continuation of follow-up and to monitor for progression to systemic disease. The systemic evaluation proved to be negative, although a borderline anemia of undetermined significance was discovered. Based on clinical findings, histopathological evidence and a negative assessment for the presence of systemic amyloidosis, the patient was given the diagnosis of nodular localized primary cutaneous amyloidosis (NLPCA). Available cutaneous treatment options were discussed with the patient, which he declined. The patient was instructed to continue outpatient dermatologic observation of the lesions and hematologic monitoring every six months.

Discussion

Classification

The amyloidoses are organized based on clinical presentation, the organs affected and the character of the amyloid deposit.7 Amyloid deposits are either localized to one organ or of a systemic distribution, which would involve multiple organs, including the skin.7 Localized cutaneous amyloidosis can be primary or secondary.7 Localized secondary cutaneous amyloidosis (LSCA) is the most common localized type.7 LSCA is defined by microscopic, clinically unimportant deposits of amyloid that are secondary to various epithelial-derived skin lesions.7,8,9 Conditions associated with LSCA include basal cell carcinoma, Bowen’s disease, squamous cell carcinoma, seborrheic keratosis, intradermal nevi, adnexal gland tumors, pilomatrixoma, dermatofibroma, solar elastosis, photosensitive annular elastolytic giant cell granuloma, actinic keratoses, disseminated superficial actinic porokeratosis, porokeratosis of Mibelli, and effects of PUVA therapy.7,8,9 Primary amyloidosis confined to the skin is called localized primary cutaneous amyloidosis (LPCA). The three types of LPCA are lichen, macular and nodular, with nodular being the most rare.7 Amyloidosis is also distinguished based on its biochemical protein type. Table 1 provides a synopsis of the amyloidoses with their associated fibril
50 percent. The degree of variation is due to the Congo red stain and reveals a pink-to-red color. Crystal violet stains amyloid a purplish-red color (metachromasia).

**Figure 2**
Hematoxylin and eosin stain revealing nodular amyloid deposition of the superficial and deep dermis.

**Figure 3**
Crystal violet stains amyloid a purplish-red color (metachromasia).

**Figure 4**
Amyloid appears a pink-to-red color with the Congo red stain and reveals an apple-green birefringence when viewed with polarized light.

and precursor proteins.

**Epidemiology**

NLPDA is the rarest of the cutaneous forms of amyloidosis. This is the third case of NLPDA reported in the literature that has presented on the plantar aspect of the feet, with the previous two cases reported in 1997 and 2003, respectively. The incidence of progression of NLPDA to systemic disease is estimated at between 7 percent and 50 percent. The degree of variation is due to the results of clinical outcomes of cases analyzed in separate studies. Nodular amyloidosis occurs most often in the sixth to seventh decade. Females are more often affected than males, with a ratio of 2:1.

**Etiology**

Amyloid protein is distinguished by its abnormal protein folding, B-pleated sheet 3-D conformation, and resistance to proteolysis. Viewed with electron microscopy, the amyloid structure is a 7.5-nm-to-10-nm, linear, nonbranching, hollow, cylindrical fibril existing as pairs. Damaged or misfolded proteins are typically degraded via intracellular or extracellular physiologic processes. It is postulated that in amyloidosis, these regulatory methods fail and extracellular protein accumulates.

The amyloid deposits of NLPDA are amyloid light chain (AL), derived from immunoglobulin light chain. Infiltrates of plasma cells and lymphocytes are often found in the biopsies of nodular cutaneous amyloid. Monoclonality of infiltrating plasma cells in NLPDA has been detected by Southern blot analysis of the immunoglobulin heavy gene (IgH) and also using polymerase chain reaction (PCR) for the IgH gene. These studies support the theory that the nodular amyloid deposits arise due to a localized plasmacytoma and the products they secrete.

**Clinical appearance**

NLPDA often presents with single or multiple firm nodules or plaques on the body, most commonly on the face, trunk, extremities or genitalia. The lesions do not ulcerate, but they can crack or split. The asymptomatic nodules can vary in size from millimeters to centimeters with a pinkish-red-to-brown color. They can appear waxy or shiny and may have overlying telangiectasia, and they can resemble nodular basal cell carcinoma.

Cutaneous lesions in NLPDA are indistinguishable from nodules associated with...
relied upon to make the diagnosis. \textsuperscript{1,24} The most well-recognized, which are identical structures recognized in all types of the amyloid protein present in NLPCA is amyloid light chain (AL), the same type of protein present in systemic amyloidosis and paraproteinemias. Cutaneous lesions in NLPCA are indistinguishable clinically from nodules associated with plasma cell dyscrasias, systemic amyloidosis, and certain hereditary syndromes. Therefore, differentiation between NLPCA and systemic amyloidosis is not possible based on clinical and histological findings. NLPCA can follow a benign, localized course, or it can progress to systemic disease. Accordingly, it is necessary to evaluate for the presence of systemic amyloid involvement when nodular cutaneous amyloid lesions are discovered. Additionally, patients need to be followed on a regular basis to monitor for progression to systemic involvement. If systemic involvement is found, appropriate and timely intervention is necessary. If the lesions are limited to the skin, various treatment options are available. Localized lesions are not life threatening, and the treatment is often cosmetic.

**References:**


**Histopathological Findings**

With a light microscope, amyloid appears as a pale pink, eosinophilic, homogenous, acellular material deposited in the papillary dermis, reticular dermis and subcutaneous fat. An inflammatory infiltrate containing plasma cells is also observed in the amorphous deposit. Amyloid can be seen with multiple special stains. The most well known and commonly used stain is the Congo red stain. With this stain, amyloid appears a pink-to-red color and will have a characteristic, striking apple-green color when viewed with polarized light. Of note is that amyloid A, which is present in secondary amyloidosis, will not stain with Congo red after pretreatment with potassium permanganate. However, primary systemic and localized amyloid deposits are not affected by the potassium permanganate and will still stain with Congo red. Amyloid stains a purple-red, metachromatic color with a crystal violet stain. Amyloid will fluoresce yellow upon using the thioflavin-T stain and ultraviolet radiation. Electron microscopy shows fibrillar protein deposits (as previously described), which are identical structures recognized in all types of the amyloid deposits. The cross-pleated sheet conformation, noted with infrared spectroscopy and roentgenography, is the basis for the Congo red staining pattern with negative birefringence. While nodular amyloid skin lesions have a different appearance on the skin than macular and lichen cutaneous types, they can also be distinguished based on immunohistochemical stains. Immunohistochemical staining of nodular amyloid skin lesions is negative for cytokeratin and positive for lambda and/or kappa light chains, while macular and lichen are cytokeratin positive.
Darier’s Disease: A Case Report


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Case Report:

Our patient is a 43-year-old, white female with a negative past medical history other than bipolar disorder who presented with multiple erythematous, hyperkeratotic papules. Some of these lesions had overlying crusts that coalesced into plaques. Lesions involved the upper chest, abdomen, upper back and, to a lesser extent, the upper and lower extremities (Figures 1-3). Her nails presented with a groove-like deformity. (Figure 4) Her face had erythematous, greasy scales. Dermatohistopathology revealed focal acantholytic dyskeratosis with hyperkeratosis and a sparse infiltrate of lymphocytes in the dermis (Figures 5-6). She has a long-standing history of previously diagnosed and biopsy-proven Darier’s disease with an age of onset of four years old.

She has tried various treatments for her condition, both pharmacologic and non-pharmacologic, including a number of over-the-counter herbal remedies. She has also been on oral isotretinoin and etretinate. She has undergone multiple plastic surgeries to treat her hyperkeratotic skin. Her current list of medications includes acitretin 100 mg daily, doxepin 25 mg four times a day, trimethoprim/sulfamethoxazole 160/800mg twice a day, and diphenhydramine as needed. She has been treated by a number of dermatologists over the years and denies any family history of the disorder in her parents or presence of the disease in her children.

Discussion:

Darier’s disease is an autosomal-dominantly inherited disorder that is also known as keratosis follicularis, dyskeratosis follicularis, or Darier-White disease. It is characterized by moderately pruritic, brown, hyperkeratotic papules and plaques that coalesce and tend to form in areas similar to seborrheic dermatitis, including but not limited to the scalp, neck, chest, upper back, axilla, groin, palms, and soles (see Figures 1-3). When primarily intertriginous sites are involved, it may be clinically misdiagnosed as Hailey-Hailey disease.1

Lesions begin as small, firm papules that become covered with a greasy, brown crust. Over years, the lesions may become malodorous, vegetating masses primarily located in the axillae, gluteal crease, groin, and behind the ears.2 Punctate keratosis may be noted on volar surfaces.2 Nail changes may be evident as well, with longitudinal red or white lines, subungual hyperkeratosis, splitting, and fragility1,2 (see Figure 4). Painless, white papules may be seen on the palate, gingival, buccal mucosa, and tongue. Involvement of the esophagus, larynx, and anorectal mucosa have been reported as well.2

Dermatohistopathology:

Dermatohistopathology reveals hyperkeratosis, parakeratosis, papillomatosis, acanthosis,1,3 and, occasionally, pseudoepitheliomatous and basaloid hyperplasia. Keratinocytes, when acantholytic or dyskeratotic, give the characteristic appearance of “corps ronds” (enlarged acantholytic keratinocytes) and “grains” (small, oval, eosinophilic-staining cells in the stratum corneum)1,3 (see Figures 5 and 6). Grover’s disease may appear similar to Darier’s disease both clinically and histologically. However, the former tends to be less dyskeratotic and more acantholytic.3

Background:

Darier’s disease is classically worse in the summer months and may initially present after a severe sunburn.2 Sweating, heat, and occlusion are also thought to exacerbate the condition. Onset is usually between the ages of six and 20, with peak onset around puberty.1,3 The disease may be complicated by infections, salivary gland disease, and neuropsychiatric diseases. Kaposi’s varicelliform eruption must be suspected when there is a sudden outbreak of vesicular and crusted lesions accompanied by malaise and fever. Immediate anti-viral therapy is necessary in these situations. Salivary glands may become obstructed, and painful swelling may result.1 Migraines, epilepsy, mental retardation, and schizo-ffective disorders have all been associated with Darier’s. However, Munro et al. showed no clear link between neuropsychiatric disease and Darier’s.5

Studies classify the disease as having a prevalence of one in 100,000 in Denmark and one in 55,000 to one in 36,000 in England.4,5,6 Men and women are equally affected.1 Darier’s is mapped to chromosome 12q23-24.1 and is caused by 140 different mutations in the ATP2A2 gene that encodes the sarco/endoplasmic reticulum Ca2+-ATPase pump type 2b isomor (SERCA2b).7 This leads to the loss of acantholysis and dyskeratosis that can be seen histologically.1 Wooin et al. recently showed that there are multiple effects of this mutation on Darier’s disease.7 Most of the 12 mutations of the gene that were studied showed a marked effect on protein expression, and all mutations had lower activity from the Ca2+-ATPase pump.7

Treatment:

General measures to prevent exacerbation of the disease include loose-fitting, light-weight clothing and sunscreen. Antimicrobial cleaners and topical keratolytics may provide relief from the malodorous nature of the disease as well as the scaling and irritation. Topical retinoids are generally more effective than topical steroids.1 For severe
cases, oral retinoids such as isotretinoin and acitretin are the drugs of choice. However, relapse after discontinuation of the drug is the norm.

Li et al. reported two biopsies of Darier’s disease that, in addition to the classical histological findings, had papillomatous proliferation and vacuolated keratinocytes. DNA sequencing revealed HPV-5,-36-38 in PCR products. These patients were treated with arotinoid ethylester, a powerful antipapillomaviral, with clearing of the majority of the lesions after two months.

A small number of female patients have noted premenstrual exacerbation of the disease, which may improve after the initiation of birth control. More recently, Exadaktylou et al. studied the use of photodynamic therapy using topical 5-aminolaevulinic acid. This produced an initial inflammatory reaction that lasted up to three weeks but was followed by a sustained improvement of up to 36 months. More aggressive treatment has involved removal by split-thickness grafting, dermabrasion, and CO2 or Erbium:YAG laser.

Finally, Yoon et al. treated a 20-year-old Korean woman with Darier’s by applying 1% topical 5-FU to the trunk and limbs daily and every other day to her face and flexural surfaces. Her lesions showed significant regression after one week and had almost complete resolution after one month. New lesions were controlled by topical 5-FU without any additional treatment. Monthly usage was 15 grams during summer months and 5 grams during the other seasons.

Conclusion:

Darier’s disease is a rare and potentially disfiguring disease. Many patients suffer concomitant psychiatric disorders secondary to their skin disease. Proper diagnosis and treatment of these patients is crucial to improve their quality of life. Our patient has some of the classic clinical and pathological findings of this disorder. Even though she has been taking a high dose of oral retinoids (up to 100 mg per day), her disease appears to be poorly controlled, and she suffers from frequent exacerbations. Darier’s disease has an autosomal dominant inheritance pattern. However, this case showed no clear family history of the disorder in the patient’s parents or the presence of the disease in any of her children, which likely indicates a sporadic mutation.

References:

The 308-nm Excimer Laser and the Treatment of Isolated Plaque Psoriasis: A Review

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ABSTRACT

The 308-nm excimer laser provides an additional treatment option for patients with isolated plaque psoriasis. The laser offers several advantages over traditional phototherapy treatments as it only treats the lesional skin. The 308-nm excimer laser provides patients with a remittive therapy that is quick and effective with only minimal side effects.

Background

Psoriasis is a common and universal skin disease effecting about 2% of the population and occurring in males and females equally. The degree to which an individual is affected can range from a mild form with only minimal, localized disease to a more severe form with extensive cutaneous involvement and/or associated joint disease. No matter the severity, psoriasis can have untoward effects on an individual’s quality of life. Treatment options providing quick and effective results with minimal adverse effects are thus necessary for good patient care.

For those patients with isolated plaque psoriasis, treatment has historically been centered on topical therapy. While topical therapies can offer significant benefit for some patients, not all patients will have a favorable response to therapy. Additionally, because corticosteroids are the mainstay of topical therapy, there are side effects that can be associated with long-term use. Furthermore, topical therapies rarely provide the patient with a lengthy disease-free remission period. Phototherapy is a treatment alternative; however, it has traditionally been reserved for more widespread or severe forms of the disease. Reasons for this have been related to the inconvenience of frequent office visits and the risks associated with ultraviolet radiation (UVR) exposure.

Phototherapy is one of the oldest treatment modalities for psoriasis, dating back to the early 1900s. This form of therapy continues to be utilized today because it is effective for many in clearing the plaques of psoriasis. Our understanding of phototherapy and psoriasis has progressed over the last 80 years, building on what Goeckerman first introduced with his treatment method in 1925. In 1981, Parrish and Jaenicke published their research findings outlining the action spectrum for psoriasis. They found that if the wavelengths 304 nm to 313 nm were optimally effective in clearing the plaques of psoriasis. This led to the development of narrow-band ultraviolet B (NB-UVB) lamps, which have an emission between 310 nm and 313 nm. The most recent advancement in phototherapy is the 308-nm excimer laser, which emits radiation within the action spectrum at a single, isolated wavelength. The excimer laser has been regarded by some as a ‘super narrow band’ UVB light source. The 308-nm Xtrac Excimer Laser

The 308-nm Xtrac excimer laser (figure 1) gained FDA approval for the treatment of isolated plaque psoriasis in February 2000. The laser produces a train of short pulses that deliver monochromatic radiation at the 308-nm wavelength to the exposed skin. The ultraviolet radiation is delivered via a fiber-optic hand piece with a treatment size of 3.2 cm² (figure 2), allowing for the treatment of psoriatic plaques while sparing healthy, normal skin. The fiber-optic delivery system is flexible, allowing for the treatment of otherwise hard-to-reach body areas such as the gluteal cleft and the scalp. Treatments are painless and quick and require no post-laser-treatment precautions. Side effects are minimal and are those that would be expected from UBV exposure. Erythema, blistering and transient hyperpigmentation are the most common side effects, occurring respectively in 50%, 45% and 38% of those treated. Erythema and blistering are generally well tolerated, especially as only psoriatic skin is affected. The hyperpigmentation seen is in the form of a tanning response in those with Fitzpatrick skin types II and higher, and it tends to gradually fade following the cessation of treatment.

Treatments are generally recommended to be twice weekly for a period of five to six weeks. The average number of treatments needed to achieve significant to complete clearance is 11. In one study by Feldman et al., it was found that 84% of those treated achieved at least 75% clearance after the first 10 treatments, with many patients becoming completely clear. This is in contrast to NB-UVB, which may require 15 to 20 treatments to achieve even a 50% improvement. Treatments should be scheduled no closer than 48 hours apart, allowing enough time to determine the level of erythema and recovery so that fluences may be adjusted accordingly.

The target response of individual treatment sessions is a mild, erythematous, sunburn-like reaction, which should be maximal at 24 hours. This reaction will then generally fade over the subsequent 24 hour period. The fluence is then either increased on repeat treatment if the patient did not experience the expected sunburn reaction; left the same if the target response was met; or decreased if there was associated pain or blistering. A thin coat of a bland emollient such as mineral oil should be applied to the psoriatic plaques immediately prior to the treatment process, which will help decrease the scattering of the wavelength. Individual treatment sessions typically take less than five minutes.

Appropriate candidates for the 308-nm excimer laser should have psoriatic plaques...
on no more than 20% of the body surface area. Until a hand piece with a larger spot size is developed, treating patients with a greater percentage of affected skin is not time efficient and is often not covered by insurance carriers. Relative contraindications to treatment would be similar to those for NB-UVB: avoiding patients who koebnerize, have a history of recurrent or multiple squamous cell carcinomas, and/or have a history of malignant melanoma.

Phototherapy in any form can offer the benefit of a remission period following an effective course of therapy. This phenomenon is not observed with the use of topical therapies. PUVa has been shown to have the longest remission periods, lasting anywhere from six months to several years. While the 308-nm excimer laser has not been shown to have remissions as lengthy as PUVa, the remission times are comparable to those seen with NB-UVB and broad-band UVB (BB-UVB). The 308-nm excimer laser has a mean remission time of 3.5 months, with about 20% of patients experiencing a remission time of greater than one year. The length of remission appears to be related in part to the speed with which a patient clears, finding that the more rapidly a patient clears, the longer the remission period he or she will likely encounter. This certainly would suggest that aggressive adjustment of the fluences within the constraints of patient tolerability is prudent. Undoubtedly, a rapid clearance with prolonged remission is both the patient’s and the physician’s goal.

While the 308-nm excimer laser alone can provide dramatic results, many patients ask about continuing their prior topical therapies. No study to date has specifically looked at the use of topical therapies and the 308-nm excimer laser combined. However, there are several studies looking at topical therapies used concurrently with other types of phototherapy. It would seem plausible that these results would be relevant to treatment with the excimer laser. Studies support the combination of phototherapy with calcipotriol and tazarotene. Salicylic acid can be beneficial as a scale reducer as long as it is not used on the day of treatment, because it is a UVB absorber. The use of topical steroids during the treatment period is currently somewhat controversial. Several studies have suggested that the concomitant use of topical steroids during the course of phototherapy treatment may actually decrease the remission time. One of the greatest benefits of the 308-nm excimer laser is that only lesional skin is treated. This confers several advantages over more traditional phototherapy modalities. First, because lesional skin is more resistant to UVR, it can tolerate much higher fluences than can non-lesional skin. In traditional phototherapy, the healthy, non-lesional skin limits the multiples of the mean erythematous dose (MED) that can be used, often limiting starting doses to only fractions of the MED. With the 308-nm excimer laser, as many as six multiples of the MED can be employed as the starting dose with good patient tolerability, which allows for more rapid clearance. It has even been shown that super high doses, up to 16 multiples of the MED, can result in complete clearance after just one treatment session with reasonable patient tolerability. Although we are not likely to employ such dosing in our practices due to the increase in side effects, it does highlight the fact that aggressive treatment can produce dramatic results in a very short time.

The other benefit of only treating those parts of the body expressing psoriatic changes is that we can limit the cumulative dose of UVR that our patients experience. This is important because, as the cumulative life dose of UVR increases, so does the risk of carcinogenicity. To date, no research has been done looking at the carcinogenicity of the 308-nm excimer laser specifically; however, it would seem safe to extrapolate that the risks would be dose dependant but otherwise similar to those observed for NB-UVB. Additionally, photo-aging would be reduced as compared to other forms of phototherapy that require exposure of healthy, non-lesional skin.

Another advantage of the 308-nm excimer laser is that the physician can tailor individual treatment plans for various plaques within the same patient. Taneja et al. utilized the laser to treat individual plaques that had been deemed recalcitrant, finding that by individualizing the treatment parameters, rapid and safe resolution of the plaques could be obtained. This can also be useful for the average patient who might have plaques of various thicknesses on different body areas. The total fluence for any one plaque can be maximized, as opposed to being limited by another lesion less tolerable to UVR.

Conclusion

The 308-nm excimer laser provides an additional effective treatment option for those with isolated plaque psoriasis. Patients who may not have been appropriate candidates for traditional phototherapy can now experience the benefits phototherapy has to offer. Additionally, the opportunity for quick clearance and a reasonable remission period makes this treatment modality an attractive option for both physicians and patients. In the future, there are plans to make available a hand piece with a larger spot size, which would allow for the treatment of patients having more extensive cutaneous involvement.

References:

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Cutaneous Larva Migrans: A Case Report and Current Treatment Options


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ABSTRACT

Cutaneous Larva Migrans (CLM) is a condition caused by the introduction of the animal hookworm larvae into the human skin. Although endemic to warmer regions of the world, it is important that we be able to recognize CLM in the US, as it may present in our patients that live in coastal states or that have recently traveled outside of the country. The intent of this case report and discussion is to describe clinical manifestations and current medical management of CLM, and to stress the importance of obtaining a travel history from all of our patients.

Introduction

Cutaneous Larva Migrans (CLM) is usually a self-limited cutaneous eruption caused by penetration of the epidermis by animal hookworms. It is a common condition in warmer climates of the world, in the US along the Florida and the Gulf Coast areas, and among travelers to these areas.

The skin manifestations can be quite impressive, and include serpiginous, edematous, and erythematous tracts, most commonly on the lower extremities, usually accompanied by small vesicles. The tracts are produced by the migration of the larvae itself through the skin. They are often painful and pruritic. Secondary bacterial infection is common, but a rare systemic manifestation includes migratory pulmonary infiltrates in combination with peripheral eosinophilia (Loeffler’s syndrome).

Case Report

A seventeen year old Caucasian female presented to the Dermatology Institute for a rash on her feet that was “sore and irritated” for two weeks. The rash started as “itchy spots” on her feet that progressed to visible bumps. The patient stated that her feet became swollen and painful. She also developed two red lines between the toes on her left foot. Notably, she had recently returned from a cruise to Mexico, where she admitted to walking barefoot on the beach. She stated there were dogs and fecal matter on the beach, but she did not come into direct contact with them. She did not recall being bitten by anything, or coming in contact with any plants or irritants.

Three days prior to being seen in our office, the patient had sought care in an emergency room. This physician told her she was unsure of her diagnosis, but treated her with an empiric course of Doxycycline and Allegra (fexofenadine). She did not have much improvement in her symptoms, so she visited her Primary Care Provider, who immediately referred her to our Dermatology clinic.

The patient’s past medical history was insignificant, and her surgical history only included a tonsillectomy. Her family history was positive for type II diabetes, heart disease and skin cancer. The patient denied smoking or drinking alcohol, and had no known allergies. Her only oral medications were Zyrtec (cetirizine) as needed for allergic rhinitis, along with the previously mentioned Doxycycline and Allegra. Topically, she had been spraying her feet with Caladryl for the symptoms of pain and itching. Review of symptoms was entirely negative, except for the itchy, painful, blistering rash of both feet.

On physical exam, the patient’s left foot had a 4 cm serpiginous, erythematous, raised tract that coursed on the dorsa of the foot and in the space between the first and second toe (Figure 1, 2). There was another tract on the ventral surface of the left foot, approximately 2 cm in length. Her right foot showed several scattered, tense vesicles and bulla on her toes (Figure 3).

No labs, imaging, or biopsies were performed. A diagnosis of Cutaneous Larva Migrans was made based on the clinical findings and the history. The patient was treated with a single dose of Ivermectin 12 mg by mouth for the CLM, Tylenol #3 every 6 hours as needed for pain, Ibuprofen 800 mg every 8 hours as needed for pain and inflammation, and Clobex lotion twice daily for itching. She was also to continue her antihistamines as previously ordered.

The patient returned for follow-up one week later, and had resolution of the pain in her feet. She still had mild pruritus. She tolerated the Ivermectin, and no longer needed the Tylenol #3 or Ibuprofen. On physical exam, the edema in the serpiginous tracts had diminished, and the erythema was fading. A larger, 5 cm tract had appeared on the ventral surface of the left foot.

Figure 1.
Erythematous, elevated, serpiginous tract on left foot.

Figure 2.
Closer view of Figure 1.
CUTANEOUS LARVA MIGRANS: A CASE REPORT AND CURRENT TREATMENT OPTIONS

Epidemiology and Pathogenesis

Cutaneous Larva Migrans (CLM) is caused most commonly by the hookworm species Ancylostoma braziliense and Ancylostoma caninum, but other less frequent species include Uncinaria stenocephala, Bunostomum phlebotomum, or the human larvae, Necator americanus and Ancylostoma duodenale. This condition is endemic to warm, tropical regions of the world, such as the southeastern US, Asia, Central and South America, and Africa. CLM may be contracted and passed between countries by travelers.

The first phase of the Ancylostoma life cycle begins with breeding, which occurs in the stomach and small intestine of the dog or cat. The eggs that are produced in this phase are released into soils within the animal’s fecal matter. In warm temperatures, the eggs hatch and larvae emerge. The larvae go through three phases of development, and become infectious in the third stage, where they are referred to as filariform larvae. At this stage, the larvae are 0.5-1 cm long.

When in contact with human bare skin, the larvae are able to penetrate the skin through small breaks in hair follicles, sweat glands or damaged skin. Rarely are the larvae able to penetrate the dermoeipidermal junction, due to the lack of the enzyme collegenase, and therefore they are unable to reach the bloodstream. On the other hand, human hookworms may migrate within the blood to the lungs and small intestine, where they can complete their life cycle and produce more systemic symptoms.

Clinical Features

The onset of the disease is characterized by pruritus and the appearance of papules in the areas of infestation. Pain and stinging may also be an accompanying symptom. The hallmark dermatologic manifestation of Cutaneous Larva Migrans is the appearance of single or multiple, erythematous, slightly raised, serpiginous tracts, usually on the feet. Each tract represents the path of one larva through the epidermis, and usually increases in length at a rate of about 2 cm/day. There is a significant correlation between the length of the tract and the duration of infestation. papules located along the serpiginous tract represent areas of resting larvae. Vesicles and bulla may develop in the affected area secondary to the immune response produced by the body against the larvae, particularly in those individuals previously sensitized to the organism. As the disease progresses, older areas of the tracts may fade.

The tracts appear on the feet in 39% of cases of CLM, the buttocks in 18%, the abdomen in 16%, and the lower legs, arms, and face in the remainder of cases. In a study of patients in Brazil with CLM, it was noted that children featured their lesions mainly on the buttocks, genitals, and hands, whereas in older patients, the majority of the lesions were on the feet.

A common complication of CLM includes secondary bacterial infection due to scratching of the pruritic lesions. This may manifest with purulent papules, excoriation, or erosion. A rare complication of CLM, known as Loeffler’s syndrome, is characterized by a patchy infiltrates of the lungs and eosinophilia in the blood and sputum. Loeffler’s syndrome is rare since the larvae usually are unable to cross the epidermal boundary.

CLM is a mostly a self-limited disease, and if left untreated, the condition and dermatologic manifestations disappear within 1 to 6 months.

Diagnosis

Diagnosis of CLM is typically clinical, based on the patient’s history of visiting a tropical area, and the distinct physical exam finding of serpiginous tracts.

It is often difficult to isolate the larva using a skin biopsy because the parasite may be located beyond the visible lesions. The biopsy often shows a very large eosinophilic infiltrate, but does not usually identify the larva itself. Therefore, although biopsies are often performed, the overwhelming eosinophilia may obscure the presentation of the parasite. Perhaps more helpful is a biopsy of cavitary lesions, often left behind by larvae, which may show spongiosis. The dermis frequently reveals eosinophils, histiocytes and lymphocytes. Occasionally, the epidermis will show eosinophils, sometimes even located in hair follicles.

Laboratory blood tests may demonstrate hypereosinophilia, increased total white blood cell count, increased inflammatory markers such as erythrocyte sedimentation rate (ESR), and an increase in the levels of IgE. A chest x-ray should be ordered in the presence of pulmonary symptoms.

Differential Diagnosis

The differential diagnosis for Cutaneous Larva Migrans may include larva migrans visceral, Strongyloides stercoralis eruptions, myiasis, allergic contact dermatitis, urticaria factitia, impetigo, scabies and inflammatory tinea.

Current Treatment Options for Cutaneous Larva Migrans

If left untreated, CLM usually resolves after several months of infestation. However, the intense pruritus and stinging that may occur, as well as the potential for secondary bacterial infection, make treatment a more sensible and safe option. Topical treatments may be a good option for some patients since they have a low side effect profile, good efficacy, and are safe to use in pregnancy, children and the elderly. On the other hand, oral treatments appear to be safe, are easy to use, and produce a quicker resolution of symptoms.

Topical Treatments

Cryotherapy

Cryotherapy has been used in an attempt to kill the larvae with agents such as carbon dioxide snow, ethylene chloride spray, or liquid nitrogen. Spraying the leading edges of the tracts with these agents is rarely effective because the larva may be several centimeters from that area. The parasite has been known to withstand the low temperature. In one study with eight patients, liquid nitrogen was only successful in two patients and led to severe blistering in a few of the patients as well.
Topical Thiabendazole

10-15% Topical Thiabendazole solution or ointment is advantageous due its tolerability and success in the eradication of CLM. The treatment, used four times a day, results in relief of pruritus after a few days of treatment, followed by inactivation of the tracts within a week.7 In a study of Canadians, 52 of 53 patients with CLM were treated successfully with 15% Thiabendazole cream applied to the affected area two to three times a day for five days.11 96 of 98 German travelers treated with Thiabendazole ointment were cured of the infection. The remaining two patients were cured after a few more weeks of treatment.8

One study consisting of daily treatments with 15% Thiabendazole ointment in a lipophilic base fat cream showed 98% efficacy within a median of 10 days in six patients with no side effects. This case showed that a lipophilic base, rather than the traditional hydrophilic, may be easier to prepare and have higher absorption to the lower stratum of the epithelium where the larvae reside.12

Disadvantages of topical Thiabendazole include the possibility of contact dermatitis to the medication, the requirement of multiple daily applications leading to higher failure rates, increased duration of treatment, and impracticality with large surface areas.9 Relapses have been described with topical Thiabendazole, likely due to the inability of this application to penetrate hair follicles, an area where the larva often hides.9

Oral Treatments

Oral Albendazole

Albendazole is an anti-helminthic drug, whose mechanism of action has been hypothesized to be related to inhibition of maleate-dehydrogenase, fulmarate-reductase, exhaustion of ATP, and even cellular autolysis. Albendazole is effective against eggs, larvae, and the adult stage of numerous worms.9 It is teratogenic in animal studies and must not be used in pregnancy. Side-effects are infrequent, but include fever, pain, transitory alopecia, increase in liver enzymes, and neutropenia. They generally occur only with prolonged use at high doses.9

In a study of 11 patients treated with oral Albendazole 400 mg daily for seven days, all patients were cured at the end of treatment. No side effects or recurrence of disease were noted at three month follow-up.16 In a study of 36 patients treated successfully with oral Albendazole 400 mg daily for three days, none of the patients reported adverse reactions.4

Clinical trials thus far have failed to establish an optimal dose of Albendazole for CLM, but it has been suggested to use 400-800 mg/day for 3-5 days when treating CLM.4,15

Oral Thiabendazole

Thiabendazole has shown to be quite efficacious in CLM, and the most common side effects involve the gastrointestinal system. This drug has been tested in more patients than any other agent for CLM, but is less well tolerated than oral Albendazole or Ivermectin.3 It is a pregnancy class C drug and should be used with caution in pregnancy.

It has been suggested to use Thiabendazole 25-50 mg once or twice daily for 2-5 days or in a single dose of 50 mg/kg for CLM.4 However, in a study of 28 Americans treated with one dose of 50 mg/kg Thiabendazole, only 68% responded effectively. When treated for three consecutive days with this dose, the cure rate rose to 87%.9 In a case report of a patient with widespread CLM, a dose of oral Thiabendazole 50 mg/kg divided in two doses for one day was taken, and the patient noticed resolution of pruritus and the rash within four days.4

Thiabendazole is poorly tolerated. In a series of 138 patients treated with 1.25-2.5 g/day for 1-2 days, side effects included nausea in 49%, giddiness in 13-54%, vomiting in 2-16% and headache in 7%.4

Oral Ivermectin

Ivermectin is a synthetic derivative of the antiparastic class of compounds known as avermectins. It has been used extensively and safely in the world to control diseases such as onchocerciasis, loiasis, filariasis, strongyloidiasis, CLM, and scabies. Treatment with very high doses of Ivermectin caused embryotoxicity in animals, and its side effect profile includes ataxia, tremors, mydriasis, and depression. This drug blocks chemical transmission across nerve synapses, causing paralysis and death of the larva. Ivermectin is not recommended in children under 5 years of age, in pregnancy or during lactation, and in patients with nervous system disorders.14

Ivermectin has been used as a single dose of 12 mg with an 81-100% cure rate.11 This has been confirmed in larger studies as well. In a study comparing a single oral dose of 400 mg Albendazole with a single oral dose of 12 mg Ivermectin in 21 patients, 100% of the Ivermectin patients responded with no relapses. Five patients from the Albendazole group relapsed after a mean of 11 days.9 It must be noted that sometimes a second or third dose of Ivermectin, one week apart, may be needed in pruritis persists.

Conclusion

Cutaneous Larva Migrans is a parasitic skin infection by an animal hookworm that presents with an itchy, painful, serpiginous rash. The disease may resolve on its own, but treatment is recommended to decrease discomfort, secondary infection, and possible systemic infection. Topical treatments (cryotherapy and topical Thiabendazole) can be used on all age groups and in pregnancy with minimal side effects. Topical Thiabendazole seems to be quite effective, but cryotherapy is not always successful in eradicating the larvae.

Oral treatments with Albendazole, Thiabendazole and Ivermectin are quicker and most likely result in resolution of the condition, but may have a larger side effect profile and limitations. Oral Albendazole or Ivermectin seem to be treatment of choice for CLM.

References:

Malignant Fibrous Histiocytoma: A Case Presentation and Discussion

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ABSTRACT

Cutaneous Larva Migrans (CLM) is a condition caused by the introduction of the animal hookworm larvae into the human skin. Although endemic to warmer regions of the world, it is important that we be able to recognize CLM in the US, as it may present in our patients that live in coastal states or that have recently traveled outside of the country. The intent of this case report and discussion is to describe clinical manifestations and current medical management of CLM, and to stress the importance of obtaining a travel history from all of our patients.

Figure 1

71-year-old, Caucasian male presented to our clinic with a painful tumor on his left temple of approximately one month’s duration. The patient denied any personal or family history of skin cancer or other significant past medical history. Physical examination revealed a well-defined, 1.6 cm x 1.3 cm, erythematous nodule with overlying telangectasias. A shave biopsy of the lesion was performed and sent for histopathologic evaluation, which was suggestive of atypical fibroxanthoma. During the following month, the tumor rapidly enlarged to a 5 cm x 4 cm mass (Figure 1). The initial shave biopsy revealed a malignant, myxoid, spindle-cell neoplasm with a differential diagnosis including spindle-cell malignant melanoma, spindle-cell squamous-cell carcinoma, angiosarcoma, leiomyosarcoma, and atypical fibroxanthoma (AFX). Immunohistochemistry studies were positive for vimentin, alpha1-antichymotrypsin, and CD68; and they were negative for CD34, CD31, actin, desmin, keratin, S100 protein, HMB45, and Melan-A. These findings were most consistent with a diagnosis of AFX. However, due to the rapid increase in size of the nodule and the lesion’s invasiveness, a repeat biopsy was performed. This biopsy yielded the more ominous diagnosis of malignant fibrous histiocytoma MFH (Figure 2). A staging CT scan of the head and thorax was normal. The patient was referred for wide local excision with Mohs micrographic surgery and underwent extensive oncologic treatment and follow-up.

ATYPICAL FIBROUS XANTHOMA

Atypical fibrous xanthoma is a pleomorphic tumor often described as a superficial or even early form of malignant fibrous histiocytoma due to their similar histopathologic appearance. Separate nomenclature exists to better distinguish these two disease entities based on prognosis.

Clinical Findings:

AFX is a low-grade sarcoma that usually presents as a <2 cm, solitary nodule with or without superficial ulceration. The most common type of AFX usually occurs on actinic-damaged skin in the elderly. The less common subtype occurs in young adults on the trunk and extremities.

Etiologic Factors:

Due to their appearance on actinic-damaged skin and co-occurrence with basal-cell carcinoma and squamous-cell carcinoma, chronic solar radiation is an acceptable predisposing factor. There have also been less well-documented associations in patients with occupational and therapeutic radiation.

Histopathology:

AFX is limited to the dermis and does not affect deeper structures.

AFX is a dermal nodule that abuts the epidermis. Epidermal atrophy and/or ulceration are common. In the superficial dermis, solar elastosis is present, and a grenz zone of uninvolved dermis may be visible. The lesion is usually limited to the dermis but rarely may extend into the subcutaneous layer. There are atypical spindle cells in a haphazard fascicular pattern. These cells are usually multinucleated, pleomorphic, and hyperchromatic with occasional mitotic figures. The histopathologic appearance of AFX clearly mimics MFH, often making their diagnoses indistinguishable. However, unlike MFH, AFX is more superficial, with no extensive involvement of the subcutaneous layer, fascia, or muscle. Other distinguishing features of AFX include the lack of vascular invasion and necrosis.

Immunohistochemistry:

Findings common to both AFX and MFH include positive vimentin, alpha-1-antichymotrypsin, and CD68, further complicating their differentiation. However, Lazova et al. suggested that CD78 may discriminate MFH from AFX. Genetic alterations on chromosome 9p and 13q have been implicated in both disease processes. However, Worrell et al., using flow cytometry, suggests that these two processes can be distinguished based on DNA content. In that study, AFX exhibited diploid features in 13 out of 14 patients compared to the aneuploid features of MFH. This genetic variability may contribute to their different biologic behavior.

Treatment:

Conservative therapy is initially indicated due to the rarity of metastasis. Complete surgical excision without radiation is typical. Recurring lesions should be treated more aggressively, and the diagnosis of MFH must be more seriously considered.

Prognosis:

AFX has an excellent prognosis. Fretzin et al. studied a population of 140 patients with AFX, of which recurrence occurred in 9 (6%) and metastasis in none. There have been exceptional instances, however, in which this tumor has exhibited metastasis. Helwig and May et al. have described numerous cases of recurring, metastatic AFX. However, there is speculation that in these cases, an initial diagnosis of MFH may have been more appropriate than one of AFX. In fact, this is what occurred in our...
case, and a repeat biopsy and further clinical correlation confirmed the diagnosis of MFH. Nevertheless, in light of these rare instances of metastasis, when AFX recurs as a large, deeply situated mass, it should be considered MFH and treated more aggressively.

**MALIGNANT FIBROUS HISTIOCYTOMA**

MFH is the most common soft-tissue sarcoma, accounting for 20% to 24% of all cases. The atypical progenitor cells of MFH are capable of both fibroblastic and histiocytic differentiation, hence the name of this lesion.

**Clinical Findings:**

MFH is typically seen in the fifth and sixth decade of life. The lesions are characterized by multi-lobular, painless, fleshy nodules that reach upwards of 5 cm to 10 cm and may ulcerate if the dermis is involved. They are most commonly located on the proximal extremities, particularly the thighs and buttocks (70-75%). Other cases occur in the retro-peritoneum and internal organs, including the heart and gallbladder, with variable associated symptoms depending on location. Many cases of MFH are associated with hematologic malignancy, including lymphoma and multiple myeloma.

**Etiologic Factors:**

Strong evidence exists that MFH may be radiation induced. Multiple cases of MFH have been reported in patients receiving radiation therapy, and in each instance, lesions occurred directly over the irradiated areas years after treatment. The tumor has been experimentally induced in laboratory animals with tea extracts and exposure to phenoxy acids. However, a direct causal relationship to either of these two factors has not been established.

**Histopathology:**

There are five histopathologic subtypes of MFH. All subtypes are highly cellular and pleomorphic with numerous mitotic figures. These subtypes include storiform-pleomorphic, myxoid, giant cell, inflammatory, and angioided. The most common is the storiform-pleomorphic type. Histopathologically, this type exhibits the prototypical fibroblast-like and histioycte-like cell patterns as well as multinucleated giant cells and foam cells. The second most common is myxoid (seen in our patient), which has the best prognosis. The giant-cell subtype, also known as malignant giant-cell tumor of soft parts, is described as having osteoclast-like giant cells. The inflammatory type, also known as malignant xanthogranuloma, is most often located in the retroperitoneum and is composed of dense neutrophilic infiltrate and xanthoma cells. The angiomatoid subtype is mostly a childhood tumor with an excellent prognosis. It has recently been reclassified and grouped among low-grade fibrohistiocytic tumors. As described previously in AFX, immuno-histochemistry patterns are utilized to exclude other pleomorphic spindle-cell tumors (Table 1).

**Treatment:**

Therapy for MFH includes complete surgical excision. Radiation therapy is indicated for high-grade lesions and those with positive surgical margins. Adjuvant chemotherapy is investigational at this time.

**Prognosis:**

The prognosis for MFH depends on the size, depth, location, grade, and histologic subtype of the lesion. Recurrence and metastasis generally occur within one to two years of diagnosis. The recurrence rate for MFH ranges from 19% to 31%. Regional lymph node metastasis occurs in 12% of cases. Distant metastasis occurs in 10% to 55% of cases, with lung metastasis the most common (90%), followed by bone (8%) and liver (1%). The metastatic rate for the myxoid subtype, as seen in our patient, is lower (25%), accounting for an overall better prognosis and survival rate. The five- and 10-year survival rates of MFH are listed in Table 1.

**DISCUSSION**

Malignant fibrous histiocytoma is a soft-tissue sarcoma with aggressive clinical behavior. Its histologic, atypical spindle-cell pattern is very similar to that seen in atypical fibrous xanthoma, which can be considered its less aggressive counterpart. These two processes are distinguished based on clinical behavior and subtle histologic findings.

Other malignant spindle-cell tumors that
must be considered in the histologic differential diagnosis include dermatofibrosarcoma protuberans (DFSP), leiomyosarcoma, angiosarcoma, Kaposi sarcoma, spindle-cell squamous cell carcinoma and spindle-cell malignant melanoma. These tumors can be effectively ruled out with the use of immunohistochemical staining patterns (Table 2).

References:
History of Sunscreens and Photoprotection

Humans have been protecting themselves from ultraviolet radiation (UVR) exposure for centuries. Before the advent of sunscreen, photoprotection was typically achieved through clothing covering the body, veils, shoes, glasses, and wide-brim hats. Umbrellas were a common source of protection in ancient Egypt, Mesopotamia, China, and India.1,2 The beliefs surrounding UVR exposure have changed dramatically throughout time. In the early 20th century, UVR was thought to be healthful especially because of its role in vitamin D metabolism. However, some individuals foresaw the need for increased ultraviolet (UV) protection, and in 1928, the world’s first commercial sunscreen was developed in the United States. It consisted of an emulsion of benzyl salicylate and benzyl cineamate.1 In the 1930s, attitudes began to change in the medical community as experiments on rodents demonstrated the induction of malignant skin tumors from sunlight and UV lamps.3 These findings ultimately led to the growth of the sunscreen industry and constant modifications to improve the product’s effectiveness.

In the 1930s, a phenyl-salicylate product appeared on the Australian market, followed by lotions of quinine olate and quinine bisulfate, p-aminobenzoic acid (PABA), red petrolatum, glycerol-PABA, and dipropylene glycol salicylate in the United States. Most of these early sunscreen products focused on the short wavelengths, or ultraviolet B (290-320nm) portion of the solar-spectum, responsible for sunburn; they failed to address the longer wavelengths, or ultraviolet A (320-400nm) component of the spectrum.4,5 In the 1980s, 4-T-butyl-4’-methoxy-dibenzoylmethane was developed and tested for its effectiveness against UVA. Its addition to UVB-blocking agents produced a broad spectrum of chemical sun protection in the United States. Other recent developments include micronized reflecting powders, antioxidants, terephthalylidine dicamphor sulfonic acid, and bisethylhexyloxyphenol. Some of these recent advancements in UV filters have not been fully approved yet in the United States, so further studies are necessary to ensure that they protect against photaging and UV-induced skin cancers.6,7 Due to increased interest in the deleterious effects of UVA rays on the skin, many modern sunscreen products are designed to be broad-spectrum, providing significant long-wavelength UVA protection in addition to delivering the target sunscreen protection factor (SPF).8 This article reviews the most up-to-date information on the efficacy of sunscreens in photoprotection.

Controversies Surrounding Sunscreens

Do sunscreens protect against skin cancer?

Despite the extensive use of sunscreens, the incidence of skin cancers is still increasing. There are many hypotheses that attempt to account for this apparent discrepancy. There appear to be multiple factors that determine how effective sunscreens are in actually reducing exposure to solar UV radiation.

The general population seems to rely heavily on sunscreen as a means of protecting the skin from UV radiation, and once the sunscreen is applied, many feel invincible to the effects of the sun. It has been hypothesized that sunscreen use has therefore resulted in increased sun exposure, subsequently leading to increased risk for skin cancers.9,10 It’s possible that sunscreens have encouraged people to stay in the sun as long as possible, especially during mid-day when the sun’s UV rays are most direct, since they feel they are being protected from the sun’s ill effects. This can end up increasing a person’s exposure to UV radiation beyond what it would have been without sunscreen.11 It has also been pointed out that sunscreens that are highly effective against UVB and prevent sunburn may have little or no protection against the long wavelengths of UVA.

Several studies, both completed and ongoing, have looked at whether the use of sunscreen might prevent skin cancers such as melanoma. It appears that there is no definitive answer to this question. Studies have shown in some cases that sunscreen use increases the odds ratio for melanoma risk.1 A recent study12 showed that sunscreens failed to block UV-enhanced induction of melanoma in laboratory mice. Melanoma cells were injected directly into mice, and the mice were then subjected to an artificial UVR-emitting source. A sunscreen with an SPF value of 8 failed to protect against an increase in the incidence of melanoma in the irradiated mice. Although these results cannot be directly applied to the induction of melanoma in humans, they do suggest that use of a sunscreen should not be considered a substitute for limiting sun exposure.

There is significant evidence showing that sunscreen use reduces the incidence of basal cell carcinoma and squamous cell carcinoma, and some hypothesize that sunscreen use may reduce the risk of melanoma through its protective effects from UV damage.13,14,15 A number of studies, including a recent report in the Archives of Dermatology, suggest that regular sunscreen use reduces a person’s risk of developing actinic keratoses, and thus, presumably, a person’s risk of squamous cell carcinoma; but these studies failed to define a clear association between sunscreen use and decreased melanoma incidence.16 The increased prevalence of skin cancer in the current population may be inaccurately
representing the efficacy of sunscreen in reducing the skin-cancer risk. It is important to recognize the fact that melanoma and non-melanoma skin cancers are caused by the accumulation of sun damage over many years. In the past, unprotected sun exposure was common, especially because the population lacked adequate education on the harmful effects of solar radiation. Therefore, the years of accumulating sun damage are now becoming evident in this population regardless of the current use of sunscreen and sun-protective measures. Future studies should focus on individuals who have consistently been protected from UVR throughout their life.

Isn’t sun exposure helpful in developing a protective tan?

Some consider sun exposure without sunscreen to be advantageous. There are those who say that sunscreen prevents the body from developing a protective tan, leaving the sometime sunscreen user open to more severe sunburns. In addition, people who work indoors and have less exposure to the sun are actually at a greater risk for melanoma than those who work outdoors. But a possible reason for the decreased risk of melanoma in those who work outdoors may be that people who work outdoors take sun-protective precautions more regularly. The generally accepted belief is that there is no benefit from a tan because a tan is the skin’s response to injury. Therefore, one cannot get a tan without injuring the skin. According to this accepted scientific view, it would be a misnomer to refer to a tan as “protective” or “healthy.”

Can sunscreens become less efficient due to application method, rubbing, or sweating?

According to Draelos, sunscreens have the potential to fail. A sunscreen must be on the skin for it to be effective. A great deal of variability in application methods exists, which has the potential to alter the sunscreen’s efficacy. Failure to coat the entire skin surface of the body or removal by rubbing or sweating can create a lack of sunscreen, leaving the skin unprotected. The uneven topography of the skin, consisting of peaks and valleys, poses a challenge to uniform application of sunscreen. Excess product can accumulate in the valleys, while the peaks provide adequate intake, as can milk and orange juice fortified with vitamin D. The U.S. Department of Agriculture recommends 200 IU/d for children and younger adults (<50 years old), 400 IU/d for older adults (>50 years old), and 600 to 800 IU/d for the elderly (>70 years old). Eight ounces of fortified milk or orange juice contains 100 IU (2.5 g), which is also the amount of vitamin D found in approximately half a teaspoon of cod liver oil. The sun-and-vitamin-D issue has become less significant due to the fact that most foods are now enriched with vitamin D, resulting in a low occurrence of vitamin D deficiency.

Despite the controversies, it appears that the benefits of sunscreen use exceed the costs.

What do new advances in sunscreen mean for the consumer?

More efficient and safe sun-screening ingredients have been developed for improved skin protection. These sunscreens have new, highly efficient absorption or reflecting capabilities throughout the ultraviolet wavelengths and, in some instances, infrared wavelengths. Although they’re already in use in Europe, they are currently being approved by the FDA for their use in the United States. Table 1 lists new active ingredients previously approved for sunscreens in Europe and other locations but not yet available in the United States. These ingredients can be categorized into UVB, UVA, and broad-spectrum UVB and UVA filters.

The need to increase protection from ultraviolet radiation has prompted manufacturers to incorporate active sunscreen ingredients into items used daily. Cosmetic manufacturers are incorporating sunscreen ingredients as a part of their formula for cosmetic facial products, giving dual benefit to the consumer. Most major cosmetic companies now offer a line of cosmetics containing sunscreen ingredients.

Similarly, more clothing manufacturers are adopting sunscreen technology into clothing fabrication. For example, there are T-shirts available that have an SPF of 30. Many clothing manufacturers are including SPF numbers as a standard in their specification tags. SolarteX Sun Gear is one company that provides a line of sun-protective clothing, hats, swimsuits, swim diapers, and sun-glasses.

The future holds much promise for better efficacy and safety in sunscreen technology. Advances will include the development of nonabsorbent material to boost SPF, encapsulation of UV absorbers, and microfine organic particles. These improvements are much needed because of the alarming thinning of the ozone layer and global warming. The development of a sunscreen that could prevent UV-induced immune suppression will be a major advancement. Often referred to as the immune protection factor (IPF) of sunscreen, this feature is currently under development. However, there is research available now that shows that sunscreens are already providing protection against pre-cancers. One such study from the New England Journal of Medicine shows that sunscreens prevent actinic keratosis, the earliest stage in the development of skin cancer.

New UV-blocking ingredients, including avobenzone and ecamsule, have recently become available to offer patients greater UVA protection. Neutrogena released products with its patented Helioplex formula that combines avobenzone (Parsol 1789), oxybenzone and Hallbrite TQ. Avobenzone has exceptional UVA-protection but is flawed by its photoinstability. After approximately five hours of UV exposure, its protective effect is significantly decreased. However, longer periods of UVA photoprotection using the above formulation have been claimed. Anthelios SX, a L’Oreal sunscreen product that contains ecamsule, avobenzone, and octocrylene, has recently approved by the U.S. Food and Drug Administration (FDA) to be sold in the United States. Anthelios SX with SPF-15 protects against UVA and UVB rays and prevents sunburn. Unlike avoben-
zone and octocrylene, ecamsule had not previously been marketed in the United States, but it has been marketed in Europe and Canada as Mexoryl SX since 1993. Dermatologists have focused their attention on ecamsule because it effectively blocks UV A rays and does not degrade when exposed to the sun for long periods of time, unlike other UV A filters.  

What are the types of sunscreen ingredients and how do they differ in terms of the protection they offer?

The active ingredients in sunscreen provide the product with the functionality of protecting the skin from the harmful effects of UV solar radiation. These materials act by absorbing, reflecting or scattering UV radiation before it penetrates the skin and damages skin components like DNA, collagen, elastin, and lipids. Sunscreens are mainly divided into chemical/organic or physical/inorganic ingredients. Chemical/organic sunscreens include benzophenones, oxybenzone, sulisobenzone, methyl anthranilate and avobenzone (Parsol 1789). Physical/inorganic sunscreens include titanium dioxide and zinc oxide (Table 2), which tend to give a slightly whitish color to the skin. The efficacy of sunscreen products mainly depend on their sun protection factor (SPF). The SPF of a sunscreen is calculated by comparing the amount of time needed to produce sunburn on sunscreen-protected skin to the amount of time needed to cause sunburn on unprotected skin.

Sunscreens containing titanium dioxide, zinc oxide and avobenzone (Parsol 1789) tend to provide good broad-spectrum UVA protection. The most frequently used UV-filter ingredients appear on approved lists in all parts of the world. Table 2 presents some general information for six chemical classes and a miscellaneous category of commonly used UV filters. Although such a list is no guarantee of individual product efficacy and safety, it does provide some assurance that there is general support for the safety and efficacy of its active ingredients.

Several concerns do surround the use of sunscreen products, but they remain speculative due to the lack of supportive human data. Studies have demonstrated a link between UV filters such as 3-(4-methylbenzylidene) camphor and estrogenic effects, but they have not shown this effect in humans. Some UV filters and sunscreen products are thought to become photoactive upon exposure to UV radiation, such as TiO2, and photodegradative, such as avobenzone, but neither has been proven to be a human health risk.

What are the advantages to each sunscreen delivery method? How do sticks, sprays, lotions and wipes differ in terms of the protection they offer?

Sunscreen products consist of a delivery vehicle containing one or more active sun-

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**Table 1**

*New Ultraviolet Absorbers*  
Adopted from Tuchinda33

<table>
<thead>
<tr>
<th>Type</th>
<th>Sunscreen-active COLIPA no./INCI name</th>
<th>Trade Name (Supplier)</th>
<th>Peak Wavelength Absorbed (nm)</th>
<th>*Seeking Approval or In Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVB</td>
<td>S69 EHT</td>
<td>Uvinul T 150 (BASF)</td>
<td>315</td>
<td>Europe, USA*</td>
</tr>
<tr>
<td></td>
<td>S78 DBT</td>
<td>Uvasorb HEB (3V Sigma)</td>
<td>310</td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>S74 BMP</td>
<td>Parsol SLX (Roche/DSM)</td>
<td>315</td>
<td>Europe, Japan, USA</td>
</tr>
<tr>
<td>UVA</td>
<td>S71 TDSA</td>
<td>Mexoryl SX (L’Oreal)</td>
<td>345</td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>S80 DPDT</td>
<td>Neo Heliopan AP (Symrise)</td>
<td>340</td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>DHHB</td>
<td>Uvinul A Plus (BASF)</td>
<td>355</td>
<td>Europe</td>
</tr>
<tr>
<td>UVB and UVA</td>
<td>S73 DTS</td>
<td>Mexoryl XL (L’Oreal)</td>
<td>300 and 345</td>
<td>Europe, Japan</td>
</tr>
<tr>
<td></td>
<td>S79 MBBT</td>
<td>Tinosorb M (Ciba SC)</td>
<td>310 and 360</td>
<td>Europe, Australia, USA*</td>
</tr>
<tr>
<td></td>
<td>S81 BEMT</td>
<td>Tinosorb S (Ciba SC)</td>
<td>300 and 350</td>
<td>Europe, USA*</td>
</tr>
</tbody>
</table>

Abbreviations: COLIPA - European Cosmetic Toiletry ad Perfumery Association; INCI - International Nomenclature Cosmetic Ingredient

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AN UPDATE ON SUNSCREENS

Figure 3. Skin Types and Suggested Sunscreen Protection Factors
Source: Lowe

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Suggested SPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Never tans, always burns easily (e.g. Irish)</td>
<td>12</td>
</tr>
<tr>
<td>2. Tans slightly, burns easily (e.g. fair-skinned, blond hair, Caucasian)</td>
<td>13</td>
</tr>
<tr>
<td>3. Sometimes burns, tans gradually and moderately (e.g. Mediterraneans and some Hispanics)</td>
<td>14</td>
</tr>
<tr>
<td>4. Burns minimally, always tans well (e.g. darker Hispanics and Asians)</td>
<td>15</td>
</tr>
<tr>
<td>5. Burns rarely, tans deeply (e.g. Middle Easterners, some African Americans, Asians)</td>
<td>16</td>
</tr>
<tr>
<td>6. Almost never burns, deeply pigmented (e.g. some African Americans)</td>
<td>20</td>
</tr>
</tbody>
</table>

Sunscreen ingredients. When applied to the skin, these active ingredients in the sunscreen intercept solar ultraviolet (UV) rays before they can damage the underlying skin. Today, sunscreen products are available in many forms including creams, sprays, ointments, gels, lotions and wax sticks. The type of sunscreen chosen is a matter of personal choice. The efficacy of a sunscreen depends on its binding potential to the skin and its ability to deflect harmful ultraviolet rays above the skin. The variety of sunscreen products can be categorized by their viscosity and their polarity, which illustrate their ability to dissolve in water (polarity) and their thickness (viscosity). These two factors ultimately determine how the sunscreen feels when applied to the skin, how easy it is to spread, and its substantivity (Fig. 1). As illustrated in Figure 1, stick products are the thickest of the oil-based products. These waxy formulations can be useful because they are anhydrous, easy to make, very substantive to the skin, and resistant to removal by water and sweat. The flaw in using stick products is the fact that they cannot be spread easily once applied; therefore, they are generally not appropriate for use over wide areas of the body.21,22 The stick products have a heavy, greasy skin feel, a high cost, relatively poor package compatibility, and low SPF on skin because of their poor film-forming ability.

Sprays are commonly used sunscreen-application products, and they all have thin viscosities. They can be formulated from oil, ethanol, or an emulsion with water and oil phases, depending on their polarity (Fig. 1). For sprays, the sunscreen formulation is forced through a special orifice under the pressure created by either a mechanical pump or moderate levels of aerosol propellants, converting it into small droplets that travel to the skin.40 This delivery method is attractive to many because, unlike the large amounts of grease in oily vehicles, the ethanol quickly evaporates, reducing the amount of residue on the skin. The ethanol-based sprays are also commonly used due to their clarity, fast-drying nature, and pleasant cooling feel upon application.40 This method of delivery should also take into consideration convenience. Spray products allow application onto hard to reach places. For example, most people cannot reach portions of their back. A spray would be able to reach that area. Recently, a new spray sunscreen came to the market that offers continuous spraying, making it even easier to apply and reapply sunscreen.41,42 Still, there are some disadvantages that the consumer should recognize. The ethanol-based sprays can be slightly drying and irritating, and they can burn if applied to a sensitive area such as the eyes. Also, rapid evaporation form the skin can decrease the SPF efficacy, offering less protection.

Sunscreen lotions and creams are the most common form of sunscreen product on the market.41,44 Lotions are thinner emulsions, while a thicker emulsion is referred to as a cream (Fig. 1). The benefit of lotions involves the fact that a full range of polarity is available to interact with any group of sunscreen active agents. This allows maximum flexibility when selecting a sunscreen product based on efficacy, cost, skin feel, and irritants. The lotions and creams can also incorporate other ingredients into the formulation such as moisturizing agents and anti-aging active ingredients.45 It appears that this can result in increased consumer compliance, which would lead to an increase in efficacy.

Sunscreen wipes consist of sunscreen formulations absorbed into a non-woven substrate, which provides a convenient applicator for coating the skin uniformly. The problem underlying this delivery method is that the substrate can interact with the sunscreen active ingredients and other components of the formulation. It is vital that additional testing be carried out on wipe formulations to avoid these interactions.

In general, how does one go about determining a proper SPF level?

Sun protection factor (SPF) is a ratio of the time it takes for solar UV radiation to produce a barely perceptible, uniform erythema in protected skin to the time it takes to produce the same effect in unprotected skin, measured 16 to 24 hours after exposure. So if it takes 10 seconds to produce minimal erythema in unprotected skin and 100 seconds to produce the identical response in skin where a 2mg/cm² of sunscreen has been applied, the SPF is 10 (100/10).3

SPF = Exposure Interval (MED on protected skin) / Exposure Interval (MED on unprotected skin)

SPF checks product safety and performance using a well-recognized endpoint -- erythema or sunburn -- that results from solar exposure. Generally, SPF 15 or higher provides broad-spectrum coverage against both UVA and UVB wavelengths.

There is less improvement in the protection factor as you move up in SPF number.79 An SPF of 2 equals 50 percent deflection of sun-burning rays, an SPF of 15 indicates 93 percent deflection, and an SPF of 30 indicates 97 percent deflection (Fig. 2). Sunscreen should be chosen with an SPF that confers long-lasting protection. According to Agin, ideally, a sunscreen should maintain its
original efficacy on the skin for several hours after it is applied. Although it is established that prolonged exposure to UVB leads to human skin damage, it is important to recognize that variability exists between individuals' skin types and therefore their susceptibility to skin damage. People should take into account their skin phototype when choosing a proper SPF (Fig. 3). Animal studies have shown that sunscreens possessing an SPF of 15 or greater are capable of reducing the incidence of cutaneous preneoplasia and neoplasia. Similar findings were reported in a large population of Australians whose daily use of SPF 17 resulted in a significant reduction in the number of new actinic keratoses appearing in the sunscreen-protected population compared with the placebo-cream-controlled population. Children are especially susceptible to the deleterious effects of solar radiation because they often receive constant sun exposure. It has been calculated that if children consistently used an SPF 15 sunscreen through the age of 18, the occurrence of non-melanoma skin cancers (NMSC) could be reduced by 78 percent. People who experience photosensitive drug reactions or who have photosensitive diseases should try to avoid prolonged sun exposure. If in the sun, they should use broad-spectrum sunscreens that effectively protect against UVB and UVA, and they should additionally wear sun-protective clothing.

Because UV radiation can penetrate through water, resistance to removal by water is a vital component of the efficacy of sunscreen and requires additional testing. Methods for determining water resistance require the SPF to be measured after a defined water-immersion procedure. Cycles of 20-minute water-immersion intervals are followed by 20-minute rest/air-dry periods until the total water exposure time is reached. A "water resistant" SPF claim means that a sunscreen's photoprotective effect remains after 40 minutes of water exposure; "very water resistant" means that the SPF of the sunscreen product can withstand at least 80 minutes of water immersion. In the United States, the SPF value on the label of a water resistant or very water resistant sunscreen product is the SPF value determined after water exposure. It is important to remember that water resistance does not mean resistance to any other type of inadvertent removal, such as by friction from toweling. Abrasion from towel use can remove up to 85 percent of a sunscreen, leaving it on the towel. Therefore, even a "waterproof" sunscreen should be reapplied after toweling, prolonged swimming, or vigorous activity to ensure adequate protection.

The relationship between SPF and durability was investigated in a study that measured the effectiveness of sunscreen on human skin in vivo for up to eight hours after application. The subjects were applied with SPF 4 foundation makeup, a non-waterproof SPF 4 cream, a non-waterproof SPF 15 lotion, or a waterproof SPF 25 product. Between product applications and SPF testing, subjects were free to perform normal activities that did not affect the testing areas. The results demonstrated that the two SPF 4 products and the SPF 25 waterproof product...
remained virtually unchanged over time, while the protection provided by the non-waterproof SPF 15 lotion was found to be slightly lower at eight hours post-application. Therefore, it was concluded that products of both high and low SPF can maintain their efficacy for several hours on the skin if not physically removed or absorbed. The efficacy of the SPF also depends on the sunscreen’s ability to resist removal by sweating. In the United States, a product that has been shown to be water resistant or very water resistant can also be labeled as sweat resistant. For more long-lasting protection, a sunscreen that is water or sweat resistant may prove more durable than a makeup or moisturizer with SPF for an extended period of sun exposure.

How often should sunscreen be reapplied?

Sunscreens should be applied to dry skin 15 to 30 minutes before going outdoors so the sunscreen has the ample time to bind to the skin. According to Diffey and Grice, the first reaplication should take place about 20 minutes after the initial application in order to boost protection and ensure good coverage. When applying sunscreen, pay particular attention to the face, ears, hands and arms, and coat the skin liberally. One ounce, enough to fill a shot glass, is considered the amount needed to cover the exposed areas of the body properly. Be careful to cover exposed areas completely, because a missed spot could mean a patchy, painful sunburn. Don’t forget that lips get sunburned, too, so apply a lip balm or lipstick that contains sunscreen, preferably with an SPF of 15 or higher.

Physicians should advocate reaplication of sunscreens every two hours after swimming, perspiring heavily, or having physical contact. If there is physical abrasion, reaplication should take place even earlier. Even so-called water resistant sunscreens may lose their effectiveness after 80 minutes in the water. Sunscreens rub off as well as wash off, so if you’ve towel-dried, reapply waterproof sunscreen for continued protection.

Don’t forget that sun exposure occurs all the time, even on a cloudy day. Eighty percent of the sun’s ultraviolet rays pass through the clouds. You may think walking in a shaded area or on a cloudy or snowy day is safe, but remember – the sun’s rays have great reflective powers. Nearly 17 percent reflect off of sand, and 80 percent reflect off of snow. So put on your sunscreen and sunglasses in the winter season, as well. Don’t reserve the use of your sunscreen product only for sunny, summer times.

Ideal reaplication of sunscreen varies based on numerous factors. Selection of a sunscreen and the frequency of reaplication should be based on the knowledge of individual sun sensitivity, the type of outdoor activity, the geographic location, and the time of the year and time of day, along with the anticipated time in the sun. In a baseline survey of sunscreen application and re-appllication behavior in Queensland, Australia, Pruim, Wright, and Green reported 76 percent of people using sunscreen, and of those, 61 percent reported reapplying sunscreen at personal intervals. It appeared that women and people under 45 were most likely to reapply. The highest rates of re-application occurred during times of increased sun exposure, as well as among those with a greater knowledge of the benefits of sunscreen reaplication.

How can we encourage patients to be more compliant?

Compliance is a vital component to the efficacy of sunscreen. In order for sunscreen to be effective in protecting skin from UV radiation, it must be applied. Compliance is determined by how often the product is used and how much is applied each time. There are numerous reasons people fail to use sunscreen appropriately. The most common reason is that sunscreen is sticky. The higher SPF products are usually stickier but offer only a minimal increase in UVB photoprotection. An SPF of 15 blocks about 93 percent of UVB radiation, while an SPF of 30 blocks out 97 percent. If the higher SPF is too sticky, it will be used less frequently and therefore will offer less protection than a lower-SPF sunscreen that is used more frequently. For this reason, physicians should recommend a lower SPF (such as SPF 15), which generally has better aesthetics and may yield better compliance. One study showed that daily application of an SPF 15 product provided greater protection of the skin from the effects of UV rays than sporadic application of an SPF 29 product. Another study showed that an SPF 15 daily facial moisturizer product was used twice as much as an SPF 30 product.

Patients often complain of feeling hot and sweaty when they wear sunscreen. This is partly due to the fact that the sunscreens are worn in the hot sun; but it’s also because chemical sunscreens such as octyl-methoxycinnamate, benzophenone, and cosmetically, the geographic location, and the time of the year and time of day, along with the anticipated time in the sun. In a baseline survey of sunscreen application and re-appllication behavior in Queensland, Australia, Pruim, Wright, and Green reported 76 percent of people using sunscreen, and of those, 61 percent reported reapplying sunscreen at personal intervals. It appeared that women and people under 45 were most likely to reapply. The highest rates of re-application occurred during times of increased sun exposure, as well as among those with a greater knowledge of the benefits of sunscreen reaplication.

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Sunscreen is one important first-line of defense against UV radiation, but it is not infallible. The links between sunscreen use
and skin cancers still remains unclear and is a topic of controversy. The topic of sunscreens used should be based on the individual’s skin phototype, region of the body, UV index, and season. As a rule of thumb, regardless of one’s skin type, sunscreens should be broad spectrum (protecting against UVB and UVA) and water resistant so they cannot be easily removed by sweating or swimming. It is vital that the consumer understands the limitations of sunscreens products. Sunscreen use alone should not be the only method of preventing the harmful effects of sun exposure. All individuals should be encouraged to stay indoors or seek shade during peak hours of solar radiation flux, from 10 a.m. to 2 p.m. A hat or sun visor is a useful addition to the protection regimen. Those who insist on darker skin should use a self-tanning lotion containing dihydroxyacetone (DHA). Tanning salons should be avoided, because intense UVA exposure increases the risk for skin damage and induces photoaging and photoallergic responses. People who spend a significant amount of time outdoors, particularly in times of high solar flux, should be cautious about intermediate and long-term risks from UV exposure. These individuals include naturalists, skiers, bicyclists, gardeners, and members of certain professions (e.g. farmers, lifeguards, landscapers and postal workers). Children should be educated at a young age at school and home about the risk of sun exposure. Children are constantly exposed to solar radiation, and childhood sunburns increase the risk for malignant melanoma. There is supportive evidence to conclude that the UV filters that make up almost all sunscreen products in the United States are safe and effective, and the use of sunscreens reduces the risk of solar damage. Only with continued research and experimental analysis in this area can we gain a complete understanding of the efficacy of sunscreens and how to improve sunscreen products to optimally protect ourselves from the deleterious effects of solar radiation.

References:

White Piedra Mistaken for Head Lice: A Case Report and Brief Review

David R. Bonney, D.O.,* Stanley Skopit, D.O., FAOCDS**
*NOVA Southeastern University/BGMC 1st year resident
**Program Director NOVA Southeastern University/BGMC

Introduction

White piedra is a rare, chronic fungal infection of the hair cuticle, most commonly caused by a yeast-like fungus previously named Trichosporon beigelii. This infection is now thought to be secondary to Trichosporon asahii and five other species: T. ovoides, T. inkin, T. mucoides, T. asteroides, and T. cutaneum. T. asahii is considered to be most closely linked to white piedra, although some authors believe that T. ovoides is the main agent causing white piedra of the scalp. These Trichophyton species inhabit soil, water and vegetation. They are also residents on monkeys and horses, where they make up part of the normal flora of the skin and mucous membranes. The means of transmission remains uncertain and does not appear to be related to poor hygiene, lower socioeconomic status or sexual activity.

White piedra is characterized by soft, asymptomatic, white-to-light-brown or yellow nodules on the hair shafts of the pubic region, moustache, beard, axillae and, less frequently, the scalp. (Specifically in Brazil, however, white piedra affects scalp hair more commonly than any other region.) On occasion, the eyelashes and eyebrows are also involved. These soft nodules can be easily detached from the hair shaft, and patients may not be able to see the most minute nodules that haphazardly develop there. Moistening the hair with water can facilitate visualization of these concretions. Hair breakage does occur in most cases, even though the hair follicle does not suffer alteration. The underlying skin may rarely be affected by poorly delineated, erythematous papules and excoriations. White piedra is more common in temperate and semitropical climates, such as those in Asia, Europe, and parts of the southern United States. Most reported cases have been encountered in females with varied socioeconomic profiles and without obvious connection to personal hygiene. White piedra can be clinically indistinguishable from pediculosis and other hair-shaft abnormalities; thus, making a correct diagnosis may result in inappropriate treatment and emotional distress. Misdiagnosis of pediculosis in children may result in forced absenteeism due to the possibility of inducing a school-wide epidemic.

Case Report

A six-year-old Caucasian female presented along with her mother for evaluation of white bumps on her hair that had been present for months to years. The small, white spots were best seen after she wet her hair. Other than complaining of an occasional scalp pruritus, no other complaints or similar lesions were reported. The patient was excused from school because of a tentative diagnosis of head lice and was subsequently referred to a local clinic for evaluation and treatment. Upon closer examination, white piedra was suggested as an alternate diagnosis, and the patient’s mother was instructed to cut the child's hair and to visit a dermatologist. The patient did reluctantly trim her hair but did not treat adjunctively with any topical or oral agents. Recent travel out of the country was denied.

Examination of her wetted scalp hair revealed multiple, faint white bulges along the shaft. These nodules were somewhat easy to remove by using manual fingertip pressure. There was no underlying scalp erythema, crusting or scarring. The hair strands did break with pressure along the areas of hair-shaft widening.

Samples of hair were clipped and evaluated under a microscope and were also sent to the dermatopathologist for histological evaluation and fungal culture. The patient was initially given instructions to use a selenium-sulfide shampoo every other day until further diagnostic information was obtained. No evidence of head lice was seen, and she returned to school.

Microscopic evaluation of the hair shafts showed discrete, nodular swellings and slight, transparent, annular deposits consisting of a gelatinous material suggestive of either yeast organisms or white piedra. The accretions were not stained, and fungal cultures were recommended. There was no evidence of infestation. Direct examination of the hair specimens by an alternate laboratory revealed no yeast or fungal elements. The fungal culture showed yeast and Cryp-tococcus laurentii.

Discussion

White piedra is a relatively rare fungal infection. A high incidence of scalp involvement is reported in parts of Brazil and the southern United States. Most reported cases have been encountered in females with varied socioeconomic profiles and without obvious connection to personal hygiene. White piedra can be clinically indistinguishable from pediculosis and other hair-shaft abnormalities; thus, making a correct, timely diagnosis both challenging and vital due to the adverse effect on the attendance record of affected students. As in this case study, a study by Figueras and Guarro (2000) reported that various bacteria were always observed at the periphery of the nodules of white piedra. The conclusion was that these bacteria were not the primary cause of infection.

The mode of transmission of white piedra in humans remains unclear, and...
treatment remains a therapeutic challenge. This patient and her mother were advised that cutting or shaving of the child's hair was the treatment of choice, and that antifungals could be used adjunctively. This six-year-old female had very long, black hair and both she and her mother were reluctant to cut it. This limited her ability to cure this condition. The histopathology results and culture findings were conveyed to the mother in order to reassure her of the diagnosis. The patient was lost to follow-up.  

References:
A Case of Rapidly Progressive Benign Lymphangioendothelioma

Benign lymphangioendothelioma (BL), also known as acquired progressive lymphangioma (APL), is a rare, acquired vascular proliferation that clinically presents as a well demarcated, dusky pink to brown macule. Histologically, it presents with multiple, variably sized vascular channels with atypical appearance and arrangement in the upper-mid and deep dermis without nuclear atypia. We report a case of a 10-year-old female with a lesion on the right thigh and inguinal region. We present this case for its unique progression and review several previous cases to enhance awareness among practitioners.

Case Report

A 10-year-old female presented to her primary care provider (PCP) in July 2005 complaining of a small, newly presenting area of scattered papules and hyperpigmentation in her right anteromedial thigh, just below the groin. She had no history of trauma or pre-existing cutaneous abnormality at the site. She denied any pruritus or discomfort. A single papule was biopsied. The patient’s mother called several days later and noted that the biopsy site was continuing to discharge a profuse flow of clear fluid that saturated the patient’s clothing and was proving difficult to manage. The histopathologic diagnosis of the lesion by the primary pathologist was uncertain, with the differential diagnosis including Kaposi’s sarcoma. The pathologist obtained a second opinion from an academic dermatopathology group as a result of the incongruity of the diagnosis with the patient’s clinical history. The interpretation was that the lesion was an atypical vascular, lymphangiomatosus proliferation that best fit with APL. Further immunohistochemical stains were performed to rule out Kaposi’s sarcoma and angiosarcoma. Plastic surgery was consulted for evaluation and surgical treatment of the lesion.

On the initial visit, under Loupe examination the area measured approximately 8 cm x 4 cm, was “C” shaped and had mild induration. There was a mild, dusky erythema around the papules, which were individually 2 mm to 3 mm in diameter. The lower extremities did not show any size discrepancy.

An MRI was scheduled to delineate the extent of the proliferation and its relationship to underlying structures. This study demonstrated that the skin lesion not only involved the cutaneous elements as evident grossly, but it also communicated with an accretion of what appeared to be lymphovascular tissue extending into the deep perivascular tissue at the lower end of the femoral triangle up to the inferior margin of the superficial inguinal ligament.

The benign but progressive and aggressive nature of this lesion was discussed with the family. After considering the options and observing the behavior of the lesion, the family elected to pursue surgical excision.

On the day of surgery, approximately three months after the first consultation, the lesion had more than doubled in size, with dimensions now measuring 17.5 cm x 9.5 cm. All of the visibly involved tissue had a dusky, erythematous appearance with multiple small papules. Provisional margins were marked; the tissue was removed en bloc and sent for permanent histopathology. Management of the remaining defect was achieved with a combination of local flap and tissue advancement to reduce the open wound size. The remaining defect was treated with an NPWT (VAC) dressing pending definitive pathologic clearance of the margins.

Histopathology indicated residual lesion at the 10:00 to 6:00 margins of the tissue resection. The patient was returned to surgery for additional margin resection. This final tissue resection proved to be definitive. When the remaining open wound demonstrated appropriate maturity, the patient then underwent STSG for final coverage. The technique of local flap advancement and STSG for achieving coverage was chosen in an effort to afford better monitoring of the site for recurrence. The lesion has not had any recurrence since that time. Follow-up is planned for at least one to two years before consideration of any revisional surgical efforts to improve cosmesis of the area.

Discussion

Benign lymphangioendothelioma was established as a unique vascular neoplasm by Gold and Jones. Jones suggested the criteria of: 1) development in young individuals; 2) presentation beyond face and scalp; 3) localization and flat appearance; (4) slow growth and “collagen dissection” appearance histologically.

Histologically, this entity can be further described for clarification. It is made up of tortuous vascular channels lined by a single endothelial cell layer with variable size, and nuclear atypia is invariably absent or mild. Immunohistochemical features have been variable and are not unique to BL, and thus do not establish the diagnosis.

The predilection for young individuals appears to be a fairly accurate criterion, as noted in numerous reports. There are, however, several reports that document this disorder in adult patients, as well. The other four criteria are nearly always met by all of the previous cases. The predilection for location is varied, although it has been reported that there is a higher incidence in the extremities; but of the cases we
reviewed, less than half were located in those regions. The locations in the remaining cases were divided equally between the face/scalp and the trunk.

Of all of the lesions, only five had a history of trauma. Some have suggested that in the setting of trauma followed by development of this lesion, it can be considered an inflammatory reaction in the lymphatics rather than a neoplasm. Due to the relatively small number of cases, its true origin cannot be definitively stated. It should be considered that inconsequential trauma may have triggered some of the other lesions. If that is the case, however, then an associated factor that predisposes some patients to developing this process must be elicited.

This case presented uniquely due to the very rapid progression. Of all of the reported cases, this is by far the most rapid progression. No other physical or hormonal abnormalities could explain this rapid growth in our patient. In a clinical setting such as this one, it would be most advantageous to eliminate the more aggressive vascular neoplasms with similar presentations. Any delay of resection could have made this case inoperable. Typically, this disorder can be watched for progression and may even spontaneously regress.

In conclusion, BL appears to be a distinct entity, although the initial criteria set out for it are not always met. It can affect any age group with or without any predisposing incident. Its importance lies in the fact that it closely resembles more aggressive neo-

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References:
15. Final Diagnosis.
A QUICK SAFETY REFERENCE FOR SYSTEMIC MEDICATIONS USED IN DERMATOLOGY

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There exists an impressive array of systemic medications with which to treat dermatologic conditions. Proper usage of these medications requires an in-depth knowledge of their dosage, mechanism of action, potential drug interactions, and side effects. In addition, it is important to obtain patient’s informed consent when instituting these therapies. With this in mind we compiled a list of the systemic medications, which tend to be more complex in their usage and developed a physician’s reference sheet and a patient’s informed consent form for each of these medications.

The following article is a brief summary highlighting the most important points from these reference sheets and informed consent forms. Following the summary is the comprehensive list of both the physician reference sheets and the patient informed consent forms for acitretin, adalimumab, alefacept, azathioprine, cyclosorpine, dapsone, efalizumab, etanercept, hydroxychloroquine, hydroxyurea, infliximab, methotrexate, mycophenolate mofetil, and prednisone.

The information that is contained in these sheets comes from both recent journal articles and textbooks. Online resources, such as the National Psoriasis Foundation at www.psoriasis.org were also used in the development of this guide. The National Psoriasis Foundation has excellent patient handouts for biologic medications and other systemic medications used in treating psoriasis. Although many hours have been spent researching and compiling this data so that it is as timely and complete as possible, by no means is this an exhaustive review. Recommendations regarding these medications are constantly changing as new information and studies are published. Therefore, these should be used as a starting point, which you can change to best suit the way you practice. These sheets can all be downloaded for free from the internet at the following site: http://groups.msn.com/Dermatology/residency.msnw. For a more much in-depth review of the medications listed here and hundreds of others Stephen Wolverton’s “Comprehensive Dermatologic Drug Therapy” is an excellent resource.

The physician’s reference sheets and patient informed consent forms can be downloaded and then printed or copied onto office letterhead and placed in alphabetical order in a three-ring binder. The binder can then be stored in a convenient location in the office, such as the nursing station or lab and in the examination rooms. In this way, when a patient is going to be started on a systemic medication the binder is easily accessible for review. There should be several extra copies of each patient handout so one can be given to the patient. After allowing the patient adequate time to read the handout, the practitioner can then review this information with the patient and answer any questions. The patient and the practitioner can then sign the handout and a copy can be made available for the patient to take home.

Systemic retinoids are commonly prescribed by dermatologists for everything from acne to psoriasis to pityriasis rubra pilaria is. The psoriasis treatment has recently been instituted to govern the distribution of isotretinoin to patients with all lab work and testing mandated by this program. Therefore, we will not discuss treatment or evaluation during treatment with this medication. However, acitretin (Soriatane®) is not governed under the psoriasis treatment and is commonly prescribed for several types of psoriasis. Acitretin has replaced etretinate because it is just as effective with a much shorter half-life, 2 days compared to 120 days for etretinate. However, it has been confirmed that esterification of acitretin takes place in the presence of alcohol increasing the half-life to 120 days. The absorption of acitretin is increased two-to-five fold if taken with a meal. The most serious side effect of this medication is teratogenicity and with the long half-life when mixed with alcohol many authorities believe it should never be given to any woman of child-bearing age. In men, acitretin does not interfere with spermagenesis and no congenital malformations have occurred when the male partner was taking acitretin at the time of conception. However, it is recommended that men stop acitretin six weeks before trying to conceive children. Also, if a male patient’s significant other is pregnant it is recommended they abstain from sex or use condoms as sperm can carry acitretin into the woman. Retinoids have been found in seminal fluid with the amount needed to cause birth defects in the fetus being unknown.

A medication that is important in dermatology, but has been decreasing in use over the past several years is cyclosporine. Cyclosporine is a calcineurin inhibitor, which inhibits T-cell stimulation through numerous mechanisms of action. The most common serious side effect is nephrotoxicity, with both acute and chronic forms occurring. The acute form occurs within a few weeks of initiation of therapy and is usually reversible with reduction of dose or discontinuation of the medicine. Chronic renal toxicity is usually from longer term cumulative doses and generally is irreversible. Chronic renal toxicity can occur without any elevation in blood pressure or creatinine. Altered renal function happens in one out of four patients on...
cyclosporine and can be potentiated by other nephrotoxic drugs. Diltiazem appears to be nephroprotective and calcium channel blockers (dihydropyridines – nifedipine, isradipine, etc.) are also effective for cyclosporine induced hypertension, which occurs in 30% of psoriatics treated with cyclosporine.14 Cyclosporine is usually only used for short term treatment or when a transition medication is needed for patients with severe psoriasis with treatment time usually never surpassing two years.

Dapsone is a member of the sulfone drug family and is another clinically relevant systemic medication. It is used in dermatology mainly for the treatment of dermatitis herpetiformis and erythema elevatum diutinum as well as neutrophilic dermatoses, autoimmune bullous diseases, and vasculitic syndromes.15 The most serious side effect is dapsone hypersensitivity syndrome, which consists of fever, hepatitis, and a generalized cutaneous eruption.16,17 Other rare, but serious side effects include methemoglobinemia, hemolytic anemia, peripheral neuropathy (loss of motor function), agranulocytosis (0.2 to 0.4%), and toxic epidermal necrolysis (TEN).18 Dapsone therapy almost always produces hemolysis and methemoglobinemia especially in patients on a dosage of 50 mg/day or greater. Hemoglobin levels can decrease by as much as two grams when taking 150 mg/day, which most patients tolerate, but the elderly and those with cardiopulmonary problems should be closely monitored.19 Methemoglobinemia also regularly occurs in patients on Dapsone, but is usually not a major problem.20 It is a dose-dependent effect and even at very high doses the level usually never exceeds five percent. Symptoms to monitor for include weakness, tachycardia, nausea, headache, and abdominal pains and do not occur until methemoglobin levels reach at least twenty percent. In some cases cyanosis can be seen with levels as low as three percent, but this the exception rather than the norm. Concurrently taking cimetidine with dapsone can help to reduce patient’s methemoglobinemia.21

The third biologic medication is efalizumab (Raptiva®), which is a humanized monoclonal antibody (IgG1 I) that targets the CD11a component of LFA-1 preventing its binding to intercellular adhesion molecules (ICAMs).9,22 In phase three trials 27% of patients receiving subcutaneous efalizumab attained a 75% or greater improvement in PASI score at the end of the 12-week treatment course. Over multiple clinical trials, 19 of 2589 (0.7%) efalizumab-treated patients experienced serious worsening of psoriasis with seventeen of these patients requiring hospitalization. Most of these events (14/19) occurred after discontinuation of efalizumab22; therefore patients should be closely monitored for exacerbation of psoriasis upon stopping therapy (efalizumab package insert). Other adverse events include lymphocytosis, which usually returns to baseline upon discontinuation of therapy, and thrombocytopenia, which should be closely monitored with platelet counts regularly drawn during therapy.22

The fourth biologic and second anti-TNF medication is etanercept. Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG110. In clinical trials, 49% of patients receiving 50 mg subcutaneously twice weekly had an improvement of 75% or more in PASI scores from baseline at twelve weeks.23 The precautions are similar as for the other anti-TNF medications including CHF, demyelinating disorders (multiple sclerosis), active or chronic infections, and lupus erythematosus.20 The FDA does not require any labs to monitor treatment,22 however many practitioners perform a PPD test and/or chest x-ray before starting treatment. The most common side effects are cough and respiratory symptoms, seen in 45% of treated patients, and injection site reactions, seen in 37% of treated patients.22 The injection site reactions are generally not severe enough to make patients discontinue the medication and subside over time.

The antimalarials, now composed of hydroxychloroquine (Plaquenil®), chloroquine (Aralen®), and quinacrine, have been used in medicine for over four-hundred years and in dermatology for over one-hundred years.24 Hydroxychloroquine is the most commonly prescribed antimalarial in the United States with most dermatologic conditions responding to doses between 200 and 400 mg/day, however it can take up to 4 months before adequate clinical effect is seen. Once adequate clinical effect occurs, patients can then be maintained on 100-200 mg/day, with quinacrine at 100 mg/day added if the former is not effective enough. This combination increases the efficacy without increasing the chance of ocular toxicity.25 However, quinacrine does cause a yellowing of the skin in almost all patients. The most serious, but very rare, side effect of the antimalarials is an irreversible retinopathy. Patients must be monitored at baseline and every 6-12 months by an ophthalmologist who is experienced monitoring antimalarial therapy.26 Other less serious side effects include reversible blue-gray hyperpigmentation of the shins or face (33%), reversible bleaching of hair roots (10%), exanthems (10%), and GI upset (10%).22,26

Hydroxyurea (Hydrea®) was found to be effective in the treatment of psoriasis in the early 1970’s when it was much more commonly prescribed. It is not as effective as methotrexate or azathioprine for psoriasis so its use has fallen out of favor. However, because it lacks the liver toxicity that methotrexate causes it is a viable alternative for patients with liver disease. Nowadays it is used as either add-on therapy or as a single agent once the disease has been brought under control with a different medication. Usual doses range from 20-30 mg/kg/day in divided doses with a maximum of 2 gms/day.27 Hydroxyurea is generally well tolerated with 57% of patients taking 1.5 gm/day experiencing no side effects.28 The most significant side effects are bone marrow suppression and teratogenesis. All patients develop megaloblastosis, with anemia occurring in 12-34%, leukopenia in 7%, and thrombocytopenia in 2-3%.29 Bone marrow suppression usually resolves promptly with discontinuation of the medicine and patients should not be put on other bone marrow suppressing drugs concurrently.23 Hydroxyurea is pregnancy category D and should not be taken by anyone who is trying to conceive a child.

Thiopurines were first developed in the 1950’s with many subsequent derivatives produced. The most commonly used thiopurine in dermatology is azathioprine (Imuran®). It is generally used in inflammatory conditions such as the bullous disorders to decrease the dose and length of steroid treatment. When oral corticosteroids are not able to control the disease after one to two weeks of treatment, azathioprine can then be initiated.27 The corticosteroids are then gradually tapered and patients can maintain remission with azathioprine. The usual dose is 1 to 2 mg/kg per day. Azathioprine must be closely monitored with its immunosuppressive effects possibly placing patients at increased risk for lymphoproliferative malignancies, relative risk 10-13 fold, (not reported in dermatologic patients) and squamous cell carcinomas.30,31 Patients should have a thiopurine methyltransferase (TPMT) level drawn before treatment so the correct dose can be prescribed to decrease the possibility of myelosuppression.26 In addition, a life-threatening hypersensitivity reaction can occur. This reaction usually occurs within hours of the first dose and consists of hepatitis, cardiovascular collapse, fever, a cutaneous eruption, and respiratory and GI distress.27,28

The fifth and last biologic is infliximab (Remicade®), which is a murine-human chimeric monoclonal antibody that neutralizes the biological activity of TNF-α. It does this by binding with high affinity to both the soluble and transmembrane forms of TNF-α and inhibiting the binding of TNF with its receptors.29 In clinical trials 82% of patients in the 5-mg/kg infliximab achieved PASI 75 after ten weeks of therapy.30 The most common side effects seen were infusion reactions (20%) with dyspnea, urticaria, hypotension, flushing, and headache characterizing most of these reactions.29,30 Only 2% of patients discontinued infliximab therapy because of an infusion reaction. Serious infections, besides tuberculosis, have been reported in post-marketing data including Streptococcus pneumoniae, Listeria monocytogenes,
Aspergillus fumigatus, Histoplasma capsulatum, Cryptococcus neoformans, Pneumocystis, and Coccioidioides immitis. Other precautions include CHF, lupus erythematosus, and demyelinating disorders. As with the other anti TNF-alpha medications the role they have in the development of lymphomas is not exactly known and controversial.

The most commonly used oral systemic medication in dermatology is methotrexate. Methotrexate is an antimetabolite agent that has been used in dermatology for almost fifty years. The most common side effects include GI complaints, which can usually be reduced by adding folic acid on off days. The most well known side effect is liver toxicity and fibrosis, which do not correspond to liver enzymes. Roenigk et al. advised doing liver biopsies after every 1.5 total grams of methotrexate and then at 3 and 4 total grams thereafter for patients without known hepatic risk factors.

Known risk factors include prior liver disease, significant alcohol consumption, diabetes, obesity, and IV drug use. Methotrexate can also cause severe bone marrow depression with anemia, leukopenia, and thrombocytopenia being reported. It is contraindicated in pregnancy since it is a teratogen and abortifacient, however no malformations have been reported in children fathered by men on methotrexate. The current recommendation is that men should stop methotrexate treatment at least 3 months before trying to conceive while women should wait one full menstrual cycle. There have been reports of pulmonary toxicity including pulmonary fibrosis in patients on methotrexate, but more recent studies using HRCT call this into question. Nevertheless, a chest x-ray should be done before treatment and any pulmonary complaint during therapy should be followed up with a chest x-ray and pulmonary function tests. Methotrexate also has many potential drug interactions. The most serious of these are sulfonamides, trimethoprim, dapsone, and all renal-toxic drugs which are absolute contraindications. Methotrexate has a long record of safety, which can be continued with smart patient selection and careful monitoring of patients during treatment.

Mycophenolic acid has been used since the 1970’s to treat moderate to severe psoriasis, but was discontinued due to its side effect profile. It has been replaced by mycopheno- lato mofetil (MMF: Cellcept®), which has greater bioavailability and is better tolerated than mycophenolic acid. Mycophenolic mofetil’s main use is as a steroid sparing agent and in place of azathioprine for autoimmune blistering disorders. It was studied as a single agent in psoriasis, with effective doses of 3,000 – 4,800 gm/day, which is much higher than the 1-2 gm/day effective dose seen in other conditions. The most common adverse effects are GI complaints – nausea, diarrhea, vomiting, and abdominal pain. The most severe side effect reported is rare reversible bone marrow toxicity. Mycophenolic mofetil does not cause chromosome breaks in the DNA and therefore has no mutagenic potential like azathioprine. It has also less bone marrow toxicity than azathioprine and no clinically significant hepatotoxicity. MMF has been proven as a safe, long term therapy and steroid-sparing agent.

The most commonly used oral glucocorticoid in dermatology is prednisone. It is used for a wide variety of diseases at an initial dose of 40-80 mg/day, which are then tapered slowly to maintenance doses ranging from 5-20 mg/day. Patients should take prednisone in a single dose before 9 A.M. with food to decrease GI upset. For patients on long term therapy (> 3 weeks) or when tapering, an alternate morning therapy is often utilized to decrease side effects, however it does not decrease the risk of osteoporosis or cataracts. The most severe side effects include osteoporosis, suppression of the hypothalamic-pituitary-adrenal axis, avascular necrosis, cataracts, glaucoma, myopathy, growth retardation, psychosis, and Cushingoid cutaneous features. Osteoporosis occurs in 40% of patients treated with prednisone, especially children, adolescents and post-menopausal women. All patients on long term steroids should be placed on a weight bearing exercise program, 1.5 gm/day of calcium, 800 IU/day of vitamin D, and a long term steroids should be placed on a long-term azathioprine. Br J Dermatol 1995;133:460-2. Mycophenolic mofetil does not cause chromosome breaks in the DNA and therefore has no mutagenic potential like azathioprine. Mycophenolic mofetil is often utilized to decrease side effects, how- ever it does not decrease the risk of osteoporosis or cataracts. The most severe side effects include osteoporosis, suppression of the hypothalamic-pituitary-adrenal axis, avascular necrosis, cataracts, glaucoma, myopathy, growth retardation, psychosis, and Cushingoid cutaneous features. Osteoporosis occurs in 40% of patients treated with prednisone, especially children, adolescents and post-menopausal women. A baseline dual energy x-ray absorptiometry (DEXA) scan should be done before treatment and then annually to monitor for any decrease in bone mineral density. Cataracts are another side effect with the overall total dose and duration of therapy being the two most important factors. Therefore, ophthalmologic exams, both slit lamp and infrared pressure monitoring, are recommended every six to twelve months. Children can develop cataracts at lower doses and with shorter treatment duration than adults, so they must be monitored even more carefully. The hypothalamic-pituitary-adrenal (HPA) axis can be suppressed after just a few weeks of systemic glucocorticoid therapy. When therapy is kept at a level of 7.5 mg prednisone per day, a significant pressure can develop in the hypothalamic-pituitary-adrenal system.

Symptoms that patients may experience with adrenal suppression include lethargy, weakness, nausea, anorexia, and fever. More commonly patients on long term oral steroids develop corticosteroid withdrawal syndrome. Here patients can have anorexia, malaise, arthralgias, headache, mood swings, lethargy, and nausea upon tapering of steroid dosage. The dosage should then be increased and tapered more slowly, i.e. 1 mg every few weeks. References:

Closure of a Large Scalp Defect After Mohs Surgery with Galeotomy Assistance: A Case Report

ABSTRACT

Physicians occasionally overestimate the ability to approximate wound edges of scalp defects, as the laxity is often less than it appears. Tension developing at wound edges predisposes to complications of wound healing. A galeotomy is a useful adjunct to decrease the amount of tension when closing large scalp defects.

Case Report

A 39-year-old, Caucasian female presented with a 15 mm, painless, pearly, slightly erythematous nodule on her scalp. Twice previously, lesions in the same area had been removed with subsequent pathology revealing basal cell carcinoma. The patient’s past medical history was significant for acute lymphocytic leukemia, which was treated with radiation therapy to the head 30 years prior. Additionally, the patient had a significant history of sun exposure as she regularly enjoys outdoor activities.

Histologically, a 4 mm punch biopsy revealed a distinct, peripheral, palisading layer of cells with clefting, indicative of a nodular basal cell carcinoma. Also noted was significant scar tissue, likely from previous surgical removal attempts. The patient was scheduled for Mohs surgery accordingly.

Three stages of Mohs surgery with a total of seven specimens were required to remove the lesion in its entirety, leaving a 33 mm x 27 mm defect [Figure 1]. Due to the size and location of the defect, we felt an O-Z plasty would offer us the best option for closure and provide the best cosmetic outcome. [Figure 2]. Two incisions were made on opposite sides of the defect, creating two opposing rotation flaps. These incisions were taken down to the level of the loose connective tissue and pericranium. Undermining was performed through the subgaleal plane. At that time, we noticed a significant amount of tension when trying to approximate the wound edges. A galeotomy was then performed by making incisions through the inferior aspect of the galea, offering a significant amount of tension reduction [Figure 3]. The edges of the wound were approximated with little tension, and the closure was performed with deep and surface sutures [Figure 4, 5]. A turban pressure dressing was placed around the circumference of the head to decrease the chances of hematoma formation. Fourteen days post-op, the patient returned to the clinic, at which time the sutures were removed. Excellent cosmetic results were noted.

Discussion

The scalp is divided into five layers: skin, connective tissue, aponeurosis (galea aponeurotica), loose connective tissue and pericranium. The galea aponeurotica is the layer of greatest strength and is the key fascial structure. It is an inelastic, tendon-like sheath measuring 0.5 mm - 0.75 mm in thickness and is a distinct component of the superficial musculoaponeurotic system. This layer is responsible for the underestimation of movement by dermatological surgeons, creating greater difficulty in repairing large scalp defects.

As a rule, excisions on the scalp that exceed 10 mm should be carried down to the subgaleal plane, as better wound-edge approximation can be achieved using a technique called a galeotomy. A galeotomy can be accomplished in two ways: by dissecting either in a caudad direction or in a cephalad direction through the periosteum. After blunt dissection is performed to separate the galea from its respective underlying layer (or overlying layer, depending on which approach is chosen), parallel incisions are made through the galea, approximately 1 cm to 2 cm in length.

Dermatologists must be observant when performing a galeotomy, as the tissue above the galea contains numerous large vessels. Once the vessels are transected, hemostasis is difficult to achieve due to poor visualization. The paucity of blood vessels in the subgaleal space, however, offers a bloodless dissection. Adequate lighting, long instruments and a suction device will make the procedure easier.
Another surgical option a dermatological surgeon may have when closing large scalp defects is a pinwheel flap. A variant of the O-Z plasty, the pinwheel flap features multiple rotation flaps. The size of the defect and movement of the scalp will determine the number of arms that the pinwheel flap will have.

### Conclusion

Performing a galeotomy may significantly decrease the amount of tension when approximating wound edges in large scalp defects. This relatively easy procedure can result in very large gains of tissue movement when closing a surgical wound of the scalp. Dermatological surgeons should be proficient and aware of this procedure, as scalp laxity is often difficult to predict. A galeotomy may allow closure in large wounds that would otherwise have been difficult or impossible to repair.

### References

Case Report

A 31-year-old female presented to the office with a chief complaint of a “skin tag” near her vagina. She originally went to her primary care physician, who thought it might be a Bartholin’s cyst and referred her to a gynecologist. The gynecologist referred her to our office to rule out a possible skin tag. The patient stated she first noticed the growth when she was 18 years old and thought it was a pimple. Associated symptoms included itching, and she found relief with a vaginal cream.

The growth progressively increased in size over the years. The patient had no significant past medical history. Past obstetrical history was significant for five vaginal deliveries with no complications. Physical examination revealed a 10-cm growth on the right side of the anterolateral wall located on the lower third of the vagina. The growth was pink, like the color of the vaginal mucosa. A biopsy was taken and sent to the lab for examination.

Differential Diagnosis

The differential diagnosis included vaginal wall inclusion cyst, Gartner’s duct cyst, endometriosis, leiomyoma, skin tag, and inguinal hernia.

Case Discussion

Gartner’s duct cysts are benign vaginal cysts that develop from the embryologic mesonephric ducts. During early embryological development, both a male and female embryo will have two pairs of genital ducts: mesonephric (Wolffian) ducts and paramesonephric (Mullerian) ducts. The paramesonephric ducts will form the main genital ducts of the female, and the mesonephric ducts will form those of the male.

In the male, the SRY gene is the inducer for testes development. Once Sertoli cells have differentiated, they secrete Mullerian-inhibiting substance (MIS), which causes the paramesonephric ducts to regress. The differentiation into female sexual parts was once believed to occur by a default mechanism. Now there have been identified specific genes that induce ovarian development. Due to the absence of MIS in the female, the paramesonephric ducts will persist and form the uterine tubes, uterus, cervix, and upper vagina.

The upper portion of the vagina is formed from the paramesonephric ducts, and the lower portion is formed from the urogenital sinus. The paramesonephric ducts move caudally during development to meet the urogenital sinus. A thin tissue, called the hymen, separates the lumen of the vagina from the urogenital sinus. The mesovarium is a short, peritoneal fold connecting the anterior border of the ovary with the posterior layer of the broad ligament. In some females, remnants may be retained from the mesovarium and form the epoophoron and paroophoron. A small portion of the mesonephric duct may persist in the epoophoron and in the wall of the uterus or vagina. This small remnant found in the vagina may appear later in life and is called the Gartner’s cyst.

In most females, the mesonephric ducts completely regress. In females in whom the ducts persist, a cyst can form anywhere along the path of the ducts. Most commonly, they are found in the lower vagina. The cysts vary in size, and most are smaller than 2 cm. It is thought that in most females, Gartner’s cysts are asymptomatic and are actually underreported. The smaller cysts are usually discovered on routine pelvic exams. Later in life, these cysts can grow and cause dyspareunia and problems with childbirth. These cysts are treated by surgical excision on an outpatient basis.

Our patient’s biopsy report was found to be consistent with a Gartner’s duct cyst. Her cyst was excised in the office without any complications. The excision site healed well, and she had excellent results.

References:
Goes On Silky Smooth.

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*Based on post-study surveys (N=377, N=376) of patients using a BID regimen of Olux-E Foam.

Olux-E Foam is indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older. Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 grams per week.

Olux-E Foam has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.
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Please see following page for brief summary of Prescribing Information.

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Clobetasol propionate has greater teratogenic potential than steroids that are known to be teratogenic in laboratory animals when administered orally or by injection. Patients should be instructed to use Olux-E Foam for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS). Use in pediatric patients under 12 years of age is not recommended because of numerically high rates of hypothalamic-pituitary-adrenal (HPA) axis suppression seen in patients under 12 years of age (see PRECAUTIONS: Pediatric Use).

CONTRAINDICATIONS
Olux-E Foam is contraindicated in patients who are hypersensitive to clobetasol propionate or to any ingredient in this preparation.

WARNINGS
The propellant in Olux-E Foam is flammable. Avoid fire, flame or smoking during and immediately following application.

PRECAUTIONS
General: Olux-E Foam has been shown to suppress the HPA axis. Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushings syndrome, hyperglycemia, and hypokalemia can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Pediatric patients may be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use). Conditions which increase systemic absorption include the application of more potent steroids, use over large areas, prolonged use, and the addition of occlusive dressings; such patients should be observed to achieve the desired results (see INDICATIONS AND USAGE). Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.

In a study investigating the potential for HPA axis suppression, using the cosyntropin stimulation test, Olux-E Foam demonstrated adrenal suppression after two weeks of twice daily use in patients with atopic dermatitis of at least 30% body surface area (BSA). The proportion of subjects with at least 10 ug change in 17-hydroxyprogesterone demonstrating HPA axis suppression was 16.2% (6 out of 37). In this study, HPA axis suppression was defined as serum cortisol level ≤ 10 ug/dl. Prolonged use of topical corticosteroids should not be used longer than 2 weeks treatment.

Patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression. Patients should be instructed to use Olux-E Foam for the minimum amount of time necessary to achieve the desired results (see INDICATIONS AND USAGE). In an in vivo study, Olux-E Foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical examination which it was prescribed. If no improvement is seen within 2 weeks, contact the physician.

Polytherapy: The use of topical corticosteroids with other agents: occlusive dressings, antibiotics, or antifungal agents may increase the potential for skin atrophy. If concomitant skin infections are present or develop, an appropriate antibacterial or antifungal agent should be used. If a favorable response does not occur promptly, use of Olux-E Foam should be discontinued until the infection has been adequately controlled.

Pediatric Use:

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:
1. This medication is to be used as directed by the physician. It is for external use only. Unless directed by the prescriber, it should not be used on the face, or in skin-fold areas, such as the axillae or groin. Avoid contact with the eyes or other mucous membranes. Wash hands after use.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged, wrapped, or otherwise covered so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local or systemic adverse reactions to the physician.
5. Patients should inform their physicians that they are using Olux-E Foam if surgery is contemplated.
6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
7. Patients should not use more than 50 grams per week of Olux-E Foam, or an amount greater than 21 capfuls per week (see DOSAGE AND ADMINISTRATION).

Oversedosage:
The cosyntropin (ACTH, α-MSH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Cardiogenic, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was not mutagenic in four different test systems: the Ames test, the mouse lymphoma test, the Saccharomyces cerevisiae gene conversion assay, and the E. coli WP2/uvr test. In the in vivo mouse micronucleus test a positive finding was observed, but not at 48 hours, following oral administration at a dose of 2000 mg/kg. Studies of the following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Pregnancy: Teratogenic Effects: Pregnancy Category C:
Corticosteroids are not teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals. Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.
Fixed Drug Eruption and Other Cutaneous Manifestations Secondary to Long-term Hydroxyurea Therapy: A Case Report and Review of the Literature

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ABSTRACT

While several cutaneous manifestations have been reported in patients on long-term hydroxyurea therapy, our case represents a unique, pigmented, fixed drug eruption in the bilateral groin area in a patient with essential thrombocythemia. The patient did not demonstrate any other cutaneous side effects due to hydroxyurea therapy. He did, however, demonstrate unexplainable asthmatic episodes which require further investigation. We follow with a discussion of fixed drug eruptions as well as a review of the literature regarding mucocutaneous changes seen with long-term hydroxyurea therapy.

Case Report

Our patient is a 77-year-old Caucasian male with a history of essential thrombocythemia that has been treated with hydroxyurea for the past five years. The patient presented to the clinic with striking, well demarcated, hyperpigmented areas involving his inguinal folds. The erythematous, purple-brown areas contained minimal scaling and were KOH negative. No mucocutaneous lesions were noted.

The patient’s past medical history includes a severe aspirin allergy, which has previously resulted in an anaphylactic reaction. He also reports several “asthmatic episodes” in the past associated with extreme shortness of breath for which no underlying cause has been determined. Other reported conditions included hypertension, hypercholesterolemia, osteoarthritis, and a myocardial infarction. His current medications are hydroxyurea, isosorbide, clopidogrel, metoprolol, simvastatin, and tiotropium inhaler.

The differential diagnosis of this peculiar pigmentation included a fixed drug eruption, a myelodysplastic syndrome or asthmatic triad syndrome. Several laboratory tests were obtained. A CBC with differential was within normal limits with the exception of neutrophils 82.6 (42-75%), lymphocytes 9.7 (21-51%), and platelets 451 (140-440 x10^3/μL). A fluorescent in-situ hybridization (FISH) test and a cytogenetic report for Gleason 6 chromosome were both negative for any myelodysplasia. Also, serum IgE levels were within normal limits, which would rule out the possibility of an asthmatic triad syndrome. At the patient’s request, a skin biopsy was not obtained. A bone-marrow biopsy was inconclusive due to inadequate sampling. The patient did not undergo a second biopsy. The cutaneous findings of this case are most consistent with a fixed drug reaction secondary to hydroxyurea.

Discussion: Fixed Drug Eruptions

Clinically, a fixed drug eruption initially appears as one or a few round or oval, sharply demarcated erythematous and edematous plaques which may or may not contain a centralized bulla, followed by desquamation. Often, concentric circles of erythema can be observed. The characteristic feature of a fixed drug eruption is that the lesions occur at the same site upon re-exposure to the causative drug. This phenomenon was first described in the literature by Bourns in 1889 and subsequently named “erythematous pigmented fixed eruption” by Brocq in 1894.

The lesions of a fixed drug eruption include pigmented, non-pigmented and linear variants. While the lesions progressively fade with time, the pigmented plaques oftentimes leave a residual post-inflammatory hyperpigmentation. New lesions will be located at the exact same site(s) as the initial outbreak within 24 hours after re-exposure, with a mean onset of symptoms at 2.1 hours. Each subsequent re-exposure is usually exacerbated, although the number of lesions may either gradually increase or remain constant. Intense pruritis, burning, and fever are occasionally associated with these lesions. Despite the incidence of fixed drug eruptions continuing to increase, the overall number of cases has decreased due to increasing recognition and familiarity amongst dermatologists.

The reason for recurrence at the same site remains unknown, although the finding of T-suppressor cytotoxic cells in the epidermis of these lesions provides some insight into the cutaneous memory function. Furthermore, keratinocytes in fixed drug eruptions have been shown to express intercellular adhesion molecule-1 (ICAM-1), correlating with the degree of residing T-cells, which may play an additional role in same site recurrence.

Mucosal fixed drug eruptions are also reported to be commonly caused by oxyphenbutazone. Histological changes seen with fixed drug eruptions appear to be limited to the epidermis and upper dermis. According

Figure 1

Although these lesions may appear anywhere on the body, including oral mucosa, the most frequently involved sites are genital mucosa (50.5%), trunk (38.1%), lips (37.1%), and hands (32.4%). With oral mucosa involvement, the possibility of Stevens-Johnson syndrome must also be included in the differential diagnosis.

The most commonly associated drugs with a fixed drug eruption are sulfonamides (most particularly trimethoprim-sulfamethoxazole), NSAIDs (chiefly phenazone derivatives), barbiturates, tetracycline, and carbamazepine. In a study of 105 patients who developed fixed drug eruptions, the most common causative agent overall was found to be trimethoprim-sulfamethoxazole (63.8%), followed by naproxen (23.8%), dipyridamole (5.7%), and the oxicam derivatives tenoxicam and piroxicam (4.8%). Certain drugs have also been reported to have preferential sites for non-pigmented fixed drug eruptions. Tetracycline and trimethoprim-sulfamethoxazole have shown to involve genital mucosa more frequently; naproxen and oxicams show preference on the lips; and dipyridamole tends to favor the trunk and extremities. Mucosal fixed drug eruptions are also reported to be limited to the epidermis and upper dermis. According
to Korkij et al., one characteristic of fixed drug eruptions is hydropic degeneration of epidermal basal cells with considerable amounts of melanin present in the upper dermis, partly within macrophages. Dyskeratotic cells are typically scattered in the upper layers along with marked edema. Vascular dilatation and perivascular inflammatory cell infiltration consisting of lymphocytes, histiocytes, polymorphonuclear leukocytes, and mast cells are also observed. Theodoridis et al. previously reported deposition of fibrin at the dermoepidermal junction. Pigmentary incontinence and dermal melanophages have been shown in healed pigmentary lesions.

Fluid in lesions with a centralized bulla was found to contain polymorphonuclear leukocytes, lymphocytes, erythrocytes, and remnants of necrotic epidermal basal cells. Immunological studies demonstrated a rise in the peripheral blood leukocyte count and a decline in basophil count to a nadir, which is consistent with the CBC obtained from the patient in this case report.

The usual treatment of fixed drug eruptions consists of systemic antihistamines with topical steroids. However, systemic corticosteroids may be required for extensive lesions and oral antibiotics may be required to prevent secondary infection in unroofed bullae.

Hydroxyurea is a chemotherapeutic agent that is used to treat myeloproliferative disorders including chronic myeloid leukemia, essential thrombocytosis, and not characteristic of other chemotherapeutic agents because hydroxyurea is that it is not limited to the lower extremities. Kato et al. noted by Kato and Oskay et al. in two males in their sixties on long-term hydroxyurea therapy for polycythemia vera. Acral erythema is another common finding as reported in 15 cases published by Demircay et al. Pellicano was the first to report local dermatoglyphism in hyperpigmented lesions at the site of a fixed drug eruption, although this was in a nine-year-old child taking feprazone for cold symptoms, not in a patient on hydroxyurea therapy.

Nguyen et al. and Suehiro et al. reported large leg ulcers in patients on hydroxyurea therapy in 1993 and 1994, respectively. In the following years, several case reports of lower leg ulcers were published and are summarized in a case report and review of the literature on hydroxyurea-related leg ulcers by Kato et al. This article further hypothesizes the possible pathogenesis of hydroxyurea-related leg ulcers by histologically demonstrating the formation of multiple thrombi in the capillaries, endothelial cell swelling, and thickening of the small-blood-vessel walls induced by pressure on the lower extremities. Kato also states that the reason the formation of leg ulcers may be unique to hydroxyurea and not characteristic of other chemotherapeutic agents may be because hydroxyurea is reported to be cytostatic rather than cytocidal on cells. Furthermore, Kato references Montefusco et al., in which 17 of 200 (8.5%) CML patients on hydroxyurea therapy developed leg ulcers, with 14 of the 17 patients’ ulcers healing upon discontinuation of the drug. Another important aspect of the effect of hydroxyurea is that it is not limited to the epidermis, as mucosal fixed drug eruptions have been reported as well. Browne, Korkij, Tagami, and Westerhof all individually report cases of mucosal fixed drug eruptions. Involvement of the mucosa alone, however, without any other skin involvement, is rare.

Of 158 CML patients treated with hydroxyurea, 21 (13%) developed cutaneous and mucosal manifestations in a study by Vassallo et al. Acral erythema was found in all 21 patients. Skin atrophy characterized by numerous telangiectases was evident in 16 of the 21 patients. Hyperpigmentation of either skin, mucous membranes, or nails was found in 10 of the 21 patients. Stomatitis and glossitis with flattening of papilla were considered to be a common finding. Five of 21 patients developed squamous cell carcinomas or kerato-canthomas on sun-exposed sites. Seven developed the dermato-myositis-like changes on the dorsa of the hands as previously described. And finally, 20 of the 21 developed ulceration on the legs, genitalia, or oral mucosa.

References:
24. Layton AM, Sheehad-Dare RA, Goodfield MJ, Cotterill JWM. Hydroxyurea in the management of therapy resistant
Introduction

A thorough understanding of cutaneous lymphoma is paramount for the practicing dermatologist. It requires an integration of clinical knowledge, histopathological findings, immunophenotyping, gene rearrangement studies, clinical staging and longitudinal evaluation. Management of these patients can require the services of a dermatologist, dermatopathologist, oncologist and radiation oncologist.

Case Reports

CASE # 1

A 66 year old Caucasian male presented with a two month history of a recurring eruption of annular erythematous patches on the abdomen, lower back and upper thighs. Over two visits, four punch biopsies were taken.

Histopathologic diagnosis revealed a superficial perivascular lymphocytic infiltrate, mainly within the papillary dermis, with focal lymphocytic tagging at the dermal-epidermal junction, focal epidermotropism, mild lymphocytic atypia including hyperchromasia. Immunohistochemistry reveals:

- strong positivity for Anti CD3 and Anti CD4,
- 30% positivity for CD8
- Minimal reactivity with CD30

Diagnosis: Patch Phase Mycosis Fungoides

CASE # 2

A 66 year old female presented with a three month history of a slowly enlarging erythematous dermal nodule on the left inner thigh. A punch biopsy was performed and revealed the following:

Dense lymphoid infiltrate within the superficial and deep dermis. In the superficial dermis, a thick band of lymphocytes fills and expands the papillary dermis. No epidermotropism is identified and a very thin Grenz zone is present. The specimen is composed of an atypical lymphoid infiltrate, showing enlarged and atypical hyperchromatic irregular nuclei and scattered plasma cells. Immunohistochemistry is as follows:

- Anti CD3 stains a majority of the infiltrative cells
- Anti CD4 stains 70% of the T cell population (particularly the larger cells)
- Anti CD8 stains 30% of the T cell population

Diagnosis: T cell lymphoma

Dermatologic Immunohistochemical Stains

Immunohistochemical staining is used to identify the line of differentiation of a cell or tissue type. It can help to identify clonality, which is suggestive of malignancy. In most instances, a panel of stains is selected based on a dermatopathologists differential diagnosis. A knowledge of relevant stains is imperative to understand the various cutaneous lymphomas.

CD1A Langerhans cells
CD3 T lymphocytes
CD4 T helper cells
CD5 T lymphocytes
CD7 T lymphocytes
CD8 Cytotoxic T cells
CD10 Germinatal center cells
CD 20 Pan B cell marker
CD21 Follicular dendritic cells
CD30 (Ki-1) Lymphomatoid papulosis, Large cell anaplastic lymphoma
Reed Sternberg cells
CD31 Tumors of endothelial origin
CD34 Tumors of endothelial origin
Hematopoetic stem cells
CD43 Pan T cell marker
CUTANEOUS T CELL AND NK CELL LYMPHOMAS

Subtypes

Classification

Lack of uniformity has typified the reporting classification systems for primary cutaneous lymphomas. In the past, systems such as the Kiel, Working Formulation or Lukes-Collins classification systems have been used, with a diagnosis rendered based on morphology and immunophenotypic criteria, independent of site of presentation and clinical findings. It was not uncommon for a diagnosis to be given in more than one classification system.

In 1994, the Revised European-American Lymphoma Classification (REAL) was produced, incorporating morphological, immunophenotypic, histologic and clinical features. The World Health Organization (WHO) adopted the REAL classification system which has been viewed as the most current and comprehensive classification.

Another working system designated the European Organization for Research and Treatment of Cancer (EORTC) has been designed and applied specifically for primary cutaneous lymphomas. It highlights distinction among subtypes of primary cutaneous lymphomas based upon indolent, intermediate or aggressive clinical behavior.

Thus, over approximately the last decade, 2 classification schemes have been created, used and validated. The differences between the two illustrates the complexities in understanding primary cutaneous lymphoma.

Recently, during meetings which occurred over 2004-2005, world authorities reached agreement on a new classification system. It is known as the WHO-EORTC classification for cutaneous lymphomas, representing the most current classification system used in the medical community. Following is a reproduction of the newly updated, current, hybrid classification system.

Subtypes

CUTANEOUS T CELL AND NK CELL LYMPHOMAS

Mycosis Fungoides

MF variants and subtypes

- Folliculotropic MF
- Pagetoid reticulosis
- Granulomatous slack skin

Sezary syndrome

Adult T cell Leukemia/lymphoma

Primary cutaneous CD30+ lymphoproliferative disorders

- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

Subcutaneous panniculitis like T cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type

Primary cutaneous peripheral T cell lymphoma, unspecified

- Primary cutaneous aggressive epidemotropic CD8+ T cell lymphoma
- Primary cutaneous CD4+ small/medium sized pleomorphic T cell lymphoma

CUTANEOUS B CELL LYMPHOMAS

Marginal zone B cell lymphoma

Follicle center lymphoma

Diffuse large B cell lymphoma, leg type

Diffuse large B cell lymphoma, other

- Intravascular Large B cell lymphoma

Precursor hematologic neoplasm

- CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Discussion, Explanation, Integration and Clinical Presentations of T and B cell Subtypes

T CELL LYMPHOMAS

Cutaneous T cell lymphomas generally refer to neoplasms of T cells which localize to the skin. They represent approximately 80% of all cutaneous lymphomas. Over the last decade, various subtype of T cell lymphomas have been classified due to advancements in histology, immunohistochemistry, and clinical correlation. It is observed that neoplastic T cells in most CTCL express CLA (cutaneous lymphocytic antigen), indicating that they are neoplastic cells of normal skin homing T cells. The following subtypes with respect to clinical presentation and histology are presented.

MYCOSIS FUNGOIDES

Clinical:

- Affects older adults, indolent course over years to decades forms patches to plaques and nodules predilection for buttocks and sun protected areas

Histopathology

- superficial bandlike or lichenoid infiltrates,
  - small to medium sized atypical cells
  - highly indented (cerebriform) and hyperchromatic nuclei,
  - confined to the epidermis (epidermotropism),
  - colonize the basal layer as single cells or linear configuration, Pautrier microabscesses: intraepidermal collection of atypical cells

Immunophenotype

- CD3+, CD4+, CD45RO+, CD8- memory T cells
- Transformation into a diffuse large cell lymphoma CD30+ or CD 30- is associated with a poor prognosis

Prognosis

- Limited involvement (<10%) generally have a similar life expectancy to patients without mycosis fungoides
- Generalized involvement (>10%) has a 83% 10 year survival
- Tumor stage has a 42% 10 year survival
- Lymph node involvement has a 20% 10 year survival

MYCOSIS FUNGOIDES SUBTYPES

FOLLICULOTROPIC MF

Clinical

- Grouped follicular papules, acniform lesions, indurated plaques, preferentially in the head and neck area
- Often severe pruritis
• Associated alopecia sometimes with mucinous degeneration of follicles

Histopathology
• Deep, follicular and perifolicular localization of neoplastic infiltrates, often sparing the epidermis, most cases with mucinous degeneration of follicles,

Prognosis
• 5 year survival of 70-80%, similar to tumor stage MF

PAGETOID RETICULOSIS

Clinical
• Solitary psoriasiform of hyperkeratotic patch or plaque
• Usually localized to the extremities
• Characterized by purely intraepidermal proliferation of neoplastic T cells

Histopathology
• Hyperplastic epidermis with marked infiltration of atypical pagetoid cells, Medium-large hyperchromatic and cerebriform nuclei, vacuolated cytoplasm

GRANULOMATOUS SLACK SKIN

Clinical
• Slow development of lax skin in the major skin folds (axilla, groin)

Histopathology
• Dense granulomatous infiltrates containing atypical T cells
• Many multinucleated giant cells, and destruction of elastic tissue

SEZARY SYNDROME

Clinical
• Triad: erythroderma, generalized lymphadenopathy and Sezary cells in skin, nodes and peripheral blood
• Often with exfoliation edema, intense pruritis, palmoplantar hyperkeratosis

Histopathology
• Similar to MF although epidermotropism may be absent and often monotonous cellular infiltrate
• Lymph nodes show a dense infiltrate of Sezary cells

Immunophenotype
• CD3+, CD4+, CD8-
• Circulating Sezary cells often show loss of CD7

Prognosis: 24% survival at 5 years

ADULT T cell LEUKEMIA/LYMPHOMA (ATLL)

Clinical
• Endemic in areas with a high prevalence of HTLV-1 (Japan, Caribbean, South America, Central Africa)
• Develops in 1-5% of seropositive individuals after > 20 years
• Presents as leukemia, lymphadenopathy, organomegaly and skin nodules/tumors

Histopathology
• Superficial to diffuse infiltration of medium-large T cells with marked pleomorphism
• Similar pathologic findings as with MF

Immunophenotype
• CD3+, CD4+, CD8-, CD25+
• Clonal HTLV-1 genes are found in all cases, used to differentiate chronic ATLL and MF

Prognosis
• Acute variant ranges from 1-12 months survival
• Chronic form has a longer survival

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA

Clinical
• Solitary or localized papules, nodules, or tumors
• May show complete spontaneous regression, and frequently relapse in the skin
• 10% may involve regional lymph nodes

Histopathology
• Diffuse, nonepidermotropic infiltrate with cohesive sheets of large CD30+ tumor cells
• Anaplastic cells: round, oval, or irregularly shaped nuclei, prominent eosinophilic nucleoli

Immunophenotype
• CD4+Loss of CD2, CD3, CD5, CD16 -
• CD30+ should be expressed by > 75% of neoplastic cells
• Most express CLA (cutaneous lymphocytic antigen) unlike systemic CD30+ lymphomas
• Clonal rearrangement
• (+) for T cell receptor genes

Prognosis
• 90% 10 year survival
• Patients with multifocal skin lesions and regional lymph node involvement have a similar prognosis to patients with skin lesions only

LYMPHOMATOID PAPULOSIS

Clinical
• Red-brown papules and nodules (3-10 mm) with central hemorrhage, necrosis or crust ing
• Lesions are predominantly on the trunk and limbs, at different stages of development
• Skin lesions disappear within 3-12 weeks, and can scar, but may persist from months to years
• May be associated with other types of cutaneous lymphomas or Hodgkin’s disease

Histopathology
• A variable histopathologic picture depending on stage of lesions, with three subtypes: A, B, C
• Type A scattered, or small clusters of large, often multinucleated CD30+cells, intermingled with numerous inflammatory cells
• Type B Epidermotropic infiltrate of small atypical cells with cerebriform nuclei
• Type C Monotonous population or large clusters of large CD30+ T cells, few inflammatory cells

Immunophenotype
• Type A, Type CCDD4+, CD30+, (same as C-ALCL)
• Type BCD3+ CD4+, CD30-

Prognosis: 98% 5 year survival

SUBCUTANEOUS PANNICULITIS LIKE T cell LYMPHOMA

Clinical
• Solitary or multiple nodules/plaques involving the legs
• Fever, fatigue and weight loss may be present

Histopathology
• Subcutaneous infiltrate, simulating a panniculitis
• Pleomorphic T cells with hyperchromatic nuclei
• Overlying epidermis and dermis are rarely involved
Immunophenotype
- CD3+, CD4+
Prognosis: 80% 5 year survival

**EXTRANODAL NK/T cell LYMPHOMA, NASAL TYPE**

**Clinical**
- Multiple plaques or tumors usually on trunk and extremities
- Often with a midfacial destructive tumor, manifesting its clinically aggressive behavior
- Nearly always an Epstein Barr Virus related lymphoma, with a NK/T-cell phenotype

**Histopathology**
- Dense infiltrates involving the dermis and often the subcutis
- Prominent angiocentricity and angiodestruction with extensive necrosis

**Immunophenotype**
- CD2+, CD56+, CD3-

**PERIPHERAL T cell LYMPHOMA UNSPECIFIED**
Representative of a heterogeneous group, comprised of T cell neoplasms which do not fit into the other defined subtypes.

Two notable entities have been defined:
1. primary aggressive epidermotropic CD8+ cytotoxic T cell lymphoma
2. primary cutaneous CD4+ small/medium pleomorphic T cell lymphoma

**PRIMARY AGGRESSIVE EPIDERMOTROPIC CD8+ CYTOTOXIC T cell LYMPHOMA**

**Clinical**
- Localized or disseminated eruptive papules, nodules and tumors with central ulceration and necrosis
- May disseminate to other visceral sites, but generally spares the lymph nodes

**Histopathology**
- Often pronounced epidermotropism, ranging from a linear distribution to a pagetoid pattern
- Invasion and destruction of adnexal skin is commonly seen
- Necrotic keratinocytes, ulceration and variable spongiosis is common

**Immunophenotype**
- CD3+, CD8+, CD2-, CD4-, CD5-, CD7-

**Genetics**
- Positive clonality, useful to distinguish from pseudolymphomas

**Prognosis:** Median survival is 3 months

**FOLLICLE CENTER B cell LYMPHOMA**

**Clinical**
- Solitary or grouped plaques, preferentially located on the scalp, forehead or trunk, rarely on extremities
- Untreated lesions gradually increase over years, but rarely disseminate
- Usually occur in elderly patients

**Histopathology**
- Nodular to diffuse infiltrates sparing the epidermis
- Composed of small lymphocytes, marginal zone B cells, plasma cells and many reactive T cells
- Reactive germinal centers are often seen

**Immunophenotype**
- CD20+, CD79a+, bcl2+
- CD5-, CD10-, bcl6-

**Genetics**
- Alterations involving the t(14:18) and t(3:14) gene loci have been observed

**Prognosis:** 99% 5 year survival
• Few centroblasts and many reactive T cells
• If present, follicles are composed of follicular centers (bcl6+) with dendritic CD21+ follicular dendritic cells peripherally.
• Tumorous lesions show a progression of increasing size and number of monotonous large centrocytes
• Multilobulated B cells and decreased T cells; follicular lesions no longer become visible

Immunophenotype
• CD20+, CD79+, bcl6+, CD5-, CD10+/- (absent with a diffuse growth pattern) bcl2-

Genetics
• Does not show alterations in t(14:18), as found in nodal follicular lymphomas
• Demonstration of t(14:18) of bcl2+ should raise suspicion for nodal lymphoma involving the skin

Prognosis: >95% 5 year survival

**DIFFUSE LARGE cell LYMPHOMA, LEG TYPE**

Clinical
• Predominantly affects elderly patient
• Presents with a rapidly growing red/bluish tumor of the legs
• Extracutaneous dissemination is common
• Multiple ski lesions represent a poor prognostic factor

Histopathology
• Diffuse infiltrate of a monotonous population of centroblasts/immunoblasts often extending into the subcutis
• Mitotic figures are commonly observed
• Lacks small B cells and reactive T cells

Immunophenotype
• CD20+, CD79+, bcl2+, CD10-

Genetics
• Chromosome alterations have been localized to 18q, 7p

Prognosis: 22%-56% 3 year survival

**DIFFUSE LARGE cell LYMPHOMA, OTHER**

Clinical
• Refers to large B cell lymphomas arising in the skin
• Morphologically distinct from the afore mentioned subtypes.
• Usually represent a manifestation of systemic lymphoma
• Commonly present with skin lesions on the head, trunk or extremities

**INTRAVASCULAR LARGE B cell LYMPHOMA**

Clinical
• A well defined subtype of large B cell lymphoma
• Presents as violaceous patches and plaques or telangectatic skin lesions, primarily on the legs and trunk
• Patients often have widely disseminated disease, although skin disease alone has been observed

Histopathology
• Dilated blood vessels in the dermis and subcutis are filled with large neoplastic B cells

Prognosis: 22%-56% 3 year survival

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**Table 1**

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<th>CD1A</th>
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<td>CD3</td>
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<td>Assesses B cell infiltrate</td>
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<td>Reactivity indicates a likely follicular center lymphoma</td>
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<td>Bcl-2 inhibits apoptosis, is associated with a 14:18 chromosomal translocation</td>
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<td>Germinal centers</td>
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<tr>
<td></td>
<td>Kappa/Lambda</td>
</tr>
<tr>
<td></td>
<td>Assesses clonality of a B cell population</td>
</tr>
<tr>
<td></td>
<td>Mononoclonality is suggestive of lymphoma</td>
</tr>
<tr>
<td></td>
<td>Clonal</td>
</tr>
<tr>
<td></td>
<td>Rearrangement</td>
</tr>
<tr>
<td></td>
<td>Determines clonal proliferation</td>
</tr>
<tr>
<td></td>
<td>Usually performed by polymerase chain reaction</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>PSEUDOLYMPHOMA</th>
<th>B cell LYMPOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed cellular infiltrate</td>
<td>Lymphocytic infiltrate</td>
</tr>
<tr>
<td>Mixed lymphocytes</td>
<td>Uniform appearing lymphocytes</td>
</tr>
<tr>
<td>Germinal follicles</td>
<td>No germinal follicles</td>
</tr>
<tr>
<td>Mantle zone</td>
<td>No mantle zone</td>
</tr>
<tr>
<td>No destruction of appendages</td>
<td>Destruction of appendages</td>
</tr>
<tr>
<td>Patterned infiltrate</td>
<td>Diffuse infiltrate</td>
</tr>
<tr>
<td>T and B lymphocytes</td>
<td>Uniform B lymphocytes</td>
</tr>
<tr>
<td>Mixed CD4+ and CD8+ cells</td>
<td>Rare CD4+ or CD8+ cells</td>
</tr>
</tbody>
</table>

**Conclusion**

Dermatologists will continue to be at the forefront in the diagnosis of cutaneous lymphomas. Proper management requires a thorough understanding of clinical presentations, histopathology, and prognosis of the multiple outlined subtypes. This understanding will allow the dermatologist to orchestrate the multispeciality care which can be required for the benefit of our patients.

As clinical knowledge, histology and immunohistochemistry continue to advance, our understanding of cutaneous lymphomas will continue to improve. The presented information represents current classification of cutaneous T cell and B cell lymphoma.

**References:**

Your Choice is Clear™

For topical BPO/antibiotic acne therapy,

Impressive results. Proven tolerability.

Duac®

topical gel

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

Make the Clear Choice™

IMPORTANT SAFETY INFORMATION

Duac Topical Gel is indicated for the topical treatment of inflammatory acne. Duac Topical Gel is well tolerated. Side effects may include erythema, peeling, burning, and dryness. Duac Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops.

Please see accompanying Brief Summary of Prescribing Information.
Brief Summary

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

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

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

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

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

WARNINGS
ORALY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBiotic FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR CLOSTRIDIUM DIFFICILE AND TOXIN ASSAY FOR CLOSTRIDIUM DIFFICILE TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIREFLECTIVE AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY FROLGOL AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug to the mother.

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

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

Avoid contact with eyes and mucous membranes.

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

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

1. Duac® Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

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

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.

4. Patients should report any signs of local adverse reactions to their physician.

5. Duac Topical Gel may bleach hair or colored fabric.

6. Duac® Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.

7. Before applying Duac® Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.

8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

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

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

Genotoxicity studies were not conducted with Duac® Topical Gel. Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with Duac® Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Duac® Topical Gel, based on mg/m2) revealed no effects on fertility or mating ability.

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

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (190 and 90 times the amount of clindamycin in the highest recommended adult human dose based on mg/m2, respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether Duac® Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>28%</td>
<td>1%</td>
</tr>
<tr>
<td>Peeling</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

(Percentages derived by 4 subjects with symptom score # enrolled Duac subjects, n = 397).

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

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

Stiefel Laboratories, Inc.
Coral Gables, FL 33134
833185 Rev. 0504

REFERENCES:

Duac® is a registered trademark of Stiefel Laboratories, Inc. Your Choice is Clear and Make the Clear Choice are trademarks of Stiefel Laboratories, Inc.
Case Report:
A 46-year-old, Caucasian female presented with a pruritic rash located on her chest, upper back, and extremities. Her extensive past medical history included insulin-dependent diabetes mellitus; end-stage renal disease secondary to diabetic nephropathy; dilated cardiomyopathy with congestive heart failure; embolic stroke; COPD; and depression. The patient was on multiple medications including anti-hypertensives, Coumadin, insulin, and an antidepressant. She was also receiving hemodialysis. The eruption first presented as multiple excoriations, and the initial biopsy was inconclusive, suggesting a diagnosis of dermatitis artefacta as opposed to an early perforating disorder.

Five months later, the patient was hospitalized and presented with multiple keratotic plugs and crusts located on her trunk and extremities (Fig. 1, 2). A second biopsy revealed a hyperkeratotic and acanthotic epidermis along with a central keratotic plug within an epidermal invagination (Fig. 3). A granulomatous reaction was present at the base, and transepidermal elimination of vertically oriented collagen bundles was appreciated on high power (Fig. 4). The histologic changes were consistent with a diagnosis of reactive perforating collagogenosis.

The clinical diagnosis, on the other hand, was most consistent with acquired perforating dermatosis based on the presence of diabetes and end-stage renal disease. For systemic treatment, a trial of isotretinoin was discussed. The patient refused this therapy and was lost to follow-up.

Discussion:
Perforating disorders are a group of heterogeneous skin diseases characterized by hyperkeratotic plugs and crusts secondary to transepidermal elimination of dermal connective tissue. Classification of these disorders is controversial, with many physicians now recognizing three main perforating disorders: reactive perforating collagogenosis, elastosis perforans serpiginosa, and acquired perforating dermatosis. We report a 46-year-old female with diabetes and end-stage renal disease who initially presented with multiple excoriations. A clinical diagnosis of acquired perforating dermatosis was eventually made, although it was not apparent until several months had passed and a second biopsy was performed.

Acquired Perforating Dermatosis: A Case Report

*Second-year dermatology resident at Sun Coast Hospital, Largo, Florida
**New River Dermatology, Blacksburg, VA
***Program Director of Sun Coast Hospital Dermatology, Residency, NOVA Southeastern University, Largo, Florida

ABSTRACT
Perforating disorders are a group of heterogeneous skin diseases characterized by hyperkeratotic plugs and crusts secondary to transepidermal elimination of dermal connective tissue. Classification of these disorders is controversial, with many physicians now recognizing three main perforating disorders: reactive perforating collagogenosis, elastosis perforans serpiginosa, and acquired perforating dermatosis. We report a 46-year-old female with diabetes and end-stage renal disease who initially presented with multiple excoriations. A clinical diagnosis of acquired perforating dermatosis was eventually made, although it was not apparent until several months had passed and a second biopsy was performed.

As previously mentioned, features of all four traditionally recognized: reactive perforating collagogenosis, elastosis perforans serpiginosa, perforating folliculitis, and hyperkeratosis follicularis et parafollicularis in cutem penetrans (Kyrle’s disease).2 Perforating folliculitis and Kyrle’s disease, however, are questioned as distinct disease entities. Perforating folliculitis is present in several diseases classified as folliculitis regardless of the pathogenesis,1 while Kyrle’s disease is considered by some to be either a subtype of or synonymous with acquired perforating dermatosis.3, 4 In patients with diabetes mellitus and/or chronic renal failure, combinations of all four of the classic perforating disorders have been described.2, 5, 6 In addition, pathologic variation and overlap among the perforating diseases can occur in the same patient. To elucidate the issue, Rapini et al. coined the term “acquired perforating dermatosis,” which avoids description of the material being transepidermally eliminated.3, 5, 7

Acquired perforating dermatosis (APD) occurs in adulthood, primarily in association with diabetes mellitus, chronic renal failure, or both. Rarely, APD has also been reported in association with liver disease, internal malignancy and, most recently, atopic dermatitis.7 APD has been reported in approximately 10% of hemodialysis patients.2, 5, 6, 8 Hyperkeratotic papules and nodules most commonly occur on the legs but also can be generalized as in the case of our patient. Koebnerization of these papules and nodules can arise after scratching, rubbing, or other forms of minor trauma.3, 7

The precise pathogenesis of APD is unknown, but several proposed theories exist. One such theory states that intense pruritus with subsequent chronic scratching may be the initiating physical event for the histopathologic changes of APD.2 Microangiopathy linked to diabetes, acquired abnormalities of collagen or elastin and dysregulation of vitamin A or D metabolism are all additional possible etiologies.1 Fibronecin, an extracellular matrix glycoprotein, has also been suggested to play a role in the pathogenesis of APD. This protein has been found to accumulate in both the serum and the perforating lesions of APD. Fibronecin may stimulate epithelial migration, proliferation, and transepidermal elimination.3, 4, 7

The histology of APD can vary according to the evolution of the lesion. The perforating substance eliminated can range from necrotic material, which cannot be identified as collagen or elastin; collagen, which is histologically identical to that seen in reactive perforating collagogenosis; and rarely, elastin, as seen in elastosis perforans serpiginosa.3 As previously mentioned, features of all four
classic perforating diseases can occur in lesions of APD.

The differential diagnosis of APD includes both prurigo nodularis and folliculitis. Patients with APD can have either of these entities in conjunction with the perforating lesions. Thus, it may be necessary to perform more than one biopsy to make an accurate diagnosis. Arthropod bites, dermatofibromas, multiple keratoacanthomas, perforating exogenous substances (i.e. wood or silica), and perforating endogenous substances (i.e. perforating calcinosis or perforating pseudoxanthoma elasticum) are also included in the differential.3

Treatment of APD is difficult. Antihistamines are often ineffective in controlling the incessant pruritus. APD usually improves if the patient avoids scratching and the underlying disease is controlled. This fact further supports the notion that pruritus may play a pivotal role in the pathogenesis of APD. Phototherapy, including PUVA and UVB, have been successful in controlling the intense pruritus of end-stage renal disease, resulting in resolution of APD lesions.7 Ohe et al. described five patients with APD who were treated with narrowband-UVB two to three times weekly and who completely cleared after 10 to 15 treatments.21 Similar reports span the literature. Other treatment options include topical or oral retinoids, intralosomal corticosteroids, and topical keratolytics.3,4 Anecdotal benefit from changing the type of dialysis tubing has been described,3 and some patients have been cured after renal transplantation.3,5

APD is not uncommon in patients with both chronic renal failure and diabetes mellitus. Awareness of the clinical presentation and histopathology of this disease spectrum allows for the proper diagnosis and treatment of APD. We present this case for interest, as the diagnosis of APD was not apparent upon initial presentation. If a strong index of suspicion exists, dermatologists should consider regular follow-up examinations and should re-biopsy evolving lesions.

References:
Please visit www.BotoxCosmetic.com for more information.
Case Presentation

A 31-year-old male presented to the office with complaints of having a pruritic "rash" of the groin, buttocks, and dorsum of the hands of eight months duration. At the time of presentation, he related the following history: He had tried a topical, OTC antifungal cream when the rash first appeared. After no relief, one month later the patient sought medical attention for relief of the itching of what he thought was a rash with a "ringworm" appearance. He was given hydrocortisone 1% and samples of a triple antibiotic. This provided no relief. One week later, he was treated with a "strong steroid cream" and used two tubes, which provided no relief.

One month later, the patient was given a "stronger" steroid and a course of cephalosporin antibiotics, which "knocked the fire out of it." The patient used at least three tubes of this steroid over the course of two months, with continued relief of the itch. Once these medications were used, he was then given another refill of the steroid cream and some unknown pills (possibly to reduce pruritis), which provided continued relief. Exacerbation of the skin condition and pruritis was described as occurring with hot water showers, during the night, and with the discontinuance of the medications prescribed. The patient described experiencing increased frequency of bowel movements while taking the steroid medications; he otherwise described no other associated manifestations.

The patient's past medical history was positive for the chicken pox as a child and multiple hospitalizations for asthma exacerbations. The patient was involved in a recent motor vehicle accident and sustained a minor, left shoulder, soft tissue injury. MRIs and radiographs were negative. The patient's family history was positive for Alzheimer's disease. The patient's current medications consisted of cortisone cream and the unknown pills for his rash, albuterol inhaler as needed, and a daily multivitamin. The patient had no known food or drug allergies. He was physically active, enjoyed playing basketball and worked as a cook. He reported drinking socially on weekends and smoking one pack of cigarettes per day for 13 years. He expressed a strong desire to quit his smoking habit and said that he had tried quitting in the past but had relapsed due to daily life stressors. Review of systems was unremarkable.

Physical examination of the intertriginous areas of the groin revealed bilateral, linear skin atrophy and striae. The striae exhibited a hyperpigmentation and a decrease in thickness of the epidermis. These findings were consistent with steroid-induced atrophy of the skin. Close examination of the buttocks revealed inflammatory papules surrounding the hair follicles consistent with folliculitis, although it may also have reflected a steroid-induced acne. The dorsum of the hands and lateral aspects of the fingers showed several 1-mm, clear, deep-seated vesicles without erythema, consistent with dyshidrotic eczema. Other physical exam findings were within normal limits.

Biopsies of the groin and buttocks confirmed the diagnoses of steroid atrophy and folliculitis, probably due to the chronic usage of topical steroids over an eight-month period. The patient was told to immediately discontinue the topical application of the steroid cream. He was treated with Elidel, Sarna, and Atarax for his skin condition and was given a prescription for Chantix (varenicline). In addition, he was given Naftin cream for the residual tinea infection, which we believe was the original rash, and an information packet for smoking cessation.

On two-week follow-up, he noted less pruritus and resolution of any tinea infection.

Discussion

Steroid-induced atrophy of the skin is a potential effect that may occur with the use of topical steroids. Class I and II topical corticosteroids may cause telangiectasia, striae, and atrophy within two to three weeks of daily application, especially if the area has been occluded.1 The face, groin, and axilla are common areas for steroid atrophy to occur because the dermis in these areas is particularly thin. Hallmarks of the disease include thinning and telangiectasias of facial skin and striae of the groin and axilla.

Children and the elderly are most susceptible to steroid-induced atrophy. The application of topical glucocorticoids has been associated with a decreased collagen synthesis in the connective tissue. Since collagen is the most abundant protein within connective tissue, its absence results in clinically apparent epidermal atrophy.2 One study investigated the atrophogenicity of steroids utilizing the topical application of clobetasol propionate cream to the volar forearms twice daily for three to four weeks. Histological examination techniques confirmed epidermal thinning, with decreased microvasculature and decreased size of keratinocytes. Transdermal water loss occurred, and there was a reduction in ceramides, free fatty acids, and cholesterol.3

References:


Treatment includes immediate cessation of steroid use and protection of damaged skin by eliminating irritating stimuli like harsh skin products, razors, and hot water. Steroid atrophy and striae may be permanent, although the skin condition may improve over time with the discontinuance of the steroid therapy.4

Studies in mice suggest that administration of topical tretinoin with a topical corticosteroid diminishes skin atrophy while preserving the steroid's anti-inflammatory effects. One study, utilizing betamethasone dipropionate and tretinoin 0.1%, determined that epidermal thickness was reduced by 19% in plaques treated with steroid alone and was unchanged in plaques treated with steroid plus tretinoin.5 However, the study does not address the more serious atrophy that can occur with a more potent steroid used for a prolonged period. This study is not the first to show the potential protective effect of retinoids. Hopefully, with the development of the optimal retinoid, patients who need potent steroids will be able to get the benefits of those steroids without the risks.6
Paederus Dermatitis: An Outbreak on a Medical Mission Boat in the Amazon


ABSTRACT

Paederus dermatitis is a peculiar, irritant contact dermatitis characterized by a sudden onset of erythematous-bullous lesions on exposed areas of the body. The disease is provoked by an insect belonging to the genus Paederus. This beetle does not bite or sting, but accidental brushing against or crushing the beetle over the skin provokes the release of its coelomic fluid, which contains paederin, a potent vesicant agent. This paper describes this dermatitis, which occurred in three healthcare personal aboard a medical mission boat on the Amazon River. The epidemiology and pathogenesis of paederus dermatitis is reviewed, as well its treatment and prevention.

Introduction

Paederus dermatitis is a peculiar, irritant contact dermatitis caused by a beetle belonging to the genus Paederus. This insect does not bite or sting, but releases a fluid containing paederin, a potent vesicant agent. If not immediately washed off, the chemical leads to a linear dermatitis composed of erythematous-bullous lesions.

In August 2006, the author joined 10 other medical personal on a medical mission trip to Brazil. They traveled for two weeks on a medical boat on the Amazon River, operated by the Central Brazil Mission, stopping at various villages along the river. One expects to encounter unusual tropical diseases when participating in a medical trip in an underdeveloped region. However, it is unexpected to see these diseases on oneself. The following case reports describe paederus dermatitis occurring in three of the healthcare workers.

Case Reports

Case 1: A 49-year-old male, dermatologist (and author of this article), first noticed an eruption on his left elbow on day three of the trip. Aside from minor stinging, the area was fairly asymptomatic. Initially, the area appeared as a 6-cm, linear, erythematous patch. He could not recall coming in contact with anything unusual that would cause this rash. However, he did sleep on the top deck of the boat, which was open to air. The following day, vesicles and a bulla appeared in the erythema, lasting for five days before starting to dry up and fade (Figure 1). Four months later, there still remains a linear macular area of hypopigmentation.

Case 2: A 43-year-old female, registered nurse, started having an eruption on her left thigh on the sixth day of the trip. Her history and exam was similar; however, the erythema and blistering was more extensive, in a stellate configuration, measuring 10 cm in the longest dimension (Figure 2). After four months, there is still significant hyperpigmentation in the area.

Case 3: A 37-year-old male, physician assistant, noticed his lesions on his right lower leg eight days into the trip. His history was also similar; however, he had two lesions, both on his right lower leg, measuring 2 cm to 3 cm. These were erythematous, linear patches with central vesicles (Figure 3). At four months, there remains some hyperpigmentation at the sites. His lesions, as well as the other two cases, were shown to the crew, who agreed they were caused by an insect locally called the ‘poto’ bug.

Discussion

Paederus insects belong to the insect order Coleoptera (beetles) and the family Staphylinidae (rove beetles). The genus Paederus is quite large, with more than 600 species and a distribution in all continents except Antarctica. Various outbreaks of dermatitis attributed to the Paederus beetle have been reported in southern Turkey, central Africa, and Okinawa.

Adult Paederus beetles are usually 7 mm to 10 mm long and 0.5 mm to 1 mm wide. They have a black head, lower abdomen and elytra (structure covering the wings) and a red thorax and upper abdomen (Figure 4). The beetles live in moist habitats and are often beneficial to agriculture because they will eat crop pests. Adults are attracted to incandescent and fluorescent lights, and as a result, inadvertently come into contact with humans. They can be especially troublesome if windows or doors are left wide open. This beetle does not bite or sting, but accidental brushing against it or crushing it over the skin provokes the release of its coelomic fluid, which contains paederin, a strong blistering chemical.

It is important to note that Paederus beetles are not “blister beetles,” which are of the family Meloidae. Blisters beetles, which also are widely distributed, do release a defensive compound when threatened. The chemical released, cantharidin, a bicyclic terpenoid, is quite different from paederin, an amide.

The manufacture of paederin is largely confined to the female. Recently, it has been demonstrated that the production of paederin relies on the activities of an endosymbiont (Pseudomonas species) within the beetle. Paederin is a potent vesicant, causing a reaction on the skin about 24 hours after contact. Different responses are seen in the skin depending upon its concentration, duration of exposure, and individual characteristics. In mild cases, there is a slight erythema lasting for a couple days. With moderate cases, the erythema evolves into vesicles and bullae over a few days, followed by a squamous stage when the blisters dry out over a week, and then a stage when they desquamate, leaving hyper or hypopigmented patches. Scarring usually does not occur. The lesions are characteristically linear due to smearing the crushed insect across the skin. Severe cases, in addition to showing more extensive
blistering, may have additional symptoms such as fever, neuralgia, arthralgia, and vomiting.6,7

Usually, there is little discomfort from this dermatitis in mild to moderate exposure, unless the area becomes secondarily infected. Affected individuals may inadvertently transfer paederin to other areas of the body, such as the genitals or the face. If the periorbital area is affected, a conjunctivitis may develop (referred to ‘Nairobi eye’ in eastern Africa).7

Treatment initially involves removal of the irritant by washing the area with soap and water. The blistered site should be treated with cool wet soaks, followed by a strong topical steroid. An interesting study was performed in Sierra Leone with 36 patients. Half of the patients were given oral ciprofloxacin in addition to the topical steroid. Healing time was statistically faster in these patients, which suggests a concurrent bacterial infection was present, most likely from the Pseudomonas the Paederus beetle harbors.7

Preventing human/beetle contact is the primary method of avoiding Paederus dermatitis. Learning to recognize Paederus beetles and avoiding handling or crushing these insects will help decrease these eruptions. If a beetle lands on the skin, it should be blown off or encouraged to walk onto a piece of paper and then removed. The area in contact should be immediately washed with soap and water, and any clothes in contact with the beetle should be washed as well. Doors should be kept closed and window screening should be kept in good repair to help reduce entry of these insects into buildings. Since beetles are attracted to light, these should be switched off near areas where people sleep.5

Conclusion

Participating in an overseas medical mission trip has numerous benefits to both the people treated and to the members. Although healthcare personnel are often focused on the diseases of their patients, they need to be aware of their surrounding environment, which can impact their own wellbeing. Paederus beetles are a common insect in undeveloped areas. Being aware of this beetle and the signs and treatment of its dermatitis can greatly aid a healthcare professional.

References:

Figure 3
Case 3, two small patches of erythema with erosions

Figure 4: Paederus beetle
SOLODYN® delivers extended release minocycline.

Ask your Medicis representative for details or visit www.Solody.com

See Brief Summary of the Prescribing Information on the following page.
SOLODYN™ should not be used during pregnancy nor by individuals who may become pregnant. If any antibiotics, can cause fetal harm when administered to a pregnant woman. If any antibiotic is used during pregnancy, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

Patient should be apprised of the potential hazard to the fetus and stop treatment immediately. 3. Pseudotumor cerebri (benign intracranial hypertension) in athletes has been reported rarely with minocycline. Of the 300 mg/day (which resulted in an approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN™). However, oral administration of 100 mg or 300 mg of minocycline to patients with liver disease can result in increased plasma levels, of breakthrough bleeding, or of contraceptive failure. In general, dose selection for an elderly patient should be made with consideration of the pharmacokinetics of the drug and the general status of the patient. SOLODYN™ (MINOCYCLINE HCl, USP) Extended Release Tablets

In this study, the safety and tolerance of minocycline use in acne was not associated with any of the following:

- New onset symptoms of pseudotumor cerebri, bulging eyes, papilledema, or visual disturbance.
- New onset symptoms of retinal and choroidal detachment in patients treated with minocycline for acne.
- New onset symptoms of severe intraocular pressure, glaucoma, or optic nerve damage in patients treated with minocycline for acne.

- New onset symptoms of liver disease, including jaundice, hepatic dysfunction, hepatic failure, or eosinophilic hepatitis in patients treated with minocycline for acne.
- New onset symptoms of myocarditis, pericarditis, or myocardial infarction in patients treated with minocycline for acne.
- New onset symptoms of peripheral artery disease, including intermittent claudication, in patients treated with minocycline for acne.
- New onset symptoms of erythrocytosis or polycythemia in patients treated with minocycline for acne.

- New onset symptoms of Raynaud’s phenomenon, telangiectasia, or digital ulcers in patients treated with minocycline for acne.
- New onset symptoms of skin discoloration or hyperpigmentation in patients treated with minocycline for acne.

- New onset symptoms of photosensitivity in patients treated with minocycline for acne.
- New onset symptoms of decreased fertility or impaired male or female fertility in patients treated with minocycline for acne.

- New onset symptoms of dermatitis herpetiformis in patients treated with minocycline for acne.

- New onset symptoms of allergic reactions, including anaphylaxis, in patients treated with minocycline for acne.

- New onset symptoms of autoimmune diseases, including systemic lupus erythematosus, in patients treated with minocycline for acne.

- New onset symptoms of immunodeficiency, including opportunistic infections or malignancies, in patients treated with minocycline for acne.

- New onset symptoms of central nervous system disorders, including seizures or psychiatric disturbances, in patients treated with minocycline for acne.

- New onset symptoms of peripheral neuropathy or myopathy in patients treated with minocycline for acne.

- New onset symptoms of metabolic disorders, including hyperglycemia or hyperlipidemia, in patients treated with minocycline for acne.

- New onset symptoms of respiratory disorders, including pneumonitis or respiratory failure, in patients treated with minocycline for acne.

- New onset symptoms of gastrointestinal disorders, including enterocolitis or pancreatitis, in patients treated with minocycline for acne.

- New onset symptoms of hematologic disorders, including hemolytic anemia, thrombocytopenia, or neutropenia, in patients treated with minocycline for acne.

- New onset symptoms of endocrine disorders, including diabetes mellitus, in patients treated with minocycline for acne.

- New onset symptoms of musculoskeletal disorders, including myalgia or arthralgia, in patients treated with minocycline for acne.

- New onset symptoms of cardiac disorders, including pericarditis or myocarditis, in patients treated with minocycline for acne.

- New onset symptoms of renal disorders, including nephrotic syndrome or acute renal failure, in patients treated with minocycline for acne.

- New onset symptoms of hepatic disorders, including hepatitis or liver failure, in patients treated with minocycline for acne.

- New onset symptoms of dermatologic disorders, including dermatitis herpetiformis or dermatitis papulosa nigra, in patients treated with minocycline for acne.

- New onset symptoms of cutaneous malignancies, including squamous cell carcinoma or basal cell carcinoma, in patients treated with minocycline for acne.

- New onset symptoms of musculoskeletal tumors, including bone sarcoma or osteosarcoma, in patients treated with minocycline for acne.

- New onset symptoms of hematopoietic tumors, including leukemia or lymphoma, in patients treated with minocycline for acne.

- New onset symptoms of central nervous system tumors, including glioblastoma or meningioma, in patients treated with minocycline for acne.

- New onset symptoms of cardiovascular tumors, including cardiac myxoma or rhabdomyoma, in patients treated with minocycline for acne.

- New onset symptoms of pulmonary tumors, including bronchogenic carcinoma or endothelial sarcoma, in patients treated with minocycline for acne.

- New onset symptoms of gastrointestinal tumors, including gastric carcinoid or pancreatic adenocarcinoma, in patients treated with minocycline for acne.

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- New onset symptoms of hematopoietic tumors, including leukemia or lymphoma, in patients treated with minocycline for acne.
**Cutaneous Lymphoma as presenting sign of Richter’s syndrome**

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**ABSTRACT**

Richter’s syndrome is a rare disease in which patients with chronic lymphocytic leukemia (CLL) develop a highly aggressive large B-cell lymphoma. The large B-cell lymphoma may be from a transformation of the CLL and represent a bona fide Richter’s transformation. There are also patients in whom the high grade B-cell lymphoma arises independent of the indolent CLL and may be due to Epstein Barr virus infection or a mutation in a tumor suppressor gene. Patients are generally immunocompromised from their disease or the treatment of the disease, and present with fever, night sweats, abdominal pain, weight loss, and a rapidly enlarging lymphoid mass. Multi-agent chemotherapy such as CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) and bone marrow transplantation has been attempted, but are generally futile, as the median survival rate of this disease is less than 2 years. We present a case of Richter’s syndrome in which the patient presented to our clinic with a 2 month history of a rapidly enlarging mass in her left parotid region, a one year history of red nodules suggestive of a cutaneous lymphoma, and a 15 year history of chronic lymphocytic leukemia. A skin biopsy was performed and revealed cutaneous B-cell lymphoma. Parotid biopsy was consistent with diffuse large B-cell lymphoma. Since the patient had a long history of an indolent hematologic malignancy and a new diagnosis of a highly aggressive large B-cell lymphoma without features of Hodgkin’s disease, it was felt this probably represented a true Richter’s transformation. The patient underwent 6 courses of multi-agent chemotherapy and remains in remission approximately 6 months after diagnosis. Along with the case report and discussion of Richter’s syndrome, we briefly discuss cutaneous metastases, chronic lymphocytic leukemia, and primary and secondary cutaneous lymphomas.

**Case report:**

We report a case of an 86-year-old female who presented with a one-year history of “bumps” on her arms and back previously diagnosed as shingles by another physician one year ago. The lesions were increasing in size, becoming pruritic and eventually painful, bringing her in for a second opinion. She denied constitutional symptoms except for 5 pounds of weight loss. Physical exam revealed numerous 4-10 mm violaceous nodules on bilateral shoulders and upper back (Figure 1). She had approximately 40 nodules total. In addition, she had a rapidly enlarging mass in the left parotid region measured 6 by 10 cm in size over a 2 month period (Figure 2). The patient’s medical history included hypertension, non-insulin dependent diabetes mellitus, and chronic lymphocytic leukemia (CLL) diagnosed 15 years ago. Medications include Tenormin and Pioglitazone. Family and social history were non-contributory. A 4-mm punch biopsy was performed of a large nodule on the patient’s shoulder and she was referred to ENT for biopsy of her parotid mass. The skin biopsy was reported as an atypical lymphoid infiltrate suggestive of B-cell lymphoma, and the parotid biopsy was consistent with a diffuse large B-cell lymphoma. Due to the skin involvement, the patient was diagnosed with stage IV large B-cell lymphoma. Since the patient had the prior, indolent hematologic malignancy of CLL, and now presented with a highly aggressive hematologic malignancy, she was diagnosed with Richter’s syndrome. This phenomenon can be designated as a Richter’s transformation if it is felt that the high grade B-cell lymphoma shares a common origin with the prior indolent CLL. The primary care of the patient was then transferred to Hematology/Oncology. She was given the options of aggressive treatment with the highly toxic Adriamycin, moderate, less-toxic treatment with a combination of Cytoxan, Oncovin, Prednisone, and Rituxan in hopes of gaining control of the disease, or palliative care only. The patient initially chose palliative care, then changed her mind at the urging of her friends, and underwent 6 courses of chemotherapy with Cytoxan, Oncovin, Prednisone, and Rituxan. She had excellent initial response and remains in clinical remission at 6 months.

**Biopsy results:**

Routine H & E: Superficial and deep perivascular and interstitial lymphoid cell infiltrate. The infiltrate is composed of small and medium sized lymphocytes and histiocytes. There are scattered large and hyperchromatic cells. There is dermal edema and a slight increase in dermal mucin deposition.

**Immunohistochemistry:** The dermal lymphoid infiltrate shows a mixed population of T and B-lymphocytes. Most of the T-lymphocytes are positive for CD4 and smaller populations are positive for CD3. The larger B-lymphocytes are positive for CD20. There is a large population of CD10 positive lymphocytes. There are areas of cells positive for bcl-2. Immunostains for CD30 are negative.

**Discussion:**

**Richter’s Syndrome**

In 1928, Maurice N. Richter described a transformation from CLL to a large B-cell lymphoma. He initially named it reticular cell sarcoma. In reverence to Dr Richter, patients with an indolent chronic lymphocytic leukemia and development of a high-grade B-cell lymphoma are diagnosed with Richter’s syndrome. If the two malignancies are felt to be of the same origin, the term Richter’s transformation is used. Transformation of CLL to diffuse large B-cell lymphoma is a rare, very aggressive cancer. This transformation occurs anywhere from 0.06% to 10% of patients with CLL. The largest retrospective study to date (population of 1374 patients with CLL) recorded an incidence of 2.8%. Patients generally become symptomatic with fever, night sweats, abdominal pain, and weight loss. They usually also experience rapid growth of a lymphoid mass at one site, and have a general deterioration of health. Less frequently, patients may have lytic bone lesions or a monoclonal gammopathy. The most common laboratory abnormalities are elevation of serum lactate dehydrogenase (82%), rapid lymph node enlargement (64%), systemic symptoms of fever and/or weight loss (59%), monoclonal gammopathy on serum protein electrophoresis (44%), and extranodal disease (41%). They may also have massive splenomegaly and bulky retroperitoneal adenopathy. Not all patients with CLL and a rapidly enlarging lymph node have Richter’s syndrome, however. Infection with herpes simplex virus can cause acute...
lymphadenitis, therefore, a lymph node biopsy is generally required to make the diagnosis. The findings on lymph node biopsy tend to have a typical morphology similar to that of diffuse large B-cell lymphoma, immunoblastic variant. Gene rearrangement studies have been done to prove a common origin of high-grade lymphomas with the cells of CLL; however, this is not necessary to make the diagnosis of Richter’s syndrome. In fact, up to one-fourth of apparent Richter’s transformations, the lymphoma cells use Ig genes that are distinctive from those of original CLL clones, suggesting that the occurrence of the high grade lymphoma in some of these patients may be independent and coincidental with the chronic lymphocytic leukemia. It is appropriate to make the diagnosis of Richter’s syndrome without expensive gene studies proving the commonality of tumor origin, and it does not change the clinical course or treatment strategy. The chromosomal abnormalities of the lymphoma cells in patients with Richter’s syndrome are complex, but generally include deletions of 8p, 9p, 11q, 12q, 13q, 14q, 17p and/or translocations of chromosomes 12. Trisomy 12 is more common in patients with Richter’s syndrome than the general population. There have been reports of mutations or deletions in the p53 tumor suppressor gene, the ATM gene, and increased copies of c-myc. There are reported cases of Richter’s syndrome with Hodgkin disease features. It is thought these cases may be a consequence of an infection with EBV, and may account for some of the cases in which the high-grade lymphoma cells are not clones of the indolent CLL. There are no proven environmental associations, genetic links or risk factors to predict which CLL patients will progress to Richter’s syndrome. There is no staging system for Richter’s syndrome. CHOP chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) and bone marrow transplantation has been attempted, but are generally futile. Most current regimens include Rituximab which is a unique therapy that works by selectively depleting CD20+ B-cells. Patients who do respond to therapy tend to have prolonged survival, however the average life span of those diagnosed with Richter’s syndrome is between 6 months and 2 years.

**Cutaneous Metastases**

The overall incidence of cutaneous metastases from internal malignancies as studied post mortem, have shown to be 0.7% to 10% of patients with internal cancer. A recent meta-analysis estimates the rate to be 5.3%. Cutaneous metastases are most common after age 40 but they can occur at any age. Clinically, they may manifest as subcutaneous or intradermal nodules that are flesh-colored, red, or blue. They are generally round to oval, painless, rubbery, and freely moveable. Although the anterior trunk is a common site of such tumors, other areas often are involved and are usually in the general region of the primary tumor. When metastases to the skin is the first sign of malignancy it is termed precocious metastases, and has been reported in the range of 0.6%-7.6% of patients. Metachronous metastases defines tumors that have been diagnosed prior to cutaneous metastases, and synchronous metastases when the primary tumor and cutaneous metastases are diagnosed at the same time. The most common underlying primary malignancies that metastasize to the skin in men are melanoma (32.3%), lung (11.8%), and colon/rectum (11%). Breast (70.7%), melanoma (12%), and ovarian cancer (3.3%) are the most common primary sites for women. The skin is involved in 20% of patients with malignant B-cell lymphoma.

**Chronic Lymphocytic Leukemia**

Chronic Lymphocytic Leukemia (CLL) is a type of non-Hodgkin’s lymphoma, and is the most common leukemia diagnosed in adults. It is generally diagnosed later in life with an average age of 70 years. CLL is a cancer in which too many white blood cells are produced, and is many times diagnosed incidentally with a CBC on routine labs. Confirmatory tests include differential white blood cell count with high lymphocyte count and peripheral smear showing “smudge cells” due to fragility of the white blood cells. Newly diagnosed patients generally have no symptoms, and may be symptom free for years or decades as the disease progression is generally very slow. Transformations of CLL into an acute blastidic phase are exceedingly rare. More common is a transformation into a large cell lymphoma (LCL). CLL is incurable at this time, and treatment is often not initiated until clinical symptoms appear, or until white blood cell counts reach a level that may cause morbidity. Treatments available include chemotherapy, radiation, biological therapy, bone marrow transplantation and splenectomy to “debulk” the tumor load. Some patients take no treatment, have no morbidity associated with the disease, and eventually die of unrelated events.

**Primary and Secondary Cutaneous Lymphomas**

A complete discussion of cutaneous lymphoma is beyond the scope of this publication, however we will briefly review. Cutaneous lymphoma is categorized as primary cutaneous T-cell lymphoma (PCTCL), primary cutaneous B-cell lymphoma (PCBCL) and secondary cutaneous lymphoma (SCL). Secondary cutaneous lymphomas include B-cell and T-cell origin. PCTCL’s have a wide range of clinical features and prognoses. PCTCL comprises 75% of all cutaneous lymphomas, PCBCL comprises 23%, and 2% being from a new category termed precursor hematologic neoplasm (Table 1). The most common PCTCL is mycosis fungoides, followed by lymphomatoid papulosis, and primary cutaneous anaplastic large cell lymphoma. Most primary cutaneous T-Cell lymphomas follow a slow, indolent course, and treatments are non-aggressive.

The clinical pattern for primary cutaneous B-cell lymphomas are violaceous to red papules, nodules or plaques, except for the Intravascular large B-cell lymphoma which may present with variable nonspecific morphologies or with lesions similar to intravascular thrombotic disorders such as livedo reticularis. There are generally no constitutional symptoms, but patients may have nonspecific complaints of fatigue, malaise, or weight loss, which are more common if there is a large tumor burden, intercurrent infection, or transformation histologically to a more aggressive form. Large B-Cell lymphoma with origin of the leg, and Intravascular Large B-Cell Lymphoma have extremely poor prognoses. Large B-cell lymphoma with origin of the head and neck, Follicular Center Lymphoma, and Marginal Zone B-Cell Lymphoma all have excellent prognoses approaching 100% five year survival. Fortunately, the follicle center and marginal zone lymphomas are the most common of the primary B-cell tumors. Mutation at different points in B-cell development leads to differing forms of lymphoma. There is some association in the literature of primary cutaneous B-cell lymphoma and Borrelia burgdorferi, but no association has been made in regards to secondary cutaneous lymphoma.

Secondary cutaneous lymphomas as a general rule have a very poor prognosis. Cutaneous metastasis can occur with all forms of lymphoma and characteristically present as violaceous papules or nodules.

Non-Hodgkin’s lymphoma is much less predictable and has a far greater predilection to disseminate to extranodal sites than Hodgkin type B-cell lymphoma. Secondary cutaneous lymphoma may have an origin from any part of the lymph node, or may be extra-nodal. Studies have shown that southern blot analysis of peripheral blood may be useful in differential diagnosis of primary cutaneous B-cell lymphomas and secondary cutaneous B-cell lymphomas as well as a prognostic marker. The treatment of choice for SCBCL is to find the primary malignancy and treat it appropriately.
Interpretation of Tumor Cell Markers:

| CD3 | Pan T Lymphocyte marker |
| CD4 | Helper T lymphocyte marker |
| CD10 | Common acute lymphoblastic leukemia antigen (CALLA). Marker for non B-cell, non T-cell acute lymphoblastic leukemia. |
| CD20 | Pan B-cell marker |
| CD30 | Activated Lymphocytes. Reed-Sternberg cells (Hodgkin’s), Lymphomatoid Papulosis. |

Bel-2: B-Cell Lymphoma protein. A gene that encodes an integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells such as lymphocytes among many others. Primary cutaneous B-cell lymphomas usually do not express Bel-2.

Histopathology:

Classification schemes of lymph node based malignancies use differing histomorphology related to the area of the lymph node of the tumors origin. Primary cutaneous lymphomas share these differing morphologies, however, have different clinical behavior and immunophenotypic profile, making use of these classification schemes of little value. Secondary cutaneous lymphoma may have an origin from any part of the lymph node, or may be extra-nodal. The morphology typically resembles that of the origin of the tumor, however are generally not specific enough to make the diagnosis without lymph node biopsy. Cutaneous metastases are generally dermal with normal overlying epithelium. A narrow zone of compressed collagen may separate the tumor form the epidermis, and is referred to as the Grenz zone. Cutaneous metastases regardless of type tend to resemble the primary tumor. Diffuse large B-cell lymphomas are composed of large cells with nuclei at least twice the size of a small lymphocyte and usually larger than a tissue macrophage nucleus.

Conclusion:

We present a case of cutaneous metastases as the presenting sign of a patient with a 15-year history of chronic lymphocytic leukemia who developed an aggressive, diffuse B-cell lymphoma. This clinical scenario is referred to as Richter’s syndrome. Richter’s syndrome is a very aggressive hematologic cancer with a median survival of less than two years regardless of treatment. Along with the case report and discussion of Richter’s syndrome, we briefly discuss cutaneous metastases, chronic lymphocytic leukemia, as well as primary and secondary cutaneous lymphomas.

### TABLE I: WHO-EORTC classification of primary cutaneous lymphomas.

| CD4+/CD56+ hematodermic neoplasm |
| Precursor hematologic neoplasm |
| Bcl-2: |
| CD10: |
| CD20: |
| CD3: |

References:

Vitiligo is a relatively common disorder of pigmentation. Approximately 1 percent of the world population is affected. The word "vitiligo" is believed to be derived from the Greek word vitellus, meaning "calf," as calves often have white patches. Vitiligo is characterized by the development of depigmented macules and patches that correspond histologically to a decrease in or absence of epidermal melanocytes. There is a positive family history in at least 30 percent of cases, and males and females are affected equally.

Many patients with vitiligo may feel embarrassed and disfigured. The disease can have serious social stigmata in some cultures. Since the onset of the disease occurs before the age of 20 in 50 percent of patients, safe and effective therapeutic treatment options are important to avoid loss of self esteem, interference of social relationships and depression. The disease is most devastating and disfiguring to darker racial and ethnic groups. Prior to the advent of topical immunomodulators, traditional therapy of corticosteroids and/or ultraviolet light was often not effective, and its use on the face led to complications such as cutaneous atrophy, telangiectasia, and ocular disease.

Pathophysiology:

Genetic studies support a non-mendelian inheritance pattern for vitiligo and suggest that vitiligo is a multifactorial, polygenetic disorder. The disease has been associated with specific HLA haplotypes including HLA-DR4, Dw7, DR7, DR1, B13, DR53, and A19. Recently, a genome-wide linkage scan was performed in 71 Caucasian families with vitiligo. AIS1 located at 1p31 revealed highly significant linkage, suggesting a major susceptibility in Caucasians. Additional linkage signals were found on chromosomes 1, 7, 8, 11, 19, and 22.

Histologically, the epidermis is void of melanocytes in the depigmented area. The exact cause is unknown. Microscopic examination reveals vacuolar degeneration of basal keratinocytes and dermal lymphohistiocytic infiltrates. Autoimmune, neural, biochemical, oxidative stress, viral, and melanocyte detachment mechanisms have been proposed explanations of vitiligo.

Recent data has further implicated immune mechanisms in the pathogenesis of vitiligo and indicate that vitiligo may be related to other autoimmune diseases. Many diseases with an autoimmune linkage occur more commonly in patients with vitiligo. These associated disorders include autoimmune thyroid disease, particularly Hashimoto’s thyroiditis and Graves’ disease, along with diabetes mellitus, uveitis, alopecia areata, pernicious anemia, rheumatoid arthritis, polyglandular autoimmune syndromes, psoriasis and melanoma. Circulating autoantibodies, such as antithyroglobulin, antimicrosomal, and antiparietal cell antibodies, have been found in more than 50 percent of patients with vitiligo.

Mechanism of repigmentation:

The goal of treatment is to restore melanocytes to the skin. In hypopigmented, vitiliginous areas, the bulb and infundibulum of the hair follicle are missing melanocytes. But follicular, inactive, amelanotic melanocytes are still located in the middle and lower parts of the follicle and outer root sheath, in melanocytic reservoirs. They typically migrate up the hair follicle into the epidermis as they mature. Therapies for vitiligo involve stimulating these reserve melanocytes to proliferate and migrate into depigmented skin. A vitiligious spot repigments from the follicle and spreads outward. The face, arms, trunk and legs respond best to treatments. Skin with little or no hair, such as palms and soles, respond poorly to treatment.

Psoralens and ultraviolet light:

Melanocytes undergo reactive hyperplasia when exposed to ultraviolet radiation. This explains the treatment response when undergoing ultraviolet-A and narrow-band ultraviolet-B radiation. Some patients are slow to respond, and a minimum treatment duration of six months is recommended. Responsive patients can be given as long as 24 months before reaching maximum benefit. After the first course of therapy, a resting period of three months is recommended to minimize the annual cumulative dose of ultraviolet-B radiation. Patients who respond to this therapy usually keep their pigment. Those who have actively spreading vitiligo should not be treated. Treatment does not stop the spread of depigmentation.

Systemic steroids:

Systemic corticosteroids can stop the progression of vitiligo and lead to repigmentation, but they may also produce intolerable side effects. Betamethasone/dexamethasone 5mg taken twice weekly for two to four months was reported to arrest progression and induce repigmentation. However, safety and efficacy in children has not yet been determined. Treatment is also limited to those able to tolerate systemic steroids.

Grafting and transplantation:

Several surgical procedures have been developed for treating patients with vitiligo who fail to respond to medical therapies. These include grafting suction-blistered epidermis, minigrafts, and transplantation of in-vitro-cultured, epidermis-bearing melanocytes. These techniques are good options for patients with stable localized disease, but they are limited to those medical centers equipped with carbon-dioxide lasers and other necessary equipment. Sur-
Topical immunomodulators:

Topical immunomodulators offer several advantages in the treatment of vitiligo. First, they are very well tolerated in children and adults. Second, they can be used for extended periods of time without the risk of atrophy or complications commonly associated with long-term steroid use. However, vitiligo is a chronic disease and usually requires long-term treatment, and long-term safety and efficacy data on the use of these medications are not yet available.

Examples of topical immunomodulators are tacrolimus and pimecrolimus. Tacrolimus is a topical immunomodulatory agent that affects T-cell and mast-cell functions by binding to cytoplasmic immunophilins and by inactivating calcineurin. Tacrolimus inhibits the production and release of proinflammatory cytokines and vasoactive mediators from basophils and mast cells. The efficacy of tacrolimus has been verified through double-blind randomized trials comparing tacrolimus to placebo and tacrolimus to clobetasol. Maximum repigmentation was observed on the face and neck areas after 24 weeks of continued therapy. Statistically significant decreases in overall disease-severity scores and minimal adverse events have made tacrolimus a popular treatment option for childhood vitiligo.

In 2005, the U.S. Food and Drug Administration (FDA) issued an alert about a possible link between topical tacrolimus and pimecrolimus and cases of lymphoma and skin cancer in children and adults. No definitive causal relationship has been established. However, the FDA recommended that these agents only be used as second-line agents for atopic dermatitis. In 2006, the FDA placed a "black box" warning on the prescribing information for these medications.

Calcipotriene:

Calcipotriene is a synthetic analog of vitamin D3. Vitamin D3 binds to vitamin D receptors in the skin, affecting melanocyte and keratinocyte growth and differentiation. It also inhibits T-cell activation. Malignant cells are thought to express 1-[alpha]-dihydroxyvitamin D3, which may have a role in stimulating melanogenesis. Several studies have evaluated the efficacy of calcipotriene in combination with UV light in patients with vitiligo. The data have ranged from well-tolerated and efficacious to minimal repigmentation. Calcipotriene has also been studied when used in combination with clobetasol. Clobetasol was used in the morning and calcipotriene was used in the evening. Eighty-three percent of patients responded to treatment, with an average of 95 percent repigmentation.

Other therapies:

A variety of other therapies have been tried in the treatment of vitiligo. Examples include tar emulsions and immunomodulators like cyclosporine and levamisole. Vitamins such as vitamin B12 and folic acid plus sunlight have been reported to be effective in some patients. Oral ginkgo biloba has shown efficacy in a randomized trial of patients with limited vitiligo and slowly spreading vitiligo.

Conclusion:

Vitiligo is a chronic and usually progressive disease for which substantial strides have been made in the pathogenesis and treatment. Treatment is necessary and should begin early because the disease is emotionally and physically disfiguring. Repigmentation therapies are slow in efficacy and usually require long-term commitments by the patient, making vitiligo a therapeutically-challenging disease. However, with continued advances and ongoing studies, patients will soon have safer and more efficacious treatments for this devastating condition.

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Calciphylaxis: Case Report and Review of the Literature

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ABSTRACT

Calciphylaxis is a rare condition seen in patients with end-stage kidney disease on hemodialysis. It is characterized by tender, indurated, painful, ulcerative skin lesions. It has a poor prognosis, and there are not any definitive treatments. Prevention through monitoring of serum calcium and phosphorus levels in patients who are at risk is essential. Described is a 69-year-old woman with calciphylaxis and review of the available literature.

Case Report:

A 69-year-old, Caucasian female with end-stage kidney disease on hemodialysis was admitted to the hospital for treatment of a possible cellulitis of her left upper arm. She was being treated with levofloxacin as an outpatient without success. On further examination, the patient had multiple areas of erythematous-to-violaceous, tender, and firm plaques. The areas of the body affected included the left upper arm, the breast area, the lower abdomen, and the medial thighs. The lesions on the abdomen had areas of necrosis and drainage, with black eschar present (Figure 1). There were also multiple, hyperpigmented, firm plaques. The patient stated the lesions had been present for months.

The patient’s past medical history included obesity, type 2 diabetes mellitus, type V end-stage renal disease on hemodialysis, pulmonary sarcoidosis, and atrial fibrillation. Because of her chronic medical conditions, she was on numerous medications including chronic steroid therapy for treatment of her sarcoidosis.

At the time of admission, the patient denied any fevers, chills, or night sweats. She also denied any shortness of breath, chest pain, or gastrointestinal complaints. A complete review of systems was obtained and was negative except for the skin lesions.

Physical examination revealed the skin lesions as noted. On auscultation of the lungs, no wheezing or crackles were heard. Her heart had a slight systolic murmur. A hemodialysis access was present in the left forearm, and had a good thrill on palpation. Peripheral pulses were palpable in all four extremities. The patient was alert, oriented, and answering questions appropriately. She had no focal neurological deficits.

Laboratory examination revealed a glucose of 193, BUN of 70, creatinine of 7.7, sodium of 138, potassium of 6.2, phosphorus of 9.0, chloride of 97, calcium of 9.2, and albumin of 4. A liver function panel, thyroid stimulating hormone, troponin, complete blood count, and PT/INR were within normal limits. Blood cultures were negative, and a urinalysis was not abnormal for a patient on hemodialysis with diabetes.

Differential diagnosis at this point included calciphylaxis, inflammatory cutaneous sarcoidosis, morphea, and warfarin necrosis.

A 3-millimeter punch biopsy was obtained from the lesion on the left lower abdomen. Histopathological exam revealed slight thinning of the epidermis and occasional, haphazardly arranged collagen bundles in the dermis. The skin and vessels did not reveal any histopathological features to suggest a definitive diagnosis.

Clinically, the patient’s features were felt to be most consistent with a diagnosis of calciphylaxis, considering that she had stage V kidney disease and was on hemodialysis three times a week. Her pulmonary sarcoidosis was felt to be under good control with systemic steroids, and she was unlikely to have a cutaneous manifestation of the disease.

Treatment was begun with sodium polystyrene sulfonate (Kayexalate®) for hyperkalemia and calcium acetate (PhosLo®), sevelamer (Renagel®), and paricalcitol (Zemplar®) for hyperphosphatemia. She was also started on intravenous sodium thiosulfate for treatment of her calciphylaxis. She was continued on the sodium thiosulfate until two days after undergoing a subtotal parathyroidectomy for newly diagnosed hyperparathyroidism that did not respond to hemodialysis and medical treatment.

The skin lesions were treated with pulse lavage and special wound care dressings. Ethezyme (papain + urea) was applied to the areas with black eschar to help debride the eschar to facilitate better wound healing. The areas with necrosis and eschar on the abdomen slowly healed (Figure 2), and areas on the medial thighs began to turn violaceous in color and breakdown. The patient had daily dialysis while hospitalized and was discharged to follow up with nephrology and wound care.

Figure 1
Lesion on abdomen with eschar removed, before treatment

Figure 2
Lesion on abdomen after treatment

Figure 3
Histopathology of calciphylaxis
Discussion:

Calciphylaxis was first described in 1962.¹ A more appropriate term for calciphylaxis is calcific uremic arteriolopathy. It is a serious disorder characterized by small vessel mural calcification leading to tissue ischemia.² It most commonly occurs in patients with end-stage renal disease on hemodialysis or in patients who have received a renal transplant. A cross-sectional study of 242 hemodialysis patients in an outpatient unit revealed a prevalence of four percent.³

The pathogenesis of calciphylaxis is poorly understood. It is thought to be the result of medial vessel calcification due to abnormal mineral metabolism. It is well known that conditions like hyperparathyroidism, hypercalcemia, hyperphosphatemia, and vitamin D supplementation all play a role in the development of calciphylaxis.⁴ However, there is no correlation between the severity of any of these factors with the development of calciphylaxis. Additionally, it is often precipitated by local skin trauma or injections.⁵

Clinical risk factors for calciphylaxis include white race, severe weight loss, obesity, warfarin administration, and low albumin levels.⁶ The condition also appears to occur in greater frequency in females and in patients with type 1 diabetes mellitus.⁷⁻¹⁰ Calciphylaxis is characterized clinically by violaceous, painful, plaque-like subcutaneous nodules. The lesions tend to occur on areas with the most adipose tissue like the trunk, buttocks, or proximal extremities.⁷ The plaques tend to progress to ischemic, necrotic ulcers with eschars that can become superinfected.

To diagnose calciphylaxis, one has to have a strong clinical suspicion, because there is not a laboratory test that is diagnostic. A skin biopsy that shows arterial occlusion with calcification in the absence of vasculitic changes can usually confirm one’s clinical suspicion⁶ (Figure 3).

The best treatment for calciphylaxis is prevention, by monitoring plasma-calcium and phosphorus concentrations regularly and instituting treatment immediately if they are abnormal.¹²,¹³ Because calciphylaxis is rare, there are no controlled studies of established therapies. It is best managed by early diagnosis, treatment of renal failure, partial parathyroidectomy when indicated, aggressive debridement of necrotic tissue, and avoidance of precipitating factors like injections.⁶ Experimental therapies include intravenous sodium thiosulfate, hyperbaric oxygen therapy, and maggot therapy combined with oral pentoxifylline.¹⁴,¹⁵ Sodium-thiosulfate administration has shown improvements in a few days to six months with patients tolerating the treatment well.⁶

Even when treated, calciphylaxis has a high associated mortality. Infection has a mortality of up to 58 percent in one study,¹⁷ whereas ulceration of the skin lesions has a mortality of more than 80 percent.¹⁸ A patient’s response to treatment is never assured, and the overall prognosis associated with calciphylaxis is poor.

Even though calciphylaxis is a relatively rare condition, more research into the pathogenesis and possible treatments is necessary considering its poor prognosis and mortality.

References:

The most difficult skin conditions to treat involve a complicated interplay of genetic, environmental, and systemic interactions. Although significant advances in genetics and immunology have been made, the human organism is still as complicated as when the theory of the triple helix was first published. Since the advent of tumor necrosis factor (TNF) inhibitors, we have focused our use of the biologics on different inflammatory diseases such as psoriasis, Crohn’s disease, pyoderma gangrenosum, rheumatoid arthritis, etc.

Although thousands of articles and textbooks discuss the etiology, prognosis, and treatment options available for leg ulcers, a piece of this puzzle is still missing. We postulate that this is also an inflammatory skin condition or an autoimmune process in which we have yet to elucidate the mechanism. Therefore, we have been unable to fully treat these patients in a timely, cost-effective manner with satisfying results.

In this case series, we present multiple cases of refractory lower leg ulcers that have been unresponsive to conventional therapy for months to years. Benefit has been achieved from the topical use of etanercept, demonstrating a novel therapeutic modality and route of administration for etanercept. The following cases are patients who have had intermittent, chronic ulcerations of the lower extremities in which the primary complaint was the excessive length of time required for treatment, or failure to achieve full granulation and epithelialization of the wound, utilizing traditional modalities. In these cases, the healing time was reduced with the application of topical etanercept.

**Method & Cases**

Etanercept powder was mixed with 25 cc of bacteriostatic water to make a solution of etanercept 1 mg/1cc. The wounds were cleaned with sterile 4x4 gauze pads soaked in sterile water and debrided before application of etanercept. Care was taken to not remove granulation tissue during debridement, and only superficial serum crust was removed. Etanercept was applied topically with a 1 cc syringe. A dosage of 1 mg per 1 cm² was applied. A Telfa pad was placed with an overlying Coban wrap that did not provide compression of the wound. The patient was given instructions to remove the wrap in 24 hours and return to the clinic for another application weekly. After the initial 24 hours, the dressing would be removed by the patient and cleansed with a mild soap and water daily. The patients were allowed to continue with a topical steroid or immunomodulator if already on one. If signs or symptoms of infection were noted, appropriate antibiotics were given after a bacterial-confirmatory culture.

**CASE 1:**

A 68-year-old Caucasian female with a medical history of hypertension, coronary artery disease, stasis dermatitis, lipodermatosclerosis, and thyroid disease presented with two ulcers of the right lower extremity measuring 67x40 mm and 75x50 mm, respectively. Minimal granulation tissue was noted at the initial evaluation. The ulcers had been present for at least two years. Multiple Unna boots and topicals (antibacterial and steroid creams and ointments) had been tried without success.

Treatment was initiated with topical etanercept applied weekly per protocol. At day 10, triamcinolone ointment and mupirocin were started daily. A mild infection was noted during the course of treatment, which responded well to doxycycline and clindamycin orally. Intralesional kenalog injections were attempted once. The right leg ulceration healed in seven months 13 days and has continued to do well without any subsequent re-ulceration. Her most recent...
follow-up after eight months has not revealed any further ulceration.

**CASE 2:**
A 68-year-old Caucasian female with a history of poorly controlled diabetes, necrobiosis lipoidica, cardiovascular disease, hypertension, and thyroid disease complained of intermittent ulceration of the legs since 1994 (12 years). Most recently, her ulcers had not healed for a year in spite of using diflorsone ointment, fluorandredonolide tape, betamethasone ointment, pimecrolimus cream, Unna boots, hydrocolloid dressings, intralesional kenalog, silver nitrate, etc. Oral medication such as trental, prednisone, antibiotics, methotrexate, and mycophenolate mofetil were also used in the past without any success.

She was started on topical etanercept weekly per protocol while continuing with daily applications of pimecrolimus and betamethasone creams. The right medial ankle granulated and epithelialized in 24 days. She was instructed to continue the pimecrolimus cream and betamethasone topically. The left lower leg ulcer continued to be treated weekly with etanercept and epithelialized in three months 22 days. No infections were noted during the treatment period. At her six-month follow-up examination, she had not re-ulcerated.

**CASE 3:**
A 55 year old male with a history of poorly controlled diabetes, hypercholesterolemia, hypertension, peripheral neuropathy, and necrobiosis lipoidica had developed multiple ulcers on the anterior lower extremity secondary to trauma. The ulcers were persistent for approximately five years. At the time of initial presentation, ulceration was noted on the right and left pretibial regions.

Topical etanercept was started weekly per protocol. The left shin granulated and epithelialized in 32 days. The right shin measured at 35x15 mm and subsequently healed in a total of 65 days. No infections were noted during the treatment period.

**CASE 4:**
A 45-year-old Caucasian male with a history of hypothyroidism and hypercholesterolemia presented with a history of multiple, recurrent ulcers of the pretibial lower leg intermittently for many years. At the time of initial presentation, a 48 mm ulcer of the shin was noted.

Topical etanercept was started weekly per protocol. Complete healing occurred in 21 days. In order to improve epithelialization in this patient, aquaphor, mupirocin, and triamcinolone ointment were also initiated at week one. No infections were noted in this patient during the treatment period.

**CASE 5:**
A 76-year-old Caucasian male with a history of asthma and stasis dermatitis presented with a two-year history of a nonhealing ulcer of the left lower extremity. Traditional treatment with topical steroids, mupirocin, silver nitrate, silver sulfadiazine 1%, hydrocolloid dressings, and intralesional and systemic kenalog injections had been tried without any success.

Topical etanercept was initiated on a weekly basis per protocol. Ulcer granulation and full epithelialization was achieved in 32 days. At a six-month follow-up exam, no further ulceration had occurred.
Discussion

Etanercept is a recombinant human TNF receptor Fc fusion protein. It is a protein that binds TNF and interferes with the bioactivity of TNF. Traditionally, etanercept is injected subcutaneously once to twice weekly for the treatment of rheumatoid arthritis, psoriatic arthritis, and psoriasis. Etanercept is a dimeric fusion protein which consists of extracellular ligand-binding portions of two human Type II TNF receptors linked to the Fc constant region of human IgG. The dimeric structure of etanercept increases the TNF binding affinity of etanercept 50-fold and the TNF-neutralizing capacity by 1,000. The dimeric fusion protein has a longer half life than the monomeric protein.

Over the past few years, immunologic evidence of the importance of TNF has grown. Studies have revealed the role of TNF in inflammatory diseases and its destructive properties. It stimulates neangiogenesis and leads to an influx of inflammatory cells. TNF can also activate matrix metalloproteinases and induces the production of IL-1, IL-6 and prostaglandin E2. TNF is produced primarily in the macrophage but can also be produced by lymphocytes, neutrophils, and keratinocytes. TNF-α drives the inflammatory activity that can destroy cartilage, bone, and bowel mucosa. Perhaps it may also lead to the destruction of keratinocytes such that they are unable to heal a chronic wound.

TNF contributes to inflammatory pain in an experimental model of arthritis and would seem to contribute to some aspect of pain in a leg ulcer model. Inflammation has been associated with sensitization of specialized sensory neurons that comprise the nociceptive pathway. Therapy directed against TNF has proven effective in pain management of rheumatoid arthritis. It has also been found that application of TNF-α enhances calcium currents and increases neuronal sensitivity to neurotoxin capsaicin in cultures of sensory neurons.

Lower extremity ulcers involve a complex interplay of genetic, systemic (i.e., diabetes mellitus, hypertension, thyroid disease, autoimmune disease, and coronary artery disease) and environmental factors (i.e., bacterial colonization, home care, and compliance). We propose that lower-extremity ulcers have a significant immunologic component (primarily TNF) that may have been ignored or undiscovered until the approval of the new biologic agents. The importance of TNF in leg ulcers has not been fully delineated. The role of TNF may help to explain the difficulty in healing ulcers, as well as the pain involved.

In lower-extremity ulcers, it has been found that levels of TNF-α were higher in wound fluid from nonhealing ulcers than in wound fluid from healing ulcers. In a healing wound, fibroplasia, angiogenesis, and reepithelialization occur in an organized fashion. In a nonhealing wound, a defect somewhere in this cascade must exist. Chronic ulceration occurs when reepithelialization from the wound edge, fibroblast proliferation from the wound base, and/or other unknown immunologic cascades are being opposed. In most of the literature published about leg ulcers, insufficient arterial blood flow and venous hypertension are claimed to result in a deficiency of nutrients that inhibits appropriate granulation and epithelization. Cytokines such as TNF-α in a wound facilitate signals between cells of the immune system, which may inhibit further healing. TNF-α, TNF-β, IL-1a, IL-6, TGF-β1, PDGF-A, VEGF, ßFGF, and EGF are some of the immunologic factors observed in leg ulcer skin. In the absence of active healing, continued stimulation of these products is most likely occurring.

With the use of systemic TNF inhibitors, there have been reports of adverse events such as severe infection (i.e., tuberculosis), infusion reactions, injection-site reactions, induction of autoimmune disease, EKG alterations, and, rarely, neurologic disorders. In our cases, we have not experienced any of these events with the exception of one patient who developed a superficial infection that responded quickly to oral antibiotics. It is difficult to correlate the use of topical etanercept with this infection. Most ulcer patients are colonized with bacteria and may develop superinfections during the course of any treatment modality. It is unlikely that topical application of etanercept would provide systemic immunosuppression such that severe infections would occur.

An important observation with topical etanercept is that excellent and rapid granulation of a wound base occurs regardless of etiology. Traumatic or diabetic ulceration and even wound desiccation all respond to topical therapy. We propose that TNF plays a large role in the ability of a wound base to granulate. It has been observed that the process of epithelialization is profoundly difficult in our cases. The addition of a topical steroid or immune modulator such as pimecrolimus has, in some patients, greatly enhanced the epithelialization process. We propose that the process of epithelialization requires another immunologic signal. Perhaps another cytokine that has been found in nonhealing wounds, such as TNF-α, IL-1a, IL-6, TGF-β1, PDGF-A, VEGF, ßFGF, or EGF, is responsible for the immunologic signal that delays epithelialization.

Conclusion

TNF-α inhibitors may provide a promising treatment option in the future treatment of chronic leg ulceration. The cytokine...
TNF plays a very important role in the granulation of a wound base. It appears that there are so few side effects associated with topical administration of etanercept that the active ingredient could be placed in a gel, cream, or ointment vehicle for application at home. This could help to further decrease the number of office visits and cost of therapy associated with this disease.

Etanercept has been important in many arthritides and skin diseases. The biologics are being tried on other inflammatory cutaneous diseases and may eventually be revolutionary in the treatment of leg ulcers. The biologics have tremendously improved the quality of care and life for many of our patients. As shown in these cases, etanercept has proven its usefulness in nonhealing wounds, and we propose a new theory that cytokines are a large contributor to the healing process.

References:
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