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Contents

Letter from the JAOCd Editors ........................................................................................................................................... 4
Letter from the President ...................................................................................................................................................... 5
Aggressive Angiomyxoma: A Rare Perineal Tumor ........................................................................................................... 6

Angela Combs, D.O.,* Stanley Skopit, D.O., FAOCD**

Confluent and Reticulated Papillomatosis ....................................................................................................................... 7

Robert A. Norman, DO, MPH, MBA,* Daniel R. Johnson, OMSIV**

Minocycline-induced Hyperpigmentation in a Patient with Hidradenitis Suppurativa: A Case Report ....................... 9

Chris Buckley, D.O.,* Stanley Skopit, D.O., FAOCD**

Lichen Aureus: A Case Report and Review of the Traditional, Nutritional, and Alternative Treatment Options .... 13

Raymond R. Knisley, D.O.,* Bruce F. McDonald, D.O., F.A.O.C.D.**

Cholesterol Embolism Syndrome: A Case Report and Review of the Literature ...................................................... 15

Laura DeStefano DO,* Janet Allenby DO**

Acute Generalized Exanthematous Pustulosis: A Case Report and Review ................................................................. 17


Malignant Glomus Tumor: A Case Series and Review of the Literature ........................................................................... 21


A Rare Morphoeform Complication of a Black Ink Tattoo ............................................................................................. 24

Scott Deckelbaum, DO,* Jack Griffith, DO,** Paul Shitabata, MD,*** Mark Horowitz, DO,****

David Horowitz, DO, FAOCD, FAAD*****

Lessons in Dermatoscopy: Dermatoscopic Pattern of Facial Melanoma in Situ (Lentigo Maligna) ................................. 26

Theresa Cao, DO,1 Margaret Oliviero, ARNP,2 Stanley Skopit, DO, FAOCD,3 Harold Rabinovitz, MD, FAAD2

A Bump on a Child’s Foot: Infantile Digital Fibromatosis ............................................................................................. 28

Angela Combs, D.O.,* Stanley Skopit, D.O., FAOCD**

A Case Report of Muir-Torre Syndrome ....................................................................................................................... 30

Theresa Cao, DO,1 Verena Ahlgrimm-Siess, MD,2 Margaret Oliviero, ARNP,3 Stanley E. Skopit, DO, FAOCD,4 Harold S. Rabinovitz, MD, FAAD5

Review of Stevens-Johnson Syndrome and Toxic Epidermal Necrosis: A Case Report and Discussion ................... 32


Removing a Gun Powder Tattoo From a Cannon Blast: A Unique Approach with Laser Therapy .......................... 37


Charlene Snyder, M.S.P.A.-C., James A. Bailey, PhD

Melanoma Epidemiology ................................................................................................................................................... 38

Megan Morrison, BS,* Daniel Hogan, MD,** Jarvis Tseng, DO, PGY-3***

Erythema Dyschromicum Perstans: A Case Report and Review of the Literature ...................................................... 41

Rupa Reddy, DO,* Stanley Skopit, DO, FAOCD**

Low-molecular-weight Heparin: A Novel Treatment Option for Ashy Dermatosis ...................................................... 43

Magaly Vitiello, MD,* Alejandra Vivas, MD,** Andleeb Usmani, DO,*** Janet Allenby, DO, FAOCD,****

Francisco A. Kerdel, BSc, MBBS*****

Cutaneous Larva Migrans: A Case Report and Discussion ............................................................................................ 45

Robert Levine, DO,* Suzanne Sirota-Rozenberg, DO, FAOCD,** Marvin S. Watsky, DO, FAOCD****

An Unusual Presentation of Antiphospholipid Syndrome .............................................................................................. 49

Shari Sperling, DO,* Suzanne Sirota-Rozenberg, DO,*** Marvin S. Watsky, DO,**** Lewis Cuni, MD*****

Extranodal Rosai-Dorfman Disease Presenting with Progressive Nasal Congestion .................................................. 51

Brooke Reemer, D.O.,* Lynn Sikorski, D.O.,** Annette LaCasse, D.O.****

Rheumatoid Neutrophilic Dermatitis ............................................................................................................................. 55

Leah M. Schammel, D.O.,* Steven K. Grekin, D.O., FAOCD**
The JAOCD continues to improve with each issue. We thank all of the authors who have contributed articles. The use of Editorial Manager for submission, review, and editing has made it easier to produce a quality journal. The journal provides the unique opportunity for residents and dermatologists in our college to contribute to the dermatology literature and improve the status of our college through education.

In order to achieve our goal of becoming an indexed publication and producing more issues annually, we need your help. Our reviewers do a fantastic job of helping to make each article the best and most complete it can be. A small group of reviewers is not enough to handle the large number of articles that are submitted. We are in desperate need of more reviewers. If you have just become a fellow of the AOCD, becoming a reviewer with the JAOCD is a great way to become involved in our college. It allows you to give back to the profession that has given so much to you. You will be listed as a member of the editorial review committee in each issue of the journal. Generally, you will be asked to review an article about once every three to four months. The review process is easy and is done completely online through Editorial Manager. Please contact us at JAOCD@aol.com if you are willing to help us by becoming a reviewer.

We encourage our fellow members, residents, and those applying for dermatology residency to continue to submit articles to the JAOCD.

Sincerely,

Jay S. Gottlieb, DO, FAOCD (Senior Editor)
Jon Keeling, DO, FAOCD (Editor)
Andrew Racette, DO, FAOCD (Editor)
Greetings. I take this opportunity to thank all of you in the College for the honor of representing you as president this year, beginning in San Francisco. I initially became involved with this college while vying for a residency. And now I find myself president. Along the way on several committees, I have met and been mentored by several outstanding members of our College.

The furthest thing from my mind during my training was to add more to my plate. Further training with fellowship, marriage, children, and business opportunities are the usual and primary factors in most people’s lives. Now, as I’m wiser, I’ve come to the realization that professional commitment is also important and requires that I give back to the organizations that have enabled me to be where I am.

This brings me to my first message as president – it’s a request, or a plea. Please give back to the AOCD. I’m not asking for a monetary donation. I’m asking for your time and consideration. It is especially important that our residents have the interest and desire to become involved and give back to the College for the opportunities provided them. Our college is growing in number of residents, programs, and members. We need to have committed individuals ensuring the future of the AOCD. We need to develop and improve as we grow, and not only in numbers. Dr. Epstein has started this process by rescheduling the business meeting to better enable the residents to attend. This will provide them the opportunity to become more aware of and involved in the workings of our College. Remember that our ability to practice in our specialty is due to the hard work of the members who came before us.

Thank you for this opportunity to address all of you.

Leslie Kramer, DO, FAOCD
President, AOCD 2010-2011
Aggressive Angiomyxoma: A Rare Perineal Tumor

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ABSTRACT

Aggressive angiomyxoma (AAM) is a rare, slow-growing myxoid tumor that typically occurs in the genital area of women of child-bearing age. It has a high recurrence rate, and metastasis has been reported but is considered a very rare phenomenon. We present a case of a 34-year-old female who presents with an AAM of the left perineum.

Case Report

A 34-year-old female presented to our clinic for evaluation of a lesion in the groin area that had been present for approximately four months. The patient denied pain or discharge of the lesion. The patient also denied any fever, chills, nausea, vomiting, bowel-movement changes, or weight changes. The patient denied a history of sexually transmitted diseases. The patient did not have a significant past medical history. Her past surgical history included one cesarean section and a knee replacement. The patient had no known drug allergies, and she was not on any medications.

Physical exam revealed a well-nourished, well-developed African-American female in no acute distress. Physical exam of the genital area revealed a 3.0 x 1.5 cm nodule of the left perineum. No discharge or tenderness was elicited by palpation. A biopsy performed for histopathologic evaluation was consistent with an aggressive angiomyxoma (AAM).

Discussion

AAM is a rare neoplasm, with about 150 cases reported, first described by Steeper and Rosai in 1983.2 The tumor is derived from mesenchymal tissue, typically in the pelvic region of adult females, with a peak incidence during the third decade of life.3 This tumor has been reported to develop in the inguinal region of men, but the male to female ratio is 1:6.4 AAMs are skin-colored, rubbery nodules that need to be clinically differentiated from a Bartholin’s cyst, periurethral cyst or hernia.1 Histologically, AAMs are composed of spindle- and stellate-shaped cells with round to oval hyperchromatic nuclei in a myxoid stroma (Fig. 1 and 2).4 There are prominent thin- and thick-walled blood vessels (Fig. 1 and 2).1 The immunohistochemical profile of AAMs includes positivity for desmin, smooth muscle actin, estrogen receptor and progesterone receptor.1 However, S-100 is negative.1 This immunohistochemical profile helps differentiate AAMs from other myxoid neo-

Figure 1. Hypocellular tumor in myxoid and mucinous stroma.

Figure 2. Spindle-shaped cells in a myxoid stroma with thin- and thick-walled blood vessels.

References

Confluent and Reticulated Papillomatosis

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ABSTRACT

Confluent and reticulated papillomatosis is a rare disease in which multiple, small, grayish-blue, and hyperkeratotic papules erupt and coalesce on the truncal skin regions. The disease commonly originates from the intermamillary, epigastric, and mid-back regions of the body. Studies suggest that the disease is selective for females with darkly pigmented skin. It has a broad age range at onset, between 5 and 63 years of life, but most commonly presents in post-pubertal patients between the ages of 18 and 21. Microscopically, local hyperpigmentation is explained by an increased number of melanocytes in the hyperkeratotic, horny layer of the epidermis. Histopathologic analysis reveals mild hyperkeratosis, papillomatosis, and focal acanthosis surrounded by a superficial infiltrate of lymphocytes within the local capillary bed. A six-week regimen of minocycline appears to be among the most effective treatments for the disease.

Presentation

A 16-year-old male presented to our clinic with the chief complaint of acne. He indicated that his acne was poorly localized and involved his chest, back, and face with varying degrees of severity. The distribution was poorly contained and had been gradually worsening in severity for several years despite various treatment regimens. He indicated that his facial acne began as small, white papules which were non-pruritic, erythematous, and mildly tender. During the comprehensive dermatologic history, the patient mentioned a slow development of multiple dark spots primarily involving his chest and abdomen that he stated had not been specifically treated. He had tried various over-the-counter topical creams, benzoyl peroxide facial washes, and topical retinoid cream without success. The patient was interested in a more effective treatment modality.

When further questioned about the rash involving his chest and abdomen, he reiterated that it had been there for some time and seemed to be expanding more rapidly over the past months. He denied related pruritus or concerns with hair loss in the affected region of his chest. The spread had been slow. The patient also denied any related familial dermatologic diseases. No one in his family reports to have had similar symptoms. It was decided to treat his acne, and a biopsy was taken of the hyperpigmented region of his chest. During his two-week follow up, the biopsy report was histopathologically identified as confluent and reticulated papillomatosis.

The patient’s past medical and surgical history were significant only for asthma with no reported controller medications. Per family history, the patient reported no known dermatologic, genetic, or predisposing autoimmune disease.

On physical examination, this was a well-developed 16-year-old male who appeared his given age. He paid appropriate attention to hygiene. Cognitive, sexual, and physical maturity was consistent with age. Cardiac, pulmonary and abdominal examinations were all within normal limits. There was no lymphadenopathy, oral ulcerations or rashes involving the head and neck. On dermatologic examination, the patient had numerous, open and closed comedones over the facial region, with mild circumferential erythema around the closed comedones. The acne pattern was non-cystic in character and consistent with pubertal acne. His hair growth and distribution were both normal. There were multiple, hyperpigmented, bluish-brown patches diffusely involving the chest, abdomen and central back (Fig. 1). Inspection of eccrine and apocrine glands revealed no evidence of hyperhidrosis, chromhidrosis or bromhidrosis.

Discussion

Confluent and reticulated papillomatosis (CARP) was first identified by Gougerot and partner Carteud in 1927. The disease was originally called papillomatose pigmentée innominée but was later renamed papillomatose pigmentée confluent et reticule after diagnostic criteria were specified.1 Wise described the first case in the United States in 1937 and renamed the disease confluent and reticulated papillomatosis.2 Because of its close histological similarity to acanthosis nigricans, confluent and reticulated papillomatosis went largely unidentified for many years. However, the disease is now generally accepted as a distinct dermatologic entity. CARP is characteristically described as “papuloverrucous lesions” which eventually convalesce into a reticulated pattern.3

Confluent and reticulated papillomatosis is a rare disease in which multiple, smaller than 0.5 centimeter, grayish-blue, and hyperkeratotic papules erupt and eventually coalesce on the truncal regions of the body.4 The disease most commonly erupts within the intermamillary, epigastric, and mid-back regions of the body. Lesions isolated to the chest may eventually spread to include the breasts, lower abdomen, flanks, and the suprapubic skin regions. Eruptions covering the back typically arise in the infrascapular region and may spread to include the shoulders, nape of the neck, and may even descend inferiorly to involve the gluteal cleft. Prior studies suggest that the disease is primarily selective for dark-skinned females but will also frequently appear in light-skinned individuals. It most commonly manifests in post-pubertal patients in their late teens but may have a broad range of onset, between 5 and 63 years of life. Pathophysiologically, local hyperpigmentation is identified by melanosomes within the hyperkeratotic, horn layer of the epidermis. Histopathologic identification is also typically positive for hyperkeratosis, papillomatosis, and acanthosis.5 The above figure illustrates a typical plaque containing hyperpigmented, hyperkeratinized skin with epidermal sloughing. Tissue biopsies may also describe elongated dermal papillae surrounded by a superficial infiltrate of lymphocytes surrounding the local capil-
lary bed. If left untreated, the mixed patch-plaque lesions coalesce into a characteristic reticular pattern on the truncal skin.

CARP is commonly associated with diseases of endocrine origin such as hypothyroidism and diabetes mellitus, dermatologic infections, and familial autoimmune diseases. In rare cases, amyloidosis has been associated with CARP. The inciting cause is yet unknown. In some cases, the skin takes on a phenotypic identity that can imitate Malassezia furfur infections. Moreover, tissue biopsies may test positive for Pityrosporum orbiculare, a skin colonizer that is commonly found in Tinea versicolor infections.

Although infectious triggers, genetic selection, and amyloidosis have all been postulated, the link to a “disorder of keratinization” seems most compatible. Under electron microscopy, Miescher first proposed that “confluent and reticulated papillomatosis is due to a defect in keratinization.” He supported his studies by demonstrating increased lamellar granules in the stratum granulosum layer of the epidermis on dermatopathological analysis. Lamellar granulation is specific to diseases characterized by rapid cellular turnover in the epidermis. Diagnostically, Miescher characterized the majority of CARP tissue biopsies as having a thickened transitional cellular layer. This layer represents the epidermal zone where granular cells are converted into cornified epithelium.

During identification of potential medical diseases, the differential list should include but not be limited to the following: acanthosis nigricans, amyloidosis, macular dyskeratosis, congenital epidermal nevus syndrome, epidermodysplasia verruciformis, keratosis follicularis, pityriasis rubra, and atypical tinea versicolor.

The treatment of CARP is relatively effective with a single, six-week course of minocycline 100 milligrams twice daily.7 Our patient was discharged with a six-week course of minocycline and instructed to return for follow-up evaluation after treatment completion. At his six-week follow-up, he showed marked regression of his underlying confluent and reticulated papillomatosis. In past studies, topical tretinoin has proven its utility as an adjunctive therapy option. Topical applications may also be substituted with oral retinoids such as etretinate and isotretinoin. A 1996 trial by the American Academy of Dermatology found some success with combined use of daily oral isotretinoin and topical 10% lactic acid.9 As with use of all oral retinoid formulations, patients must be warned about toxicities related to oral retinoid therapy, and females specifically must be warned about teratogenic effects during gestation.

In summary, confluent and reticulated papillomatosis is a unique dermatologic disease with successful treatment options. CARP can be identified quickly if the evaluating clinician has a high index of suspicion that is based on many well-defined criteria for diagnosis.

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4. Schwartz R, MD, MPH. Professor and Head, Dermatology, Professor of Pathology, Pediatrics, Medicine, and Preventive Medicine and Community Health, UMDNJ-New Jersey Medical School. Confluent and Reticulated Papillomatosis. March, 2010.
5. Mafong E, MD. Confluent and Reticulate Papillomatosis. Dermatology Online Journal. 7(1): 13. Dept. of Dermatology, New York University. (Fig. 2)
Minocycline-induced hyperpigmentation in a patient with hidradenitis suppurativa: A case report

**Abstract**

Minocycline-induced hyperpigmentation is an uncommon adverse effect of chronic minocycline ingestion which can result in large areas discoloration of the body. This is a case presentation of a 59-year-old female who developed ashy-gray discoloration of her body after chronic treatment of hidradenitis suppurativa with minocycline. Additionally, a review of the literature and discussion of the common causes, cutaneous and histologic findings, differential diagnoses, diagnostic techniques, and various treatment options for this disease will be presented.

**Introduction**

Minocycline-induced hyperpigmentation is an uncommon adverse effect of chronic minocycline ingestion. It results in large areas of the body being discolored. This is a case presentation of a 59-year-old female who developed ashy-gray discoloration after chronic treatment of hidradenitis suppurativa with minocycline. Additionally, a review of the literature and discussion of the common causes, cutaneous and histologic findings, differential diagnoses, diagnostic techniques, and various treatment options for this disease will be presented.

**Case Report**

A 59-year-old Caucasian female presented to our clinic complaining of asymptomatic, red-brown spots which had been occurring on her arms episodically for the past several months. She stated these lesions occurred with trauma, lasted several days and then slowly disappeared. She stated she otherwise felt well and denied complaints. She admitted to a history of chronic hidradenitis suppurativa (HS) for which she had taken many months of minocycline over the past several years, but it had been stable for the last two months. She denied any minocycline ingestion for two months. She denied any itching, fever, malaise, fatigue, and unusual joint pains. She also specifically denied the use of cancer chemotherapeutic agents, amiodarone or dietary supplements, unusual diet, or heavy metal exposure.

Physical exam revealed a few scattered, red to violaceous, fairly well-circumscribed macules on her bilateral forearms. She was noted to have several scattered, blue-black, irregular, ill-defined patches on her upper and lower extremities, abdomen, face, and oral mucosa. There was a slate-gray darkening of her sclera, nails, and lips, and there were firm, atrophic nodules on the right axilla. No drainage or open lesions were noted. The patient was completely unaware of the dark areas on her body.

A 3mm punch biopsy was conducted on the left mid-forearm hyperpigmented lesion. H&E stains revealed dermalpigmentation deposition consistent with drug-induced hyperpigmentation. The pigment stained with Fontana-Masson stain for melanin and Perl’s stain for iron. This pattern was consistent with that seen in association with certain medications such as minocycline. Lab workup, including CBC, CMP, serum iron, and thyroid panel, was within normal limits.

The patient was diagnosed with minocycline-induced hyperpigmentation. All minocycline and other tetracycline use was discontinued. When the patient returned to the office for three-month follow-up, slight improvement was noted in the scleral and mucosal discoloration, and a decrease in prominence of dark patches was seen. No flare-up of HS was noted.

**Discussion**

Drug-induced pigmentary abnormalities are a common cause of dermatologic consultations and account for 10-20% of cases of acquired dyspigmentation worldwide. They are generally not associated with increased morbidity or mortality, there is no age- or sex-related prevalence, and there is no race predilection, although pigmentary change is often more dramatic in darker-skinned individuals (1).

A careful history should be undertaken to rule out other underlying disorders and association with sunlight, and to establish a temporal relationship between medication use and symptoms. Minocycline use is a common culprit, but a large number of other drug groups are implicated, including antimalarials, chemotherapeutics, heavy metals, amiodarone, AZT, psychotropic drugs, and clofazimine.

Minocycline is a highly lipid-soluble antibiotic that turns black with oxidation. Hyperpigmentation occurs in up to 3-5% of patients with long-term use. In addition to prolonged period of use, high cumulative dose, excessive sun exposure, and prior incidence of inflammatory skin change.

**Figure 1**

Increases the risk of minocycline-related hyperpigmentation (2). Many metabolic, depositional, and endocrine diseases can cause pigmentary disorders. If history and clinical presentation indicate, then a further workup is needed, including a CBC, CMP, serum iron products or copper levels, thyroid hormones, and a corticosteroid stimulation test (3). Treatment consists mainly of identification and discontinuation of the inciting agent. Most pigmentation is reversible, although this process may take several months. Sun avoidance may enhance recovery time.
References:


Figure 4

Figure 5
Congratulations to our co-editor, Jon Keeling, his wife Julie and big brother Jack on the birth of Nate Keeling
Born on Sept 12, 2010. 7 lbs, 12 oz. 21 inches.
We wish them all the happiness in the world.

Best Wishes,
Jay Gottlieb, Andrew Racette and the staff of the JAOCN
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**Lichen Aureus: A Case Report and Review of the Traditional, Nutritional, and Alternative Treatment Options**

Raymond R. Knisley, D.O., a Bruce F. McDonald, D.O., F.A.O.C.D. b
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**ABSTRACT**

This is a case report of a 73 year old Caucasian female with biopsy proven Lichen Aureus on her thighs, knees, ankles, feet, and forearms. When she could not tolerate traditional medical treatment, she was switched to nutritional and alternative therapies to treat her disorder. Her condition was noticeably improved with Vitamin C and Rutin without any undue side effects. We, as Osteopathic physicians, suggest that a holistic approach to patients’ health concerns- to include nutritional and alternative therapies- be used to treat every patient whenever feasible.

**Case Report**

This is a case report of a 73-year-old Caucasian female with complaints of pink to light-brown, well-circumscribed macules and patches on bilateral lower legs, from her knees to her ankles, of one year duration (Fig. 1 and 2). She also had some golden-colored patches on her forearms (Fig. 3), feet (Fig. 4), ankles (Fig. 5), lower legs, and thighs (Fig. 6). She denied pruritus or scaling.

The skin of her lower legs showed fine-line wrinkles, mottled pigmentation and cayenne-pepper-like staining, and light-brown to golden macules with mild telangiectasias on her ankles, feet, knees, calves, and thighs, with excoriated plaques over her knees. Her forearms showed brawny, erythematous, edematous, lichenified plaques over the bony prominences. There was mild atrophy of the skin consistent with photoaging.

Skin biopsy of the golden macule on her right thigh showed an infiltrate of lymphocytes with extravasated erythrocytes and siderophages in the dermis, compatible with lichen aureus.

The patient was started on pentoxifylline 400mg by mouth three times daily. She noticed some improvement in the lesions, but chose to stop the medicine because of constant nausea. At this point, traditional therapy was discontinued because of unwanted side effects. Thus, nutritional and alternative therapies were initiated. Vitamin C 500mg by mouth twice daily and rutin 250mg by mouth daily were prescribed. Within one month, the patient noticed a visible improvement in her lesions with no side effects from the medications.

This case was chosen for publication not only for its rarity and unusual pathophysiology, but also for its difficulty of therapeutic management.

**Discussion**

Lichen aureus was first described by Martin in 1958. It is an uncommon and chronic skin disease that is part of the pigmented purpuric dermatoses. These disorders represent a collection of diseases portrayed by petechial hemorrhage considered to be secondary to capillaritis. Lichen aureus typically consists of a solitary, well-circumscribed lesion, although segmental and linear patterns have also been reported. It can be found commonly on a lower extremity, many times overlying a perforator vein. These chronic patches or plaques are most often rust to purple-brown in color but may have a golden hue with occasional petechiae. They are typically asymptomatic, slow to evolve, and usually persist for many years unchanged. Complete resolution is a rarity. They have no systemic findings and classically lead to patient evaluation to exclude thrombocytopenia or vasculitis because of the purpuric or petechial features of the lesions.

**Pathophysiology**

The exact cause of lichen aureus is unknown. Its pathophysiology typically results from minimal inflammation and hemorrhage of superficial papillary dermal vessels, usually capillaries. The reason for the inflammation is not known for certain. There is no association with any abnormality of coagulation. Venous hypertension, exercise, and gravitational dependency are important contributors influencing the disease presentation. It has a predilection for children or young adults, with males being affected greater than females.

The dermatopathologic report of the case presented was classic.

**Differential Diagnosis**

Clinically, other similar-appearing diagnoses include small vessel vasculitis, mycosis fungoides, allergic contact dermatitis, non-allergic reaction to topical medications, drug eruption, suction-induced purpura, hypergamaglobulinemic purpura of Waldenström, and dermal hemorrhage from venous hypertension.

**Treatment**

Treatment of lichen aureus can be a challenge. Very potent topical glucocorticoids are occasionally helpful when pruritus or more marked erythema is present. Antihistamines are used for pruritus if present. PUVA and narrowband UVB have been successful in at least one case. Successful therapy with ascorbic acid 500mg twice daily and rutin 50mg twice daily has been reported. Resolution with topical pimecrolimus 1% twice daily has been reported in a 10-year-old child. A combination of pentoxifylline and prostacyclin has been reported to be successful. Without treatment, lichen aureus is considered a chronic dermatosis.

**Pharmacology**

Rutoside (rutin) is a citrus flavonoid glycoside found in buckwheat, the leaves and petioles of Rheum species, and asparagus. It is used as a nutritional or perhaps as an alternative medical therapy. It inhibits platelet aggregation, making the blood less viscous, and improves circulation. Rutin also strengthens the capillaries and therefore can reduce the symptoms of hemophilia. It also may help to prevent venous edema of the legs. Rutoside can be found in “health food” stores and nutritional centers.

Ascorbic acid (vitamin C) is a water-soluble vitamin essential in the formation of collagen in bones, cartilage, muscle, and...
blood vessels. It is a necessary requirement for collagen formation, tissue repair and to prevent scurvy. Vitamin C participates in collagen hydroxylation, which adds hydroxyl groups to the amino acids proline or lysine in the collagen molecule. This reaction uses vitamin C as a cofactor and allows the collagen molecule to assume its triple helix structure, thus making vitamin C crucial to the development and maintenance of scar tissue, blood vessels, and cartilage.

Pentoxifylline (Trental) improves the flow properties of blood by decreasing its viscosity and improving erythrocyte flexibility. This increases blood flow to the affected microcirculation and enhances tissue oxygenation. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. The specific mode of action and the series of events leading to clinical improvement are unknown.

Pimecrolimus (Elidel) 1% cream binds with high affinity to macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase calcineurin. As a result, it inhibits T-cell activation by blocking the transcription of early cytokines. Specifically, pimecrolimus inhibits interleukin-2 and interferon gamma (Th1-type) and interleukin-4 and interleukin-10 (Th2-type) cytokine synthesis in human T cells at nanomolar concentrations. Pimecrolimus also prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE.

Prostacyclin (PGI₂) primarily prevents the formation of the platelet plug involved in primary hemostasis by inhibiting platelet aggregation. It is also an effective vasodilator.

References
Cholesterol Embolism Syndrome: A Case Report and Review of the Literature

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ABSTRACT

Cholesterol Embolism Syndrome (CES) is a disorder affecting multiple organ systems and is characterized by the embolization of cholesterol crystals from disrupted atherosclerotic plaques. The triggering events are varied and common. The initial symptoms may prompt a patient to visit a dermatologist where the patient’s medical history is very important. Here we present a case report with the classic cutaneous findings.

Introduction

Cholesterol embolism syndrome (CES) is a disorder affecting multiple organ systems and is characterized by the embolization of cholesterol crystals from disrupted atherosclerotic plaques. The triggering events include anticoagulation, angioplasty, fibrinolytic therapy and spontaneous occurrences. There are acute, subacute and chronic forms. In the early stages the cholesterol embolism directly occludes the small arterioles. In the later stages the emboli cause a severe local inflammation which eventually causes tissue ischemia. The initial symptoms may prompt a patient to visit a dermatologist, at which point the patient’s medical history is very important.

The incidence of CES is still unclear. Reports from early studies show incidence rates of 8.6%-12.3% in older patients with severe atherosclerosis. The one-year mortality rates have been reported as 21%-58%, and even higher with multiorgan involvement.

Diagnosis is based on clinical findings, which can include livedo reticularis, blue toe syndrome, renal insufficiency/failure, and eosinophilia. A definitive diagnosis can be confirmed by taking a biopsy of an affected region. Most patients have skin involvement, and it is an easy and accurate way to get a sample. The histology demonstrates the cholesterol clefts where the crystals are dissolved during tissue processing. Here we present a classic case of CES that was clinically diagnosed, with dermatologic findings being a key factor, and highlights the difficulties of choosing an appropriate treatment plan.

Case Presentation

A 66-year-old female presented to the ED complaining of dyspnea for one day. She was admitted for further workup. The patient had not seen a doctor in 35 years. She smoked a pack a day for 45 years. During that admission she was diagnosed with atrial fibrillation, CHF, HTN, COPD, NIDDM and hyperlipidemia. Bilateral adrenal incidentalomas were also found. The patient was discharged on ASA, CCB, ACEI, diuretic, statin, and B2 agonist.

An endocrine workup showed the adrenal adenomas were non-functioning. Despite aggressive medical treatment, the patient’s blood pressure continued to rise. Angiogram of the renal arteries revealed a 60% stenosis of the left renal artery. Angioplasty and stenting of the left renal artery was performed.

Four weeks later, the patient was admitted for uncontrolled HTN. She stated that she had been nauseous for several days and unable to take her BP meds. Her condition was stabilized, and she was discharged to follow up with her PCP. Labs were drawn by her PCP, and the patient was sent immediately to the ER due to acute renal failure. Creatinine at admission was 5.5, baseline was 1.3. The white-cell count was 16,000 with 6.6% eosinophils. The patient developed livedo reticularis and blue toe syndrome (Fig. 1) on the day of admission. The diagnosis of cholesterol emboli syndrome was made. Skin necrosis occurred several days later (Fig. 2). Renal function did not improve, and she was started on dialysis. The patient refused a statin, stating that they caused her myalgias in the past. The data on corticosteroids was controversial, so supportive measures were continued. The livedo reticularis waxed and waned during the course of hospitalization. Several days later, she began to complain of severe abdominal pain, and a CT scan, without contrast, was performed. It showed dilated loops of large and small bowel as well as free fluid. This was thought to be due to mesenteric infarction from cholesterol emboli. The patient was transferred to the ICU, where she expired shortly after.

Discussion

This case illustrates a clinically diagnosed case of CES. The physical exam findings of livedo reticularis and blue toe syndrome, as well as the history of renal angioplasty, progressive renal failure and the laboratory data, all supported the diagnosis. A skin biopsy was not performed but could have confirmed the diagnosis histologically. The patient also had multiple risk factors including her age, hypertension, and hyperlipidemia.

The clinical dermatologic feature of livedo reticularis occurs when the venous blood becomes visible due to sluggish flow and significant deoxygenation as well as venous dilatation. It is normally bilateral, and the location depends upon where the embolization originates.

Much of the current literature focuses on the recognition of risk factors, incidences of CES, and the outcomes of patients. This case is unique in that it illustrates the difficulties of choosing an appropriate treatment plan.
dence, and accurate and timely diagnosis. There also have been some case reports and small trials of different therapies including LDL apheresis, corticosteroids, statins, and iloprost. There are no large randomized studies. The importance of recognition of these dermatological features and their association with the underlying, possibly fatal complications is underscored here. These patients may not have any other complaints and may show up at the dermatologist’s office. It is important to know what history to obtain and what further testing is required, and to involve other specialists early in the care of these patients. This allows for supportive care and minimization of further aggravating factors.

References

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS: A CASE REPORT AND REVIEW

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ABSTRACT

Acute generalized exanthematous pustulosis is a rare eruption of the skin with many etiologies, most commonly systemic medications. It is characterized by nonfollicular, sterile pustules occurring on diffusely erythematous skin. We present a case of an 82-year-old man with a recent history of having received influenza vaccine developing acute generalized exanthematous pustulosis, which resulted in a hospital admission and confusion as to the diagnosis among other specialists. Whether or not his eruption was secondary to influenza vaccine is not known; however, it is interesting that symptoms followed the vaccine by several days.

Introduction

In 1968, Baker and Ryan reviewed 104 cases of pustular psoriasis and found a subgroup of patients that exhibited a pustular eruption without a prior history of psoriasis but having had drug intake, and termed this finding exanthematic pustular psoriasis.1 Acute generalized exanthematous pustulosis (AGEP) was first termed by Beylot et al. in 1980.2

Acute generalized exanthematous pustulosis is a rare eruption of the skin that is most commonly caused by systemic medications. It is characterized by nonfollicular, sterile pustules occurring on diffusely erythematous skin. The acute eruption typically begins on the face and intertrigonous regions, typically affecting between one and five people per million per year.3 AGEP is often associated with fever and leukocytosis (mostly neutrophilic).4 In a few cases, the etiology of AGEP was attributed to a viral infection (enterovirus or parvovirus B19) or a hypersensitivity reaction to mercury; however, 90% of cases of AGEP are in association with the intake of medications, particularly antibacterial agents.5 The onset of AGEP is typically acute, usually within two days of drug exposure, and it generally resolves in less than 15 days, followed by generalized desquamation.4

Case Presentation

An 82-year-old white male presented with a three-day history of a nontoxic, migratory, intermittent pruritic rash suggesting urticaria. Clinical examination was negative for any cutaneous lesions, but the patient was treated for urticaria based on history. He was given prednisone, 20mg Aristocort IM, Allegra, and Atarax without improvement of lesions. Several days later, the patient returned with severe pruritus and a generalized rash. Two biopsies were performed along with KOH studies to rule out fungus. The patient’s unbearable pruritus didn’t resolve, and the rash became more intense, resulting in an emergency room visit and a subsequent hospitalization. Two additional biopsies were performed in the hospital. He had been vaccinated for influenza several days prior to hospitalization.

The patient’s past medical history was significant for high cholesterol and hypothyroidism, for which he had been taking Lipitor and Synthroid for five years. His allergies included oranges, grapefruits, and tomatoes.

The primary two biopsies revealed a lichenoid dermatitis with an atypical lymphoid infiltrate. The second two biopsies revealed a prominent subcorneal pustular dermatosis without atypical lymphocytes.

Physical exam on the last visit to the office prior to hospital admission revealed generalized, non-blanching, erythematous, maculopapular lesions scattered diffusely, with predominance on the V-neck area and on the forearms (Figure 1). A few 1-2mm pustules were present on the abdomen and chest. KOH was negative for scabies. Three days after admission to the hospital, the patient developed 1-2mm pustules diffusely scattered about the torso and extremities, including his palms. Also, there were pustules on his abdomen and legs, surrounded by a generalized erythoderma (Figure 2). Blood tests included a WBC count of 36,100 with 90% neutrophils, a negative ANA and a negative ESR. Epstein-Barr virus panel was positive, indicating an infection at some point in the patient’s past.

After an infectious disease and hematology-oncology consult, broad spectrum antibiotics were recommended along with IVIG. Based on our clinical exam and histological evidence, we diagnosed the patient with AGEP and recommended discharge from the hospital with symptomatic treatment. Our recommendations were followed, and the patient improved dramatically over the next two weeks, experiencing a generalized desquamation involving the acral areas (Figure 3).

Histopathology

Histopathology of AGEP typically shows spongiform subcorneal and/or intraepidermal pustules, marked edema of the papillary dermis, perivascular infiltrates of neutrophils, and some exocytosis of eosinophils. Additionally, some keratinocyte focal necrosis or vasculitis may be present.6

Etiology

Acute generalized exanthematous pustulosis is most frequently caused by medications. Antibiotics, especially beta-lactams, are the most common causative agents of reported medications.4 It has also been reported that AGEP was triggered by acute viral infections, most notably enteroviruses and parvovirus B19.7 Spider bites have also been reported in three cases to possibly induce AGEP.8 Mercury and pneumococcal vaccine have also been named as possible etiologies leading to AGEP.9

Many patients with AGEP have a history of prior sensitization to the causative drug. Britschgi et al. described involvement of T cells in drug-induced AGEP, evident due to positive patch tests and lymphocyte transformation tests. Following exposure, cell-bound drug presentation elicits the drug-specific CD4 and CD8 immune reaction, causing the expression of CXCL8, which is a dominant chemokine, leading to the attraction and accumulation of polymorphonuclear neutrophils (PMNs).9 Sidoroff et al. found in a multinational case-control study that the drugs most often associated with AGEP were ampicillin/amoxicillin, quinolones, hydroxychloroquine, sulphonamides, terbinafine and dilitiazem.10 Aquilina et al. reported AGEP in a human immunodeficiency virus-seronegative man potentially due to a reaction to prophylactic therapy, including zidovudine, lamivudine and protease inhibitor, for human immuno-
deficiency virus. Prior reports have also identified clindamycin as a causative agent of AGEP.

**Treatment**

The main form of treatment for AGEP is to stop the offending agent. After withdrawal of the presumed offending agent, pustules usually resolve spontaneously in less than 15 days, and a generalized extensive desquamation tends to occur. Administrations of intravenous corticosteroids, antihistamines, and broad-spectrum antibiotics have also been used in treatment.

**Discussion**

Acute generalized exanthematous pustulosis is a rare, acute eruption that is characterized by non-follicular sterile pustules occurring on a diffuse, edematous erythema, predominately on the intertriginous folds and on the face. Patients often present with fever and leukocytosis, and may describe having a burning or itching sensation. Antibiotics, particularly beta-lactams and macrolides, are the most common causes of AGEP; however, a wide range of offending drugs have been reported. Other etiologies reported to attribute to AGEP include mercury, viruses (B19 and enterovirus), spider bites and pneumococcal vaccine. Roujeau et al. found that the median time frame of onset of AGEP following ingestion of the offending drug was one day. Patch testing has been used to identify the cause of AGEP due to T-cell involvement in the pathogenesis of the disease. However, the sensitivity of patch testing is only 50%. Lymphocyte transformation tests (LTT) may also be positive due to involvement of T cells.

Differential diagnosis of AGEP includes pustular psoriasis, subcorneal pustular dermatosis (Sneddon-Wilkinson disease), pustular vasculitis, and toxic epidermal necrolysis (TEN). AGEP can be differentiated from pustular psoriasis mainly through history, particularly assessing the time frame from exposure to the offending agent. Furthermore, AGEP also characteristically exhibits a briefer course of fever and pustules, with a shorter duration of systemic involvement that is less severe than pustular psoriasis. Sneddon-Wilkinson can be differentiated from AGEP as being characteristically a cyclic disease in an afibrile patient with recurrent, flaccid pustules that are localized. Toxic epidermal necrolysis (TEN) can be separated from AGEP as usually presenting with significant mucosal involvement, including full-thickness epidermal necrosis and sparse inflammatory infiltrate.

Acute generalized exanthematous pustulosis may potentially manifest as a severe disease, with up to 5 percent mor-

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**References**

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Glomus Tumor is a rare benign, painful, tumor of subcutaneous tissue. Malignant Glomus Tumor is an even much less reported malignant variety of the aforementioned tumor. These aggressive malignant tumors typically arise in pre-existing Glomus Tumors, but may also arise de-novo. We present two cases of Malignant Glomus Tumors occurring in two separate patients. We provide a thorough review of the clinically and pathologically relevant aspects of Malignant Glomus Tumor.

Introduction

The glomus tumor (GT) is a rare, benign neoplasm consisting of cells that resemble modified smooth-muscle cells of the normal glomus body. The glomus body is a specialized form of arteriovenous anastomosis related to thermoregulation, located in the stratum reticularis of the dermis and most frequently found in the subungual region, lateral portion of the digits, and the palm, areas where GTs are therefore most commonly encountered. Most glomus tumors are benign and treated with simple local excision, with a 10% risk of local recurrence due to incomplete extirpation. The malignant counterpart of GT is an uncommon, recently described neoplasm with only a few reported cases. An estimated 1% of glomus tumors are reported to be malignant. Malignant glomus tumors (MGT) have been termed glomangiosarcomas when arising from a previously benign GT, but may also develop without any preexisting glomus tumor, designated glomangiosarcomas de novo. MGTs are recognized to arise from a discernible, benign precursor lesion in roughly half of the reported cases. We present two cases of malignant glomus tumor found in two different patients. Both cases of glomangiosarcoma arose within a preexisting benign glomus tumor.

Case 1

A 46-year-old man presented with a tumor on the left arm. Microscopic pathologic findings showed sections of encapsulated neoplasm, with a portion of benign counterpart of glomus tumor, and cellular areas showing organoid neoplastic cells with pleomorphic, vesicular nuclei and frequent mitoses. The tumor was deeply seated in the subcutaneous tissue, measuring 0.7 cm, and was partially encapsulated. There were no signs of necrosis or hemorrhage or evidence of infiltrative border. Immunoperoxidase stains revealed tumor cells immunopositive for smooth-muscle actin, vimentin and chromogranin, while negative for pancytokeratin and S-100.

Case 2

A 55-year-old male presented with a tumor on the left elbow. Microscopic pathologic findings showed glomangiomatous with focal atypia. Although the epidermis was unremarkable, within the reticular dermis and extending deeply to closely involve the deep and peripheral margins was proliferation of glomus cells, some in the characteristic perivascular nest arrangement. The vessels ranged in size from thin-walled capillary spaces to ecstatic vascular spaces with secondary thrombosis. The glomus cells had a spindled configuration and were more cellular, with a much greater degree of cytologic atypia. At least three mitotic figures per 10 high fields, including atypical mitotic figures, were appreciated. Additionally, cytologic pleomorphism was pronounced, with occasional multinucleated bizarre tumor cells. The entire tumor was circumscribed, and the area of greatest cytologic atypia comprised approximately 15 to 20 percent of the tumor volume. Other foci revealed larger ecstatic spaces with considerable areas of hemorrhage. Immunoperoxidase studies showed tumor cells strongly immunopositive for smooth-muscle actin, while negative for CD34, cytokeratin, and S-100.

Discussion

Glomus tumors are rare, distinctive neoplasms that resemble the normal glomus body. They comprise less than 2% of soft-tissue tumors. In 1924, Masson first described the clinical presentation of glomus tumor as excruciating pain out of proportion to size, localized tenderness, and cold sensitivity that subsided abruptly following removal of the tumor. Most commonly, patients complain of episodic paroxysms of pain that radiate away from the lesion, which are triggered by changes in temperature, specifically cold exposure, as well as minor tactile stimulation. However, in some cases patients may also have clinical manifestations of hypertension, muscle atrophy or osteoporosis of the affected region in addition to symptomatic pain. Studies have demonstrated that the glomus tumor’s nerve fibers consist of substance P, a vasoactive peptide associated with pain, suggesting pain production and mediation as a possible result of the release of this substance.

Characteristically, glomus tumors occur as solitary or multicentric lesions in the deep dermis or subcutis of the upper or lower extremity, most commonly in the subungual region of the finger; however, occurrences at unusual sites where normal glomus bodies may be sparse or even absent have been reported, such as the gastrointestinal tract, respiratory tract and gynecological regions. Clinically, GTs are small, blue-red nodules often on the upper or lower extremity and usually <1 cm in diameter, but lesions up to 3 cm have been reported. Glomus tumors accounted for 1.6% of 500 consecutive soft-tissue tumors reported by the Mayo Clinic, and they occur equally in both genders but with a female predominance among patients with subungual lesions (3:1). Most glomus tumors are diagnosed between 20 and 40 years of age, with approximately 70% of solitary tumors occurring by age 30. Multiple subungual glomus tumors have been reported in neurofibromatosis type 1.

The malignant variant of glomus tumors is extremely rare and may arise from a preexisting benign lesion or de novo. A recent classification suggests that this term should be reserved for those tumors with discernible risk of metastasis. In 2001, Folpe et al. identified the following histopathologic criteria for malignancy in glomus tumor based on a 52-case study: large size (>2 cm) and deeply located lesions, or moderate to high nuclear grade and increased mitotic rate (>5 mitoses/50 cells).
high-power fields), or displaying atypical mitotic figures. Of the 21 GTs meeting the criteria for malignant classification, 38% developed metastases, supporting the importance of this classification system. In 1972, Lumley and Stansfeld reported a case of MGT that produced metastases with no prior benign glomus component. Additional reports have detailed patients with malignant glomus tumors arising from preexisting benign GTs, one of which produced pulmonary metastases within two years.

Histologically, GTs are well-circumscribed lesions that contain tight convolutes of capillary-sized vessels surrounded by glomus cells set in a hyalinized or myxoid stroma, and may exhibit a highly vascular appearance. Glomus cells are uniformly round to ovoid and form nests, sheets and trabeculae, interspersing the branching vascular channels that are lined by endothelial cells. The glomus cell is distinctive, allowing for the differentiation of this tumor from other similar lesions. The cells are regularly shaped, with sharply punched-out, rounded nuclei set off from the cytoplasm and well-demarcated borders that are accentuated with periodic acid-Schiff (PAS) or toluidine blue stain. Eosinophilic granular cytoplasm is a unique oncocytic feature that has been described in some glomus tumors. In half of the cases of malignant glomus tumors, a compressed rim of benign glomus tumor is observed bordering malignant regions. The tumor may maintain a structurally similar form to benign GT but is composed of sheets of round cells with high nuclear-to-cytoplasmic ratio, high nuclear grade, and typical or atypical mitotic figures, resembling round-cell sarcomas. Contrarily, the malignant tumor may structurally differ from its benign counterpart and consist of spindle or fusiform cells arranged in short fascicles. The presence of pseudocysts of varying size, consisting of proteinaceous material secondary to cystic degeneration, is a characteristic feature. Occasionally, confluent zones of necrosis are also appreciated. GTs are histologically distinguished from leiomyosarcomas with epithelioid change and from round-cell tumors such as rhabdomyosarcomas. Epithelioid leiomyosarcomas consist of larger cells with greater eosinophilic cytoplasm and characteristically display thick-walled blood vessels, in contrast to GTs, which demonstrate small branching vessels. Rhabdomyosarcomas will histologically demonstrate nested growth patterns, consist of multinucleated large cells with substantial eosinophilic cytoplasm, and are absent of perivascular growth, differentiating them from glomus tumors. Glomangiosarcomas also histologically resemble Ewing's sarcoma, but are differentiated by the characteristic intracellular glycogen, as well as the necrosis and crushing artifact commonly observed in Ewing's sarcoma.

Immunohistochemistry is also diagnostically useful in identifying both benign and malignant glomus tumors. Hidradenomas are adnexal tumors most closely resembling glomus tumors, but are appropriately differentiated through immunostaining, as they characteristically contain immunoreactive keratin and frequently express carcinoembryonic and epithelial membrane antigens, which are absent in GT. The S-100 immunostain is useful in distinguishing between melanocytic and glomus tumors, as highly cellular GTs may occasionally be mistaken for intradermal nevi or even malignant melanomas. Immunostains exhibiting cytoplasmic actin and the intricate chicken-wire pattern between cells of collagen type IV are features strongly suggestive of both benign and malignant GTs. Atypical glomus tumors may also be confused with primary cutaneous round-cell tumors such as Merkel cell carcinoma and eccrine spiradenoma, or more rare tumors such as cutaneous extraosseous ES/primitive neuroectodermal tumor (PNET). Unlike atypical GTs, Merkel cell carcinoma and eccrine spiradenomas will express cytokeratins, and although muscle-actin expression may be observed in eccrine spiradenomas, it is limited to the basal cells. Furthermore, actin is not demonstrated in cutaneous ES/PNET, and pericellular type IV collagen is not expressed. Cutaneous neuroblastomas may also be confused with glomus tumors; however, neuroblastomas will express neurofilament proteins, synaptophysin and chromogranin, which are markers for neural differentiation. In deep soft tissue, atypical GTs may need to be differentiated from hemangiopericytomas, which do not commonly express muscle actin and will histologically demonstrate the characteristic staghorn vessels as well as both spindleled and epithelioid cells. Studies suggest that actin and myosin immunohistochemical stains are more intensively highlighted in benign GTs than in MGTs, whereas the contrary is evident for vimentin stains. Additionally, other markers have been proposed to predict malignant behavior and differentiate MGTs from benign glomus tumors, such as overexpression of Bcl2, Ki-67, and p53.

Glomangiosarcomas are typically considered low-grade sarcomas. Complete local excision may be used for treatment, but there is a risk of recurrence and potential metastasis. Recent studies suggest the treatment of choice is wide excision with negative margins. Studies have shown that despite chemotherapeutic regimens, patients have rapidly died of the de novo glomangiosarcoma when widespread metastasis has resulted. Therefore, patients should be monitored closely following excision of these tumors.

In conclusion, although they are rare entities, malignant glomus tumors do in fact exist and have potential for widespread metastasis, specifically when meeting the criteria for classification set by Folpe et al. Approximately half of these malignant tumors have a discernable preexisting benign component, while the remainder...
arise de novo. When obtaining samples, careful sectioning is important, as histologic changes may only be focal. Appropriate clinical and pathologic correlation, in addition to immunohistochemical examination, is essential for the correct diagnosis in such soft-tissue tumors.

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A RARE MORPHEAFORM COMPLICATION OF A BLACK INK TATTOO

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Introduction

Many cultures have a long history of tattooing themselves for various symbolic reasons. Radiocarbon dating has identified mummies as old as 5,200 years with tattoos.1 Complications from tattoos are likely to have been occurring since that time. Kazandjieva noted that M. Hutin reported the first data on complications from the tattooing process in 1853.2 Since that time, there has been an extensive amount of medical literature documenting the complications of tattooing. We are reporting a rare complication of a black-ink tattoo.

Case Report

A 39-year-old male presented to our clinic for evaluation of a rash involving his right upper extremity. It was described as a warm, itchy and tender rash that had been present for about four to five months. His past medical history was notable for diabetes, hypertension and hyperlipidemia. He denied any significant history of alcohol, tobacco or drug use. He was taking the following medications: pravastatin, metformin, glipizide, lisinopril, insulin detemir, exenatide and omega-3-acid ethyl esters. He denied any medication changes within the year prior to onset of the rash. The patient noted his symptoms arose within a tattoo that was placed approximately five years before onset of the rash. He had no adverse reactions to the initial tattoo placement and one year later had a second tattoo placed just proximal to it. During the previous several years, he had had several other tattoos placed in various areas of his body.

Physical exam revealed an obese male with a firm sclerodermoid patch on his right upper extremity within a black-ink tattoo (Figure 1). There was no involvement of skin outside of the tattooed area, and his other tattoos remained free of clinical findings. The differential diagnosis at the time of presentation included: hypersensitivity reaction, scleroderma, lupus profundus, morphea and Well’s esoinophilic cellulitis. A biopsy revealed a diffuse, superficial and deep, perivascular, perinodular and interstitial infiltrate composed of numerous plasma cells. An immunohistochemical evaluation of the plasma cells demonstrated a kappa/lambda light-chain ratio of 4:1, suggestive of a plasmacytoma. AFB and PAS were negative for microorganisms. A second biopsy was obtained to further explore the possibility of a cutaneous plasmacytoma. A urine and serum protein electrophoresis was also obtained. The repeat biopsy demonstrated a superficial and deep, mixed lymphoid infiltrate with numerous mature plasma cells, an increased number of eosinophils, and dermal sclerosis. Immunohistochemical staining demonstrated a kappa/lambda light-chain ratio of 2:1, consistent with a reactive plasma-cell infiltrate. The urine and serum protein electrophoresis revealed no monoclonal gammopathy or light-chain disease. The final histopathology was interpreted as morphea arising within a tattoo. The plasma-cell infiltrate was interpreted as an exuberant inflammatory response to the tattoo pigment.

Discussion

Tattoos have become increasingly common, resulting in a multitude of adverse reactions and complications being reported in the literature. These include infections, granulomatous reactions, allergic reactions, photosensitivities, lichenoid reactions and pseudolymphomatous reactions.3 There have been few reports of morpheaform or scleroderma-like reactions in the literature.4,5 Ours is an interesting case of a morpheaform reaction arising in a tattoo, mimicking a cutaneous plasmacytoma. Our patient’s initial biopsy (Figure 2) was suggestive of a monoclonal proliferation of plasma cells. There are reports in the literature documenting pseudolymphomatous tattoo reactions.5 These have been attributed to several etiologies, including tattoo ink.6 Our patient was reevaluated, and clinically his plaque had progressed to a larger sclerodermoid plaque that extended into an adjacent tattoo. A repeat biopsy did not confirm the presence of a monoclonal plasma-cell infiltrate or significant light-chain restriction. Given the histologic changes and clinical findings, we believe the patient developed a localized morphea.

Early-stage morphea findings consist of closely packed collagen fibers in the dermis with a lymphocytic infiltrate at the dermal-subcuticular junction. In this case, the lymphocytic infiltrate was plasma-cell predominant. This is known to occur especially in the early developmental stage of morphea.4 Repeat biopsy on our patient suggested the progression to a later-stage morphea, with hyalinized collagen bundles and a paucity or decrease in adnexal structures (Figure 3). In addition, there is a marked decrease in cellularity, especially when compared to the first biopsy. This progression is noted by comparing the early biopsy in Figure 2 to the repeat biopsy in Figure 4. Unfortunately, the biopsy did not include the subcuticular junction. However, our histologic findings do suggest the progression of morphea through an early stage to a later stage. Our patient lacked any clinical findings to suggest CREST syndrome or progressive systemic sclerosis, and given the localization of symptoms within his tattoo, we speculate his findings were secondary to an inflammatory reaction to the pigment, demonstrated in Figure 5.

Our patient has undergone several treatment modalities, including topical corticosteroids, intralesional injection of corticosteroids, and UV phototherapy, to which he failed to respond. Laser tattoo removal at the present time would not be considered due to the potential risk of developing systemic complications with the release of pigment from macrophages.7 There are reports of generalized reactions following laser treatment,6 so we believe...
recommending laser treatment would not be appropriate. A trial of dapsone was given for its anti-inflammatory effect, and thus far, the patient has had mild improvement in his plaque. Failing this, surgical removal may be considered.

References

Lessons in Dermatoscopy: Dermatoscopic Pattern of Facial Melanoma in Situ (Lentigo Maligna)

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ABSTRACT

Facial melanoma in situ on sun damaged skin, or lentigo maligna, often presents as a subtle, indolent, irregular macule or patch that may mimic other benign or malignant neoplasms. Dermatoscopy may aid in the early diagnosis when features of dark brown or black asymmetrically pigmented follicular openings, slate-gray dots/granules (dermatoscopic regression), streaks, and rhomboidal structures are identified.1 In this article, we describe a 56-year-old man with an irregular brown macule on the cheek that showed dermatoscopic features consistent with melanoma in situ on sun-damaged skin.

Case Report

A 56-year-old white male presented with a brown, irregular lesion on his right cheek. Clinically the lesion was a flat, ill-defined, light and dark brown macule approximately 9 mm in diameter (Figures 1 and 2). Dermatoscopically, the lesion had asymmetric, pigmented follicular openings and subtle blue-gray pigmentation (Figures 3 and 4).

Discussion

Melanoma in situ on sun-damaged skin of the face, or lentigo maligna, is also known as Hutchinson’s melanotic freckle and premalignant melanosis of Dubreuilh.4 It is a histogenetic subclass of a melanocytic malignancy usually found on sun-damaged skin, often on the face, of middle-aged and elderly persons.4 Initially, melanoma in situ on sun-damaged skin presents as a flat brown or black, irregularly shaped lesion that often thins out at the edges.4 It grows slowly over months to years and may show central regression, so patients may give a history of a changing lesion with increasing size.4

Early diagnosis of facial melanoma in situ can be difficult, as many other skin lesions, such as solar lentigines, flat seborrheic keratoses, pigmented actinic keratoses, and early pigmented basal cell carcinomas, can mimic melanoma.1 The dermatoscope is a useful tool and can help identify the diagnostic features for differentiating between malignant and benign skin lesions.

The differential diagnoses in this case included malignant melanoma in situ (lentigo maligna) or a solar lentigo. Dermatoscopically, the lesion had the malignant features of asymmetric, pigmented follicular openings, focal gray-brown dots, and blue-gray pigmentation. An excisional biopsy was performed to rule out malignant melanoma in situ. Histopathologically, the lesion indeed was diagnosed as malignant melanoma in situ. Step sections were performed and showed nests of melanocytes confined to the epidermis. The nests were not equidistant from one another and varied in size and shape. In addition, there were increased numbers of individual melanocytes, and the dermis contained marked solar elastosis.

The dermatoscopic features for melanoma on sun-damaged skin consist of the following: The dark brown or black, asymmetrically pigmented follicular openings represent atypical melanocytes descending unevenly down individual hair follicles.3 Other features include slate-gray dots/granules (dermatoscopic regression), streaks, and the formation of rhomboidal structures.1

Schiffner described a model for the progression of lentigo maligna. As the malignant cells proliferate around and down hair follicles, aggregated dots and globules intertwine to form short streaks.3 Streaks lengthen and connect to form rhomboidal structures, resulting in the annular-granular pattern, and eventually coalesce into homogeneous areas.3 Early on, asymmetric follicular openings are seen; however, as melanoma cells invade the follicle and dermis further, the hair follicles eventually become obscured.3

Sometimes other lesions can share some of the features of melanoma on sun-damaged skin. Melanocytic nevi in adolescents and lichen planus-like keratoses may demonstrate slate-gray streaks and dots/granules.3 Another melanoma simulator is pigmented actinic keratoses, which are considered by some as collision tumors of actinic keratoses and solar lentigines.3 They often have dermatoscopic features of asymmetric follicular openings, rhomboid-
dal features, and gray dots/granules. The helpful clues to the diagnosis include the additional clinical features of a fine scale, moth-eaten borders, fingerprinting, and fine, interrupted lines. Melasma may also have an annular-granular pattern, but is usually differentiated clinically. The take-home message is that no single criterion reliably makes a specific diagnosis; therefore, using a combination of criteria is the best approach. Schiffner’s four features of asymmetric, pigmented follicular openings, dark brown/black rhomboidal structures, slate-gray dots, and slate-gray globules provides a specificity of 96% and a sensitivity of 89%.

Finally, the selection site of biopsy is important for obtaining histological confirmation of melanoma on sun-damaged skin. If possible, an excisional biopsy should always be performed. If, however, the lesion is too large, an adequate biopsy should be taken from within the dark-brown, black, or slate-gray areas, as the changes in other parts of the lesion may be too subtle for a definitive diagnosis. If the histopathology is equivocal or negative but the dermatoscopic suspicion is high, the clinician should repeat the biopsy.

References
A BUMP ON A CHILD’S FOOT: INFANTILE DIGITAL FIBROMATOSIS

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ABSTRACT

Infantile digital fibromatosis is an asymptomatic growth of myofibroblasts with a unique histological finding of eosinophilic intracytoplasmic inclusion bodies. These nodules mostly occur on the dorsal and lateral aspects of the fingers or toes of young children, with one-third being congenital. The lesions frequently recur following excision and have been reported to spontaneously regress. We present a 2-year-old boy with two large nodules on his right foot that have been present for about one year.

Case Report

A 2-year-old male was seen in our office for a growth on his right foot that was initially noticed by his mother at approximately 1 year of age (Fig. 1). Then, within the previous three months, a second growth adjacent to the initial lesion was noticed. The mother reported that her son did not seem to be bothered by the nodules, and she denied that her son scratched or guarded them or that the growths exhibited signs of bleeding or drainage of any exudative material. The mother additionally reported that her son could not wear shoes due to the size of the lesions. The mother also reported that she had a normal pregnancy with a non-complicated vaginal delivery and that her son was up to date with all of his immunizations. The mother stated that there were no other previous medical problems with her son, who lived with both parents and an older brother. The mother denied any trauma to the affected foot. The mother also denied any recent travel. The family history was non-contributory.

Figure 1. Two-year-old boy with two large, fleshed-colored nodules on right foot.

Physical exam revealed a healthy-appearing 2-year-old male who interacted appropriately for his age and development. A firm, non-tender, fleshed-colored, 5-cm nodule with an adjacent 1-cm firm nodule was appreciated at the base of the third and fourth digit of the right foot (Fig. 1). The nodules were non-erythematous and non-fluctuant. The patient was noted to ambulate without difficulty.

An X-ray of the affected foot revealed no boney involvement. A 3mm punch biopsy revealed spindle cells in interlacing bundles in the dermis containing eosinophilic intracytoplasmic inclusion bodies consistent with infantile digital fibromatosis (Figs. 2 and 3).

Figure 2. Spindle cells in interlacing dermal bundles.

Figure 3. Eosinophilic perinuclear intracytoplasmic inclusion bodies.

Discussion

Infantile digital fibromatosis (IDF) was first described by Reye in 1965 as a recurring fibrous tumor of childhood (1). It is also known as Reye’s tumor and inclusion body fibromatosis (2). This rare tumor behaves in a benign manner, with no reports of metastases, and is clinically asymptomatic (2). It typically presents as a firm, fleshed-colored nodule that almost always occurs on the dorsal or lateral aspects of fingers or toes with sparing of the thumbs and great toes (2). Although the cause is unknown, it has been proposed that deregulation of the transforming growth factor-β superfamily may play a role (3). Myofibroblasts are the primary cell type in IDF, and transforming growth factor-β1 mediates the differentiation of myofibroblasts from fibroblasts (3).

Clinically, IDF may resemble keloids or knuckle pads and must be differentiated from lymphoma, fibrosarcoma, sarcoidosis, or other malignancy. Thus, a skin biopsy is recommended, as IDF has a unique histology. The characteristic finding that distinguishes IDF from other fibromatoses is eosinophilic inclusion bodies in the cytoplasm of the myofibroblasts (4-6). These inclusion bodies are believed to be composed of actin and vimentin and stain pink with H&E, red with Masson’s trichrome, and purple with phosphotungstic acid hematoxylin (4-6).

This case presents unusually large tumors, as most are less than 2 cm. IDF can present with single or multiple nodules that are typically on the dorsal or lateral aspects of the fingers or toes. Males and females are equally affected. IDF has a classic growth pattern, with about one-third being congenital and most cases presenting in early childhood (2). Adult cases of IDF have been reported but are considered very rare (8). IDF has also been reported to spontaneously regress without scarring over several years, although larger lesions may cause joint contracture or functional impairment of the digit.

Conservative treatment is the mainstay, as IDF is considered benign in behavior and has a reported 60-75% recurrence rate after surgery (9). Surgical intervention should be considered if possible joint mobility problems due to IDF is an issue. Mohs micrographic excision using immunohistochemical stains has been reported as a successful treatment modality (9). Most IDF can be monitored clinically for signs of aggressive behavior. Due to the large size and possibility of functional impairment, our patient was referred for possible surgical management.
References

A Case Report of Muir-Torre Syndrome

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ABSTRACT
In this case report of Muir-Torre syndrome (MTS), we describe a 63-year-old man with a personal and family history of MTS with multiple colon cancers and sebaceous tumors who presented with a recent sebaceous carcinoma. The lesion was examined clinically, dermoscopically, with in-vivo reflectance confocal microscopy (RCM), and histologically. The features of his sebaceous carcinoma are described here as well as a topic review of MTS.

Case Report
A 63-year-old gentleman with a known history of Muir-Torre syndrome (MTS) and non-melanoma skin cancers presented for routine skin cancer screening and was noted to have a 7 mm, ulcerated, pink-brown papule on his right lower back (Figure 1). His diagnosis of MTS was made in the 1990s, when he had numerous skin cancers and sebaceous neoplasms that prompted his previous dermatologist to refer him for genetic testing for MTS. The patient’s past medical history revealed at least three colon cancers, the first of which presented at age 48, and a duodenal cancer. His family history also included colon cancer in both of his parents and a sister with at least three colon cancers, the first of which presented before age 48. His past medical history revealed at age 30 a CAse report of muir-torre syndrome (MTS) and non-melanoma skin cancers in both of his parents and a sister with multiple colon cancers and sebaceous tumors who presented with a recent sebaceous carcinoma. The lesion was examined clinically, dermoscopically, with in-vivo reflectance confocal microscopy (Figure 2). In vivo reflectance confocal microscopy (RCM) of the lesion was similar to that of sebaceous hyperplasia—the sebaceous glands appeared as granulated clusters of round cells with central, round, dark nuclei and a rim of brightly speckled cytoplasm due to the highly refractive lipid droplets within the sebaceous acinar cells (Figure 3). Additionally, there were some dendritic cells and dilated linear vessels around the aggregates of sebaceous cells (Figure 3). To date, the RCM features of sebaceous carcinomas have not been described, and more cases must be examined to look for possible features to distinguish sebaceous carcinomas from sebaceous hyperplasia or other lesions of sebaceous differentiation. Histopathologic evaluation showed proliferation of sebaceous glands in the dermis consisting of sebaceous, basaloid, and squamoid cells as well as an associated proliferation of hyperplastic squamous epithelium, confirming the diagnosis of sebaceous carcinoma (Figures 4 and 5).

Discussion
Muir-Torre syndrome (MTS), first described by Muir in 1967 and Torre in 1968, is a rare, autosomal-dominant genodermatosis characterized by sebaceous skin neoplasms, or multiple keratoacanthomas, and internal malignancies. Over 200 cases have been reported, with a male to female ratio of 2:1. The condition is also thought to be a phenotypic variant of hereditary nonpolyposis colorectal cancer (HNPPC), also called Lynch syndrome. HNPPC is also an autosomal-dominant predisposition to colorectal cancer and other malignancies. Both diseases are caused by germline mutations in the DNA mismatch repair genes MSH2 or MLH1, resulting in tumors with microsatellite instability. MSH2 is located on chromosome 2p, and MLH1 is on chromosome 3p. Though the incidence of mutations in MSH2 and MLH1 are nearly equal in HNPPC, mutations in MSH2 are much more common than mutations in MLH1 in MTS. Recently, cases of MTS with MSH6 mutations have also been reported, where MSH2 and MSH6 were often linked with both gene proteins intact or both deficient. A less common subtype of MTS lacks microsatellite instability and mismatch repair gene defects but is associated with mutations in MYH homo-log (MYH), a base excision repair gene. Inactivation of the fragile histidine triad (FHIT) has been linked to MTS. Sporadic cases of MTS have also been reported. The sebaceous skin neoplasms found in MTS include sebaceous adenomas, sebaceous epitheliomas (sebaceomas), basal cell epitheliomas, cystic sebaceous tumors, and sebaceous carcinomas. Sebaceous adenomas are the most common type, but the presence of any of these lesions should prompt consideration of MTS and evaluation for visceral malignancies. Cystic sebaceous adenomas and sebaceous adenomas with keratoacanthoma features, termed seboacanthomas, are highly specific markers for MTS, whereas sebaceous hyperplasia and keratoacanthomas (KAs) are found in the general population and are nonspecific. On the other hand, KAs with sebaceous differentiation, KAs in non-sun-exposed areas, KAs in younger patients, or multiple KAs present in a patient with colon cancer are highly suggestive of MTS. Sebaceous neoplasms that are difficult to classify also should be considered markers for MTS.

Most sebaceous tumors of MTS occur in the head and neck region and are of low malignancy. They can occur before, during, or after the onset of internal malignancies, including decades before or after the visceral malignancy. Sebaceous carcinomas constitute 30% of sebaceous neoplasms in MTS and can have a more aggressive growth pattern and metastatic potential, especially if located on the eyelid, but generally lack the infiltrative growth pattern and marked cellular atypia of true carcinomas. They can be treated by wide local excision or Mohs micrographic surgery. Benign sebaceous neoplasms can be treated with curettage, excision, cryosurgery, or radiotherapy. Oral retinoids alone or in combination with interferon alpha may be used to prevent new sebaceous lesions.

The most common internal malignancies in MTS are colorectal followed by genitourinary. Both the visceral and sebaceous malignancies in MTS reportedly have a more indolent course than those in the general population, even after metastasis. Additional characteristics are that colorectal carcinoma in MTS patients usually presents 10 years earlier (median age,
50 years) than the general population (age range 55-65 years) and occurs proximal to the splenic flexure. Other less frequently associated cancers are breast carcinoma, hematologic malignancies, head and neck cancers, and small intestine cancers. Endometrial cancers develop in about 15% of women with MTS. Although there are no universal screening guidelines, some experts have recommended that all MTS patients should have frequent screening colonoscopies, biennial according to some sources while others recommend every one to two years, beginning at age 20-25 or 10 years before age of colon cancer diagnosis in a first-degree relative. Other important tests are annual history and physical examination including complete skin exam, serial urinalyses, and complete blood counts. In addition, women with MTS should undergo routine gynecologic evaluations including breast and pelvic examinations with Pap smear at least by age 30, and endometrial biopsies and transvaginal ultrasounds if indicated.

The clinical diagnostic criteria for MTS include at least one visceral malignancy plus at least one sebaceous adenoma, sebaceous carcinoma, sebaceoma, or keratoacanthoma with sebaceous differentiation. Alternatively, MTS can be diagnosed if a patient has multiple keratoacanthomas, multiple visceral malignancies, and a family history of MTS. Molecular genetic analysis for germline mutations in DNA mismatch repair genes and examination of tumor tissue for microsatellite instability are both expensive and time-consuming methods, whereas immunohistochemical testing of tumor tissue for MSH2 and MLH1 protein is fast, reliable, and cost-effective, making it a useful screening tool with a high predictive value for identifying patients with mismatch repair defects.

In summary, a histopathologic diagnosis of sebaceous neoplasms should lead to immunohistochemical studies to look for loss of mismatch repair gene expression. Such cases then should be confirmed with molecular genetic analysis as well as referral for genetic counseling and other diagnostic procedures to screen for internal malignancy, namely colorectal or genitourinary cancers.

References

Case Report

A 49-year-old male with a past medical history of HIV/AIDS (CD4 count of 5) for 17 years, tuberculosis for two months, hypertension, illicit drugs and alcohol abuse, and gout presented to the emergency room with a three-day history of severe swelling of the left foot and a progressively worsening rash for three weeks. The patient had been started on allopurinol one month prior to the rash.

On presentation, the ill-appearing patient had a low-grade fever along with widespread purpuric macules and atypical targets with skin detachment of greater than 30%. Flaccid bullae were also present with a positive Nikolsky’s sign. Mucosal involvement included bilateral conjunctiva, oral mucosa, and genitalia. Based on the history of allopurinol use, multiple comorbidities, and the clinical picture, a diagnosis of TEN was made with a SCORTEN score of 2. Histopathology revealed basal cell hyperplasia, lymphocytic infiltration, and epidermal necrosis. The patient was admitted to the ICU, allopurinol was discontinued, and supportive care was initiated. IVIG at 1 gm/kg/day was initiated for a total of five days. The patient’s skin sloughing ceased to progress, and re-epithelialization occurred 10 days after IVIG was initiated. The patient continued to improve and achieved near normal cutaneous regeneration.

Discussion

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are dermatological emergencies with surrounding nosologic controversies. Due to the fact that the pathogenesis of these disorders is not well understood, there is a lack of consensus as to whether the two conditions are within a spectrum of disorders or if they are completely separate entities. The most widely accepted criteria, which will be used herein, demonstrates a continuum between SJS and TEN and separates both of these conditions from severe erythema multiforme (EM).

The continuum of SJS and TEN is classified by the percent sloughing of the body surface area. SJS is less severe and involves less than 10% of the body surface area; TEN involves 30% or more of the body surface area. SJS/TEN overlap constitutes between 10% and 30% desquamation of the total body surface area. Mucous membranes are involved in over 90% of SJS cases and nearly all TEN cases. There are usually more than two mucous membranes involved. Ocular complications are generally the most concerning and require prompt consultation.

These two conditions are relatively rare. The estimated incidence ranges from two to seven cases per million people per year, in which SJS is more common.2 Both may occur at any age, but TEN patients tend to be slightly older, ranging from 46 to 63 years of age versus 25 to 47 years of age in SJS.21 HIV patients are more susceptible to SJS and TEN. The exact reason is not known; however, it is postulated that it could result from multiple exposures to medicines and infections, as well as a derangement in the immune system. Another theory relates to these patients being “slow acetylators,” which causes excess toxic metabolites from medicines and depleted glutathione reserves, which act as potent antioxidants.4 Systemic lupus erythematosus patients appear to experience greater rates of SJS and TEN. In addition, it has been thought that malignancy may increase the risk of these two conditions; however, it is uncertain whether it is the malignancy itself or the exposure to multiple causative medicines.

Medications are the leading etiology in both SJS and TEN. Children account for a slightly higher percentage of SJS cases related to infections, such as mycoplasma pneumoniae. The medication list involved in these two conditions is extensive. The most common groups of medicines include anti-gout agents, antibiotics, anti-psychotics, antiepileptics, analgesics, and NSAIDS, particularly piroxicam. The most common anti-gout agent is allopurinol. Sulfonamides are also the most common anti-biotic, followed by penicillins and cephalosporins. Patients with the HLA-B-1502 allele are at increased risk for SJS and TEN due to carbamazepine and other aromatic anticonvulsants.8 Due to the fact that the presence of this allele is quite high in patients of Asian and South Asian descent, the United States Food and Drug Administration has issued a regulation to screen these patients prior to carbamazepine use. Furthermore, higher doses and more rapid administration of these medications may increase the risk of SJS or TEN. For example, allopurinol doses higher than 200 mg/dL per day were associated with a greater risk of developing SJS or TEN.27 Also, lamotrigin was associated with higher incidences of severe skin reactions when it was initially introduced. Therefore, recommendations were made for gradual titration of the medication, resulting in fewer reports of SJS and TEN.27

The exact mechanism of sloughing is not well understood. The quicker onset of symptoms with recurrent exposure of an offending agent suggests an immunologic process. Granulysin, a cytolytic protein, was the most highly expressed molecule isolated from SJS and TEN patients’ blisters.29 There was a direct correlation between the amount of granulysin and severity of the disease. Other theories include the interaction of the Fas ligand with the Fas receptor, which induces apoptosis. The Fas ligand was elevated in 5 of 7 patients with SJS and TEN.26 As previously mentioned, SJS and TEN belong to a spectrum of desquamative skin disorders and are completely separate entities from bullous erythema multiforme. Bastuji-Garin et al. classified these disorders into five categories:27

1) Bullous erythema multiforme (EM): characterized by typical (three different zones) or raised atypical (two different zones and/or poorly defined border) target lesions. Epidermal detachment is less than 10% of the total body surface area.
2) SJS: diffuse purpuric or erythematous macules or flat atypical targets in association with less than 10% total body surface area epidermal detachment.
3) SJS/TEN overlap: widespread purpuric macules or flat atypical targets with 10%-30% body surface area epidermal detachment.
4) TEN with spots: greater than 30% epidermal detachment with flat atypical target or purpuric macules (Fig. 1).
5) TEN without spots: large sheets of epidermal detachment involving greater than 10% of the body surface area without

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targetoid lesions or purpuric macules.

Skin biopsy is helpful in determining the diagnosis of SJS or TEN versus the differential diagnosis, which most commonly includes erythema multiforme, erythematous drug eruptions, acute generalized exanthemezutis, putulosis, photo-toxic eruptions, paraneoplastic pemphigus, and staphylococcal scalded skin syndrome. An appropriate sample should be obtained with a 4 mm or greater punch biopsy or deep shave biopsy, although some argue that a regular shave biopsy is sufficient due to the fact that these are epidermal diseases. Two biopsy specimens should be taken: one for formalin-fixed hematoxylin and cosin processing, and one for immediately frozen section.

The earliest finding in SJS is that of perivascular mononuclear inflammatory infiltrate, primarily of T-lymphocytes. This, however, is not diagnostic, as it may be seen in many other conditions, such as simple drug-related exantheme. Clusters of lymphocytes progressively surround dying basal keratinocytes, a phenomenon termed satellitosis. Subsequently, frank subepidermal vesiculation develops with full thickness epidermal necrosis. Once fully developed, SJS demonstrates full thickness detachment with splitting above the basement membrane. There is minimal inflammatory infiltrate and normal immunofluorescence. The histopathology of TEN is very similar, with sweat duct involvement, basal cell hyperplasia, lym

phocytic infiltration, and necrosis (Fig. 2).

Although there are clinical and histological clues to the diagnosis of SJS and TEN, there are no widely-accepted diagnostic criteria. There should be suspicion for the above disorders if there is a history of a potential causative medicine, a proctome of an acute onset febrile illness and malaise, targetoid lesions, erythroderma progressing to vesicles and bullae, or necrosis and sloughing of the epidermis.

Treatment of SJS and TEN is just as controversial as the nosology. However, there are universally accepted recommendations, which include immediate removal of potential causative agents, supportive care with fluid and electrolyte management, nutritional support, wound care, pain management, and treatment of infections. It must be understood that SJS and TEN involve multi-specialty teams, and appropriate, prompt consultation should be initiated. Transfer to a burn unit also improves prognostic outcome.

Beyond supportive care, there are no established therapies. There are two schools of thought on the administration of glucocorticoids. The therapy behind this treatment is that pooled human IVIG contains antibodies that block the Fas ligand from its receptor, and thus prevent target cell death. The survival rate was found to be 88% in a retrospective study over a three-year period in 48 patients treated with IVIG. This regimen is also well-supported in the pediatric population.

The prognosis of TEN is assessed through a scoring system referred to as SCORTEN, which is based upon seven independent and easily measured clinical variables and laboratory values. This scoring system must be used on days one to four. The criteria include age over 40 years, pulse greater than 120 beats per minute, presence of cancer or hematologic malignancy, greater than 10% total body surface area epidermal detachment on day one, blood urea nitrogen greater than 28 mg/dL, blood glucose greater than 252 mg/dL, and bicarbon

or less than 20 mEq/L.

Table 1

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<th>Score</th>
<th>Mortality</th>
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<td>1-1</td>
<td>32.2%</td>
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<tr>
<td>2</td>
<td>12.1%</td>
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<tr>
<td>3</td>
<td>35.3%</td>
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<tr>
<td>4</td>
<td>58.3%</td>
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<tr>
<td>5 or greater</td>
<td>90.0%</td>
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1. Each variable is assigned one point, and mortality significantly increases with each additional point (Table 1). A SCORTEN of 0-1 correlates to 3.2% mortality, whereas a score of 5 or greater correlates to 90% mortality.

In conclusion, cases of SJS and TEN need emergent attention, as they have proven to be fatal, especially in the elderly and immunocompromised. These life-threatening mucocutaneous diseases are usually drug-related. Although optimal treatment remains to be clarified, it is universally agreed upon to stop the offending agent and provide supportive care.

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References:


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

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

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DESCRIPTION
Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.3%), and isobutane propellant.

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

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

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifested as Cushings syndrome, hyperglycemia, and glucocorticoid in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression is noted, the patient should be withdrawn from the use of the drug, or a less potent steroid, or a less occlusive dressing may be used. In patients on immunosuppressant therapy, an increase in frequency of infections may occur.

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

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient
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; avoid contact with the eyes and inhalation of the spray.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests
A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone showed negative results.

Pregnancy: Teratogenic Effects
Category C. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

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

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

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

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (frequent dabs on a small area are a frequent cause) burning, itching, irritation, dryness, folliculitis, pustulosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and milia.

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

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

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

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

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Lowila® care cleansing bar
Pernox® salicylic acid and sulfur cleanser
Sebulex® salicylic acid and sulfur shampoo
Balnetar® therapeutic tar bath

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Case Presentation

A 52-year-old white female was enjoying 4th of July festivities at “River Fest” in Wilmington, NC, when her husband lit the fuse on a cannon containing black powder. Unfortunately, this patient stepped in front of the cannon as it was firing; as a result, she was left with a significant amount of black-powder tattooing forming dark spots over her right cheek and neck.

Discussion

The patient presented to Atlantic Dermatology Associates, P.A., for evaluation and removal options for the black pigment tattoo.1 James A. Bailey, PhD, was consulted in this case to discuss the powder composition by-products. It was determined that removal of the black pigment, or the tattoo removal, would be safe to treat with laser. Because of the deep pigmentation of the impregnated foreign material, the Candela GentleLASE, which emits its energy at a wavelength of 755 nm, was chosen for the treatment. This particular wavelength has an affinity toward melanin, the primary determinant of skin and hair color. When treating traumatic tattoos with lasers, the gun powder mimics the naturally occurring melanin and is preferentially absorbed by the laser energy.2,3 By absorbing the energy, the powder is heated rapidly and disintegrates.

Typically, a Q-switched 755 nm laser is used to treat tattoo inks, traumatic tattoos such as the one described here, and unwanted pigmented lesions.4 Q-switched devices can deliver very short pulse durations of laser energies, creating more of a photo-acoustical impact on the tattoo or pigmented lesion. This allows the pigmented material to more readily be absorbed. Lacking a Q-switched device but possessing a very powerful alexandrite laser, treatments were delivered at monthly intervals for two months with the expectation that a few more treatments may be required to completely clear the tattoo. The Candela GentleLASE 755 nm laser was set at 18 mm spot size, 20 fluency, and cooling spray 50 with a 50-millisecond delay for treatment.

Impressively, the patient demonstrated over 80% clearance after only two treatments.—Monthly treatments will continue until the patient’s traumatic tattooing sustained from an accidental cannon blast injury is totally clear.

References

Malignant melanoma is one of the most rapidly increasing cancers in the US in older populations, while in younger populations the incidence is beginning to stabilize. The lifetime risk for melanoma has been increasing significantly over the last few decades. We examined population-based data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute and the State Cancer Profiles to compile the newest changes in the epidemiology of melanoma. Various risk factors can affect the prognosis of melanoma, and steps can be taken by patients to avoid melanoma early on. With patient education and screening, physicians can continue to assist in the early diagnosis of melanoma and lead the fight to decreased morbidity and mortality.

**Introduction**

Malignant melanoma is one of the most rapidly increasing malignancies in the United States in older age groups, while in younger groups the incidence is beginning to stabilize. The lifetime risk for melanoma has been increasing significantly over the last few decades. For persons born in 1935, the risk of developing invasive melanoma was 1 in 1,500, for persons born in 1960 the risk was 1 in 600, for persons born in 1980 the risk was 1 in 150, and it is estimated that for people born in 2006 the risk is 1 in 62. We examined population-based data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute and the State Cancer Profiles to compile the newest changes in the epidemiology of melanoma. Various factors can affect the prognosis of melanoma, and steps can be taken by patients to prevent melanoma early on. With patient education and screening, physicians can continue to assist in the early diagnosis of melanoma and lead the fight to decreased morbidity and mortality.

**Incidence, Mortality and Survival**

Melanoma of the skin accounts for 4% of skin cancer cases but 80% of all skin cancer deaths. According to the most recent statistics from SEER based on data from 2002-2006, the average age for melanoma of the skin is 59 years. Men have a higher risk for melanoma than women at 25 per 100,000, with the risk for women at 15.8 per 100,000. The national incidence from 2000-2005 has increased by 2.5 cases per 100,000 a year for men and women, whereas in Florida there has been a slight decline of -0.7 annual percent change (APC). As of 2005 in Florida and nationally, melanoma ranks as the 8th most common cancer, 5th for men and 7th for women. For men, the incidence of melanoma is highest on the back, which is a difficult area for early diagnosis due to difficulty viewing the back during self-exams. For women, melanoma most frequently occurs on the lower legs. Lightly pigmented Caucasians with blue/green eyes and blond/red hair have a higher incidence than Hispanics, Asians and African Americans.

The average age of death from melanoma of the skin from 2002-2006 was 68 years of age. The rates of death are declining for both men and women. The five-year rate change nationally and for Florida from 2001-2005 showed a slight increase in annual percentage change (Table 1), but is still a stable rate of change. This elevation can be due to increased recognition of melanoma-induced deaths due to increased diagnosis. It has been stated that one American dies from melanoma every hour, and that it is one of the leading cancers in terms of average years of life lost per death from the disease. This scary statistic is due to the fact that it affects more younger people than most cancers.

The staging system for melanoma was updated by the American Joint Commission on Cancer (AJCC) in 2002 and is based on the TNM (tumor, nodes, and metastasis) system (Table 2). The T stage is based on the microstaging of the primary tumor, which can be categorized by two methods: Breslow depth or Clark’s levels. Breslow depth is the measurement of the thickness of the primary tumor, while Clark’s levels (Table 3) are categorized by the level of invasion into the dermal layers of skin and subcutaneous fat. Five major changes were made in the staging system: (1) Clark’s level was replaced by Breslow depth as the prognostic variable of primary tumor invasion that best predicts survival, (2) ulceration of the primary lesion was included in the staging for each T stage, (3) the size of the lymph nodes was replaced by the number of lymph nodes involved for the N stage, (4) patients were categorized into clinical and pathologic staging to include lymphatic mapping data and micrometastatic disease within lymph nodes, and (5) stage IV was subcategorized based on anatomic site and inclusion of an elevated serum LDH.

If melanoma is detected in stage I or II there is an excellent chance for cure, but the five-year survival rates of stage III and IV melanomas (metastatic) are less than 10%. According to SEER, the overall five-year survival has been improving, and during 1999-2005 was 91.4%. Table 4 shows the five-year national survival rates based on race and sex, while Table 5 shows the national five-year survival rate based on stage at diagnosis. Table 6 shows the national five-year survival rate based on depth at diagnosis.

**Risk Factors**

Many studies have reconfirmed the common risk factors for melanoma, i.e. a tendency to freckle, light hair color and light skin pigmentation. Baumert et al. pointed out that fairer skin types have a significantly increased risk for developing melanomas with greater tumor thickness. Because of this known increase in risk, physicians should be sure to emphasize the importance of self skin exams (SSEs), especially to those with elevated risk factors. These have been studied and proven to be more effective when discussed with partners together. Robinson et al. determined that wives were more likely than husbands to be aware of the melanoma criteria (ABCDE rules, Table 7), read information about skin cancer detection, perform skin self-examination, and use sunscreen regularly. They were also more proactive about new suspicious lesions than their husbands. Since melanomas are also most common on the backs of men, the assistance of a partner in self skin exams is invaluable. In a study done by Baumert et al., increased tumor thickness was associated with subjects who live alone and subjects with a low education level (no high school diploma or equivalent). Of the 217 subjects in the study who presented with a tumor thickness > 1.5 mm, 38.8% lived alone, and 35.4% had a low education level. There has also been a correlation made with unemployment status and an increased risk of developing melanoma > 1.5 mm.

The risk factor for non-melanoma skin cancer and its relationship with ultraviolet (UV) irradiation has been well documented, but studies are still being carried out to determine the exact relationship between ultraviolet irradiation and melanoma. It is widely understood that there is interplay of genetic mutations and the UV exposure causing the melanocytes to transform into malignant melanomas. In a study performed by Garland et al. reviewing melanoma cases in the Navy from 1974-1984, a few occupational risks were...
established. People with primarily indoor occupations had a higher age-adjusted incidence rate of melanoma, whereas people with mixed indoor and outdoor jobs had the lowest age-adjusted incidence rate of melanoma. Interestingly, people with mixed indoor and outdoor jobs had a higher age-adjusted incidence rate of melanoma, whereas people with primarily outdoor jobs had only a moderate age-adjusted rate of melanoma. This relationship has been linked to the protective role of vitamin D, and the benefit of exposure to sunlight in small doses. As discussed by Garland et al., a mechanism has been proposed in which previously initiated melanocytes are inhibited by vitamin D from presenting clinically. It was also noted that people with a high level of lifetime sun exposure actually had a decreased risk for melanoma. Even though there has been a link established between sun exposure and melanoma protection, a time limit of 10-15 minutes has been set as the optimal time limit.

**Clinical Presentation, Diagnosis and Prognosis**

The clinical presentation of a melanoma can be an evolving mole or a new lesion growth. There are different presentations depending on the subtype of melanoma. Most cases of melanoma are found by the patient or spouse, leaving less than a third of melanomas to be discovered first by the physician. When they are found by the physician, the melanoma is usually at an earlier stage. Melanomas are usually first detected when they change in accordance with the ABCDE rule (Table 7: asymmetry, irregular borders, color variation, diameter > 6 mm, evolving over time).

Garland et al. noted a few studies that pointed out the fact that melanomas do not always occur in the areas of the body most often exposed to sunlight. This confirms that there are other factors besides UV exposure that play a crucial role in the development and malignancy of melanoma. As previously mentioned, vitamin D has been studied for its protective role in melanoma. When exposed to UV light, the vitamin D levels remain high for seven days. For this reason, Garland et al. made the correlation that sun-exposed areas are more protected from the damage, where as unexposed areas (i.e. the back) are less protected. Even though vitamin D is protective, 10-15 minutes a day of sun exposure is sufficient, and any more than that should be avoided. On the other hand, a case study was carried out by Weinstock et al. to determine the level of protection from melanoma afforded by supplemental vitamin D. The study found no evidence to suggest that supplemental vitamin D was protective against melanoma. Studies have been carried out to see if photoprotection from sunscreen and protective clothing reduces the serum vitamin D level by blocking conversion of 7-dehydrocholesterol in the skin to pre-vitamin D, which is induced by UV-B. A two-year follow-up study showed that individuals who regularly used SPF 15 sunscreen had slightly lower levels of serum vitamin D than controls that used no skin protection, but none of the subjects had abnormal parathyroid or calcium levels.

There are several major subtypes of melanoma. The most recently reported SEER data reported 153,124 cases of malignant melanoma in 17 SEER registries between 1988 and 2006. The majority of these cases were described as melanoma not otherwise specified (47%), superficial spreading melanoma (34%) (Figure 1), nodular melanoma (7%) (Figure 2) and lentigo maligna melanoma (6%) (Figure 3). Other types of melanoma are acral lentiginous melanoma (Figure 4) and amelanotic melanoma (Figure 5), which are less common.

The depth at diagnosis is an important predictor of the prognosis. From 1988 to 1993 and 2000 to 2006, the number of thin (<1 mm) and thick (>4 mm) melanomas increased from 68% to 71% and 4.7% to 5.4%, respectively, while the number of intermediate thickness tumors (1.01-4 mm) decreased from 17% to 15%.

Baumert et al. pointed out that the most important prognostic factor is tumor thickness at the time of diagnosis, and also noted that the most effective way to improve melanoma prognosis is to detect it in an early stage. Prevention of melanoma is possible, but unfortunately most of the damage is done in childhood. Garland et al. stated that the highest predictive risk for developing melanoma would be high exposure to sunlight as a child, followed by an adulthood spent in an office.

The most important proactive measure an adult can take is to wear sunscreen or sun-protective clothing that has UV-A and UV-B protection, and to do self skin exams. Garland et al. pointed out that 40% of UV-A can reach the melanocyte, and at least 10 times more UV-A acts on the melanocyte than UV-B. This makes UV-A a more important factor in the initiation and progression of melanoma than UV-B. The most common sunscreens (homomenthyl salicylate and PABA) primarily block UV-B, which inhibits the erythematous response but allows excess exposure to UV-A. Sunscreens are measured based on sun protective factor (SPF), which is mostly a reflection of protection against UV-B. Studies used to evaluate SPF are based on a dose of 2 mg/cm², while most people use a lower dose. Because of under-application, the actual SPF of applied sunscreen is usually significantly lower than the advertised amount. In 1999, the FDA sunscreen monograph mandated that for a sunscreen to advertise as water resistant, it must maintain the labeled SPF value after two to four sequential immersions in water for 20 minutes. Sunblock is commonly advertised as a stronger form of sunscreen, but the FDA sunscreen monograph does not sanction the term, as it is a misnomer. Sunblock has additional inorganic filters to reflect and scatter UV radiation, but a portion of radiation is always absorbed. It is never fully “blocked.” Patients must also be reminded that sunscreen only has a shelf life of three years and should be replaced after this time period. Patient education should be heavily emphasized for individuals living alone, older than 70, and with a lower education level.
References


Table 1. Five-year Rate Changes for 2001-2005. All ages, both sexes, all races (including Hispanic)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>USA</th>
<th>FL</th>
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<tbody>
<tr>
<td>1.01-2 mm</td>
<td>2.5</td>
<td>-0.7</td>
</tr>
<tr>
<td>2.01-4 mm</td>
<td>0.8</td>
<td>1.2</td>
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</table>

Table 2. Stages of Melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II</td>
<td>Localized disease</td>
<td>98.10%</td>
</tr>
<tr>
<td>III</td>
<td>Regional disease</td>
<td>84%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastatic disease</td>
<td>61.90%</td>
</tr>
</tbody>
</table>

Table 3. Clark’s Levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor cells in epidermis only (melanoma in situ)</td>
</tr>
<tr>
<td>II</td>
<td>Tumor cells extend into, but do not fill, papillary dermis</td>
</tr>
<tr>
<td>III</td>
<td>Tumor cells fill epidermis and papillary dermis</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor cells extend into reticular dermis</td>
</tr>
<tr>
<td>V</td>
<td>Tumor cells extend into subcutaneous fat</td>
</tr>
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</table>

Table 4. Overall five-year national relative survival rates for 1999-2005

<table>
<thead>
<tr>
<th>Age</th>
<th>Caucasian</th>
<th>Black</th>
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</thead>
<tbody>
<tr>
<td>Man</td>
<td>89.00%</td>
<td>73.30%</td>
</tr>
<tr>
<td>Woman</td>
<td>93.90%</td>
<td>80.40%</td>
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Table 5. Stage distribution with national five-year survival rates

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>Spread to regional lymph nodes or directly beyond primary site (stage III)</th>
<th>Metastasized (distant stage, stage IV)</th>
<th>Unstaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>84%</td>
<td>8%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>5-year survival</td>
<td>98.10%</td>
<td>61.90%</td>
<td>15.30%</td>
</tr>
</tbody>
</table>

Table 6. Five-year national survival based on tumor thickness (1988-2006)

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>&lt; 1 mm</th>
<th>1.01-2 mm</th>
<th>2.01-4 mm</th>
<th>&gt; 4 mm</th>
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<tbody>
<tr>
<td>1988-1992</td>
<td>96.8</td>
<td>86.0</td>
<td>72.3</td>
<td>55.4</td>
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<tr>
<td>1993-1997</td>
<td>97.2</td>
<td>87.8</td>
<td>71.3</td>
<td>56.8</td>
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<tr>
<td>1998-2002</td>
<td>97.1</td>
<td>89.1</td>
<td>74.4</td>
<td>58.1</td>
</tr>
</tbody>
</table>

Table 7. ABCDE rules of melanoma

<table>
<thead>
<tr>
<th>Rule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Asymmetry</td>
</tr>
<tr>
<td>B</td>
<td>Irregular borders</td>
</tr>
<tr>
<td>C</td>
<td>Color variegation</td>
</tr>
<tr>
<td>D</td>
<td>Diameter &gt; 6mm</td>
</tr>
<tr>
<td>E</td>
<td>Evolving over time</td>
</tr>
</tbody>
</table>
ABSTRACT

Abstract: Erythema dyschromicum perstans (EDP), also known as ashy dermatosis, is a distinct clinical entity that was first described in 1957. Patients may present with chronically progressing asymptomatic blue-gray hyperpigmented patches involving the face, trunk, and extremities. While there is no known association with underlying disease, frustration often occurs due to lack of an effective treatment. While various options exist, further research may help to elucidate other treatment modalities.

Case Report

A 58-year-old Hispanic male presented to the office with complaints of darkish discoloration of his skin for several years. There was no associated pruritus, pain, or previous skin disorder. His past medical history included hypertension; however, he was not on any medications. Family history and review of systems were non-contributory. Physical examination revealed a hyperpigmented, blue-gray, macular eruption without erythema or scale over the anterior neck, bilateral shoulders, mid-chest, upper back and bilateral arms (Figure 1, Figure 2, and Figure 3). Examination of the nails and oral mucosa was normal. Blood work including CBC, chemistry, renal, liver and thyroid functions were within normal limits. Shave biopsies performed on the right base of neck and right anterior shoulder revealed interface changes with scattered apoptotic bodies and numerous dermal melanophages, consistent with erythema dyschromicum perstans (ashy dermatosis) (Figure 4). After discussion of treatment options along with risks and benefits, the patient declined further treatment.

Discussion

Erythema dyschromicum perstans (EDP), also known as ashy dermatosis, was first described by C. Oswaldo Ramirez in El Salvador in 1957. It is a chronic hyperpigmentation disorder characterized by asymptomatic, blue-gray patches with slightly elevated erythematous borders in the early stages. Usually it presents as a symmetrical eruption involving the face, neck, trunk, and proximal extremities, although there have been reports of asymmetric unilateral EDP affecting the lower extremity. EDP can affect persons of all ages; however, it usually presents before the age of 40. Women tend to be affected more than men, and there is a predilection for intermediate to darker skin types, in particular Latin Americans. Differential diagnosis includes exogenous ochronosis, lichen planus pigmentosus, contact dermatitis, mycosis fungoides, drug-induced hyperpigmentation, post-inflammatory hyperpigmentation, syphilis, and endocrinopathies.

The histopathology of EDP may show vacuolated changes in the basal cell layer of active lesions, edema of the dermal papillae, and a perivascular lymphohistiocytic dermal infiltrate with pigment incontinence. Inactive lesions may exhibit epidermal atrophy, a slight perivascular infiltrate and an increase in dermal melanophages.

The etiology of EDP remains unknown; however, several predisposing factors have been suggested: ammonium nitrate ingestion, whipworm infection, oral ingestion of radiographic contrast material, treatment of hookworm infection, and HIV infection. There have been proposed immunological and genetic associations with EDP. A study performed by Baranda et al. found an appreciable expression of intercellular adhesion molecule 1 (ICAM-1) and major histocompatibility complex (MHC) class II molecules, HLA-DR, in the keratinocytes within the basal layer. ICAM-1 is not found in normal skin, but it is present in the epidermis in patients with inflammatory skin conditions such as psoriasis, lichen planus, allergic contact dermatitis, and graft-versus-host disease, implicating an inflammatory process for EDP. Also found was expression of CD36, a thrombospondin receptor not found in normal skin, in the strata spinulosum and granulosum of active lesions of patients with EDP. CD36 serves as a marker for activated T cells in the dermis, supporting an inflammatory process for EDP. CD94, a cytotoxic T cell marker expressed by natural killer cells, was also noted to be present in the dermal infiltrate of active EDP lesions, suggesting a cytotoxic phenomenon against the basal keratinocyte layer. These findings support an immunologic basis, suggesting that there may be a possible genetic component. A study performed in Mexican mestizo patients by Correa et al. reported an association between HLA-DR alleles and EDP. A correlation between the HLA-DR4 allele, in particular the HLA-DRB*0407 subtype, was found in Mexican mestizo patients with ashy dermatosis, a finding that may help to further elucidate the ethiopathogenesis in future studies.

There is no standard treatment for EDP. Past treatments have included sun protection, topical retinoids, topical and systemic corticosteroids, keratolytics, in particular the HLA-DRB*0407 subtype, was found in Mexican mestizo patients with ashy dermatosis, a finding that may help to further elucidate the ethiopathogenesis in future studies.
Clofazimine 100mg/day for three months was shown to be effective in a study by Baranda et al., proposed to be due to the anti-inflammatory effects as exhibited by a disappearance of ICAM-1, HLA-DR, CD36 and CD94 from active lesions of patients treated with clofazimine. Clofazimine is a lipophilic rhimophenazine dye with antimicrobial and anti-inflammatory properties, originally used to treat tuberculosis. It has also been used to treat noninfectious inflammatory skin disorders such as discoid lupus erythematosus and pyoderma gangrenosum. Dapsone is another antimicrobial that has anti-inflammatory properties and has shown to be effective for neutrophilic dermatoses and lymphocyte-rich dermatoses. Multiple case reports have documented varying degrees of success with Dapsone 100mg/day, possibly via mechanisms that alter immunologic aspects of the disease. Nonetheless, there is no treatment of choice for EDP, and potential therapeutic options may broaden upon further insight into the pathogenesis of the disease.

References

LOW-MOLECULAR-WEIGHT HEPARIN: A NOVEL TREATMENT OPTION FOR ASHY DERMATOSIS

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ABSTRACT

Ashy Dermatosis (AD) is a chronic hyperpigmentary disease of unknown etiology with characteristic and usually asymptomatic ash-gray macules affecting mainly type IV skin individuals. There is not established treatment for this condition although multiple therapeutic options have been used. Multiple studies suggest that AD is only a Lichen Planus (LP) variant, since they share similar clinical presentation and both have lichenoid dermatitis with vacuolization of basal cells as histopathological findings, although these are not pathognomonic. The successful use of low doses of low-molecular-weight heparin (enoxaparin) for the treatment of LP based on its inhibition of activated T-lymphocyte heparanase, an enzyme that allows the lymphocytes to penetrate through vascular barriers and migrate to target tissues, in LP and possibly AD; its similarities with AD and the minimal risk of side effects, led to the use of enoxaparin in two of our AD patients with promising results.

INTRODUCTION

Ashy dermatosis (AD), or erythema dyschromicum perstans, is an acquired, benign and chronic hyperpigmentary disease. Its etiology is unknown, but it seems to be more prevalent in Latin Americans, type IV skin individuals, and females in the first to third decade of life.

AD patients develop asymptomatic but sometimes pruritic, ash-gray macules that may have erythematous borders in the initial presentation. It usually involves the neck, trunk and extremities and may become disfiguring over time.

Different treatment modalities have been used for this disease, including topical and systemic steroids, sun blockers, keratolytic agents, antimalarials, daiminophenylsulfone, griseofulvin, dapsone, antibiotics, ascorbic acid, retinoids, estrogens, clofazimine and laser therapy, all with variable results. Unfortunately, no universally accepted therapy exists for this disease.

AD has also been described as idiopathic eruptive macular pigmentation and lichen planus pigmentosus, with multiple studies, including immunofluorescence, suggesting that AD is a lichen planus (LP) variant given that they share similar clinical and histopathological findings.

Since there is no established therapy for this condition, we describe our experience treating two AD patients with low-molecular-weight heparin (enoxaparin) on the basis of AD’s similarities with LP, with promising results.

CASE REPORTS

Case 1: A 30-year-old Latin American woman presented with a seven-month history of asymptomatic, large gray patches over her back, abdomen and extremities, treated in the past with antifungals without improvement. A skin biopsy revealed basal vacuolar alterations and few necrotic keratinocytes with superficial dermal melanophages and mild perivascular lymphocytic infiltrate (Figure 1). There was no neutrophilic exocytosis in the stratum corneum, and PAS was negative. AD diagnosis was made, and the patient started with enoxaparin 30 mg weekly (we chose this dose because enoxaparin in the USA is dispensed as preloaded syringes of 30 mg to make it convenient for the patients), triaminolone ointment 0.1% BID, and an intramuscular injection of triaminolone acetonide (40 mg). After two months, the dose was increased to 30 mg twice a week, and the lesions were almost gone after six months of treatment (Figure 2).

Case 2: A 50-year-old Indian woman presented with a nine-month history of asymptomatic, large gray patches over her neck, chest and arms. She had received no previous treatment for this condition and denied any recent history of exposure to a new drug. Antibacterial antibodies, including Sjogren’s antibodies (anti-SSA, anti-SSB), were all negative. A skin biopsy was performed that showed vacuolar and lichenoid changes with a perivascular lymphocytic infiltrate, melanin incontinence, and epidermal atrophy. After the diagnosis of AD was made, the patient was started on enoxaparin 30 mg weekly. The dose was increased to twice a week after a month, with lighter-looking lesions after three months of treatment (Figure 3).

None of the patients developed any side effects.

DISCUSSION

Several immunopathological studies of active AD lesions have shown that AD may involve a cell-mediated abnormal immune response, which results in damaged melanocytes and disruption of the basal membrane zone.

Histopathological findings, which are not pathognomonic, demonstrate lichenoid dermatitis with vacuolization of basal cells, colloid bodies and a moderate infiltrate of lymphocytes and histiocytes in the papillary dermis along with melanophages.

It has been demonstrated by immunofluorescence studies that there is a great similarity between AD and lichen planus (LP). Clinically, they also have similar initial presentation. Therefore, authors have suggested that AD may be a subset of idiopathic LP or a lichenoid drug reaction. Although there is no definitive treatment for LP, enoxaparin (3 mg subcutaneously) has been successfully used based on the fact that heparin at low doses inhibits activated T-lymphocyte heparanase. This enzyme is expressed by activated T lymphocytes, allowing them to penetrate vascular barriers and migrate to target tissues in LP and possibly in AD. The lymphocytes attracted attack the keratinocytes and melanocytes, leading to the lichenoid reaction. By inhibiting heparanase, enoxaparin prevents T cell migration and penetration into the subendothelial basal lamina and possibly T cell-mediated immunity in delayed-type hypersensitivity reactions.

Enoxaparin has also been associated with suppression of the standard patch test reactions in patients with allergic contact dermatitis. However, the ability of this drug to inhibit these immune reactions is not related to its anticoagulant activity.

The great resemblance to and connection with LP was the rationale for the use of enoxaparin in our patients with AD. Such low doses of enoxaparin are devoid of anticoagulant activity

CONCLUSION

As shown in these cases, the administration of enoxaparin was effective and safe for the treatment of Ashy Dermatosis. More studies need to be done to determine whether this drug may be a therapeutic option for this chronic condition.
for both patients, demonstrating sustained improvement in a relatively short period of time. We propose the use of this drug for AD, as it may be a successful alternative treatment, and propose more studies to confirm the positive response of this drug for the treatment of this condition.

References

Cutaneous Larva Migrans: A Case Report and Discussion

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***Program Director, SJEH, Far Rockaway, NY

ABSTRACT

A rare case of cutaneous larva migrans in a 21 year old male with an intensely pruritic rash presented to the office. The rash started one month after his recent vacation to Jamaica. This skin condition usually occurs in individuals who go barefoot on the beach, children playing in sand boxes, carpenters and plumbers working under homes, and gardeners. These individuals are more often exposed to the hookworms, Ancylostoma caninum and A. braziliense, which is often found in dog or cat feces. The characteristic skin lesions are erythematous twisting and winding burrows on the dorsal aspects of the feet. Cutaneous larva migrans responds well to oral albendazole and symptomatic treatment with topical steroids and antihistamines.

Introduction

Cutaneous larva migrans is caused by penetration and migration within the epidermis of nematode parasites. It is characterized by erythematous, pruritic, serpiginous plaques usually occurring on the feet or other exposed sites.1,2

Although cutaneous larva migrans has a worldwide distribution, it is most commonly seen in warm climates, such as the southeastern U.S., Central and South America, Africa, and other tropical areas.3 Occasionally, cases have been observed in cooler climates, but usually these patients had previously traveled to the tropical areas.1,5

The infection is acquired by walking barefoot on ground contaminated with animal feces. The larvae enter the skin and begin a prolonged process of migration within the epidermis. Ancylostoma braziliense and Ancylostoma caninum are the two species most frequently involved.2 Except in rare cases, the parasite remains confined to the epidermis, producing visible tracts and intense pruritus. It is self-limited because the larvae lack the lytic collagenase enzymes needed to cross the epidermal basement membrane.6 Disease of extended duration is uncommon because the larvae are unable to complete their life cycles in the human body and usually die within two to eight weeks.

Case Report

This is a case report of a 21-year-old Caucasian male who presented to a busy private dermatology practice with an intensely itchy rash on his left foot for one month. Prior to the rash starting, he was vacationing in Jamaica, where he had walked barefoot on the beach. The rash started as a red bump and then gradually became an erythematous, serpiginous, twisting and winding eruption on the dorsal and dorsolateral aspects of the left foot (Figure 1).

He had been to the emergency room a week prior and was misdiagnosed with a fungal infection and treated unsuccessfully with an antifungal regimen. He was referred to infectious disease but could not get an appointment for a month. Luckily, he was able to get an appointment to see us, and we were able to make the diagnosis of cutaneous larva migrans. Within a week of his five-day course of albendazole, along with symptomatic treatment with topical steroids and antihistamines, his rash was resolved.

Discussion

In addition to intensely pruritic, serpiginous “tracts,” lesions may be associated with vesicles and bullae in previously sensitized patients, as seen in our patient on day three of five of treatment with oral albendazole (Figure 2).

Besides the typical location of the distal extremities, additional sites of involvement are the hands, buttocks, and, rarely, the perianal area. Each larva produces one tract and migrates at a rate of 1-2cm/day. In severe infections, hundreds of such lesions may be found on a single person. Systemic manifestations such as migratory pulmonary infiltrates and peripheral eosinophilia (Loeffler’s syndrome) are rarely seen. Due to intense itching and scratching, superimposed infections may complicate the clinical picture, as can impetigo and allergic reactions.

Although usually a clinical diagnosis, biopsies are sometimes done. Scale crust, spongiosis or intraepidermal vesicles with eosinophils are common epidermal findings. Dermal edema with perivascular lymphocytes, histiocytes and numerous eosinophils are common dermal findings.4 It is unusual to see the parasite in biopsy specimen, but occasionally the parasite can be identified within the epidermis. More commonly, cavities left by the parasites are located in the stratum corneum.5

Although optimal treatment is controversial and most treatment trials have been of low quality, it is generally agreed that the most effective agents in treating cutaneous larva migrans are topical or oral antihelminthics, including albendazole, thibendazole, and ivermectin. The more common regimens include (1) topical thiabendazole 10% to 15% cream two to three times daily for five to 10 days; or (2) oral albendazole 400mg daily for three to five days; or (3) one dose of 12mg oral ivermectin.9,10 Freezing the leading edge of the skin track with ethylene chloride spray, solid carbon dioxide, or liquid nitrogen rarely works, as the larva is usually located several centimeters beyond the visible end of the trail. In one series, cryotherapy (repeated applications of liquid nitrogen) was unsuccessful for six patients and resulted in severe blistering or ulceration in two patients. In another series, none of seven patients treated with liquid nitrogen was cured. Because this method is both ineffective and painful, it should be avoided.12
Acknowledgements

The authors would like to acknowledge and thank Dr. Richard Berry for letting us use this case.

References


ZIANA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

Important Safety Information for ZIANA Gel

- The most commonly reported adverse events were nasopharyngitis, pharyngolaryngeal pain, dry skin, cough, and sinusitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. ZIANA Gel should be discontinued if significant diarrhea occurs. Systemic absorption of clindamycin has been demonstrated following topical use of this product.
- If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued.
- Avoid exposure to sunlight and sunlamps. Patients with sunburn should not use the product. Use with caution in patients who require considerable sun exposure due to occupation or who are inherently sensitive to the sun. Avoid excessive exposure to the sun, cold, and wind, which can irritate skin. Daily use of sunscreen and protective clothing are recommended.
- Keep away from eyes, mouth, angles of nose, and mucous membranes.
- This drug is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.
- Concomitant use of topical medications with a strong drying effect can increase skin irritation. Use with caution.

See reverse side for a Brief Summary of the Full Prescribing Information.
be associated with the passage of blood and mucus. stool cultures for studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis.

with atropine may prolong and/or worsen severe colitis. severe colitis may result in death.

to several weeks following cessation of therapy. antiperistaltic agents such as opiates and diphenoxylate in the 12-week studies. eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

related to drug use for approximating rates. in the clinical trial may not reflect the rates observed in practice. the adverse reaction information from the package insert for Full Prescribing Information

Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the systemic absorption of clindamycin has been demonstrated following topical use of this product. Colitis

BRIEF SUMMARY

ZIANA® Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

CONTRAINDICATIONS

ZIANA® Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of this product. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. When significant diarrhea occurs, ZIANA® Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

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. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure

Exposure to sunlight, including sunlamps, should be avoided during the use of ZIANA® Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may have had some sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel in, e.g., a hat are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with ZIANA® Gel.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use for approximating rates.

The safety data presented in Table 1 (below) reflects exposure to ZIANA® Gel in 1,853 patients with acne vulgaris. Patients were 12 years and older and were treated once daily for 12 weeks. Adverse reactions that were reported in >1% of patients treated with ZIANA® Gel were compared to adverse reactions in patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the vehicle gel alone:

<table>
<thead>
<tr>
<th>N (%)</th>
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Table 1: Adverse Reactions Reported In At Least 1% Of Patients Treated With ZIANA® Gel: 12-Week Studies

<table>
<thead>
<tr>
<th>Local Reaction</th>
<th>Baseline N=1805 N (%)</th>
<th>End of Treatment N=1014 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>636 (35)</td>
<td>416 (26)</td>
</tr>
<tr>
<td>Scaling</td>
<td>237 (13)</td>
<td>280 (17)</td>
</tr>
<tr>
<td>Itching</td>
<td>189 (10)</td>
<td>70 (4)</td>
</tr>
<tr>
<td>Burning</td>
<td>38 (2)</td>
<td>56 (4)</td>
</tr>
<tr>
<td>Stinging</td>
<td>33 (2)</td>
<td>27 (2)</td>
</tr>
</tbody>
</table>

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and 2, 1,277 subjects enrolled with moderate to severe acne, 854 subjects treated with ZIANA® Gel and 423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were slightly higher for the ZIANA®-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA® Gel showed a similar adverse reaction profile as seen in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

DRUG INTERACTIONS

Concomitant Topical Medication

Concomitant topical medication, such as emollients or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution. When used with ZIANA® Gel, there may be increased skin irritation.

Erythromycin

ZIANA® Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vivo antagonism is not known.

Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ZIANA® Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA® Gel. ZIANA® Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ZIANA® Gel was tested for maternal and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA® Gel at 600 mg/kg/day (approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA® Gel for two weeks prior to artificial insemination and continuing until gestation day 18, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA® Gel applied daily to a 60 kg person.

Clindamycin

Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/ day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin up to 180 mg/kg/day (175 and 88 times the amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin

In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (~ 78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on a body surface area comparison.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of ZIANA® Gel. 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. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIANA® Gel is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ZIANA® Gel in pediatric patients under the age of 12 have not been established.

Clinical trials of ZIANA® Gel included patients 12–17 years of age.

Geriatric Use

Clinical studies of ZIANA® Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Manufactured for:

Medics, The Dermatology Company

Scottsdale, AZ 85256

U.S. Patents 5,721,275 and 6,387,383

ZIANA® is a registered trademark of Medics Pharmaceutical Corporation.

Prescribing Information as of October 2008.

300-13B

Table 2: ZIANA® Gel-Treated Patients with Local Skin Reactions

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Antiphospholipid syndrome (APS) is a multisystem disorder with vascular thromboses and/or pregnancy morbidity. We present a case report of a patient who presented to our emergency department with several purple/black blisters on her legs, buttocks, face and abdomen. She complained of pain and burning in areas of skin involvement, but otherwise denied Raynaud’s phenomenon, widespread cutaneous necrosis and vasculitis-like lesions (7). The most commonly used tests to diagnose the antiphospholipid disorder are lupus anticoagulant, anticardiolipin antibody, enzyme-linked immunosorbent assay (ELISA) and anti-beta 2-glycoprotein 1 antibody. The diagnosis of antiphospholipid syndrome is made based on at least one thrombotic event or pregnancy complication and at least one laboratory criteria of high titer of anticardiolipin antibodies, positive lupus anticoagulant test, or anti-beta 2-glycoprotein 1 antibodies on two or more occasions at least 12 weeks apart (2).

Case Report:

Our patient is a 49-year-old white female who presented to our emergency department with several purple/black blisters on her legs. Lesions began nine days prior to admission and spread to her arms, buttocks, face and abdomen. She complained of pain and burning in areas of skin involvement, but otherwise denied systemic findings of fever or infection. She denied any new exposures or travel history. She had a history of one pregnancy 20 years ago, which she ended in termination. Prior to admission, she was seen by her primary care physician and treated with bacitracin for two doses, but the lesions progressed. Her medication was then changed to doxycycline, for which the patient again took only two doses before coming to the hospital due to worsening symptoms. Past medical history was significant for Graves’ disease, asthma, and allergic rhinitis. The patient’s medications included propylthiouracil (PTU), which she had been on for five years, and albuterol. She had no known allergies to medications. Family history was significant for her mother with rheumatoid arthritis and father who had a myocardial infarction.

On physical exam, the patient had multiple black, hemorrhagic bullae with necrotic plaques and patches, in areas with surrounding erythema, on her legs, buttocks, arms, and right cheek (Figures 1-4). Lab work consisted of coagulation panel, blood culture, and chest X-ray, all within normal limits, ANA 1:80, speckled pattern, lupus anticoagulant positive, anticardiolipin IgG Ab negative, RF negative, CRP positive, hepatitis panel negative, cryoglobulins negative, anti-DNA Ab negative, P-ANCA 41, C-ANCA negative, SS-A and SS-B negative, PTT screen elevated, and dRVVT positive. Punch biopsies revealed extensive intravascular thrombi of the small vessels (Figures 5 and 6). Direct immunofluorescence showed IgG, C3 and IgM in the vascular wall, with no abnormal deposits of IgA or fibrin.

The patient was treated with solu-medrol initially and then prednisone taper, and short courses of vancomycin, ciprofloxacin, and diflucan. Once the diagnosis of APS was made, we attempted to treat the patient with anticoagulants, but she refused treatment with heparin or coumadin. She was discharged on aspirin to be followed closely as an outpatient.

Discussion:

Antiphospholipid syndrome occurs in 1-10% of the general population, 16% of patients with rheumatoid arthritis, and 30-40% of patients with systemic lupus erythematosus (SLE). Patients who are asymptomatic have a 0-4% annual risk of thrombosis, while those with other autoimmune diseases like SLE are at the higher end of the range (2). The predominant hypothesis for the origin of APS is an incidental exposure to environmental agents with beta 2-glycoprotein-1-like peptides, which induces antiphospholipid antibodies (aPL) in susceptible individuals (2). Beta 2-glycoprotein is the main target antigen for aPL (1). Thrombosis occurs through the binding of aPL to endothelial cells via beta 2-glycoprotein 1, which induces a procoagulant state. It initiates the induction of adhesion molecules, tissue factor expression and complement activation (2). Current thinking holds that once aPL are present, a “second-hit” is required for the development of the syndrome (6). Development of the second hit can be caused by smoking, prolonged immobilization, pregnancy, oral contraceptive use, malignancy, or hypertension, among other causes.

APS is characterized by venous or arterial thromboses, fetal losses and thrombocytopenia. The time interval between vascular events varies considerably, from weeks to months to years. Multiple vascular occlusive events presenting over a short period of time is termed the catastrophic variant of APS, or Asherson’s syndrome (3). Catastrophic APS is a diffuse thrombotic microvasculopathy affecting the lungs, brain, kidney, heart, skin and gastrointestinal tract. It primarily affects small vessels, and 60% of patients have a triggering factor, such as infections (3).

Small-vessel vasculitis presents with constitutional symptoms of fever, myalgias, arthralgias, and malaise with flu-like symptoms (4). The most common cutaneous finding of vasculitis is leukocytoclastic angitis of the dermal postcapillary venules. This causes purpura with occasional focal necrosis and ulceration. Necrotizing arteritis in small dermal and subcutaneous arteries causes erythematous tender nodules, focal necrosis, ulceration and livedo reticularis (4). Drug-induced vasculitis may be caused by a number of drugs including penicillins, sulfonamides, allopurinol, thiazides, retinoids, quinolones, and propylthiouracil. Propylthiouracil and hydralazine appear to cause vasculitis by inducing ANCA by an unknown mechanism (4). ANCA-associated small-vessel vasculitides include Wegener’s granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. ANCA-associated vasculitis is most common in older adults in their 50s and 60s and affects...
men and women equally (4). P-ANCA positivity may correspond to drug-induced vasculitis, microscopic polyarteritis, necrotizing and crescentic glomerulonephritis, Churg-Strauss syndrome, classic polyarteritis nodosa, Wegener’s granulomatosis, SLE, rheumatoid arthritis, or chronic IBD. Twenty percent of cases associated with drug-induced vasculitis are due to PTU (7).

This case illustrates an unusual case of antiphospholipid syndrome. Although the patient was on PTU for five years, there is no other identifiable cause of her necrotic skin lesions. With a positive lupus anticoagulant test and vascular thrombosis identified on pathology, the patient was given the presumed diagnosis of antiphospholipid antibody syndrome, most likely due to PTU, with a component of vasculitis due to positive P-ANCA and immunofluorescence results. The patient will continue to be monitored as an outpatient for the progression to rheumatologic, autoimmune or P-ANCA associated diseases.

References

Extranasal Rosai-Dorfman Disease Presenting with Progressive Nasal Congestion

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**Clinical Faculty, MSU Pontiac Osteopathic/ Botsford Hospital, Pontiac, MI; Sikorski Dermatology and Vein Clinic, Bloomfield Hills, MI
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ABSTRACT

Rosai-Dorfman disease is an idiopathic benign histiocytic proliferative disorder. It leads to massive, painless, and usually bilateral lymphadenopathy. Extranasal involvement is seen in at least 25% of cases, with the skin and nasal/paranasal sinuses being the most frequent locations. Treatment options have yet to be clearly defined, due to a variable clinical response, paucity of reported cases, and the tendency for a benign course with eventual spontaneous resolution. We report a case of a previously healthy male, presenting with nodal, cutaneous, and respiratory tract disease, successfully treated with chemotherapeutic agents.

Case Report

A 46-year-old, previously healthy African American male presented with a several-month history of progressive nasal congestion, snoring, sleep disturbances, and somnolence. Computed tomography (CT) of his skull showed mucosal thickening, obstruction of the left osteomeatal complex, and near-complete opacification of the nasal passages and ethmoidal air cells. Physical exam showed extensive polyposis of his nasal cavities. Examination of an endoscopic biopsy from the thickened respiratory tissue revealed marked inflammation and aggregates of foamy macrophages. A cause for this histologic picture was indeterminable.

Around the same time, the patient noticed several painless, enlarging lumps in his extremities. These were not felt to be related to his nasal congestion. Clinically, they were diagnosed as lipomas, and were observed. Because they became more numerous, continued to enlarge, and began to present functional impairment, he was scheduled for a diagnostic biopsy of a nodule on his right upper arm. Histology showed a lymph node with a diffuse histiocytic infiltrate. The histiocytes displayed a foamy cytoplasm and intracytoplasmic accumulation of lymphocytes. Immunohistochemical stains were positive for CD68 and S-100 protein. The clinical and histological picture combined was consistent with Rosai-Dorfman disease, which also explained his recent upper respiratory symptoms and findings.

Chest, abdomen, and pelvic CT imaging revealed extensive bilateral, cervical and right axillary lymphadenopathy. No mediastinal or inguinal lymphadenopathy was seen. There did not appear to be intrathoracic or intra-abdominal involvement of his disease. On physical exam, the patient was a healthy-appearing well-developed male with bilateral cervical and upper extremity lymphadenopathy. He had scattered 5-15mm erythematous papules and nodules on his cheeks, forehead, and scalp (Figure 1). No hepatosplenomegaly or abdominal tenderness was palpated. The rest of his physical exam was normal. On a review of systems, he admitted to night sweats and a 20-pound weight loss that had occurred over several months. He denied fever, chills, nausea, vomiting, diarrhea or other systemic symptoms.

Laboratory exam showed an elevated white blood cell count of 11.4 thou/mcl (4.0-10.0 thou/mcl), ESR 19mm/hr (0-15mm/hr), CRP 1.1 mg/dl (0-0.9mg/dl), fibrinogen 430 mg/dl (200-400 mg/dl) and a serum γ-globulin of 1.53 gm/dl (0.70-1.50gm/dl). All other labs were within normal limits.

A 2-mm punch biopsy of an erythematous papule on his right cheek showed a dense dermal infiltrate of S-100 positive histiocytes with abundant foamy cytoplasm, numerous plasma cells, intermixed lymphocytes, and very rare neutrophils and eosinophils (Figure 2). A Steiner and Steinbrunn stain was negative. These findings were compatible with the diagnosis of Rosai-Dorfman disease.

Our patient successfully underwent endoscopic nasal tissue resection, alleviating his obstructive nasal symptoms. We attempted to treat his cutaneous lesions with topical high-potency corticosteroids, intralesional triamcinolone, and oral prednisone, none of which led to improvement of his condition. He was referred to hematology/oncology, where he was treated with intravenous chemotherapy consisting of six monthly cycles of cladribine (CD2A). This has lead to an almost complete resolution of his disease.

Discussion

Rosai-Dorfman disease, otherwise known as sinus histiocytosis with massive lymphadenopathy (SHML), is a benign histiocytic proliferative disorder initially described in 1969.1 It is a rare disorder, with only about 600 cases reported to date.2 It leads to massive, painless, and usually bilateral lymphadenopathy. Most commonly, this is seen in the cervical lymph node chains, but it can also be seen in the axillary, inguinal, and mediastinal nodes.2 Most cases present in the first two decades of life, with more cases reported in males than in females.2

The cause of this condition is unknown, but histology indicates a reactive process. It has been suggested that an infectious agent such as Epstein-Barr Virus or herpes virus and an ensuing altered state of immunity may be the eliciting factor.1
Some studies have supported that the high level of histiocyte activation is the result of increased levels of macrophage colony-stimulating factor (M-CSF). It is unknown, however, what leads to these increased levels. Further study in this area is needed.

On histologic examination, lymph nodes are crowded with histiocytes, lymphocytes, and plasma cells. The histiocytes demonstrate an abundant foamy cytoplasm with emperipolysis, which is the finding of small lymphocytes engulfed within their cytoplasm (Figure 3). This finding is characteristic but not pathognomonic for Rosai-Dorfman disease. The lymphocytes become disabled after phagocytosis, leading to a suppressed state of immunity within the lesion. Cell markers have shown these histiocytes to be of macrophage lineage, but interestingly, they do not appear to be part of the dendritic antigen-presenting group of cells. Immunohistochemical staining of the histiocytes is positive for S-100 protein, variably positive for CD68, and CD-1a negative. This is important because it differentiates them from the Langerhans histiocytes, which are positive for CD-1a.

Extranodal involvement is seen in at least 25% of cases, and 75% of these cases involve the head and neck. The skin, respiratory tract, subcutaneous tissue, orbits, and bone are among the most frequently affected. The skin is the most common extranodal location, with involvement seen in up to 27.4% of patients, with nasal/paranasal sinus involvement being almost as frequent (26.8%). The histology of extranodal disease is similar to that seen in lymph nodes. A dense infiltrate of histiocytes with large nuclei and abundant foamy cytoplasm is seen, along with characteristic emperipolysis. Also, there may be an admixed accompanying inflammatory infiltrate composed of neutrophils, lymphocytes, and plasma cells.

Most commonly, nasal involvement presents as epistaxis, congestion, or rhinitis. On endoscopic examination, coarse, red-to-yellowish-brown edematous polyposis is seen. With these nonspecific symptoms, diagnosis is only established after a biopsy with subsequent histological exam. Because of the benign nature of this condition, treatment of extranodal disease in the nasal and sinus region is only required to treat symptomatic congestion once a definitive diagnosis of Rosai-Dorfman disease has been reached. Endoscopic resection is the most common and accepted procedure, although recurrence is frequent. The use of ablative CO₂ and KTP lasers has recently been reported to be successful in removing the obstructing tissue.

Extranodal skin involvement presents with clinically nonspecific lesions, which can be located virtually anywhere. The presentation is variable and can consist of solitary or multiple macules, papules, plaques, or nodules of varying coloration. Occasionally, skin lesions may be the only manifestation of this disorder. Again, the histology mimics that which is seen in the lymph nodes, making biopsy and histologic exam prudent.

Laboratory abnormalities are common in patients with Rosai-Dorfman disease and include anemia, leukocytosis, neutrophilia, increased ESR, and hypergammaglobulinemia. Also, up to 30% of patients may demonstrate moderate pyrexia. Systemic symptoms are rare and are usually secondary to compression or obstruction, which can lead to impairment of function in the affected organs. Remarkably, the disease usually follows a relatively benign course, tending to slowly wax and wane, and patients are generally healthy.

An ideal therapy for Rosai-Dorfman disease with consistently sustained remission has not yet been determined. Treatments with steroids, chemotherapy, interferon, antibiotics, radiation and surgical resection have been attempted, all with inconsistent and usually unsatisfactory results. The clinical course of this disease is variable, with a chance of spontaneous resolution. It is relatively benign and rarely leads to life-threatening complications. For this reason, conservative therapy, such as endoscopic nasal tissue debulking or cosmetic removal of skin lesions, may be the best choice.

Rosai-Dorfman disease should be considered in the differential diagnosis in any patient with unusual polyposis nasi, unexplained lymph node enlargement, nonspecific skin lesions or symptoms of internal organ compression. A combination of any of these findings, along with typical histological characteristics and/or unexplained lab abnormalities, should point the diagnostician toward this rare and interesting diagnosis.

References

In the management of rosacea, the direction is clear . . .

**POWERFUL CHANGE FOR THE JOURNEY AHEAD**

**Early efficacy**\(^1,2\) with safety for the long term\(^3\)

- Reduction in inflammatory lesion count seen as early as week \(^4,1,2\)
- Similar efficacy to doxycycline 100 mg in reducing inflammatory lesions\(^1\)
- No evidence of bacterial resistance\(^3\) and no increase in side effects over the long term (9 months)\(^3\)
- Patients pay no more than $25* for each Oracea® prescription

*For a 30-day/30-capsule prescription of Oracea® (excludes Medicaid, Medicare, or federal or state programs).

**Important Safety Information**

Oracea\(^o\) is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients.

In clinical trials, the most common adverse events reported were gastrointestinal upsets, nasopharyngitis/pain, and nasal congestion/sinusitis. Oracea\(^o\) should not be used to treat microbial infections, and should be used only as indicated. This drug is contraindicated in people who have shown hypersensitivity to any of the tetracyclines, and, like other tetracycline drugs, may cause fetal harm when administered to a pregnant woman. Oracea® should not be used during pregnancy, by nursing mothers, or during tooth development (up to the age of 8 years).

Although photosensitivity was not observed in clinical trials, Oracea® patients should minimize or avoid exposure to natural or artificial sunlight. All contraindications, warnings, and precautions associated with tetracyclines must be considered before prescribing Oracea®. The safety of Oracea® treatment beyond 9 months has not been established.

Please see brief summary of Prescribing Information on next page.

References:
Laboratory Tests:
Pseudotumor cerebri: has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has of all tetracycline-class drugs should be discontinued immediately.

Autoimmune Syndromes:
Tetracyclines have been associated with the development of autoimmune

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can result in the inhibition of bone and cartilage matrix mineralization. Although not observed during the duration of the clinical studies

Oral contraceptive failure, females are advised to use a second form of contraceptive during treatment with

As with other antibiotic preparations, use of ORACEA may result in overgrowth of non-susceptible micro-

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

Pseudotumor cerebri: Bulging fontanelles in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Drug Interactions: 1. Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In determining the dosage of ORACEA, consideration of the patient’s age, weight, body surface area, and other factors that may influence the dose in individual patients should be taken into account.

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RHEUMATOID NEUTROPHILIC DERMATITIS

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ABSTRACT

Rheumatoid Neutrophilic Dermatitis (RND) is a rare cutaneous manifestation of rheumatoid arthritis. The lesions typically present symmetrically as erythematous papules and plaques on the dorsum of the arms and hands. The disease runs a varied course, and treatment of the underlying rheumatoid arthritis can result in resolution.

A 68-year-old Caucasian female with a 10-year history of seropositive rheumatoid arthritis presented for evaluation of nontender, cutaneous lesions on her dorsal fingers (Figure 1). She also had noticed nonpruritic, nontender, swollen lesions on her posterior back and neck. All of the cutaneous lesions waxed and waned, and she had been applying Neosporin ointment without relief. Therapy for her rheumatoid arthritis included celecoxib. She had not taken methotrexate or any anti-tumor necrosis factor medications in the past.

Physical examination revealed several 0.3-0.6 cm, annular, erythematous papules and plaques on the dorsal distal interphalangeal joints of the bilateral hands. On her posterior back and neck, there were areas of grouped, yellow-to-erythematous plaques measuring 0.5-1.0 cm in diameter. A few of the lesions on the back and neck were excoriated.

A skin biopsy from the dorsal hand was performed and showed a dermal inflammatory infiltrate with numerous neutrophils. There were scattered zones of leukocytoclasia. There was no vasculitis identified. Also, a periodic acid-Schiff stain was negative for fungal elements and bacteria (Figure 2).

Based on the dermatohistopathology, history of rheumatoid arthritis, and classic cutaneous distribution, a diagnosis of rheumatoid neutrophilic dermatitis was made. Differential diagnosis included dermatitis herpetiformis, Sweet’s syndrome, and erythema elevatum diutinum.

Initially, the cutaneous lesions were treated with topical triamcinolone cream 0.1% applied twice daily. At a return visit, she had noticed minimal improvement and was told to follow up with rheumatology to check on her current medications, which only included celecoxib. We had injected Aristocort 2mg/cc into a few of the recalcitrant areas of cutaneous disease on her back and neck, with minimal improvement. We had been considering adding dapsone or an anti-tumor necrosis factor medication when her lesions spontaneously started to improve. In recent follow-up, the patient had been hospitalized for a pulmonary infection and stated that all of her cutaneous lesions had resolved. Perhaps a topical dapsone medication could be tried in the future if her lesions were to return, as she is hesitant to begin any systemic therapy.

Rheumatoid neutrophilic dermatitis (RND) is a rare cutaneous manifestation of rheumatoid arthritis. Ackerman first described this cutaneous disease in 1978. It usually occurs in patients with severe seropositive rheumatoid arthritis, but it has been reported in seronegative patients as well.

The morphology is quite varied, which hinders its immediate recognition. Some patients have presented with urticaria-like lesions localized to the back. Other cases describe annular, yellow, and erythematous papules and plaques localized to the lateral neck or extensor surfaces of the upper extremities. In general, lesions tend to be symmetrically distributed, with a predilection for the dorsum of the arms and hands. The lesions often heal without scarring, but hyperpigmentation can occur.

The dermatohistopathology of RND typically reveals a dense neutrophilic infiltrate, primarily in the mid to upper dermis (Figure 2). Papillary dermal microabscesses can be seen and confused with dermatitis herpetiformis. However, direct immunofluorescence of DH reveals granular IgA within the dermal papillae, and RND, by contrast, is negative. No evidence of vasculitis has been found, although varied leukocytoclasia has been reported.

The differential diagnosis of RND includes all neutrophilic dermatoses but mainly dermatitis herpetiformis, Sweet’s syndrome, and erythema elevatum diutinum. Other diseases to consider include pyoderma gangrenosum, Behcet’s syndrome, and bowel-associated dermatitis-arthritis syndrome. The differentiating points of RND are that it is asymptomatic, tends toward spontaneous resolution, and lacks associated fever, malaise, ocular disease, or gastrointestinal symptoms.

Treatment is based on case studies due to the rarity of the disease. Most RND resolution occurs spontaneously or with treatment of the underlying rheumatoid arthritis. Dapsone has shown efficacy in the treatment of RND. Other treatment options in the literature include topical corticosteroids, systemic steroids, and hydroxychloroquine sulfate. Certain patients have had flares of RND with discontinuation of their rheumatoid arthritis medications. There are case reports of flares of RND with discontinuation of systemic prednisone. Once the medication was re instituted, the cutaneous lesions of RND resolved. Recalcitrant lesions have also been treated with cyclophosphamide.

Currently, the pathogenesis of RND is unknown; however, immune-complex activation, cell adhesion and migration, and cytokine release all may play a role.

References