Dear AOCD Members and Resident Members,

I founded the Journal of the American Osteopathic College of Dermatology in 2002, and I have been Editor-in-Chief since its inception. I am as proud of the JAOCID as I am of the AOCD and the AOA, and as I leave the editorial helm I am confident our journal will continue to flourish.

Karthik Krishnamurthy, DO, has taken over as Editor-In-Chief. I will be working closely with him and with Julia Layton, our Copy Editor, over the next six months to make this a smooth transition, and I will be available to offer input and guidance even after this transitional period. The didactic, clinical and teaching skills that Karthik brings to this position will ensure that the JAOCID continues to grow and improve as a scientific journal.

At this time, I want to thank the membership, and in particular Stan Skopit, DO, Jon Keeling, DO, James Delrosso, DO, and Andrew Racette, DO, for all they have done to help get the journal to where it is today. Julia Layton continues to do a fantastic job working the day-to-day activities that are required to maintain this type of publication, and she will stay on as Copy Editor after my departure. I also want to thank Rick Mansfield for his excellent job in maintaining the journal’s financial records.

We always need to recognize and support the Sponsors of the JAOCID: Global Pathology, Medicis, Galderma, Ranbaxy and Bayer Healthcare, currently. Global Pathology, Medicis and Galderma are Founding Sponsors that have supported the JAOCID from even before the first issue went to press.

It has been an honor and a privilege to serve as the Editor-in-Chief for a decade. I know that Karthik will pick up where I leave off, furthering the interests of our journal and our college as we move forward.

All the best to you,
Jay

Jay Gottlieb, DO, FAOCD
Founder, JAOCID
Greetings, everyone!

Our recent Midyear Meeting in Branson was a success. It was good to see everyone again. The Board of Trustees of the AOCD voted to recommend that the Journal of the American Osteopathic College of Dermatology be an officially recognized committee of the AOCD:

**JOURNAL of the AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY (JAOCD):** This committee shall consist of the journal editor and a minimum of four additional members. This committee shall oversee the content and publication of the JAOCD.

This will require a by-laws change, and AOCD members will have the opportunity to vote on this at the Annual Meeting held in San Diego, CA, on Monday, October 8, 2012.

In 2013, in addition to our Midyear Meeting and Annual Convention, we are planning a weekend continuing-medical-education (CME) event in order to provide our members with an additional opportunity to obtain CME credit. This weekend event will be held in a location easily accessible from a major airport. We hope to provide a minimum of 12 CME credit hours during this event. Our 2014 Midyear Meeting will be held at the Ritz Carlton Dallas, and our goal is to provide 25 CME credit hours at that meeting.

**Upcoming Meetings**

Information regarding our Annual Convention in San Diego will be available soon. Check our website for updated meeting information.

**AOA Meetings**

At the recent Postdoctoral Training Review Committee meeting in Chicago on April 19, four new dermatology residency programs were approved. Additional information regarding these programs will be made available in the fall issue of the DermLine. The AOA also approved, with the help of Dr. Stephen Purcell and representatives from the AOCD, AOCP, NYCOM, and the Ackerman Academy, the first-ever Dermatopathology Fellowship with the Ackerman Academy and the New York College of Osteopathic Medicine (NYCOM).

The AOCD continues to grow and evolve, and we are no longer considered a small organization. Moving forward, our operating procedures will be further fine-tuned in order to meet that growth and better serve our members.

As always, thank you for your support of our College and the journal we're so proud of.

Sincerely,

Marsha Wise, BS
Executive Director, AOCD
Dear AOCD members, program directors, residents, and students,

This 23rd issue marks the 10-year anniversary of the *Journal of the American Osteopathic College of Dermatology* (JAOCD). I would like to share some history of the journal, as some of you may not realize or recall the tremendous efforts on the part of a few that have made the journal what it is today. First, the founding editor, Dr. Jay Gottlieb, along with his original co-editors, Drs. James Q. Delrosso and Stanley Skopit, developed the journal from scratch, crafting its architecture and premise and summoning support from colleagues, residents, students and industry. After 10 years of hard work and dedication as Senior Editor, Dr. Gottlieb is stepping down. Congratulations and thank you, Dr. Gottlieb. You developed an academically sound periodical and a tremendous legacy for our college, as the JAOCD is one of only two journals representing the specialty colleges of the osteopathic profession.

The journal will now be in the very capable hands of Dr. Karthik Krishnamurthy, who is taking over the Senior Editor position. Please continue to support the journal by maintaining regular appreciation and recognition of its sponsors and, most important, continuing to submit pertinent and academically sound articles.

I hope all attendees enjoyed this year’s mid-year AOCD meeting in Branson, MO. Dr. David Grice compiled a fantastic line-up of speakers as well as terrific social functions. As I have said previously, I welcome any comments you may have regarding our meetings. I am in constant contact with our board members and am working closely with the program chairs of our upcoming meetings, Dr. Rick Lin (Midyear Meeting in Winter Park, Colo.) and Drs. David Grice and Suzanne Rozenberg (Annual Meeting in San Diego). At the Annual Meeting, Dermpath Diagnostics is offering 10 $1,000 travel vouchers for outstanding resident research presented at the meeting. Final criteria will soon be made available to residents and program directors.

In the meantime, your Board of Trustees and various committees continue to work to better our College. The Membership Committee is currently being reorganized, and a search is underway for a replacement for Dr. Monte Fox, who served as Committee Chair for more than five years. Thank you, Dr. Fox, for your service and dedication to the AOCD.

Educationally speaking, the number of residency programs in the AOCD continues to grow, with four new programs approved this past year. Additional information regarding these programs will be made available in the fall issue of DermLine. The AOA also approved the first ever Dermatopathology Fellowship with the Ackerman Academy and NYCOM, the result of efforts by the AOCD, AOCP, NYCOM and the Ackerman Academy, and in particular Dr. Stephen Purcell. It is clear the American Osteopathic College of Dermatology is on solid ground.

I am honored and privileged to serve as your AOCD President. Once again, thank you, and please feel free to email me directly at spinsking1103@aol.com.

*Fraternally yours,*

Brad Glick, DO, MPH, FAOCD
President, AOCD
Case Report

A 23-year-old female presented to our clinic for evaluation of multiple hyperpigmented macules and papules on her thighs, arms, chest and abdomen (Figures 1 & 2). They had been present for approximately one year and were mildly pruritic. Review of systems revealed fatigue for two weeks. She had no significant past medical history, and family history was non-contributory. She did report an allergy to bee stings.

Physical exam revealed scattered 2.5 mm orange-to-tan colored macules and papules on her bilateral thighs, upper extremities, abdomen and chest. These lesions showed dermatographism with positive Darier's sign. Hyperpigmentation of the lesions was persistent with diascopy. No hepatosplenomegaly or lymphadenopathy was palpable.

Labs were taken and revealed a serum tryptase level of 70.3 ng/ml initially and 57.1 ng/ml on repeat draw one week later (normal less than 11.5 ng/ml). CBC was within normal limits.

A site was biopsied with a 3 mm punch and demonstrated superficial perivascular infiltrate of lymphocytes around slightly ectatic vessels (Figure 3). A toluidine blue stain showed significantly increased mast cells within the papillary dermis. The above was consistent with urticaria pigmentosa, macular type.

The patient was then referred to an allergist for testing. She was found to be significantly atopic with positive reactions to ragweed, weeds, grass, dust mite and cats. Her elevated serum tryptase also indicated systemic involvement, which prompted a bone marrow biopsy. The patient’s bone marrow biopsy further confirmed the diagnosis of systemic mastocytosis, although she had no GI symptoms, bone pain, diarrhea, or other systemic symptoms. She was advised to take fexofenadine in the morning and cetirizine in the evening. She also was given an epinephrine pen, and it was recommended that she be cautious with alcohol, NSAIDs, aspirin, bee stings, and local trauma to the skin lesions.

Discussion

Mastocytosis is a clonal disorder characterized by abnormal proliferation of mast cells leading to accumulation in various tissues.1,2 The World Health Organization currently recognizes seven subcategories of mastocytosis, including cutaneous mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with an associated clonal, hematological non-mast-cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma.2,3 These major categories are further divided into additional variants, where cutaneous mastocytosis, specifically, can be separated into sub-variants including urticaria pigmentosa/maculopapular cutaneous mastocytosis, typical urticaria pigmentosa, plaque form, nodular form, telangiectasia macularis eruption perstans, diffuse cutaneous mastocytosis, and solitary mastocytoma of skin.4 The overall incidence of mastocytosis is about 1/50,000-100,000 per year.2 It affects males and females equally. It occurs in all races, but is more common in whites.5 Mastocytosis affects more children (65%)6 than adults, where 80% of children present with cutaneous lesions before 6 months of age.1 Incidence of mastocytosis increases again from age 30 to 50 years.2 Most cases of mastocytosis in children are limited to the skin and resolve spontaneously.1,2 Patients with adult or adolescent-onset mastocytosis may present with cutaneous lesions, but experience a greater risk for systemic involvement and are more likely to have persistent disease.2

Mast cells originate from pluripotent...
bone marrow cells that express CD34+, CD13+, CD117+ and high affinity IgE receptor (FcεRI). The major growth factor in controlling mast cell number and those in mast cells’ final residence play a role in controlling mast cell number and differentiation. In this way, mast cells are broadly dispersed throughout the body, collecting in highest concentration in tissues that are directly exposed to the external environment, such as in the dermis, respiratory mucosa, gastrointestinal mucosa, and genitourinary mucosa. Mast cells may also surround blood vessels, lymphatics and peripheral nerves. Upon reaching their final destination, mast cells eventually mature and become fully granulated cells. Under normal regulation, both factors in bone marrow and those in mast cells’ final residence play a role in controlling mast cell number and differentiation. The major growth factor for mast cell survival and differentiation is stem cell factor. Stem cell factor links to its related receptor, a tyrosine kinase, known as KIT, which is encoded by the c-kit gene. It is postulated that a mutation in c-kit may lead to enhanced receptor function and thus result in abnormal growth and accumulation of mast cells in at least one or more organ systems. The most common mutation identified in neoplastic mast cells is a mutation involving codon 816 of c-kit mRNA, where an A to T substitution leads to an aspartic acid to valine substitution of amino acids during protein synthesis. This mutation has been found in the peripheral blood of adult patients whose mastocytosis has a hematologic component, and more currently in the skin and bone marrow of a majority of adult patients with systemic or cutaneous mastocytosis. Pediatric cutaneous mastocytosis has been thought to signify a transient dysregulation of local growth factors, but in rare circumstances, an inactivating mutation at codon 839 has been identified in children with cutaneous mastocytosis. Another genetic polymorphism identified, Q576R polymorphism, located in the interleukin-4 receptor alpha chain, may moderate disease expression as well. The discovery of these mutations may explain the varied clinical presentation and may be important in better understanding pathogenesis and determining appropriate therapies and prognosis.

Patients with mastocytosis may present with acute/chronic systemic symptoms or cutaneous lesions, where symptoms reflect the extent of mast cell disease, mediator released, and other organs involved. In about 90 percent of cases, the most common presentation of mastocytosis is limited to the skin and is characterized by single or multiple lesions that are itchy. Seventy-five percent of patients with cutaneous mastocytosis have a positive Darier’s sign, whereby rubbing the lesion leads to urtication. Additional specific findings may be present depending on the variant of cutaneous mastocytosis. Seventy-five percent of patients with cutaneous mastocytosis have a positive Darier’s sign, whereby rubbing the lesion leads to urtication. Additional specific findings may be present depending on the variant of cutaneous mastocytosis. In cases where patients present with acute or chronic systemic symptoms, tissues such as those of liver, bone, spleen, and gastrointestinal tract can be affected. Most common systemic symptoms include flushing, headache, or fatigue. Chronic systemic symptoms may involve the skeletal system, central nervous system, gastrointestinal system, or cardiovascular system and may manifest as a pathological fracture; neuropsychiatric symptoms; nausea, vomiting, or malabsorption; and syncope or flushing, respectively.

Mastocytosis is diagnosed based on clinical characteristics, and it is confirmed by histology. Biochemical data may also help support a diagnosis of mastocytosis. Cutaneous mastocytosis can be diagnosed by typical clinical skin lesions and a positive Darier’s sign. In addition, a skin biopsy is necessary to confirm the diagnosis, and it may show multifocal aggregates of mast cells in the upper dermis as well as around blood vessels. According to the World Health Organization diagnostic criteria for cutaneous mastocytosis, the skin lesion must show focal dense infiltrates greater than 15 mast cells per cluster or greater than 20 cells per high-power field in diffuse mast cell infiltrates on histology. Cutaneous mastocytosis may also be diagnosed if a c-kit D815v mutation is discovered. In patients without skin lesions, mastocytosis may be suspected if one or more of the following symptoms or findings are present: unexplained ulcer disease or malabsorption, radiographic or 99mTc bone scan abnormalities, hepatomegaly, splenomegaly, lymphadenopathy, peripheral blood abnormalities, or unexplained flushing or hypotension. While not diagnostic, elevated levels of plasma or urinary histamine or metabolites of histamine, prostaglandin D2 metabolites...
Important Safety Information

Oracea® (doxycycline, USP) 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® 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.
in the urine, or plasma mast cell tryptase may also point to a diagnosis of mastocytosis. Other markers, such as serum interleukin (IL)-6 levels, and soluble SCF receptor (CD117) and IL-2 receptor (CD25) levels may indicate presence of the disease. In the subset of patients who present without skin lesions yet are suspected to have mastocytosis, a bone marrow biopsy and aspirate is indicated for diagnosis and determination of the type. To diagnose systemic mastocytosis a patient must have certain bone marrow findings. In systemic mastocytosis, mast cells appear larger and fusiform in morphology and have loosely scattered, fine cytoplasmic granules, while normal bone marrow counterparts are round to oval in shape, have densely packed, uniform cytoplasmic granules, and nuclei that are non-lobulated. According to the WHO criteria for diagnosis of systemic mastocytosis, a patient must present with at least one major criterion and one minor criterion or else three minor criteria in the bone marrow or extracutaneous organs. Major criteria include multifocal dense infiltrates of mast cells where greater than 15 mast cells are present in aggregates. Minor criteria are as follows: greater than 25% spindle-shaped cells or other atypical morphologic features in mast cell infiltrates; c-KIT D 816V mutation; CD25 and/or CD2 expression on CD117+ mast cells; serum tryptase levels greater than 20 ng/ml devoid of an associated hematologic disorder. While bone marrow biopsy is an important diagnostic tool in adults, it is not recommended in children as systemic symptoms are rare. Bone marrow biopsy, however, is especially useful in those adult patients who have severe systemic symptoms or anaphylactic episodes. It is also helpful in adult patients with urticaria pigmentosa, especially if they have peripheral blood abnormalities, enlarged liver or spleen, or lymphadenopathy to find out if they have an associated hematologic disorder. Other tissue specimens may be obtained as indicated to define the extent of mast cell involvement. For instance, if lymphoma is considered, then lymph nodes can be biopsied, and such is the case for other organs.

Lab analysis proves to be useful in diagnosis of mastocytosis. Complete blood counts may reveal anemia, thrombocytopenia, thrombocytosis, leukocytosis, and eosinophilia in patients with systemic mastocytosis. Subclinical malabsorption may present as hypcholesterolemia or hypoproteinemia. Total tryptase level can be tested and may be helpful in diagnosis, as it is a marker of mast cell degranulation and is released with histamine. The plasma tryptase level correlates with number of mast cells in the lesions of urticaria pigmentosa in adults with systemic mastocytosis. Serum total tryptase in addition to skin biopsy should be performed in a patient with complaints of itchy cutaneous lesions, flushing, or anaphylactic reactions to drugs or hymenoptera sting to rule out idiopathic anaphylaxis, where plasma tryptase levels and mast cell proliferation would be normal in between anaphylactic episodes. A 24-h urine 5-hydroxyindoleacetic acid (5-HIAA) and urinary metanephrines may be ordered in patients with suspected mastocytosis to rule out the possibility of carcinoid tumor or pheochromocytoma.

Overall therapy for mastocytosis is conservative, and most of the current treatments will not permanently cure the skin or systemic lesions but may provide considerable symptomatic relief. First-line treatment of mastocytosis includes counseling the patient, including parents of patients under age 18 and other care providers. Patients should be instructed to avoid factors that elicit an acute mediator release from mast cells, such as heat, cold, friction, pressure, intense exercise, stress, anxiety, stinging insects and radiographic dyes. Drugs, such as aspirin, non-steroidal anti-inflammatory drugs, codeine, morphine, thiamine, and opiates should be avoided as well. Patients and their care providers should be informed of their increased risk of anaphylactoid reactions, and in such cases, epinephrine is used to treat episodes of vascular collapse. Patients should be instructed to self-administer it subcutaneously. Additional treatment is aimed at relieving an individual's specific disease symptoms secondary to mediator release. Antihistamines, including H1 and H2 blockers, may both be utilized to treat pruritus, flushing, and wheal formation, yet newer-generation antihistamines are favored over older-generation for control and anti-sedating properties. Common H1 blockers utilized include hydroxyzine, dexchlorpheniramine or doxepin, while H2 blockers include cimetidine, disodium cromoglycate may improve these cutaneous symptoms as well while also providing systemic relief, mostly of gastrointestinal symptoms such as diarrhea and abdominal pain, although they may also help reduce bone pain and disorders of cognitive function. Topical corticosteroids, leukotriene antagonists, interferon, and cyclosporine have also proven to be effective. Calcium, vitamin D, and bisphosphonates may be used to treat osteoporosis. In select patients with cutaneous mastocytosis, psoralen and long-wave ultraviolet radiation (PUVA) and targeted laser therapy for managing widespread and discrete lesions have been used successfully. In adult patients with urticaria pigmentosa with or without systemic manifestations, PUVA photochemotherapy has been associated with a decrease in whealing, lessening of Darier's sign and pruritus, and fading of pigmentary changes in existing lesions. These characteristic skin lesions, however, may return three to six months after discontinuing therapy. Due to its transient therapeutic benefits and possible side effects, it should be recommended for those patients who have extensive cutaneous disease and are unresponsive to other forms of treatment. Potent topical corticosteroids, such as 0.05% betamethasone dipropionate ointment, applied with occlusion for 8 hours per day for 8-12 weeks, may also help decrease pruritus and number of mast cells. It may be recommended as treatment for patients who have extensive cutaneous disease. In addition, a single intraskeletal injection of steroid, specifically triamcinolone acetonide, 40 mg/ml, has been associated with control of pruritus and absence of Darier's sign as well as cutaneous atrophy after four weeks. It may also clear lesions for at least one year. In a few cases, removing lesions through surgery may be curative. For patients with systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), treatment is based on the specific hematologic abnormality. Treatment with interferon-alpha 2b has been used with mixed results in patients with SM-AHNMD or aggressive systemic mastocytosis (ASM). Chemotherapeutic regimens have also been of limited success in patients with aggressive forms of mastocytosis such as ASM, mast cell leukemia (MCL) and SM-AHNMD. Cladribine, a nucleoside analogue, however, may have therapeutic benefits, as its ability to exercise its cytotoxic activity is not specific to cells that are active in the cell cycle. Thus, it can slow progressing neoplastic processes. Tyrosine kinase inhibitor, such as imatinib mesylate, may act on the mutated kit tyrosine kinase in mastocytosis, but it is thought to be of limited use as it fails to specifically
inhibit kit with codon 816 mutations associated with the most common forms of systemic mastocytosis.\textsuperscript{4,7} Splenectomy may be indicated in patients with massive splenomegaly associated with hypersplenism or portal hypertension, and it may improve the survival in patients who have grave prognoses.\textsuperscript{4,13} While long-term prognosis is unknown, bone marrow transplantation may be considered as well for this subset of patients. In advanced disease, radiotherapy may prove to be beneficial in treating refractory bone pain.

The patient’s age at time of presentation is important in determining prognosis.\textsuperscript{10} The majority of pediatric patients with cutaneous mastocytosis experience improvement of symptoms over time, and 50\% of patients’ symptoms have completely resolved by adolescence. Patients with mastocytosis should be followed depending on the type of systemic mastocytosis, occurrence of mediator-related symptoms, coexisting disorders, and treatment.\textsuperscript{13} Patients with indolent systemic mastocytosis should have a follow-up once a year, where serum tryptase levels, complete blood cell count and complete metabolic panel are checked. Patients with more aggressive forms of mastocytosis should be followed more frequently, and if disease progression is suspected, a bone marrow examination should be performed.

Overall, patients with indolent systemic mastocytosis have minimal symptoms and should remain stable with a normal life span. Patients with this form of disease do not commonly progress to severe disease. Patients with more aggressive forms of systemic mastocytosis tend to have a poorer prognosis. In patients with systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease, five-year survival is reduced, and patients with mast cell leukemia have expected survival duration of about six months.\textsuperscript{13}

Conclusion

This case describes a female patient who presented with skin lesions consistent with urticaria pigmentosa. While she did not experience systemic symptoms clinically, a bone marrow biopsy confirmed the presence of systemic disease, and her symptoms were controlled with oral antihistamines. Overall, mastocytosis represents a clonal disorder of mast cells affecting 1 in 50,000-100,000 new patients per year. In adults, mastocytosis is thought to result from a mutation in the kit receptor, and thus leads to abnormal growth of mast cells. While the most common presenting symptom is an itchy, tan-colored macule that forms a wheal after being scratched, systemic symptoms, including flushing, dyspepsia, diarrhea or hypotension, may occur as well. In order to make a diagnosis of systemic mastocytosis, a patient must have at least one major criterion and one minor criterion or else three minor criteria based on the World Health Organization’s criteria for diagnosis of systemic mastocytosis. In addition, a bone marrow biopsy helps confirm the diagnosis. Treatment is based on reducing symptoms and preventing mast cell degranulation. Histamine receptor blockers, PUVA therapy, potent topical steroids, and interferon-alpha 2b have been used with some success. In general, patients with the indolent form of mastocytosis have a relatively good prognosis, whereas patients with more aggressive forms of mastocytosis have a poorer prognosis with decreased five-year survival.

References

**ENDOGENOUS OCHRONOSIS WITHIN MELANOCYTIC NEVI**

Kurt Greleck, DO,* Vishala Sharma, MSIV** Les Rosen, MD,*** John Kartsonis, MD, FAAD,**** Layne Nisenbaum, DO, FAOCD*****

*Second-year dermatology resident, Columbia Hospital, West Palm Beach, FL
**NOVA Southeastern University, Ft. Lauderdale, FL
***Dermatopathologist, Dermpath Diagnostics, Pompano Beach, FL
****University of Florida College of Medicine, Jacksonville, FL
*****Program Director, Columbia Hospital Dermatology Residency, West Palm Beach, FL

**ABSTRACT**

Alkaptonuria is a rare autosomal recessive disease that manifests as a result of the deposition of homogentisic acid within connective tissues. Patients often present during infancy with darkening of diapers due to oxidation of homogentisic acid, or during adulthood with progressive arthritis. Skin manifestations are often subtle but may precede the onset of arthritis and be a clue to the underlying diagnosis. We describe a case of a man with alkaptonuria with evidence of ochronotic pigment deposition within dermal melanocytic nevi, which has not yet been described in the literature. The epidemiology, clinical features, pathophysiology, histopathologic characteristics, and current therapies are reviewed.

**Introduction**

Alkaptonuria (AKU) is a rare, autosomal-recessive disorder of tyrosine metabolism. Originally recognized by Garrod in 1909, alkaptonuria has been with humanity for far longer, as its signature deposition of ochronotic pigment may have been found in several Egyptian mummies. Typically manifesting clinically in the 3rd decade of life with progressive arthritis, most patients tend to eventually be diagnosed during joint replacement or repair. However, AKU can have a variety of cutaneous manifestations that often go unrecognized by the patient and the uninstructed clinician alike. The metabolic defects associated with this disease lead to the pathologic deposition of homogentisic acid (HGA) in various tissues such as the sclera, cartilage, connective tissues, heart, bone, prostate, and genitourinary system. This case illustrates the possible role that the dermatologist and dermatopathologist can play in the diagnosis of AKU, and the recognition of the fact that HGA may selectively deposit in melanocytic nevi as well.

**Report of Case**

A 54-year-old man with a history of AKU presented to his dermatologist for full body exam in February of 2011. Two biopsies of atypical nevi were taken and sent for histopathologic evaluation. His medical history was significant for hypothyroidism, but was otherwise unremarkable apart from the diagnosis of AKU and history of progressive generalized arthritis. He had both knees and ankles replaced over the previous 10 years, worked as a truck driver and had a history of previous tobacco and alcohol use. He had no history of exposure to depigmentary agents, antiarrhythmics, or antimarials. He had no history of darkened urine and his diagnosis was not made early in life; instead, it was identified after he injured his knee and underwent subsequent orthopedic surgery in December of 2002. He had a history of progressive arthritic pain to the knees and most of his joints and back. After injuring his knee he was evaluated by an orthopedic surgeon and sent for arthroscopy. During the procedure, the orthopedic surgeon was surprised to find darkened black cartilage and bone (Figure 1). Eventually, the patient required bilateral knee and ankle replacements. Following the diagnosis of AKU, the patient was referred to the National Institutes of Health (NIH) for evaluation and possible enrollment in a trial to evaluate the use of nitisinone. At the time of his initial workup at the NIH, he had a history of darkening pigmentation to the ears, face, sclera and hands which had not previously been diagnosed as AKU. During his evaluation at the NIH, a 24-hour urine specimen for homogentisic acid level was significantly elevated (see Table 1). The remainder of his bloodwork, urine, CT scan of the chest and abdomen, MRI of the brain, and echocardiogram findings were within normal limits. He was enrolled in a trial of nitisinone at 0.35mg twice a day, but had to be taken off of the medication due to increased liver function test levels after five days of treatment. Following his diagnosis and workup at the NIH, his sister was also diagnosed with AKU. Over the following years the patient’s skin continued to darken in the aforementioned areas, and his arthritic pain continued to increase. During his der-

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**Table 1**

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<td>FSH</td>
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<td>ALk Phos</td>
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<td>ALT</td>
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</tr>
<tr>
<td>HGA</td>
<td>744 [&lt;10 mmol/mol]</td>
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</tbody>
</table>

**Figure 1** Darkened ochronotic bone and cartilage are visible during arthroscopy of the patellofemoral joint
matologic exam in 2011, the patient was noted to have multiple macular, blue-gray hyperpigmented areas on the nose, bilateral helices, and bilateral elbows (Figure 2). Numerous hyperkeratotic, coalescing blue-gray papules were present over the bilateral dorsal hands, predominately over the metacarpal phalangeal joints, as well as the first web space between the thumb and second digit and the ulnar hand (Figure 3). Also present was a slight macular blue-gray pigmentation over the cheeks. Bilateral scleral pigmentation (“Osler’s sign”) was also noted (Figure 4). The chest had a hyperpigmented melanocytic nevus 6 mm in diameter with varied dark coloration and somewhat irregular borders, and the back had a 7 mm irregularly hyperpigmented papule, both of which were biopsied.

**Histopathology**

Two biopsies were examined. The first (specimen A) was from the right chest, and the second (specimen B) was from the left upper back. In both cases, histopathologic analysis revealed dermal melanocytic nevi associated with fine granules of brown ochronotic pigment interspersed throughout the melanocytes (Figures 5 & 6). No ochronotic pigment was identified within the normal skin that was not part of the dermal nevi in both specimens.

**Diagnosis**

Endogenous ochronosis; alkaptonuria.

**Discussion and Comment**

Alkaptonuria is a rare metabolic disorder, with only approximately 1,000 cases in the literature to date.5,6,7 The uncommon nature of this entity makes for a difficult early diagnosis even when clinical symptoms of darkened cartilage or arthritis begin to appear in a patient’s 30s. The systemic and progressive nature of this disease makes early diagnosis a priority; however, treatment of this disease remains in its relative infancy.

The rarity of alkaptonuria precludes a specific incidence in the population, but it is estimated to occur in 1:250,000-1,000,000 people.4 The inheritance pattern of alkaptonuria is autosomal recessive, and it is either distributed equally between males and females or has a male predominance (1:3-2:5:1).6 As Garrod noted, consanguinity is often a causative factor when detailed pedigree analysis is performed. There seems to be some degree of geographic clustering, with a reported 10-fold higher incidence in Slovakia (1:19,000 people) and Santa Domingo, where a higher degree of consanguinity may be a contributing factor.6,11 It is possibly less common in India.12 Alkaptonuria typically presents in a bimodal manner, with recognition of the disease occurring after the observation of dark urine in diapers as a child or later in life during the investigation of progressive arthritis, as was the case with the patient described herein. Alkaptonuric patients are usually asymptomatic as children and young adults,4,12-15 apart from darkening of the urine, which interestingly may not be seen during the first few days of life as the enzymatic pathway of tyrosine metabolism is not yet functioning and HGA may not be present in the urine.16 Twenty-one percent of patients present before one year of age.4 The mean age of diagnosis for AKU was 55.9 years of age, and the incidence peaked between the fourth to seventh decades of life in a review by Khaled et al.6 Skin manifestations usually present in the fourth decade of life, often as blue-black macules on the ears.6 Blue-black coloration is partly a result of the Tyndall effect. Other skin sites are often involved, and these are most generally in sun-exposed sites, cartilaginous sites, and areas with apocrine glands.17,18 Axillary skin pigmentation in the pattern of glandular orifices, as well as staining of undergarments, may be present late in the first decade. Other areas of skin findings include the nose, dorsa of the hands, palms and soles, teeth, buccal mucosa, nails, fingers, cerumen, and abdomen.5,19 Pigmented colloid milium on the dorsa of the hands has also been reported.19 We believe that this case may be the first documented deposition of ochronotic pigment within melanocytic nevi. Ocular involvement also is common, mainly manifesting as scleral pigmentation although it may also involve the conjunctiva, eyelids, tarsus, or cornea.6,16 Arthritis is likely the most common clinical finding in patients and leads to the diagnosis of AKU in 45 percent of patients.4 The earliest symptoms usually develop in the lumbar spine, hips, knees and large weight bearing joints in the third to fourth decade.6,19 The clinical presentation of arthritis often is likened to that of rheumatoid arthritis.19 Ochronotic arthropathy usually involves the spinal joints first. The radiographic changes are similar to those of osteoarthritis but instead are located in large joints, including the hip and shoulder joints, with sparing of the sacroiliac joint and smaller peripheral joints.19 Narrowing of the joint spaces with calcification of the intervertebral disks and eventual fusion of vertebral bodies are seen in the lumbar spine and result in limited range of motion and ankylosis.4,19 Fifty percent of patients have a joint replaced by the age of 55.4 Fifty-seven percent of patients have tendon-related findings, such as thickened Achilles tendons, tears following minor trauma, joint effusions, or synovitis.6 Magnetic resonance imaging (MRI) has become the imaging modality of choice for visualizing the specific bone, joint and ligament changes of AKU compared to conventional radiography.20 Cardiovascular manifestations of AKU relate to deposition of ochronotic pigment (HGA polymers) within heart valves, endocardium, aortic
The rate of aortic valve disease had a prevalence of over 40% by the fifth decade. There is controversy regarding whether there is actually an increased rate of coronary heart disease. Patients should be evaluated with echocardiography for evidence of valvulopathy and with CT scanning to screen for increased coronary calcium deposition. The genitourinary system can also be involved, with development of kidney and prostate stones in a portion of AKU patients. Renal ultrasound or CT scanning should be performed to rule out renal calculi. Incidental prostatic lithiasis commonly occurs due to the alkaline pH of prostatic secretions, and if clinically indicated, further investigation for obstruction may be warranted.

The current standard in the diagnosis of alkaptonuria is based on quantitative measurement of urinary HGA, as the clinically observed dark urine is not always present. Urine will discolor rapidly when the pH is greater than 7.0, or when reducing substances such as ascorbic acid (which normally protect HGA from oxidation) are not present. Several other tests apart from the measurement of HGA are available, such as the alkali test, photographic paper test, Benedict’s reagent test, and ferric chloride test. More commonly, HGA in urine is oxidized by the air to form a pigment-like polymeric material responsible for the black color of standing urine. However, if the urinary pH is too acidic, this reaction may never occur. Urinary and serum measurements of HGA are performed by chromatography-mass spectrometry. HGA urinary levels are typically between 1 and 8 grams per day, whereas normal excretion is usually 20-30 mg per day. Depending on the patent’s genetic carrier status, levels may be variable. Other laboratory findings in AKU patients are typically normal. DNA can be extracted from whole blood and analyzed for mutations in HGO on chromosome 3q21-q23 by polymerase chain reaction (PCR) on a research basis. Alkaptonuria is associated with a deficiency of homogentisate 1,2-dioxygenase (HGO) activity in the liver and kidney of homozygotes, resulting in a block of the metabolic pathway of tyrosine and phenylalanine (see Figure 7). AKU was the first disease to be discovered as a Mendelian autosomal-recessive single gene trait. Both compound heterozygotes and homozygotes have been found. This gene has now been completely sequenced, and a large number of AKU mutations have been identified in many different countries. Certain types of genetic sequences may represent a dynamic hot spot (CCC or GGG repeats) in the HGO gene, perhaps leading to the graphic clustering seen in Slovakia.

Homogentisic acid (2,5-dihydroxyphenylacetic acid, HGA) builds up as a consequence of HGO deficiency and is excreted by active tubular secretion of HGA in urine. HGO is normally present in the kidneys and liver of unaffected individuals, but its activity is absent in those with AKU. Although high levels of urinary HGA excretion are seen in AKU patients (active tubular excretion 400 to 500 mL/minute), HGA gradually accumulates in tissues and is oxidized, and polymerization leads to the development of ochronotic polymers. In tissues, HGA is oxidized to benzoquinone acetic acid and binds irreversibly to collagen fibers as a polymer. On H&E, ochronotic pigment has a yellow or brown “ochre” color (see histologic characteristics). The binding of benzoquinone acetic acid to collagen leads to destabilization of collagen and to loss of periodicity and homogenization of collagen fibers. This is thought to occur through inhibition of lysyl hydroxylase, an enzyme whose function is to provide sites for cross linkage between collagen fibers. Benzoquinone acetic acid is therefore thought to be the actual cause of collagen fiber degeneration. The mechanism underlying the development of arthritis is not as well understood, but is suspected to result from oxidation products, matrix microdamage, osteoporosis, and osteo-clast viability. The hyaline cartilage has increased hardness and decreased elasticity, likely resulting from the inhibition of lysyl hydroxylase and eventual cartilaginous degeneration.

Within the skin, fine ochronotic pigment granules are seen free in the dermis, in the basement membrane, within elastic fibers, within endothelial cells of blood vessels, in the secretory cells of sweat glands, and within dermal macrophages. A mild increase in basal layer melanin may also be seen. Occasional multinucleated giant cells can be seen.

Ochronotic pigment granule deposition within collagen bundles causes homogenization and swelling; formation of a jagged, fractured, or pointed appearance; and a size sometimes over 100 μm. These bodies can be distinguished from melanin by negative staining with silver nitrate and positive black staining with cresyl violet or methylene blue. Additionally, ochronotic pigment cannot be bleached by 10% hydrogen peroxide after 72 hours as melanin can be. It is interesting that in this case of AKU, ochronotic granule...
deposition is seen specifically within the dermis that is occupied by the dermal nevus, and not in the surrounding dermis. Electron microscopic analysis typically shows smaller-sized homogeneous bodies amalgamating into larger, non-membrane-bound structures. Early lesions demonstrate the deposition of electron-dense amorphous ochronotic pigment around individual collagen fibrils within collagen fibers. This deposition gradually causes individual collagen fibril degeneration and eventual replacement by ochronotic pigment throughout the entire collagen fiber.

The differential diagnosis of AKU lies mainly with acquired exogenous ochronosis. A variety of drugs, both topical and systemic, can mimic the darkening of the skin and tissues seen in endogenous ochronosis. Hydroquinone, phenol, carboxylic acid (component in cutaneous ulcer dressings), resorcinol, antimalarials, tetracyclines, phenothiazine, amiodarone, picric acid, benzene, heavy metals, chemotherapeutic agents, and minocycline are among those agents whose previous use of or exposure to must be ruled out. A medication and occupational history should be able to rule out a drug-induced history of ochronosis-like pigmentation, with confirmation by negative urinary HGA testing. An interesting aspect of this case is its initial presentation from the histopathologic perspective, with a dysplastic nevus on the chest being evaluated. As was apparent on the initial biopsy (specimen A), ochronotic pigmentation was present within the dermal nevus taken from the chest (see report of a case and histopathology). It is conceivable for a patient to have applied prescription or over-the-counter topical lightening cream containing hydroquinone on the lesion in an effort to lighten it for cosmetic improvement. However, after finding the same ochronotic pigment granules within the second biopsied nevus, which was from the back, the likelihood of a cosmetic application of hydroquinone became less probable, and a call to the clinician was made for additional history. It is possible that dermal melanocytic nevi that are biopsied and contain ochronotic pigment on histopathology could lead to a diagnosis of AKU in patients who have yet to manifest other symptoms, such as arthropathy. Pigmentation secondary to antimalarial agents usually is more prominent on mucosal surfaces, and may fluoresce under Wood's lamp examination. Other causes of mucous membrane pigmentation include argyria, amalgam tattoo, and chrysis. Amiodarone typically exhibits a slate gray-blue coloration to sun-exposed areas. Exogenous ochronosis typically resolves with cessation of the inciting agent, although in some cases the hyperpigmentation or discoloration of tissues may last for many years. Other causes of dark urine include melanuria, porphyria, myoglobinuria, bilirubinuria, and hematuria, which should be excluded with appropriate serologic and urine studies. Ocular ochronotic manifestations have been misdiagnosed as melanoma, Addison's disease, medications, exposure to silver, iron (siderosis), copper (chalcosis), arsenic (arsenic melanosis), gold (chrysiasis), aluminum, quinones, aniline dyes, and eye cosmetics containing carbon black.

The differential diagnosis of ochronotic arthritis includes ankylosing spondylitis, rheumatoid arthritis, calcium pyrophosphate dihydrate deposition, herniated disc, and osteoarthritis. These can be differentiated by radiographic studies (see clinical section), as ochronotic arthropathy tends to manifest with specific findings. A thorough history combined with failure to demonstrate the excretion of HGA in the urine should allow the clinician to rule out AKU from these aforementioned masqueraders of endogenous ochronosis.

Despite the elucidation of the pathophysiology of AKU, there are no effective therapies available. The most promising agent is 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or nitisinone. Nitisinone is a triketone herbicide that inhibits 4-hydroxyphenylpyruvate dioxygenase, the enzyme responsible for production of HGA. Nitisinone can reduce HGA production while increasing levels of plasma tyrosine and phenylalanine. A three-year phase II trial has been completed as of 12/10/2010 (NCT00107783). Interim analysis suggests positive results, but the final outcome data remain unpublished. A previous study in two patients did show a reduced excretion
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KENALOG® Spray 100g
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0.2% Triamcinolone

*After spraying, the nonvolatile vehicle remaining on the skin contains approximately 0.2% triamcinolone acetonide. Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.3%), and isobutane propellant.

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PRECAUTIONS
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.

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.

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KENALOG® SPRAY
Triamcinolone Acetonide
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DESCRIPTION
The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. The steroids in this class include triamcinolone acetonide. Triamcinolone acetonide is designated chemically as 9α-fluoro-11β,16α,21-trihydroxyprogesterone-1,4-diene-3,20-dione cyclo 16, 17-acetal with acetone. The structural formula is:

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C_{30}H_{27}FO_{6}, MW 434.50
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A two-second application, which covers an area approximately the size of the hand, delivers an amount of triamcinolone acetonide not exceeding 0.2 mg. After spraying, the nonvolatile vehicle remaining on the skin contains approximately 0.2% triamcinolone acetonide. Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.3%), and isobutane propellant.

CLINICAL PHARMACOLOGY
Topical corticosteroids share anti-inflammatory and antipruritic actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vesiculotesticular assays, are used to compare and predict potencies and clinical efficacies of the topical corticosteroids. There is evidence to suggest that a recognizable correlation exists between vesiculotesticular potency and therapeutic efficacy in man.

Pharmacokinetics
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

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, manifestations of 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 use 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 using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression is noted by the above test, the patient should be withdrawn from treatment. Reducing the frequency of application, substituting a less potent steroid, or using a sequential approach.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Intraocularly, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use). If inflammation 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 Kenalog Spray 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;

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.

5. 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.

6. Do not use Kenalog Spray on the underarms or groin areas unless directed by your physician.

7. If no improvement is seen within 2 weeks, contact your physician.

8. Do not use other corticosteroid-containing products while using Kenalog Spray without first consulting your physician.

9. Kenalog Spray is flammable. Avoid heat, flames or smoking when applying Kenalog Spray.

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

Carcinogenesis, Mutagenesis, 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 many adults 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 effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of frequency: burning, itching, irritation, dryness, folliculitis, hypopigmentation, perioral dermatitis, allergic contact dermatitis, eczematous changes, and miliaria.

OVERDOSAGE
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS, General).

DOSE AND ADMINISTRATION
Directions for use of the spray can be 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.

Spray is flammable; avoid heat, flame or smoking when using this product.

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

HOW SUPPLIED
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP) 63 g (NDC 10631-093-62) aerosol can. 100 g (NDC 10631-093-07) aerosol can.

Storage and Handling
Store at room temperature; avoid excessive heat. Contents under pressure; do not puncture or incinerate. Keep out of reach of children.

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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rate of urinary HGA of 65%, with consequent elevation in tyrosine levels. Ther-apy was discontinued as it was possible that neurologic symptoms analogous to those seen in tyrosinemia type III could have developed. A slightly larger study in nine patients was conducted with lower doses of nitisinone, and a 95% decrease in HGA was seen, without complications apart from increased liver function tests in two patients. The patient described in this case was enrolled in this trial but had to be prematurely taken off of nitisinone due to increased liver function tests.

The use of ascorbic acid has been shown to reduce the urinary levels of benzoquinone acetic acid, although the benefits of this therapy are still controversial. Studies have shown a lack of efficacy in relieving the symptoms of ochronosis, and it is possible that ascorbic acid may serve as a cofactor for the enzyme 4-hydroxyphenylpyruvate dioxygenase, which could cause an increase in HGA production and possibly lead to genase, which could cause an increase in antioxidant N-acetylcysteine (NAC), a precursor of intracellular L-cysteine and could possibly neutralize benzoquinone acetic acid. In an in-vitro human ochronotic-cell model treated with ascorbic acid and NAC, a significant increase in efficacy was seen. However, clinical trials investigating the use of this agent with ascorbic acid in combination have not yet been performed.

Management of ochronotic arthropathy is based on symptom relief with non-specific supportive treatment. Joint pain in AKU is chronic and progressive, and often requires pain management. Physical and occupational therapy help to increase range of motion and flexibility. Nonste-roidal (NSAIDS) and intraarticular st-oids are sometimes used for symptom relief.

Restriction of protein, phenylala-nine, and tyrosine are thought to reduce the production of HGA, but severe restriction of these essential amino acids is not practical in the long term and does not seem to be beneficial. Cardiovascular manifestations of AKU should be monitored after the age of 40. Echocardiography to rule out valvu-lopathy (typically aortic stenosis and less commonly mitral and pulmonary valve involvement) and CT scanning to screen for coronary artery calcification should be performed. Cardiovascular ochronosis usually runs a benign course; however, medical treatment of valvulopathy or valve replacement may be warranted. Conclusion

Alkaptonuria is an uncommon, inherited disease for which the pathogenesis and mode of inheritance has been well known to medicine from the time of Garrod. Unfortunately, an effective treatment for this disease remains an area for exploration. In the case described herein, deposition of ochronotic pigment within nevi of an adult man with AKU is reported. This histopathologic finding could be used to help diagnose endogenous ochronosis in patients who have not presented with other findings of alkaptonuria.

References

14. discussion 277.
27. Felbor U, Mutuch Y, Grein F, Müller CR, Kress W. Ocular ochronosis in alkaptonuria patients carrying mutations in the homogentisate 1,2-dioxigenase gene.


Zannoni VG, Malawista SE, La Du BN. Studies on ochronosis. II. Studies on benzoquinone-acidic acid, a probable intermediate in the connective tissue pigmentation of alkaptonuria. Arthritis Rheum 1962;5:547.


Skinnes OK. Generalized ochronosis: report of an instance in which it was diagnosed as melanomasarcoma, with resultant enucleation of an eye. Arch Pathol (Chic). 1948;45:552-8.


**Desmoplastic Melanoma: An Update on Diagnostic and Management Considerations**

Sadaf “Sabra” Waqar, DO, MPH,* Layne Nissenbaum, DO, FAOCD**

*3rd year resident, Columbia Hospital-Dermatology Residency Program, West Palm Beach, FL  
**Program Director, Columbia Hospital-Dermatology Residency Program, West Palm Beach, FL

**ABSTRACT**

Desmoplastic melanoma is rare and classically presents as a dermal tumor that is highly infiltrative, with minimal epidermal change, comprising of spindled melanocytes and prominent fibroplasia. Here we discuss clinical/histologic features, diagnostic modalities, as well as management considerations of desmoplastic melanoma.

**Background**

Accurate and early clinical diagnosis of atypical melanocytic lesions is based upon a complex interplay between the patient-derived “anamnestic data,” analytical reasoning, comparative recognition, differential recognition, and pattern analysis. The goal is early and accurate detection of the atypical or neoplastic melanocytic lesion. Practically speaking, the decision becomes whether to undertake a skin biopsy or digital mole monitoring with close follow-up.

Various logarithms, including the ABCDE rule (now utilized by physicians as well as patients) and the “ugly duckling sign” are well-established analytical approaches to evaluating clinically suspicious lesions. More specific criteria are established for dermoscopic evaluation, including the Menzies method and the seven-step checklist. These criteria and rules must of course be applied in light of each patient’s individual presentation of normal pigmented lesions. Dermatologists have undertaken a great challenge over the last decade to recognize clinical variability of “normal” pigmented lesions among individuals yet successfully develop a common language, a consistent, systematic approach to physical examination and clinical evaluation of pigmented lesions.

Similar advances have been made in the area of reflective confocal microscopy (RCM), an imaging tool that is applied in conjunction with dermoscopy to evaluate suspicious yet otherwise nonspecific lesions. When dermoscopy and RCM were used together, sensitivity (to detect atypical melanocytic lesions) is highest. Both modalities utilize study of en face cutaneous structures to ensure recognition of seemingly benign aggressive tumors.

One such aggressive tumor is desmoplastic melanoma (DM). This variant of melanoma is rare and classically presents as a dermal tumor that is highly infiltrative, with minimal epidermal change, comprised of spindled melanocytes and prominent fibroplasia.

**Clinical Features**

Clinically, the lesion presents as a nodule or plaque, sometimes depressed and often amelanotic. A pink papule or scar-like appearance is also reported, as well as a lentigo-maligna-like discoloration adjacent to the lesion.3,5

There is a high incidence of neurotropism in these tumors. Up to 78% of DM showed neurotropism in a review conducted by Lens et al. The same review also showed that the mean Breslow depth was 2.0 to 6.5 mm, and most cases presented at Clark level IV or V. Often, the diagnosis is delayed and made at an advanced stage, given a nondescript initial presentation. However, lymph node involvement is rare in this type of melanoma. The most common complications are local recurrence and systemic metastasis.

The most common associations are advancing age, male gender, and areas of sun exposure, particularly the head and neck. Clinical differential diagnosis includes basal cell carcinoma, dermatofibroma, sarcoma, or simply scar.

**Histologic Features**

There is significant variability in histologic hallmarks of DM consisting of atypical spindled cells amidst fibroplasia.4 The spindled cells can be either single or arranged in fascicles reminiscent of a nerve-derived neoplasm. The dermal-epidermal junction should be examined carefully to evaluate a possible overlying atypical endogenous melanocytic proliferation. The dermal spindled cells should be scrutinized based on cytomorphology with nuclear atypia and enhanced mitotic rate, although tumor mitotic rate is often negligible.

Regarding an inconspicuous, scar-like histologic picture, Barnhill et al. list the following warning signs as reminders to carefully consider DM: conspicuous cellularity, solar elastosis, lymphoid aggregates, retained adnexal structures, a lack of horizontal fibrosis, vertically oriented vessels and erythrocyte extravasation.3

Busam et al. have described the level of fibroplasia as “pure” or “mixed,” with pure DM having >90% fibroplasia and mixed having <90% fibroplasia and presence of other more typical histologic features of melanoma.4 The significance of this study lies in the finding that the incidence of neurotropism and lymph node involvement is different between pure DM and mixed DM. The pure DM is more likely to have neurotropism (41%) vs. mixed DM (25%). In contrast, the incidence of lymph node involvement was zero in pure DM and 12% in mixed DM. Thus, histologic-criteria subclassification of pure and mixed DM appears to have clinical utility in the management of patients with DM.

Busam et al. were also able to distinguish DM from conventional types of melanoma by hierarchical clustering of certain genes.4 Their work showed that in DM, the genes that are commonly expressed are not those that encode for pigment synthesis, but rather those for neurotropic factors (such as nerve growth factor receptor) and proteins involved in production and homeostasis of fibrous matrix (such as tissue metalloproteinase inhibitor). These findings are consistent with the staining pattern of DM, being S100 positive, P-75 positive, and vimentin positive but melan-A and HMB-45 negative.

Histologic differential diagnosis includes scar, desmoplastic nevus, desmoplastic spitz nevus, sclerosing blue nevus, dermatofibroma, dermatofibrosarcoma protubers, neural tumors, sarcomas, spindles cell squamous cell carcinoma, and atypical fibroxanthoma.
Dermoscopy and Reflectance Confocal Microscopy (RCM)\(^1,5\)

The dermoscopic features are not consistent with those of typical pigmented lesions and are highly variable among individual lesions of DM, primarily because they are often dermal tumors with varying degrees of fibroplasia, vascular hyperplasia, and amelanosis.

The seven-point checklist defines well-established, consistently reproducible criteria for evaluation of atypical melanocytic lesions. These criteria are: grey-blue areas, atypical vascular pattern, atypical pigment network, irregular diffuse pigmentation, regression, radial streaming or streaks, and irregular dots and globules.\(^1,5\)

Unfortunately, given a highly variable fibroplasia, lack of epidermal involvement, and amelanosis, these criteria have limited utility in detection of DM.

Debarbieux et al. described case reports of six DM patients focusing specifically on the dermoscopic presentation of these tumors. Their cases showed the following trends:

1. The detection of a pigment network, aggregated globules or strikes was possible only 50% of the time (3/6 patients).
2. The detection of variability in colors within the suspected lesion was more likely, with 4/6 DM lesions showing four colors.
3. The most consistent feature was detection of a white, scar-like, structureless area (6/6).
4. A blue-white veil, a classic feature of DM, was present in only 2/6 lesions.
5. Another reliable feature consistent with detection of the tumors was presence of linear atypical vessels.

Dermoscopic differential diagnosis includes scar, atypical dermatofibroma, and amelanotic melanoma. The variability in RCM parallels that of dermoscopic evaluation in DM. Pellacani et al. recently described confocal microscopic and histopathologic correlation of dermoscopic features in typical melanocytic lesions. These correlations include:

1. Atypical pigment network = non-edged papillae
2. Irregular pigment globules = irregular shaped clusters
3. Pigment dots = single large pagetoid cells
4. Streaks = radial streaming
5. Light brown pigment = regular honeycombed pattern
6. Dark diffuse pigment = bright cobblestone pattern
7. Blue-whitish veil = disarranged pattern and presence of pagetoid infiltration in superficial layers, nonedged papillae and cytological atypia in basal layer, cerebriform nests, plump cells in dermal papillae
8. Regression = thin epidermis and coarse network of ill-defined grainy bundles or fibers in the dermis, sometimes intermingled with small, bright reflecting spots and plump bright cells

However, DM is lacking in most of the typical features of a melanocytic neoplasm. As discussed earlier, the scar-like, structureless area is found to be one of the most common features in DM. This finding could possibly correlate with findings similar to those in regression, including ill-defined grainy bundles or fibers in the dermis. In addition, those DM lesions that have any degree of pigment variation or blue-whitish veil should have detectable changes if examined through RCM. Again, RCM is only an adjunctive tool for clinical assessment. Its utility becomes most sensitive in light of all the other components of clinical evaluation.

**Management**

Wide excision is standard of care. Several studies have shown that patients with melanomas of desmoplastic type have a lower frequency of sentinel-node positivity than patients with nondesmoplastic melanomas.\(^6,7\)

Some authors are not recommending sentinel lymph-node biopsy (SLNB) for pure DM, since the incidence of lymphatic spread is extremely rare in these lesions.\(^8\) DM on the trunk or lower extremity doubled the risk of SLN positivity compared with location on the head/neck or upper extremity.\(^9\)

In addition, SLN positivity decreases with age.\(^10\) In sum, a good candidate for sentinel lymph-node biopsy in addition to wide surgical excision would be a young patient with DM of the trunk or lower extremity. Otherwise, the utility of this procedure appears very low for prognostic measures. The data for mixed DM shows a different trend, and the lymphatic spread is comparable to conventional melanoma, based on tumor thickness.

The use of adjuvant therapy is not well studied. Some authors recommend post-operative adjuvant radiation treatment for better local control, given the high frequency of neurotropism and incidence of local recurrence.\(^11\)

**References**

ABSTRACT

Erosive papulonodular dermatosis was a term created to encompass three forms of irritant dermatitis that affect the genital, inguinal, and perineal regions, which may be difficult to distinguish due to overlapping clinical appearance: granuloma gluteale adultorum, pseudoverrucous papules and nodules (PPPN), and Jacquet’s erosive diaper dermatitis. We present a case of an 81-year-old Caucasian male with a painful and pruritic inguinal rash for over a year. Pathology revealed erosive papulonodular dermatosis, though no direct causative factor was determined. A review of the literature is presented to elucidate this spectrum of disease.

Case Report

An 81-year-old Caucasian male presented to the dermatology office complaining of a pruritic and painful rash in his groin for three months. During this time, the patient had used topical antifungals, topical steroids and topical antibiotics without improvement of his symptoms. He began using mupirocin cream a few days prior to presentation, which provided mild relief.

His past medical history included hypertension, hyperlipidemia, GERD, and recently diagnosed carcinoma of the bladder, for which he was being treated and followed by urology. The patient’s history was also significant for a below-the-knee amputation of his left leg as a child. His medications included simvastatin, atenolol, aspirin, chlordiazepoxide/clidinium, escitalopram and rabeprazole. He had no known allergies to medication. The patient also denied any prior topical benzocaine use.

On physical exam, there was mild erythema of the inguinal creases bilaterally (Figures 1 & 2). There were no distinct papules or nodules noted, nor was there any scaling of the skin. There was no involvement of the perianal region or buttocks. The presumptive diagnosis at that time was an irritant dermatitis. The patient was prescribed a compound of hydrocortisone-iodoquinol cream with zinc oxide paste. He complained of increased stinging and burning of the left groin and perineum. The patient was treated with various topical antibacterials and antipruritics with mild improvement but continued to complain of irritation and discomfort as well as “peeling” of the skin and new involvement of the scrotum.

Patch testing was performed (North American Series 85 Comprehensive Series Chemotechnique Patch Test Allergens) and was negative to all allergens tested. It is to be noted that at this time the patient had a relapse of bladder cancer, for which he underwent transurethral resection (TUR) with fulguration and received intra-arterial chemotherapy to the bladder. The patient had occasional episodes of incontinence following these surgical procedures, but never required the use of a diaper. He still had mild erythema and lichenification of the inguinal folds and was prescribed a topical antifungal as well as calcipotriene/betamethasone ointment without relief.

Following the patch test results, a 4mm punch biopsy of the left groin was performed, which revealed slight spongiosis dermatitis with marked hyperkeratosis (Figures 3 & 4). There were changes suggestive of a chronic irritant dermatitis synonymous with erosive papulonodular dermatosis and granuloma gluteale adultorum. These were not changes of lichen sclerosis et atrophicus, and there was no evidence of psoriasis. Furthermore, a PAS stain failed to reveal fungal elements.

The patient was prescribed mycostatin/zinc oxide ointment, which resulted in mild improvement. Due to the lack of significant response to prior topical treatment and based on the results of Frambach, et al., the patient was started on an oral antifungal once a week for 10 weeks. At the patient’s most recent visit, he stated mild to moderate improvement and was advised to continue mycostatin/zinc oxide ointment in the morning and was started on topical tacrolimus ointment to use at night. He continues to be monitored.

Discussion

Erosive papulonodular dermatosis is a term proposed by Robson et al. to encompass all variants of genitocrural irritant dermatitis, including granuloma gluteale infantum/adultorum, pseudoverrucous papules and nodules (PPPN), and Jacquet’s erosive diaper dermatitis. They had reported two patients with papulonodular and ero-
sive lesions on the diaper area associated with topical benzocaine. Both patients had lesions that were clinically similar to granuloma gluteale, PPPN, and Jacquet’s erosive diaper dermatitis. The multiple biopsy specimens taken from these patients overlapped histologically with all the aforementioned conditions. Therefore, the authors proposed the term "erosive papulonodular dermatosis" for their patients.3

Granuloma gluteale infantum is a benign skin disorder of controversial etiology manifested clinically by oval, reddish-purple, granulomatous nodules on the gluteal surfaces and groin areas of infants, classically seen between 2 and 9 months of age. Similar lesions have also been described in adults and the elderly who are incontinent, and are referred to as granuloma gluteale adultorum and diaper area granuloma of the aged, respectively. Lesions are similar to those seen in infants, typically being firm, reddish-purple, oval, or elongated nodules and plaques in the pubic area, scrotum, buttocks, and medial aspects of the thighs.3,7-9

Oclusion from diapers, paper napkins, plastic pants, detergents, starch, powder, halogenated steroids, Candida infection, and urine and feces are postulated as possible etiologies.2-6 Furthermore, benzocaine is a potent sensitizer and is a common cause of allergic contact dermatitis of the genital region. Topical benzocaine use has previously been reported to be associated with granuloma gluteale adultorum.3,4 There is no known systemic association with granuloma gluteale infantum. However, in contrast to granuloma gluteale infantum, granuloma gluteale adultorum and diaper area granuloma of the aged are observed only in the genitocrural regions and not in the intertriginous areas. In addition, the nodules of granuloma gluteale adultorum and diaper area granuloma of the aged are often eroded and do not show an arrangement parallel to skin lines.4,7,8

Granuloma gluteale has a somewhat nonspecific histology. It demonstrates epidermal hyperplasia accompanied by a densely mixed, dermal, inflammatory infiltrate of neutrophils, lymphocytes, plasma cells and eosinophils, with variable dilation and proliferation of blood vessels. The lesions of granuloma gluteale are granulomatous in clinical appearance but histologically do not demonstrate multinucleated giant cells or other features of well-developed granulomas.3,9,11

Granuloma gluteale infantum/adultorum is distinguished from PPPN and Jacquet’s erosive diaper dermatitis by the distribution pattern that overlies the convex parts of the gluteal region and the presence of a dense, mixed dermal inflammatory infiltrate. Unlike PPPN and Jacquet’s erosive diaper dermatitis, granuloma gluteale infantum/adultorum is not limited to patients with incontinence.3,5,10

PPPN is a rare condition that was first reported in association with urostomy sites. It may also occur in the perianal area secondary to urinary incontinence or encopresis, and is also believed to be an irritant dermatitis. Lesions are described as shiny, smooth, red, moist, flat-topped and round.1,3,12 The clinical appearance of PPPN is similar to that of granuloma gluteale; however, it consists predominantly of wart-like papules. In one case series, one-fifth of patients with urostomy displayed psuedoverrucous skin lesions in a peristomal location. These lesions were described as wart-like papules, or small, white-gray or reddish-to-brown erosive papules about 2 to 3 mm in size. Many of these patients also had erythematous-erosive skin lesions.3,11 On histology, PPPN demonstrates spongiotic psoriasisform dermatitis or acanthosis yet lacks significant dermal inflammation.3,11,12

In Jacquet’s erosive diaper dermatitis, lesions are localized to the genital and/or perianal skin, appearing as non-confluent, small, well-demarcated papules and nodules measuring 2 to 8 mm in diameter with central umbilication and superficial erosions or ulcers, often with heaped-up borders.10,14 The predominant lesions are the erosions. Although typically seen in infancy, Jacquet’s erosive diaper dermatitis has been reported in adults with urinary incontinence.3,10,14 Prolonged contact with urine under occlusion compromises skin integrity and renders it more permeable to irritants, the most potent being pancreatic proteases and lipases present in feces.2,10 Histopathology shows acanthosis, hyperkeratosis, spongiosis, superficial ulceration, and a mixed dermal inflammatory infiltrate consisting of neutrophils, lymphocytes, and plasma cells. However, because the histopathologic characteristics lack specificity, diagnosis remains largely clinical.10,14

Askin et al. presented an adolescent who had prolonged contact with feces due to encopresis, which was believed to be a potential causative factor. Long-term use of talcum powder also was thought to exacerbate the condition. Although non-specific, the histopathological findings of the biopsy specimen taken from a superficial, eroded, flat-topped nodule were consistent with an irritant contact dermatitis, revealing overlapping features with granuloma gluteale and Jacquet’s erosive diaper dermatitis. Pathology revealed epidermal hyperplasia and a diffuse, dermal mixed inflammatory infiltrate composed of lymphocytes, plasma cells and sparse neutrophils. The patient was instructed to discontinue the use of talcum powder, and a colostomy was created. Once the irritation caused by the stool was removed, the lesions began to resolve, leading to marked improvement in the patient’s pain and discomfort.11

Treatment options for patients with erosive papulonodular dermatosis have not been thoroughly studied. Patients with granuloma gluteale generally do not require treatment, as lesions tend to resolve spontaneously over a few months. Lesions persist for 3-6 weeks, followed by spontaneous regression over 2-4 weeks.4 Furthermore, patients with a history of granuloma gluteale associated with topical benzocaine use tend to have complete resolution once use of the offending agent is discontinued. Regardless of the final classification, management of incontinence most effectively brings about resolution of Jacquet’s erosive diaper dermatitis. Barrier agents such as zinc oxide ointment, white petrolatum, and sulcrate are useful adjuncts to protect the skin from irritants and moisture.10

Moreover, it is important to consider other differentials in the diagnosis of an inguinal eruption. Necrolytic migratory erythema is a rare syndrome that is usually associated with an islet cell tumor of the pancreas. The eruption occurs in perioreificial, flexural, intertriginous, and acral areas, and closely resembles the lesions associated with zinc or other micronutrient deficiencies. Annular and arcuate erythematous lesions coalesce to form large plaques with necrosis and sloughs of the superficial epidermis, followed by erosion or crusting. The condition is poorly responsive to topical therapy with corticosteroid and antifungal medications. Histologically, there is irregula acanthosis with parakeratosis and crust. The upper third of the epidermis demonstrates pallor and ballooning degeneration of keratinocytes. Laboratory findings may include a low serum zinc level, hypoaminoacidemia, and elevated glucagon levels. The cause of the syndrome is unknown, since some cases are not associated with glucagon-secreting tumors. Amino acid, zinc, and essential fatty acid supplementation have improved the eruption without lowering glucagon levels, suggesting these secondary consequences of hyperglucagonemia are the actual cause of the eruption.16

In conclusion, granuloma gluteale
infantum/adultorum, PPPN, and Jacquet’s erosive diaper dermatitis are all forms of irritant dermatitis affecting the genital, inguinal, and perineal regions that may be difficult to distinguish from one another due to overlapping clinical appearance. The term “erosive dermatitis” was created in order to categorize these three dermatological conditions into one disease spectrum. Although these entities are difficult to treat, it is imperative to consider a variety of treatment options, as well as diverse vehicle delivery of topical medications. Barrier repair creams and emulsions, such as Eletone, EpiCeram and Cerave, should be considered given their ability to normalize skin barrier function due to high lipid content, specifically with regard to ceramides. Acitretin, although predominantly prescribed for the treatment of psoriasis, has also been used to treat Darier’s disease, lichen sclerosus et atrophicus of the vulva, and lichen planus.

References
Case Report

A 71-year-old Caucasian male presented with a one-year history of an expanding pigmented lesion on his left upper arm. He was a non-smoker with no known drug allergies and a past medical history of well-controlled hypertension, atrial fibrillation, kidney stones, and COPD. He reported a history of several sunburns. His medications were pertinent to his above noted skin lesions. All other reviewed body systems, including constitutional, neurological, lymphatic and respiratory, were asymptomatic relating to possible metastatic melanoma.

On physical examination, there was a 1.1 cm black and brown pigmented lesion with an irregular border on his left upper arm that was highly clinically suspicious for malignant melanoma (Figure 1). Complete examination of the rest of his skin revealed no other lesions suspicious for melanoma or dysplastic nevi. Lymph node exam of the head and neck, supraclavicular, axillary, and inguinal basins revealed no lymphadenopathy. Liver and spleen were normal to palpation. An excisional biopsy with a 2 mm margin was performed.

Pathology revealed a broad, variegated, plaque-like lesion of the upper dermis. This was composed of diffuse loose regressive fibrosis and variable but focally dense and banded lymphocytic inflammation, accompanied by foci of dense collections of melanophages and melanosis. The epidermis displayed a flattened rete ridge pattern, and scattered cytoid bodies were noted. Within the inflammation were rare, small compact nests of melanocytes exhibiting low-grade cytologic atypia (Figures 2 & 3). These were confirmed as melanocytic in nature by a melan-A immunostain. Mitoses were not identified. The regressive fibrotic changes extended to a deeper level of the dermis than these nests, at a Breslow depth of 0.50 mm.

Slides of the lesion were reviewed by two board-certified dermatopathologists, including one at a regional melanoma referral center. Each concluded that the lesion represented a regressed melanocytic lesion, in the least, a regressed or halo-type dermal nevus. However, due to the breadth of the lesion, density of melanosis and cytologic atypia, regressed melanoma could not be excluded. A complete excision was recommended.

The patient was referred to a university-based melanoma clinic, where his clinical and histopathologic data, including a comprehensive melanoma profile, were presented to a multidisciplinary melanoma tumor board. A final recommendation was made to treat the lesion as a possible thin melanoma, to be excised with a 1 cm margin.

The patient was educated on the importance of follow-up with his dermatologist every six months for one to three years, and annually thereafter. The importance of and instruction in monthly self-administered skin and lymph node examinations were described, and he was educated on the early signs and symptoms of melanoma and the risk of additional skin cancer and lymphatic and distant recurrences. No further radiographic or hematological tests were indicated.

Discussion

Although regression can be seen in various benign cutaneous lesions, it is an unusual phenomenon in malignant neoplasms, seen only in three types of tumors, including melanoma, neuroblastosma, and hypernephroma. It is common for melanoma to demonstrate partial regression;
however, only around 40 cases of complete regression have been reported. This may be due to the difficulty in retrograde diagnosis of such lesions and the discrepancies in the definition. This phenomenon presents a host of dilemmas because much is still unknown about the etiology, the prognostic significance, and the treatment of regressed lesions.

In most reports of metastatic melanoma, about 2.5% have an occult primary origin. These usually present with peripheral lymphadenopathy. It is possible that complete regression could explain the origins of some of these cases. Another possibility is that these cases arise from capsular nevi within lymph nodes. Clinically, regression can be demonstrated when a preexisting nevus or other pigmented lesion begins to show a decrease in pigmentation, variation in color, fragmentation into smaller parts, and eventual scar formation. In cases of metastatic melanoma, these findings are sometimes, but not always, found in the areas of skin drained by the node that metastasis was detected in.

A set of criteria has been established to aid in the diagnosis of a completely regressed melanoma:

1. A history or clinical evidence of a pigmented lesion situated in an area drained by tumor-involved lymph nodes. This implies that in order for a lesion to be diagnosed as a regressed melanoma, metastasis must have already occurred. The diagnosis, therefore, must be made in retrospect. This criterion does not address the possibility that a melanoma could completely regress without ever metastasizing.

2. There must be an absence of any other primary lesion identifiable by history or physical examination that could represent the original lesion of malignant melanoma.

3. The must be the clinical presence of atypical pigment or depigmentation at the site of the untreated presumed primary lesion, with the typical histologic features associated with regression found on biopsy. These findings include an attenuated epidermis, dermal melanophages, lymphocytic or chronic inflammatory infiltrate, reactive vascular proliferation, and fibrosis.

4. There must be an absence of malignant melanoma cells found within the biopsy.

Pathologic diagnosis of melanocytic tumors can be one of the most difficult areas of diagnostic histopathology. The histological diagnosis of a completely regressed melanoma is fraught with pitfalls. Changes characteristic of regression can also be seen in benign regressing melanocytic nevi (halo nevi) and in inflammatory lichenoid conditions. When the findings of regression occur in the background of some residual identifiable melanoma, the diagnosis is not difficult; it becomes more challenging when no identifiable tumor is present.

A halo nevus is one of the histologic differential diagnoses that should be considered in the diagnosis of a regressed lesion. A completely regressed halo nevus clinically shows a more symmetrical annular ring, whereas a hypopigmented regressed melanoma tends to be more asymmetric. Also, halo nevi are common and considered benign in children, but are seen less frequently in the adult population. There tend to be more plasma cells and linear scarring in regressed melanoma than in halo nevi. Other histologic mimickers include benign lichenoid dermatoses, including lichen planus-like keratoses and verrucae. Usually, the clinical presentation differs, and a lesser degree of melanosis, with a more symmetric lichenoid infiltrate, is seen. Clinical correlation and step sectioning the block, looking for residual melanoma cells, may aid in this differentiation.

Finally, complete regression can be challenging to diagnose in cases with residual benign nevoid components, as in the case possibly seen in our patient. It is commonly accepted that many melanomas arise within preexisting nevi. When immune-mediated regression occurs, it may be directed toward the melanoma cells and not toward the benign nevi cells. This can give the appearance of an inflamed dysplastic or traumatized nevus. Careful evaluation of the specimen aids in the diagnosis, with the fibrosis in the benign lesions being concentric or lamellar, the inflammation being perivascular and not band-like, and plasma cells being a rarity.

In cases of other histologically ambiguous primary cutaneous melanocytic tumors that do not display clear-cut features of malignancy, molecular testing such as comparative genomic hybridization, fluorescence in situ hybridization, and polymerase chain reaction (PCR) are being increasingly used. At present, molecular testing is not always definitive or cost effective, but it is possible it may someday be of value in these cases.

The etiology of regression is thought by most to be associated with an immune phenomenon. Most data suggests a T-cell mediated cell death occurs after recognition of abnormal antigens expressed by the melanoma. Melanoma cells are known to have both cytoplasmic and cell-membrane tumor specific antigens that have the ability to stimulate both humoral antibodies and cytotoxic lymphocytes. This is supported by the finding of lymphocytes and plasma cells in the inflammatory infiltrate. It is likely that cell-mediated immunity plays the largest role in regression, with the apoptotic destruction of tumor cells mediated by cytotoxic lymphocytes. Cases of severe regression in primary malignant melanoma with nodal metastases has led to speculation that the presence of metastasis within a regional lymph node may be the initiating factor in stimulating the immune response, resulting in regression of the primary lesion.

The prognostic significance of regression in primary melanoma is highly controversial. Reported survival among the cases of patients with completely regressed melanoma is variable, ranging from 6 weeks to 11 years. Some authors indicate that regression does not increase the risk of metastasis, while others have suggested that regression is associated with a relatively worse prognosis than non-regressed lesions. Inconsistencies in the definition of regression and variations in the thickness of lesions probably contribute to the conflicting opinions. It would be intuitive that if regression were the result of a successful response from the host, that the prognosis of such lesions would be better than for lesions that escaped the body's innate ability to protect itself, but this does not always appear to be the case.

Without a consensus on the prognostic significance of regression, there have been no specific recommendations as to the management of these lesions. It could be argued that erring on the side of caution and treating these lesions as if they were melanomas would be the best solution. The sentinel lymph node (SLN) status represents an important prognostic factor in many patients with melanoma. Some have questioned the use of SLN biopsy to search for occult nodal metastasis in these cases of complete regression. To date, there is no evidence to support any benefit in doing an SLN in regressed melanocytic lesions, especially when considering the potential morbidity associated with this procedure.

As of now, a lesion that is highly suspicious for a completely regressed melanoma should probably be excised as if it were a melanoma. Physical examination of the lymph nodes, liver, and spleen are indicated, with some suggesting baseline blood work including a complete blood count.
liver function testing, and lactate dehydrogenase. Regular self- and physician-administered skin and lymph node exams are recommended every six months.

**Conclusion**

Our patient presented a diagnostic and management dilemma. Clinically, the patient presented with a melanocytic lesion that was highly suggestive for melanoma. It was asymmetrical, with an irregular border and multiple and changing colors, and had a diameter of 1.1 cm. The excisional biopsy, however, was not diagnostic for a malignant melanoma. It was interpreted by two separate dermatopathologists at different laboratories and stained with melan-A staining. Neither pathologist could definitively identify the lesion as melanoma, although the size of the regressed lesion and density of the melanosis were more than is typical of halo nevi. The depth of the regressed lesion extended to 0.50 mm. Clinically, the patient did not have palpable lymph nodes. If this had been a definitive melanoma, a re-excision with a margin of 1 cm would have been recommended. It was decided in this case to treat this lesion as such, because a definitive diagnosis could not be reached.

This case demonstrates the ability of the immune system to remove a rapidly enlarging pigmented lesion. The significance of this is unknown, especially in light of this lesion not showing metastasis so far. The possibility is raised, however, that a melanoma could indeed completely regress without metastasizing as a successful immune phenomenon. Because of the still unknown significance of this, at this time it is probably best to follow such cases with vigilant observation for future metastasis. In these cases, clinicians must use their best clinical judgment as to the management of these patients.

**References**

6. Berger AC, McClay EF, Toporcer M, Wolchok JD, Morris GJ. Completely regressed cutaneous melanocytic lesion: was it benign or was it malignant? Semin Oncol. 2009;36(5):375-9.
Think of me

ZIANA Gel is specifically designed with tolerability in mind.¹

- Indicated for the topical treatment of acne vulgaris in patients 12 years or older.
- Suspended crystalline tretinoin in vehicle designed to deliver the active ingredients to the skin.²
- Hydrogel alcohol-free aqueous base.¹

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.

2. NDA 50-802 for ZIANA Gel; Sections 4.4.1 & 4.2.5. 2006. Data on file, Medicis Pharmaceutical Corporation.

ZIANA is a registered trademark of Medicis Pharmaceutical Corporation. ZNA 11-011 07/31/12
BRIEF SUMMARY
(see package insert for full prescribing information)

ZIANA
(clindamycin phosphate 1.2% and tretinoin 0.025%) Gel

RX ONLY
FOR TOPICAL USE ONLY

INDICATIONS AND USAGE
ZIANA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age 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 (produced by clindamycin) 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. Severe constipation is another common side effect. Colitis may also be seen in patients under treatment with ZIANA Gel.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical trials are conducted under controlled conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice, and rates observed in practice may be lower or higher than those reported in clinical trials. The adverse reactions experienced by patients during clinical trials of ZIANA Gel were similar to those experienced by patients during clinical trials of clindamycin and tretinoin. The most common adverse reactions included dry skin, erythema, scaling, itching, burning, and stinging. These reactions were usually mild to moderate in severity. A higher incidence of skin reactions was seen in patients treated with ZIANA Gel compared to patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the vehicle gel alone.

Table 1: Adverse Reactions Reported in at Least 1% of Patients Treated with ZIANA Gel: 12-Week Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZIANA Gel</th>
<th>Clindamycin 1.2%</th>
<th>Tretinoin 0.025%</th>
<th>Vehicle 0.025%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENTS WITH AT LEAST ONE AD</td>
<td>407/27</td>
<td>432/24</td>
<td>225/27</td>
<td>91/22</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>65/4</td>
<td>64/5</td>
<td>10/2</td>
<td>5/1</td>
</tr>
<tr>
<td>Pharyngodyngitis</td>
<td>25/9</td>
<td>15/1</td>
<td>5/1</td>
<td>7/0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23/1</td>
<td>7/1</td>
<td>3/1</td>
<td>0/0</td>
</tr>
<tr>
<td>Graft</td>
<td>19/1</td>
<td>23/2</td>
<td>9/1</td>
<td>2/1</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>15/1</td>
<td>15/1</td>
<td>15/2</td>
<td>4/1</td>
</tr>
</tbody>
</table>

Note: Formulations used in all treatment arms were in the ZIANA vehicle gel.

Cutaneous safety and tolerance evaluations were conducted at each study visit in all of the clinical trials by assessment of erythema, scaling, itching, burning, and stinging.

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

<table>
<thead>
<tr>
<th>Local Reactions</th>
<th>Baseline N=1825</th>
<th>End of Treatment N=1671</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>199/13</td>
<td>20/4</td>
</tr>
<tr>
<td>Burning</td>
<td>39/9</td>
<td>56/4</td>
</tr>
<tr>
<td>Stinging</td>
<td>33/2</td>
<td>27/2</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS
Concomitant Topical Medication
Concomitant topical medication, such as acid or alkaline soaks 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 antibiotics. 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 50, 160 and 660 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 oral 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
Toxicology (Segment I) studies using clindamycin were performed orally in rats (up to 600 mg/kg/day) and mice (up to 100 mg/kg/day) (563 and 48 times amount of clindamycin in the recommended clindamycin topical on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin up to 190 mg/kg/day (175 and 68 times the amount of clindamycin in the recommended clinical dose based on 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 (~75 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 defects 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 (deafness 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 toxicology 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 70 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.

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Medica, The Dermatology Company
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Case Study: Psoriasis Clearing Post Stroke

Jonathan S. Crane, DO, FAOCD,* David G. Jackson, BS,** Ronald P. Benjamin, M.D.,*** Charlene Snyder, PA-C,**** Christine M. Cook, BS, CCRC*****

*Atlantic Dermatology Associates, P.A., Wilmington, NC
**University of North Carolina, Wilmington, NC
***Atlantic Dermatology Associates, P.A., Wilmington, NC
****Atlantic Dermatology Associates, P.A., Wilmington, NC
*****Atlantic Dermatology Associates, P.A., Wilmington, NC

ABSTRACT
Psoriasis occurs in approximately 2% of the population. The patients who have psoriasis tend to be genetically predisposed. Internal and external factors can result in exacerbation and remission. It is well known that streptococcus pharyngitis can trigger an episode of psoriasis. Stressful events can also precipitate psoriasis, therefore, lack of stress may help psoriasis. Many factors can exacerbate psoriasis, but what conditions can help psoriasis? Ischemic occlusion is of question. It has been reported in the past that psoriasis can clear after a stroke.1

Case Report
A 64-year-old, Caucasian male presented with a history of moderate psoriasis for nine years. During these nine years, he’d had psoriasis involving the nails, elbows, knees and back, with thick scales. He had used numerous topical steroids including clobetasol propionate 0.1% spray. When the psoriasis became severe, he was started on adalimumab. At the time he began adalimumab, he had moderate to severe psoriasis affecting 20% body surface area. The Humira significantly improved his psoriasis. At the time he began adalimumab, he had moderate to severe psoriasis affecting 20% body surface area. The Humira significantly improved his psoriasis. Within a month after beginning Humira (adalimumab), he was about 80% better. The once-thickened hypertrophic plaques were now left as thin, erythematos plaques with a mild scale. By four months into adalimumab, the lesions were extremely thin, and he felt he was 95% better as well as being very happy with his improvement. He continued with the bioinjectable for the next several years and had mild psoriasis during that time (Figure 1).

At one point, he tried just one adalimumab injection per month, but the psoriasis began to return significantly. He then returned to twice-a-month dosing and improved dramatically. Once doing well and having stable psoriasis for several months, he had a stroke. He reported that on the day of his stroke he became dizzy and had numbness in his right arm along with nausea and vomiting. A CT scan revealed an acute stroke involving the cerebellum and medulla. At that time he was admitted to the hospital and the adalimumab was discontinued. He had left-sided weakness and diminished sensory responses for several days. He was then discharged. The MRI showed acute ischemia in the right parietal lobe and right cerebellum hemisphere, as well as the medulla. It was felt that this scenario represented a complete occlusion in the left vertebral artery. This was classified as a “Wallenberg-type” stroke.

This patient had been on atenolol, Lipitor, Diovan, and amlodipine prior to the stroke as well as after the stroke. He was started on Plavix after the stroke. He did not continue the adalimumab after the stroke. He regained full neurological function without any sign of skin psoriasis (Figure 2). His psoriasis is still clear three months after his stroke. This patient inquired if we had heard of psoriasis clearance after a stroke. He was told that we would review the literature, and upon review we were able to find cases of spontaneous clearing of psoriasis after such an event.

Discussion
Psoriasis has had long-standing evidence of a link between the plaques formed by the disease and the nervous system.1 The primary elements of the neural component of psoriasis are likely peripheral nerves and neuropeptides; however, the central nervous system is probably a uniting portion of the nervous system’s role in psoriasis. One patient who had recalcitrant psoriasis for upwards of 40 years suffered “diffuse cerebral atherosclerosis and brain atrophy” secondary to a cerebral vascular accident and consequently lost some of her neural function.1 At this time, she was confused,
and her psoriasis lesions entirely disappeared within months. After this patient partially regained her cerebral function, her psoriasis reappeared on some parts of her body only (knees, elbows, buttocks, and lumbar region). This case displays some evidence of the central nervous system having a role in psoriasis, that inhibition of some functions of the central nervous system can potentially impede psoriasis, and that subsequent restoration of these functions may lead to the return of some psoriatic lesions.¹

Nerve growth factor (NGF) may also play a role in psoriasis.² NGF aids innervation of tissue and regulates some neuropeptides including SP (substance P) and calcitonin gene-related peptide (CGRP). Neurogenic inflammation plays a role in psoriasis through paths that include an increase in terminal cutaneous nerves and higher levels of substance P and calcitonin gene-related peptide in psoriatic plaques.² When psoriatic lesions form, two of the first changes are an increase in nerve growth factor and formation of more keratinocytes. These new keratinocytes in turn produce more active NGF, and NGF in turn aids innervation of tissue. This cycle strongly supports a connection between further innervation of tissue augmented by NGF and the formation of psoriatic plaques.² There also exists evidence supporting that removal of nerves from tissue, possibly by means of a stroke, leads to some clearing of psoriatic lesions, since some surgeries that have accomplished “resection of superficial cutaneous nerves” have locally eliminated psoriatic lesions.¹

A third substance may also contribute to psoriasis by acting alongside substance P and calcitonin gene-related peptide: another neurotransmitter, vasoactive intestinal peptide or VIP.³ VIP levels have been shown to increase when psoriasis spreads and decrease when the disease enters remission. This peptide causes many of the associated symptoms of psoriasis and releases histamine from the skin's mast cells. Histamine then causes “events characteristic of psoriatic plaque,” including the generation of massive amounts of keratinocytes, one of the most noticeable symptoms, along with stimulating angiogenesis and vasodilatation, two more characteristics of psoriasis. The release of VIP stimulates further release of itself along with interleukin-6, which up-regulates itself and VIP, thus making a psoriatic “vicious circle.”³ Since this process is highly dependent on neurotransmitters, a stroke has the potential to impair this process through the nerves and stop the cycle of VIP.³

Conclusion

We now know that the nervous system contributes to psoriasis, and there are many factors that can exacerbate or improve psoriasis. It appears that stroke may improve psoriasis in some patients. In addition to the immune system, the nervous system may also significantly affect psoriasis. Future studies in this area may be warranted to bring recognition of this link, and perhaps develop improved treatments.

References

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Autoimmune progesterone dermatitis is a cyclical dermatitis that occurs in women during the luteal phase of their menstrual cycle. The cutaneous eruption can vary in morphology making diagnosis a challenge. Treatment consists of suppression of ovulation through oral hormonal therapy.

History
A 47-year-old Caucasian female presented with a pruritic cutaneous eruption that started after discontinuing oral contraceptives in March 2004. The patient stated that the eruption recurred with each menstrual cycle. She stated her menstrual cycles were irregular and extremely painful. The cutaneous eruption consisted of “red bumps” on the forearms, upper thighs, and abdomen (Figures 1 & 2). The patient was otherwise healthy except for a history of tobacco use in the form of cigarettes.

Examination
Physical examination revealed a well-appearing, middle-aged adult female with excoriated red papules coalescing into a few plaques on the dorsal forearms, upper thighs, and abdomen. No lymphadenopathy or mucosal lesions were found.

At initial presentation in March 2004, the cutaneous eruption consisted of red papules coalescing into plaques along with pustules. The extent of the eruption was much more severe.

Laboratory
A complete blood count with differential, complete metabolic panel, lipid panel, and hepatitis panel revealed a slight elevation in cholesterol.

In April 2007, a bone marrow biopsy was performed that was negative. A CT of the chest, abdomen, and pelvis was also performed that revealed cysts on her ovaries.

Histopathology
3/24/04 - (CD30 negative lymphoid infiltrate) A superficial pustule containing neutrophils, erythrocytes, and fibrinous debris along with a perivascular lymphocytic infiltrate, dermal fibrosis, and psoriasiform epidermal hyperplasia.

6/18/05 - (Intra-epidermal pustular dermatitis) An intraepidermal pustule with neutrophils and an underlying superficial-to-mid perivascular and interstitial infiltrate of lymphocytes, histiocytes, and neutrophils.

4/16/07 - (Possible lymphomatoid papulosis with mixed cell infiltrate) A vertically oriented infiltrate of lymphocytes, neutrophils, and eosinophils with associated psoriasiform epidermal hyperplasia, spongiosis, and parakeratosis. Many lymphocytes were enlarged with hyperchromatic nuclei.


Course and Therapy
Currently the patient is controlled on a Medrol dose pack. She takes 1-2 tablets as needed during the luteal phase of her cycle. She has irregular cycles, and so the cutaneous eruption is not consistent. She is not a candidate for oral hormonal therapy due to her age and use of cigarettes. She also applies topical mometasone cream 0.1% as needed.

Discussion
Autoimmune progesterone dermatitis (APD) is classically described as a cyclical cutaneous eruption, occurring or worsening during the luteal phase of the menstrual cycle when progesterone levels are elevated. APD typically occurs in women between the ages of 12 and 44. Patients with APD often present with non-specific symptoms for 5-6 years before diagnosis.

The cutaneous eruption can vary in morphology. The lesions may be urticarial, papular, papulosquamous, erythematous, or multiforme-like. Mucosal surfaces may also be involved. The eruption has no predilection for any specific body site.

Symptoms generally appear or worsen within 10 days prior to menses, and resolve
or begin to improve with the onset of menses. Pruritus is typically reported, but the eruption may also be asymptomatic.

The diagnosis of APD is typically made on the clinical presentation and history of a cyclical eruption around menses. Improvement after ovulation-suppression therapy or worsening after removal of suppression supports the diagnosis.

A positive intra-dermal progesterone test performed with a small amount of progesterone suspension 50mg/ml can also support the diagnosis. The reaction can take anywhere from 30 minutes to 96 hours to become positive.

Histological features of suspected APD vary widely, and there are no clear-cut unifying features for the APD cases reviewed. Biopsy may be needed to distinguish APD from other dermatoses.

The exact pathogenesis of APD is poorly understood. It is generally agreed to represent an autoimmune condition in which the body forms a response to endogenous progesterone, manifesting itself clinically when progesterone levels are elevated. The highest levels of progesterone are typically during the luteal, or secretory, phase of the menstrual cycle.

The treatment for APD is primarily suppression of ovulation through oral conjugated estrogen therapy (oral contraceptives). Antihistamines, systemic steroids, and topical steroids are options in patients unable to take oral conjugated estrogen therapy or as adjuvant therapy along with the conjugated estrogens.

The prognosis is generally favorable, as the treatment is typically successful.

References

Primary cutaneous diffuse large B-cell lymphomas (PCDLBCL) are defined as malignant atypical B-cell proliferations presenting with cutaneous involvement alone and no evidence of extracutaneous manifestations at time of diagnosis. It most commonly presents in elderly women and are often located on the lower legs. We present a case of an 80-year-old Caucasian female who noticed a nodular lesion on her left arm and in subsequent years left lower leg and left arm that rapidly enlarged in a few months. Histological and immunophenotypical features were compatible with PCDLBCL. We also highlight the new classification system of primary cutaneous B-cell lymphomas as well as give a brief overview on prognosis and management.

**Case Report**

An 80-year-old Caucasian female presented with a 30x25 mm elevated erythematous to violaceous nodule on the left arm (Figure 1). The patient had a past medical history of hypertension. A punch biopsy was performed. Histologic sections demonstrated diffuse nodular proliferation of markedly enlarged, atypical lymphocytes involving dermis and subcutaneous adipose tissue (Figure 2). The monomorphic population showed large nuclei and prominent nucleoli with scant cytoplasm. Abundant mitotic figures and pleomorphism were also noted. Epidermotropism was not observed. Immunohistochemical stains were positive for CD20 (Figure 3), PAX5 (Figure 4), and diffusely with BCL-2, as well as BCL-6, CD-79a, and slightly for CD10. Ki-67 immunostain highlighted a large percentage of the tumor cells. A final diagnosis of diffuse large B-cell lymphoma was made.

The tumor was surgically removed by surgical oncology and received external beam radiation and chemotherapy. The patient was worked up by oncology for evaluation of any internal malignancy as well, which was found to be negative. In the subsequent years, she further developed diffuse large B-cell lymphoma of the left lower leg (Figures 5 & 6) and left arm, demonstrating a long history of left upper extremity B-cell lymphoma, which required multiple courses of external beam radiation and chemotherapy. Histologically, the findings were consistent with the aforementioned.

**Discussion**

Primary cutaneous diffuse large B-cell lymphoma is an uncommon form of cutaneous lymphoma, representing 20-25% of these lymphomas, and generally having a poor prognosis. PCDLBCL are characterized by a neoplastic proliferation of large, atypical B-lymphocytes, which clinically are most commonly present on the lower legs and are described as rapidly growing red-brown plaques. Typically, at the time of diagnosis, PCDLBCL

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**Figure 1:** 30x25mm erythematous to violaceous nodule on the left arm

**Figure 2:** Diffuse large B-cell lymphoma 400x: Tumor cells have large, irregular vesicular nuclei with prominent nucleoli with mitosis present
has no extracutaneous involvement. Nevertheless, PCDLBCL has a propensity to spread to lymph nodes and extracutaneous sites.

Cutaneous diffuse large B-cell lymphoma has the histological characterization of a diffuse infiltrate throughout the entire dermis and extending into subcutaneous tissue, usually sparing a thin subepidermal grenz zone, and consisting of large B-cells. Immunohistochemical stains of the neoplastic cells in PCDLBCL are typically positive for CD19, CD20, CD79a, Bcl-2, and MUM-1. There is an excellent correlation between CD20 and PAX-5 expression. PAX-5 is a B-cell-specific activator protein (BSAP). PAX-5 is expressed primarily in pro-, pre-, and mature B-cells, but not in plasma cells. Anti-PAX-5 has the ability to detect all committed B-cells. It is very specific to B-cell lineage and does not stain T-cells.

The characteristic predominance of the large tumor cells leads to the aggressiveness of this subtype. A histologic predominance of large cells with round nuclei, as opposed to large cells with cleaved nuclei, has a less favorable prognosis. Additionally, the expression of Bcl-2 protein also has been identified as an adverse prognostic factor.

More recently, one study showed that the five-year survival rate was decreased to a predicted 27% with the deletion of chromosome region 9p21, compared to 100% in cases without deletion. However, the location on the leg of PCDLBCL is the main negative prognostic factor for cutaneous lymphomas, representing a three-year survival rate of 43% compared to 77% in nonleg anatomic locations. Furthermore, nonleg PCDLBCL carries a less favorable prognosis than primary cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphomas, and should therefore be grouped in classification with primary cutaneous large B-cell lymphoma leg type, as proposed by the WHO-EORTC classification.

Radiotherapy is considered the treatment of choice in the management of primary cutaneous lymphomas, with 2 cm margins. There has also been reported success with the use of anthracycline-containing chemotherapies and rituximab, a chimeric monoclonal IgG1 antibody that is directed against the CD20 antigen of B cells. Additionally, rituximab has been shown to be effective in overcoming Bcl-2-associated resistance to chemotherapy, which is a poor prognostic factor when expressed.

References


KAPORIS, KASSARDJIAN, TRAN, WAY
Keratoacanthoma-Like Dermatofibroma

Zhi Zhong Wang, MD, MSc,* Andrew Simone, MD**

*Dr. Andrew Simone Dermatology Clinic, Toronto, Ontario, Canada
**Board-certified Dermatologist, Dr. Andrew Simone Dermatology Clinic, Toronto, Ontario, Canada

ABSTRACT
A solitary pretibial protuberance looked like a keratoacanthoma. Pathological report shows dermatofibroma.

Case
A Polish female, 42 years old, complained of a solitary red protuberance on the left leg for four years. She injured her left leg when she shaved it four years ago. After the injury healed, an itchy papule occurred and grew slowly into a crater-like protuberance (Figure 1). She had gestational diabetes mellitus five years ago and was treated with insulin. She has been on diabetic diet since then.

Physical Exam
There was a solitary, round, erythematous nodule on the lower one-third of the left lower extremity, one cm in diameter, well demarcated, with a crater-like surface with yellowish crust.

Pathology
Pathologic report showed parakeratosis. The epidermis was acanthotic with elongation of the rete ridges. The underlying dermis showed a fairly cellular lesion with proliferation of somewhat plump-appearing histiocytic cells with abundant cytoplasm admixed with more elongated, spindle-shaped cells (Figures 2 & 3). The surrounding stroma showed scattered mild inflammation. The morphology of this lesion was compatible with a fibrohistiocytic tumour. The features were rather suggestive of the epithelioid-cell variant of dermatofibroma. Some of the epithelioid-appearing cells had an admixture of eosinophilic cytoplasm, and foamy cytoplasm was also noted, so a xanthomatous variant of dermatofibroma was also considered in the differential diagnosis.

In order to confirm the epithelioid origin of the tumour cells, we did cell-marker tests. Immunohistochemical studies showed a cellular spindle and epithelioid proliferation of cells in the dermis, sparing the epidermis (Figures 4, 5 & 6). The tumour cells were positive for vimentin and for CD68 and factor XllIA. However, there were large epithelioid histiocytes present that were actually only focally positive for CD68 and focally positive for synaptophysin. They were negative for GFAP, neurofilament and S100 protein. The features were those of an epithelioid variant of dermatofibroma. However, while the morphology of the large cells was unusual, there was no evidence of atypia or malignancy.

Figure 1: A solitary red, keratoacanthoma-like protuberance on the left leg for four years.

Figure 2 & 3: Underlying dermis shows lesion with proliferation of cells with cytoplasm admixed with elongated, spindle-shaped cells.

Treatment
The patient declined Mohs surgical excision.

Discussion
Dermatofibroma is a common cutaneous condition of unknown etiology. It has a predilection for the lower legs of women. Characteristically, it is a solitary, firm, brown, well-defined nodule with central dimpling. It is usually asymptomatic, but pain and itching may be noted.

Some unusual clinical variants of dermatofibroma have been reported. Puig et al. reported two cases of atypical polypoid dermatofibroma on the lower extremities in 1991. The tumors were ten cm and six cm in maximal diameters, respectively, with short pedicles joining to the skin. Pathological examination showed striking atypia and scattered mitotic figures. Requena et al. reported eight cases of giant dermatofibro-
broma (greater than five cm in diameter) in 1994. They authors concluded that giant dermatofibromas usually manifest with a pedunculated appearance below the knee. They are often misdiagnosed as malignancy due to their large size. Requena et al. also reported two cases of atrophic dermatofibroma in 1995. They found out that the thinning of the lesions resulted from the depression rather than from any authentic atrophy. Hence, they suggested that delled dermatofibroma would be a more appropriate appellation than atrophic dermatofibroma. Sehgal et al. reported an unusual giant combined dermatofibroma on the scapula in 2004. The lesion was 25-30 cm in diameter and was surrounded by several similar, smaller ones (satellites). Pathological studies showed architectural features of a deep, penetrating type of dermatofibroma with xanthomatous aggregates, myxoid changes and probable myofibroblastic differentiation. This case of dermatofibroma occurred on the leg and looked like a keratoacanthoma.

The histologic appearance of dermatofibroma can show different areas with varying degrees of myofibroblastic and histiocytic differentiation. Results from immunohistochemical testing with antibodies to factor XIIIa, which label dermal dendritic cells, are frequently positive in dermatofibroma, while antibodies to MAC387, which label monocyte-derived macrophages (histiocytes), show less consistent results. In one study evaluating 28 cases of dermatofibroma, most of the spindle-shaped cells stained positively with HSP47, indicating that skin fibroblasts are a major constituent of dermatofibroma; on the other hand, the presence of CD68-positive histiocytes was inconsistent in these cases.

The cell-surface proteoglycan syndecan-1, fibroblast growth factor receptor 2, and transforming growth factor-beta may each play a role in the growth of dermatofibromas. The patient in this case had Type 2 diabetes for five years at the time of presentation and used insulin for a certain time period. Possibly, her condition was related to her diabetic diathesis and insulin use.

References

ELASTOLYTIC GRANULOMA: A CASE REPORT AND DISCUSSION

Mounir Wassel, DO,* Layne Nisenbaum, DO, FAOCD**

*Dermatology Resident, 2nd year, Columbia Hospital, West Palm Beach, FL
**Program Director, Columbia Hospital Dermatology Residency Program, West Palm Beach, FL

ABSTRACT

Annular elastolytic giant cell granuloma is a rare granulomatous dermatosis of controversial origin characterized by loss of elastic fibers and elastophagocytosis by multinucleated giant cells. Lesions of AEGCG are usually located on sun-exposed areas. We present a case of elastolytic granuloma involving the face.

Case Report

A 74-year-old woman presented with a slightly pruritic skin eruption evolving for three months. There was no family history of skin disorders. Physical examination revealed an erythematous plaque with annular configuration on the right jaw line, with central atrophy and raised erythematous margins (Figures 1 & 2). There was no mucous membrane or nail involvement. We performed a skin biopsy. Histopathologic findings showed granulomatous infiltrates in the dermis consisting primarily of multinucleated giant cells, some of which contained fragments of elastic tissue (elastophagocytosis), and loss of elastic fibers in the center of the lesion (Figures 3, 4 & 5). Special stains (PAS, AFB, Fite, GMS, Giemsa) were negative for microorganisms. Laboratory tests including complete blood cell count, chemistry panel, antinuclear antibody, urinalysis, and chest X-ray were within normal limits. The patient was treated with topical betamethasone dipropionate cream for three weeks with complete regression of the lesion.

Discussion

In 1975, O'Brien described a new type of annular skin lesion with elastolysis and elastophagocytosis, localized on light-exposed body areas. He called this entity “actinic granuloma.” The term AEGCG was proposed by Hanke et al. in 1979 and includes the lesions previously called actinic granuloma, atypical necrobiosis lipoidica, and Miescher’s granuloma. They defend the observation that solar elastosis is not always present; although less common, the lesions could be present in covered areas.

Annular elastolytic giant cell granuloma is an uncommon disease that predominantly affects older adults, with no sex predilection. Clinically, red papules and hypochromic or atrophic plaques with elevated borders and central depression are typically located on sun-exposed skin. There have been reports of lesions located on sun-protected sites. There have also been generalized forms reported with red, asymptomatic papules.

The histopathologic features are best demonstrated by a biopsy of the elevated edge of the plaque. They are characterized by granulomatous infiltrates with multinucleated giant cells in the upper and mid dermis, loss and fragmentation of elastic fibers, and elastophagocytosis by giant cells, without necrobiosis and mucin deposition. These features help to distinguish AEGCG from granuloma annulare and necrobiosis lipoidica, which are the main disorders in the histological differential diagnosis. It is speculated that solar radiation, heat or other unknown factors transform the antigenicity of the elastic fibers and induce the cellular immunological reaction. Immunohistochemical studies showing that CD4+ cells predominated over CD8+ cells in the inflammatory infiltrate also support this theory.

It has also been proposed that diabetes mellitus could be implicated in the etiology by producing structural damage of the elastic tissue. There have been reported cases of AEGCG associated with systemic sarcoidosis, cutaneous amyloidosis, molluscum contagiosum, squamous cell carcinoma of the lung, and cutaneous T-cell lymphoma.

The treatment for AEGCG remains a challenge. Variable results have been reported with therapies such as topical or intralesional steroids, cryotherapy, clofazime, antimalarials (chloroquine and hydroxychloroquine), dapsone, PUVA, and cyclosporine. Some cases resolve spontaneously. Our patient was treated with topical betamethasone dipropionate cream for three weeks with complete regression of the lesion.
References
A CASE OF A CUTANEOUS SINUS TRACT OF DENTAL ORIGIN

Garrett R. Bohrnstedt, DO,* Daniel S. Hurd, DO, FAOCD**

*1st-year Dermatology Resident, LewisGale Hospital-Montgomery, Edward Via College of Osteopathic Medicine, Blacksburg, VA
**Program Director, Dermatology Residency Program, LewisGale Hospital-Montgomery, Edward Via College of Osteopathic Medicine, Blacksburg, VA

ABSTRACT

Cutaneous sinus tracts of dental origin can be a challenging diagnosis for dermatologists. The cutaneous manifestations can mimic more common facial lesions and the patient may deny any dental or intraoral complaints. Inappropriate or delayed treatment is frequently encountered. We present a case of a young female presenting with a “cyst like” area on her right cheek. The patient had sought medical attention through primary care multiple times without resolution. Physical examination revealed a palpable cord and she was referred to a periodontist. The patient’s history was consistent with a chronic abscess involving her right first maxillary molar. Sinus tract formation was discovered extending from her right first maxillary molar to the ipsilateral nasolabial fold. This case should serve as a reminder to consider adding a dental origin to the differential diagnosis of any persistent nodular facial lesion.

We will review the typical presentation and management of this condition.

Case Report

A 19-year-old Caucasian female presented to our office with a 12-month history of a right mid nasolabial-fold nodule. She described the nodule as a “cyst like” area that would get red and irritated at times. She denied any pain or drainage from the site. She wanted the area removed for cosmetic reasons. The patient had been treated by her primary care doctor with oral antibiotics multiple times for these “cyst like” flares. She reported reduction in size of the nodule but never a complete resolution.

Her history also revealed a recent evaluation by an endodontist and an oral surgeon for the treatment of an abscessed tooth. Both physicians denied a dental origin for the facial nodule. The patient stated that a few weeks before presenting to our office, an oral surgeon had performed a root canal to her infected right first maxillary molar. The patient had just finished another course of oral antibiotics prior to her initial visit to us. She denied any other symptoms at presentation and had no major medical problems.

Examination of her right mid nasolabial fold revealed a nontender, fluctuant, partially movable dermal-based cystic nodule (Figure 1). Slight dimpling of the surrounding skin was noted. A firm, palpable cord extended downward from the region of the previous dental abscess along the right lateral maxillary buccal mucosa to the external cystic nodule. No drainage was noted on palpation. The patient was tentatively diagnosed with a dental sinus and therefore was immediately referred to a periodontist. Dental periapical radiographs (Figure 2) were obtained, and she was definitively diagnosed and treated for a chronic organized fistula of dental origin associated with the nodular lesion at her right mid nasolabial fold. The periodontist incised and drained the dental abscess and the surrounding area was dissected, explored, and curetted (Figure 3). There was no purulent discharge, and no other dental disease was identified. The patient’s condition is being followed by the periodontist until her dental disease and sinus tract have resolved. Upon complete resolution, she will follow up with us for reevaluation and treatment of any remaining cutaneous findings on her right cheek.

Discussion

Dental infection causing a cutaneous sinus tract can be a diagnostic challenge, as many patients do not present with active
primary dental disease. Often, patients seek medical attention from their primary care physician or dermatologist for evaluation and treatment of an associated cutaneous lesion. Typically, cutaneous sinus tracts of dental origin occur in the setting of chronic infection or trauma. The most common site of primary dental disease occurs at the periapical region of the tooth, which subsequently drains to the face. Eighty percent are found in the mandibular region, and 20% arise in the maxillary region. Cutaneous lesions often manifest in close proximity to the dental disease, most notably the chin, jawline, or submental area. There have been rare case reports where the tracts have been found at remote locations such as the neck and chest.

Many patients do not report dental complaints as the sinus tract permits continuous drainage from the involved tooth. This drainage does not allow for pressure to build enough to cause pain or irritation. Patients frequently present with cutaneous lesions described as erythematous, nontender, nodulocystic papules ranging from 1mm-20mm in diameter. Sometimes crusting, drainage, or ulceration is present. Drainage is not typically observed except with palpation of the cutaneous nodule or manipulation of the sinus tract, which allows expression of the contents. Perinodular dimpling or retraction of the skin may be evident and can indicate an associated healing fibrous tract.

Along with pertinent history, the main components involved in diagnosing a cutaneous sinus tract of a dental origin include a palpable cutaneous nodule with or without drainage and an attached palpable cord that extends to periapical disease found on dental radiographs. The differential diagnosis includes an infected or noninfected epidermal inclusion cyst, pilar cyst, pyogenic granuloma, foreign body reaction, mycobacterial infection, squamous cell carcinoma, furuncle, or deep fungal infection. Other entities to consider include osteomyelitis, salivary gland fistula, supplicative lymphadenitis, periauricular fistula or sinus, tuberculosis, syphilitic gumma, thyroglossal duct cyst and branchial cleft cyst.

Management consists of prompt recognition, evaluation, and treatment of the dental disease. Typically, once the dental disease is treated, the sinus tract and cutaneous lesion will resolve spontaneously. Resolution of the sinus tract should be expected to occur within 5-14 days status post definitive dental treatment. Dental infection may be treated with antibiotics, incision and drainage, tooth extraction, or root canal. Sometimes further dissection and soft tissue exploration are needed, as in our case.

If antibiotics are used, penicillin or amoxicillin are the drugs of choice. Erythromycin, clindamycin, or doxycycline may be effective for patients allergic to penicillin. Antibiotics should not be used as primary monotherapy, as disease often recurs after cessation of treatment. It has also been postulated that antibiotics do not "cure" the infection due to the lack of circulation to the necrotic pulp and sinus tract.

Potential severe complications, if disease is left undiagnosed or untreated, may include a cavernous sinus thrombosis or Ludwig's angina (a life-threatening cellulitis that can lead to airway compromise). Once the dental infection is treated, careful follow-up is necessary until full resolution. Sometimes, cutaneous scarring, retraction, or umbilication can remain even after resolution of the dental disease and sinus tract. Some patients may need surgical revision if they are concerned with cosmetic appearance of the residual cutaneous changes. This reiterates the importance of early recognition and treatment, as these cosmetic complications occur more commonly with a chronic relapsing course.

In conclusion, a high index of suspicion, proper cutaneous and intraoral inspection, palpation, pertinent dental exam, and referral for radiographic studies are imperative for early recognition of cutaneous sinus tracts of dental origin. Many patients first seek attention from a dermatologist because they have no associated dental complaints. This case serves as a reminder to include a dental etiology in the differential diagnosis of persistent nodular facial lesions. Early recognition of this disease entity will lead to prompt referral and definitive treatment, and additional complications, unnecessary surgical procedures, and distress for the patient may be prevented.

References
A Rubbery Pink-Blue Nodule on the Scalp of a 93-Year-Old Woman

Michael Centilli, DO,* Peter Saitta, DO,** Michael Whitworth, DO, FAOCD,*** Christopher Schwimmer, DO, FAOCD,**** Jean Holland, MD, FAAD*****

*PGY-1, Pontiac Osteopathic Hospital, Pontiac, MI
**PGY-4 Resident, Oakwood Southshore Department of Dermatology, Trenton, MI
***Oakwood Southshore Department of Dermatology, Trenton, MI
****Oakwood Southshore Department of Dermatology, Trenton, MI
*****Oakwood Southshore Department of Dermatology, Trenton, MI

ABSTRACT

Hidradenocarcinomas (HAC) are rare malignant adnexal tumors that develop from eccrine or apocrine sweat glands. There have been less than 100 cases documented in the English-language literature. Clinically HACs may present as firm, subcutaneous, pink to grey nodules or plaques. The skin overlying the tumor can show signs of thickening, atrophy, or appear normal; ulceration, fissuring, and crustation from hemorrhagic or serosanguinous drainage has also been present in some cases. Herein, we present a case of HAC mimicking cylindroma in a 93-year-old Caucasian female with a comorbid diagnosis of Brooke-Spiegler Syndrome.

Case Report

A 93-year-old Caucasian female presented with a long-standing history of multiple lesions on her face and scalp (Figures 1 and 2). She reported that the lesions developed during adolescence, and subsequently had increased in size and number. However, the patient was presently concerned with the largest scalp lesion, which had recently become tender. She did not report increased growth or bleeding from that particular lesion. Family history was negative for any member or child with similar lesions. A review of systems was negative for preceding illness, recent weight loss, or constitutional symptoms.

Physical examination of the patient revealed a well-appearing elderly female with multiple round, smooth, flesh-colored papules on the mid-face, ranging in size from 0.5 cm to 1.5 cm. The majority of the lesions were located on the glabella and the eyebrows bilaterally. The papules were firm and were non-tender to palpation. Numerous firm nodules and plaques were dispersed throughout the scalp, some pink in color and others grey. They ranged in size from 1 cm to 2.8 cm. The lesion of concern was on the right vertex of the scalp; it was a 2.8 x 1.2 cm firm, tender, rubbery, pink-blue nodule (Figure 2). At this time, a shave biopsy was taken of this nodule, along with shave biopsies of three other random lesions on the face.

Microscopic Findings and Clinical Course

The lesion on the right vertex scalp demonstrated a nodular and cystic collection of atypical cells with sweat gland differentiation (Figure 5). The tumor extended deeply and, though more circumscribed superficially, it demonstrated loss of circumscription in its deeper components (Figure 6). This reading was consistent with hidradenocarcinoma. The surrounding dermis showed nodules of benign spiradenoma, which suggested malignant degeneration within one of these tumors.

The remaining three biopsies demonstrated evidence of spiradenoma. The presence of multiple biopsy-proven spiradenomas, in conjunction with the clinical findings of cylindromas and trichoepitheliomas, confirmed a diagnosis of Brooke-Spiegler Syndrome.

The patient received one stage of Mohs micrographic surgery with clear margins for the hidradenocarcinoma on the scalp and is being monitored routinely for any lesion that may be suspicious for malignancy. After the case was reviewed with oncology, the patient declined further workup for metastases. The patient has had no evidence...
Hidradenocarcinomas (HAC) are rare, malignant adnexal tumors that develop from eccrine or apocrine sweat glands. There have been less than 100 cases documented in the English-language literature, and in a study reviewing 450,000 consecutive biopsies over 20 years in a dermatopathology laboratory, only two were proven to be HACs. Many of the case reports have been published using different nomenclature in addition to HAC, such as malignant acrospiroma, malignant hidradenoma, and malignant clear-cell hidradenoma, in addition to others.

Clinically, HACs may present as firm, subcutaneous, pink to grey nodules or plaques. The skin overlying the tumor can show signs of thickening, atrophy, or appear normal; ulceration, fissuring, and crusting from hemorrhagic or serosanguinous drainage have also been present in some cases. It must be stressed that these lesions do not have a distinct clinical appearance and may be easily mistaken for benign growths. The sites of predilection for HACs include the head and neck and less frequently the trunk and extremities. There is an equal distribution between both sexes, and there does not appear to be a preference for age as they have been reported in every decade of life.

Histopathologically, HACs display two main cell types, which are also features of its benign form, hidradenoma (HA). The first type is the clear cell, containing abundant glycogen, which has distinctly visible cell membranes and clear cytoplasm. These cells may have an oval or polyhedral appearance, and they contain dark, marginated nuclei. The second cell morphology is arranged at the periphery of the clear-cell line and consists of multifaceted squamoid cells with a granular cytoplasm and small, round-to-oval nuclei. These cells have been described as eosinophilic, but they have also been known to appear dark and take on a basophilic appearance. Differentiating an HAC from its benign counterpart is a difficult task, but several histologic criteria have been recommended in making the distinction. These criteria include increased mitotic activity, mitoses in clear cells, perineural invasion, angiolymphatic invasion, loss of circumscription, dispersed growth pattern, and deep extension. In addition, Ko et al. advocates further criteria to include necrosis, clefts between tumor and stoma, and p53 and Ki67 positivity with immunohistochemical staining.

Brooke-Spiegler Syndrome (BSS) is an autosomal-dominantly inherited genodermatosis caused by mutations affecting the CYLD gene on chromosome 16q12-q13. BSS is characterized by the finding of multiple adnexal cutaneous neoplasms including trichoepitheliomas, cylindromas, and spiradenomas. Spiradenocylindroma, a hybrid neoplasm consisting of features of both spiradenoma and cylindroma, may also arise in BSS. It is important to note that these lesions most commonly present sporadically as solitary neoplasms, and less frequently occur together in the setting of BSS. They are often benign, but occasionally, de novo malignancies or malignant transformations occur. Approximately 100 cases of malignant spiradenoma, cylindroma, and spiradenocylindroma exist in the medical literature. The vast majority occurred sporadically, but malignant variants were reported in cases of BSS as well. Kazakov et al. studied 24 cases of malignant neoplasms occurring in pre-existing spiradenoma, cylindroma, and spiradenocylindroma. Of the 24 cases studied, five of the patients possessed clinical features consistent with BSS. Spiradenomas were found to progress to malignancy most commonly (22), followed by cylindromas (2) and spiradenocylindromas (2). Due to the rarity of the lesions and lack of uniform criteria and terminology, it is difficult to determine a rate of malignant transformation. While no definitive portions undergo malignant transformation.
transformation, most malignant neoplasms have been found to arise in a pre-existing benign neoplasm. Consequently, these lesions should be biopsied and appropriately monitored for signs of evolution.

Conclusion

Hidradenocarcinomas are rare, malignant adnexal tumors which possess an indistinct clinical appearance. Unless signs of thickening, atrophy, ulceration, fissuring, or crusting are present, these tumors may be easily mistaken for benign growths. Upon diagnosis, these patients should be screened for metastasis, and the appropriate treatment options should be conveyed. Without detection and proper treatment, they are associated with high rates of metastasis and significant mortality.

To the best of our knowledge, there has never been a reported case of HAC arising de novo or from malignant transformation of a previously benign lesion in conjunction with BSS. Due to the rarity of HAC, it is unknown if there is any correlation or increased risk of developing an HAC from one of the characteristic lesions of BSS. Regardless of the connection between HAC and BSS, it is critically important to understand the potential for malignant transformation of the lesions associated with BSS. Repeat biopsies of lesions may be necessary if clinical suspicion exists for malignancy or complete excision is not performed.

References

ABSTRACT

Alopecia syphilitica, a rare manifestation of secondary syphilis, presents as hair loss that occurs in either a diffuse or a more common “moth-eaten” pattern and may be mimicked by other alopecias both clinically and histologically. When a patient presents with non-inflammatory, non-scarring alopecia, syphilis should be included in the differential diagnosis. A case of syphilis with alopecia as the only presenting manifestation is hereby reported and discussed.

Case Report

A 32-year-old Hispanic male presented to the dermatology office with a progressive, one-month history of patchy hair loss on his scalp. He denied loss of hair anywhere else on his body or any other skin lesions. Previously, he was seen by his primary care physician and had been using nystatin once a day for approximately five days with no improvement. The patient was otherwise healthy and had no significant past medical history or history of major medical illness in his family. He had no known allergies to medications and was only taking an over-the-counter energy supplement and Tylenol as needed. His review of systems was positive for daily headaches for a couple of weeks, but negative for fever, malaise, sore throat, muscle aches, rashes and weight loss.

Physical examination showed bilateral parietal, temporal, and occipital scalp with disseminated patches of hair loss in a moth-eaten pattern (Figure 1). The areas of alopecia were free from erythema or scale. On complete skin examination, no other cutaneous lesions were identified.

Standard hematoxylin and eosin (H&E) stained vertical sections of two 6.0 mm scalp punch biopsies were prepared. The biopsies demonstrated approximately 12 hair follicles in primarily telogen and catagen phase, and with significant miniaturization (Figure 2). Brisk lymphocytic infiltrates were identified in the peribulbar regions of each of these retracting hairs in a “swarm of bees” pattern (Figure 3). In addition to lymphocytes, scattered mast cells and only very rare plasma cells were identified as demonstrated with CD68 and CD138 stains respectively (Figure 4 and 5).

In the absence of other clinically detected signs and symptoms for syphilis, the diagnosis of alopecia areata was initially suspected histologically. Subsequent laboratory testing revealed a positive rapid plasma reagin (RPR) with a titer of 1:32 and a reactive fluorescent treponemal antibody absorption (FTA-ABS). A revised diagnosis of syphilis-induced alopecia was made. Retrospective histopathological analysis showed only rare plasma cells and an absence of eosinophils within the peribulbar infiltrates. Immunohistochemical staining for Treponema failed to demonstrate identifiable organisms in either of these biopsies.

The patient returned to the office and was notified of the results. He admitted to high-risk sexual behavior, but denied any history of sexually transmitted disease or genital lesions. The patient elected to go to the state county health department for his treatment. Further testing for HIV was recommended.

Discussion

Syphilis is caused by the spirochete Treponema pallidum. If left untreated, it becomes a chronic, systemic infection.
After penicillin was validated as an effective cure for syphilis in 1947, the rate of infections decreased dramatically in developed nations. Since 2000, there has been a rising influx of the disease in the United States amongst black and Hispanic individuals as well as men who have sex with men. These groups have a 5- to 25-fold higher incidence rate than the general population. In some developing countries, infection rates are as high as 10% of the population. There are approximately 12 million new cases per year worldwide, with the vast majority of these cases occurring in the developing world.

Syphilis progresses through four overlapping stages: primary, secondary, latent, and tertiary syphilis. Each stage is characterized by unique symptoms, clinical manifestations, and levels of infectivity. On average, the primary manifestation of syphilis first appears three weeks after exposure. Typically, it presents at the inoculation site as a solitary, painless, indurated ulcer. Other primary syphilis manifestations include condyloma lata, mucosal patches, and non-scarring alopecia. Reported estimates of the prevalence of alopecia in secondary syphilis have been remarkably disparate, ranging from 5 to 50 percent. Hair loss as the predominant or only clinical manifestation of secondary syphilis, however, is generally reported as occurring in about 3 percent of patients.

There are two types of alopecia in secondary syphilis, which were first described by McCarthy in 1940. The first type occurs in association with clinically apparent syphilitic lesions of the scalp and is termed “symptomatic syphilitic alopecia.” The second occurs in the absence of scalp lesions and is termed “essential syphilitic alopecia (ESA).” ESA can be further divided into three subtypes: as a patchy “moth-eaten” appearance, as a diffuse pattern of generalized thinning, or as a combination of both. The patchy, moth-eaten subtype occurs most frequently. While ESA most commonly involves the scalp, it may affect other places of hair growth, such as the eyebrows, eyelashes, chest, legs, axilla, or pubis. The diffuse pattern of ESA may clinically mimic telogen effluvium or androgenic alopecia. The moth-eaten form may clinically resemble other localized, non-scarring alopecias including alopecia areata, alopecia neoplastica, tinea capitis, trichotillomania, and traction alopecia. A thorough patient history as well as histopathology can help exclude these other diagnoses.

The histopathological findings of the papulosquamous lesions of symptomatic syphilitic alopecia are similar to the findings typically associated with secondary syphilis. However, the histopathologic features of ESA differ, and have been described in a limited number of biopsies available in the literature. The ESA cases reported share the common characteristics of a perifollicular lymphocytic infiltrate and frequent telogen and catagen hairs. Their main findings included a normal epidermis, follicular plugging, vasodilation, endothelial prominence, an increased number of telogen and catagen hair follicles, and follicle-orientated melanin clumping. The only universal feature present in all their cases was a perifollicular and perivascular dermal infiltrate consisting of lymphocytes and macrophages. Other cells noted in their cases included mast cells, plasma cells, melanophages, and eosinophils. Warthin-Starry stain failed to confirm the presence of T. pallidum in all cases.

In the absence of stereotypical clinical features of syphilis, the histology of ESA may be confused with alopecia areata. Lee and Hsu reported the histopathology of nine patients with syphilitic alopecia. They noted a normal dermoepidermal junction, a decreased number of hair follicles, and increased catagenization and telogenization. In addition, a key finding included a lymphocytic infiltration around the hair bulbs and the fibrous tracts. There was a notable absence of eosinophils in all biopsies, and plasma cells were noted in four specimens. This lack of eosinophils was surmised in their study to be a criterion to differentiate alopecia areata from syphilitic alopecia. Other studies, however, have refuted the specificity of eosinophils by reporting several cases of syphilitic alopecia with eosinophils present in the peribulbar infiltrate.

The histologic detection of T. pallidum has historically been challenging. The usual
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method for detecting spirochetes in tissue sections is with silver stains, using either the Warthin-Starry technique or the Steiner modification of the Dieterle technique; however, organisms are often difficult to detect with these methods.22 Nam-Cha et al. were one of the first to report finding *T. pallidum* in hair follicles by immunohistochemistry.14 This technique yields more sensitive results than the standard silver stains and may become the gold standard for the histologic detection of occult organisms. Molecular detection by polymerase chain reaction is an additional sensitive technique available for the diagnosis of *T. pallidum* in lesional scalp tissue.20

The laboratory diagnosis of syphilis is based on either direct detection of treponemes or serologic tests that assess antibody response to cardiolipin or treponemal antigens. Primary lesions can be present one to three weeks before the serologic tests become positive.3,5,8 In this phase, it is crucial to make the correct diagnosis by direct visualization of *T. pallidum* via dark field microscopy,3,6,8 Non-treponemal tests, such as the rapid plasma reagin (RPR) and Veneral Disease Research Laboratory (VDRL), are used qualitatively for screening purposes and quantitatively as a measurement to monitor antibody titers after antibiotic therapy. Although these tests are widely available and relatively inexpensive, they are limited by their lack of sensitivity in early and late syphilis and by false-positive reactions.2-5,9

Treponemal tests, due to their higher specificity, are used as confirmatory tests after a reactive non-treponemal test.3,5,6,8 Specific treponemal tests are based upon the detection of antibodies against specific treponemal antigens and include: fluorescent treponemal antibody absorption (FTA-ABS), microhemagglutination test for antibodies to *Treponema pallidum* (MHA-TP), Treponema pallidum particle agglutination assay (TP-PA), and Treponema pallidum enzyme immunoassay (TP-EIA). DNA PCR has been used to identify *T. pallidum* in clinical specimens, but is not readily available for routine use.5

The primary treatment for syphilis is a single intramuscular dose of penicillin G benzathine.1,2-5,6,8,9,11 For patients who are allergic to penicillin, alternative therapy includes doxycycline or tetracycline.7,8 For patients with latent syphilis longer than one year in duration, of unknown duration, or with cardiac involvement, or for patients with tertiary syphilis, more frequent doses of intramuscular benzathine penicillin should be given.5,6,8 Treatment may vary with a patient’s positive HIV status or with the presence of neurosyphilis, and the Centers for Disease Control should be contacted for support.2,11 Alopecia usually resolves within three months of treatment.1,11,15-17 Paradoxically, the treatment of syphilis has also been shown as a cause of alopecia and has been described in association with the Jarisch-Herxheimer reaction.22

**Conclusion**

Syphilitic alopecia usually presents with other classical findings of secondary syphilis. Only rarely is it the only presenting feature of syphilis. Syphilis is known to be a great imitator of other diseases and can be quite challenging for both clinicians and pathologists. The histologic detection of essential syphilitic alopecia is difficult and may be confused with alopecia areata, especially in the absence of stereotypical clinical features of syphilis. New adjunctive techniques, including immunohistochemistry and PCR, provide more sensitive methods of detection. Ultimately, a combination of histologic, serologic, and clinical findings are all important in order to make the proper diagnosis of syphilitic alopecia.

**References**


15. Friedli A, Chavaz P, Harms M. Alopeia syphilistica:
Syringofibroadenoma: A Case Report and Discussion

Steffany B. Steinmetz, DO,* Ryan L. Owen, DO,** Robert M. Law, M.D.,*** Bill V. Way, DO, FAOCD****

*2nd-year Dermatology Resident, Northeast Regional Medical Center, Kirksville College of Osteopathic Medicine, Department of Dermatology, Texas Division, Duncanville, Texas
**Traditional Intern, LewisGale Hospital-Montgomery, Blacksburg, Virginia
***Clinical Assistant Professor, Departments of Dermatology and Pathology, University of Texas Southwestern School of Medicine, Dallas, Texas; Pro-path Associates, Dallas, Texas
****Program Director, Northeast Regional Medical Center/Kirksville College of Osteopathic Medicine, Department of Dermatology, Texas Division, Duncanville, Texas

ABSTRACT

Syringofibroadenoma is an uncommon, benign tumor of eccrine-gland origin. This is a case presentation of a 67-year-old male with a history of multiple sclerosis who developed multiple syringofibroadenomas on his buttocks, which reoccurred after shave excision. Subsequently, full-thickness surgical excision was performed. A brief review of the literature will be presented including tumor classifications, gross as well as histopathological characteristics, and differential diagnoses.

Introduction

Eccrine syringofibroadenoma (ESFA) is a rare adnexal neoplasm of eccrine gland differentiation. First described by Mascaro in 1963, it is now considered to originate from the excretory portion of the eccrine sweat gland.1,3 Generally, the tumor is a solitary large nodule but can also manifest as multiple papules and nodules in a symmetrical or linear nevoid pattern.

Case Presentation

A 67-year-old, wheelchair-bound African American male presented with asymptomatic, growing pedunculated nodules on the buttocks. The patient had a history of primary progressive multiple sclerosis, diagnosed in 1999. He had been non-ambulatory since 2003 and was unable to assist with transfers or perform his activities of daily living.

The lesions on the buttocks had been removed five years earlier by shave excision. Physical examination revealed multiple large (average 20 mm) polyoid nodules on the buttocks near the intergluteal cleft (Figures 1 and 2). Full-thickness surgical excision was performed. The diagnosis of syringofibroadenomas was confirmed by histopathology (Figures 3 and 4).

Histopathology

Histopathological examination revealed a polyoid nodule with extension of thin basaloid cords from the base of the epidermis. Ductular differentiation is observed, with a surrounding fibrovascular stroma. Peritumoral clefting is not noted, nor is mucin deposition present. On the basis of these findings, a diagnosis of syringofibroadenoma was made.

Discussion

A variety of presentations and morphologies have been reported on syringofibroadenoma. Starink in 1997 devised a classification for ESFA dividing it into four clinical subtypes. Since then, the classification has developed into six subtypes:

1. Solitary ESFA.
2. Multiple ESFA associated with Schöpf syndrome (hidrotic ectodermal dysplasia).
3. Multiple ESFA without associated cutaneous findings.
4. Nonfamilial unilateral linear ESFA.
5. Reactive syringofibroadenomatous hyperplasia (RESFAH).
6. RESFAH associated with squamous cell carcinoma, melanocytic and vascular neoplasms.1,4

RESFAH is viewed as an epithelial reactive process of hyperplasia secondary to numerous inflammatory or neoplastic dermatoses including chronic ulceration and trauma in diabetes mellitus, neuropathy of leprosy, burn scars, venous stasis, bullous pemphigoid, sebaceous nevus and erosive palmoplantar lichen planus.1 The reactive syringofibroadenomatous hyperplasia variant may likely be the result of
repeated tissue damage and repair, as seen in the aforementioned case report regarding a wheelchair-bound, non-ambulatory patient secondary to primary progressive multiple sclerosis.

On histopathology, ESFA shows an anastomosis of cords and strands of epithelial cuboidal cells within a fibrovascular stroma mimicking fibroepithelioma of Pinkus. The difference, however, is that ESFA displays ductal differentiation and lacks palisaded dark-staining cells. Histologically and immunophenotypically, ESFA and RESFAH appear strikingly similar except that RESFAH displays MNF116-positive cytokeratins due to the hyperproliferation and underlying inflammation. Additionally, RESFAH exhibits an increased number of mast cells. In general, ESFA stains positive for epithelial membrane antigen 34βE12 cytokeratins, CK-19 and CEA.

The differential diagnosis for ESFA includes fibroepithelioma of Pinkus, clear-cell acanthoma, poroma and porocarcinoma. Recently, Cota et al. reported a case of ESFA with concomitant clear-cell acanthoma in a patient with lower-extremity stasis dermatitis; however, the relationship between the two distinct entities remains unclear. Due to the potential association between ESFA and malignancy, full-thickness excision remains the definitive treatment.

References


ABSTRACT
Calciphylaxis is a life-threatening, disabling disease that involves calcium deposition within the walls of small and medium sized arteries leading to ischemia and necrosis of the supplying tissue (1). Although this condition has been seen in other nonuremic conditions, the primary finding was first described in dialysis patients and has since been the most prevalent population (2). The development of these lesions is a slow, indolent course, most commonly seen on the lower extremities, and portends a grim prognosis (1, 2). As most of these lesions progress, the condition is complicated by severe and often fatal complications (1, 2). In addition, the pathogenesis of this disease is poorly understood and although several strategies have been aimed to treat this condition, the outcome has still been poor. Several risk factors have been identified and in this case, we evaluate the possible risks involved for the development of calciphylaxis.

Presentation of the Case
A 46-year-old Caucasian female presented to the emergency department complaining of “painful ulcers that have been spreading throughout her body” for the past few months. She handled the pain up until a few days prior to admission, when the pain had become “too intense.” This patient had an extensive past medical history, including end stage renal disease secondary to transplant rejection six months prior for which she received dialysis daily. After her initial transplant rejection, she developed diabetes secondary to pancreatic transplant failure as well as hyperparathyroidism. During her renal transplant, she had been diagnosed with a deep vein thrombosis in her right lower extremity and started on warfarin therapy. The patient was admitted for dialysis three times per week as well as pain management and wound care. After examination of the patient on admission, intravenous morphine and antibiotics were started to aid with her pain, as prophylaxis for wound infection, and for proper healing of her multiple opened ulcerations.

Examination
On complete examination of this patient, she was a largely immobile, alert, neurologically intact, cachectic-looking female with distant heart sounds and bilateral decreased breath sounds with crackles at the base of the lungs. The most remarkable finding was the tender, extensive necrotic ulcers and eschars with circumferential erythema, largely concentrated to her back, sacrum and lower extremities (see Figures 1-5). In addition, there were multiple smaller, purple, painful subcutaneous nodules and reticulated plaques as well as areas with dry gangrene on her bilateral legs and arms. The larger ulcerations ranged from the smallest at 2cm by 2 cm to 110cm by 75cm on her left flank. The patient had exquisite pain during examination of the multiple ulcerations and eschars, making it a difficult task to examine every lesion in great detail.

Further Complications and Course in Hospital

Figure 1: The largest surface area, encompassing the patient’s back, revealing one of the most impressive lesions on her left lateral flank.

Figure 2: Right dorsal foot, revealing a large eschar with ulceration. Note the great toe is largely necrotic secondary to calciphylaxis.

Figure 3: The patient's left shin

Figure 4: Left medial malleolus.

Figure 5: Right plantar surface, revealing multiple eschars with desquamation as well as areas of ulceration.
During her two-month hospital stay, laboratory work revealed elevated calcium levels and glucose levels, which remained uncontrolled despite medication optimization. Her left shin and right dorsal foot were cultured multiple times, revealing Proteus mirabilis infection; this was treated with intravenous vancomycin, piperacillin and tazobactam.

Both dermatology and plastic surgery consulted on the eschars and ulcerations to confirm the clinical suspicion and histologic diagnosis of calciphylaxis via biopsy. Additionally, warfarin was discontinued as it posed a potential threat to her condition; she was subsequently placed on sodium thiosulfate infusion with dialysis three times per week to treat the calciphylaxis. Plastic surgery recommended whirlpool therapy every day as well as surgical debridement of the larger lesions to aid with wound healing and potentiate the healing process.

Throughout her hospital stay, the rapid response team was called multiple times due to altered mental status as well as respiratory arrest, leading to multiple studies to rule out other pathologies. Her wounds continued to expand, and despite whirlpool therapy and multiple wound debridements with surgery, her condition rapidly declined. Unfortunately, due to the severity of her condition, our patient had a protracted hospital course during which she developed poorly managed sepsis in the intensive care unit secondary to wound infections, leading to her mortality.

Pathology

A biopsy was taken of the right upper extremity at the lateral edge of the lesion, including some of the erythematous rim of the lesion. The pathology report described calcification within the media of the small- and medium-sized arteries with extensive intimal hyperplasia and fibrosis consistent with the calciphylaxis. There was some lymphohistiocytic infiltrate in affected adipose lobules as well as evidence of panniculitis and subcutaneous fat necrosis of some of the biopsy site. 1,2

Discussion of the Case

Calciphylaxis is a life-threatening, disabling disease that involves calcium deposition within the walls of small- and medium-sized arteries, leading to ischemia and necrosis of the supplying tissue. 1 The etiology of the disease is largely unclear. The first condition was described in rat models by Selvey et al. in 1962. 1 By exposing the rat to a particular sensitizing agent, there was greater risk of developing calciphylaxis, and in fact more rats did develop the condition. 1,2 Some of these agents included vitamin D, parathyroid hormone, and tachysterol. In humans, the "agent" would be equivalent to large doses of parathyroid hormone, calcium or phosphate. However, this is only one of the many theories that have been proposed.

Although calciphylaxis has been seen in other, non-uremic conditions, the primary finding was first described in dialysis patients, which has since been the most prevalent population. 2 The development of these lesions is a slow, indolent course, most commonly seen on the lower extremities, and portends a grim prognosis. 1,2 As seen with our patient, as most of these lesions progress the condition is complicated by severe and often fatal complications. 1,2 Some of these fatal complications include sepsis, gangrene, and electrolyte imbalances leading to arrhythmias.

The pathogenesis of this disease is poorly understood, and although several strategies have been used to treat this condition, the outcome has still been poor. Disorders such as chronic renal failure, diabetes mellitus, hyperparathyroidism, medication usage, hypercalcemia and hyperphosphatemia are just a few of the conditions associated with this disease. Though the dysregulation of the calcium-phosphate levels in end-stage renal disease is a major factor in developing calciphylaxis, it has also been seen in the setting of metastatic breast cancer. 3 There have been several risk factors identified, including hyperparathyroidism, elevated serum calcium levels and elevated phosphate levels, diabetes mellitus, coagulopathies, warfarin and iron dextran treatment; however, not one has been identified as a major cause. 1,2

There have been reported cases of calciphylaxis that present after kidney transplantation and treatment with sodium thiosulfate. 1,2 Sodium thiosulfate has been, by and large, the first-line treatment for calciphylaxis, as the major aim of this treatment is to restore endothelial function through its antioxidant effect. When there is an absence of hyperparathyroidism, this can be a very successful adjunct to therapy. It has been shown in a small subset of patients to reduce the appearance of livedo as well as normalize the calcium-phosphate ratio. 3,4

Another way to tackle the calcium-phosphate disturbance would be to use cinacalcet, a calcimimetic that lowers the levels of parathyroid hormone in patients receiving dialysis. With careful use, it not only reduces the pain in the areas where new lesions are spreading but also decreases the level of parathyroid hormone significantly. 5 Since the side effects of this particular treatment are minimal, it may also prove to be an adequate adjuvant treatment for calciphylaxis. However, many other trials must be done to adequately gauge its efficacy.

By far the most successful yet controversial surgical option has been parathyroidectomy, which diminishes most of the external disease manifestations. It has been shown to be the best option for those without a known etiology of calciphylaxis but with associated hyperparathyroidism. However, this is still a controversial treatment, and not every patient is a candidate for it. 6 We describe a patient who was anuric, on dialysis, and post pancreatic transplant rejection with adrenal insufficiency who developed extensive calciphylaxis covering greater than 70% of her body. The treatment of choice for this patient was sodium thiosulfate three times per week for two weeks during dialysis and piperacillin and tazobactam 2.25 mg intravenous piggy-back for new onset Proteus sepsis. Although the patient may have been a candidate for a calcimimetic, she did not qualify for a parathyroidectomy because she was not medically stable. In addition, the patient's condition proved to be refractory to conventional treatment, and alternative therapy could not be implemented as she refused subsequent dialysis and further treatment, leading to her mortality.

References

Case presentation

A 79-year-old Caucasian female presented with an asymptomatic, enlarging, hyperkeratotic, ulcerated plaque on the scalp of two years duration. Her past medical history included colon cancer, diabetes mellitus with chronic kidney disease, glaucoma, hypertension, hyperlipidemia, hypothyroidism and obesity. She had no history of skin cancer or other dermatologic conditions. The patient’s medications were reviewed and non-contributory.

On physical exam, the plaque was 3cm by 1cm, located on the crown of the scalp, and appeared erythematous and hyperkeratotic within a large ulcer. The remaining skin exam revealed only a few scattered lesions on the face. To rule out malignancy, the most likely diagnosis, 4-mm punch biopsies were taken from the plaque. No signs of malignancy were identified, results showing only an ulcer with superficial fragments of neutrophilic crust, hemorrhage, hyperkeratosis and inflamed dermis with features of granulation tissue. Clinically, the plaque was still suspicious for a malignant process, but an additional biopsy rendered similar findings. The patient was lost to follow-up for one year.

Upon return, the ulcerated plaque had enlarged and developed more hyperkeratotic crusting with visible purulence (Figure 1). Three 4-mm punch biopsies were taken with concern for the possibility of an autoimmune blistering disease. A wound culture grew Pseudomonas aeruginosa, but a course of ciprofloxacin (500mg BID for 10 days) had no effect in healing the ulcerated plaque. Histopathology showed similar findings as before, with non-specific inflammation and granulation tissue. These inconclusive results led to a decision to perform a larger incisional biopsy, revealing essentially the same findings (see Figures 5 and 6). Direct immunofluorescence showed a negative immunoreactant profile (IgG, IgA, IgM, C3, C1q, C3d, C4d, C5b-9) and no features of an autoimmune vesiculobullous disease.

ABSTRACT

Erosive pustular dermatosis of the scalp (EPDS) is a rare skin disorder of unknown etiology that most commonly affects older patients. This case describes an elderly woman who presented with an asymptomatic, hyperkeratotic, ulcerated plaque on the crown of her scalp of two years duration. Basal cell carcinoma was the favored diagnosis, but histopathologic evaluation on three separate occasions showed nonspecific inflammatory infiltrate and scarring.

Direct immunofluorescence showed no significant findings. During the third visit, a wound culture grew P. aeruginosa sensitive to ciprofloxacin, yet antibiotics showed no improvement. As the diagnoses of malignancy, infection, neutrophilic dermatoses, and autoimmune diseases had been excluded, a diagnosis of EPDS was suspected. A treatment course with oral prednisone was initiated showing marked improvement within weeks and resolution over 5 months. We report this case to underscore the importance of including EPD in the differential diagnosis as to avoid delay of treatment.
lous disorder. Moderately intense dermal staining of fibrinogen was identified, a non-specific finding. The tissue was negative for S100, no atypical vascular proliferation was identified with a CD31 marker, and scattered factor XIIa positivity was seen in the areas of dermal scarring. Based on these results, with no findings of malignancy, autoimmune blistering disease, infection, or neutrophilic dermatoses, EPDS was deemed the most likely diagnosis.

The patient was started on 20 mg of oral prednisone daily, with close monitoring of her blood glucose given her concurrent diabetes. After two weeks of treatment, the pustular erosion was approximately 50 percent smaller (see Figure 2). One month after starting prednisone, the dose was reduced to 10 mg qd, and after two months of treatment a dramatic improvement was seen (see Figure 3). After the third month, the dose was further reduced to 5 mg qd, followed by two weeks of 5 mg qd, and finally two weeks of 5 mg only on Mondays and Thursdays. Complete resolution was seen five months after the initiation of treatment with prednisone, with no recurrence at two months follow-up (see Figure 4).

**Discussion**

Erosive pustular dermatosis of the scalp is an idiopathic disorder that often occurs in elderly patients. It is a diagnosis of exclusion made by negative cultures and histopathologic reports showing nonspecific inflammation and scarring. It tends to occur in elderly Caucasian women with a precipitating history of cutaneous damage, such as actinic keratoses, chemotherapy, ceryotherapy, radiation, and grafting, among others. Cases have been reported in the pediatric populations in the setting of tissue injury and atrophy. These wounds may develop years after the cutaneous damage occurs.

EPDS presents with erythema, purulence, crusting and erosive changes on the scalp that progress slowly and result in scarring alopecia. Skin cultures are usually negative for microbes; however, our case was complicated by bacterial colonization (Pseudomonas aeruginosa) due to chronically compromised tissue. Biopsies show nonspecific inflammatory changes and scarring. EPD is most commonly seen in the scalp, although it has been seen with isolated involvement of the face and in the extremities in the setting of chronic venous insufficiency. Association with autoimmune disease has also been described, although the pathogenesis remains unclear. One case reported EPD on both the scalp and leg in association with myasthenia gravis. The development of squamous-cell carcinoma has occurred in scars of EPDS, which emphasizes the need for close long-term follow-up in these patients.

Reported treatments include topical corticosteroids, retinoids, tacrolimus, calcipotriol, zinc sulphate and photodynamic therapy with methyl 5-aminolaevulinic acid. Our patient was treated successfully with oral prednisone alone. This treatment was chosen in order to quickly reduce the underlying inflammation and minimize permanent skin damage. High-potency topical steroids have been most commonly used, but recurrence has occurred when application of topical steroids is decreased or discontinued, with good response with return to treatment.

We hope that this report serves as a reminder to include EPDS in the differential for an ulcerated plaque on the scalp of an elderly person.

**References**

ABSTRACT

Sunscreens have been a topic of great debate for many decades. The development of an increasing amount of sunscreen products with more advanced sun-protective abilities seems to fuel even greater controversy regarding the safety and efficacy of sunscreen ingredients. By nature of their mechanism of action alone, organic or "chemical" sunscreens have been disputed by many to have risks that potentially outweigh benefits. Many studies have been done on the different UVA and UVB organic sunscreen ingredients to determine if these theoretical risks pose any actual threat. Because of this, it is important to review the UVA and UVB organic sunscreen ingredients, including their UV-attenuating properties, chemical properties, potential limitations to use and studies to support or refute the hypothesized risks of use of specific ingredients.

Introduction

As developments have been made in uncovering the pathogenesis of skin cancers, it is now known that ultraviolet radiation (UVR) is one of the primary contributing factors to the development of many common skin cancers. Carcinogenesis is only one of several other deleterious effects of UVR. Short-term effects from UVR include tanning of the skin, sunburn, thickening of the epidermis/dermis, increased inflammatory infiltrates, vasodilation, edema and immunosuppression. Long-term effects have been shown to include photaging and photocarcinogenesis along with further and continued immunosuppression (1,2,3,4). Sunscreens have been proven to reduce the carcinogenic and immunosuppressive effects of both short- and long-term UVR (4,5,6,7).

Despite the trusted beneficial effects, multiple studies on specific sunscreen ingredients have fueled controversies over the safety and efficacy of sunscreens (8). Sunscreen ingredients have been a topic of great debate ever since the first sunscreens were discovered over 80 years ago. Patients seek the advice of physicians, especially dermatologists, regarding which sunscreens to use, which ingredients are safe and how well each ingredient will protect skin from UVR. Therefore, it is important to be able to define the UV protection levels, outline the chemical properties and discuss the current controversies surrounding specific sunscreen ingredients.

Sunscreens are made from either inorganic or organic agents with differing mechanisms of action. Inorganic or "physical" sunscreens work to physically block UVR by reflecting and scattering photons of light. Common ingredients that work by this method are titanium dioxide and zinc oxide. In comparison, organic sunscreens are made of chemicals that prevent exposure to UVR by absorbing photons. This reaction is based on the chemical properties of the organic molecule and is limited to specific wavelengths of light. Because of this, organic or "chemical" sunscreen ingredients are generally defined as either UVA blocking or UVB blocking agents (9,10,11).

In 1999, the U.S. Food and Drug Administration (FDA) issued the Final Monograph on Sunscreen Drug Products for Over the Counter Human Use (12). In this monograph, the FDA defined 16 active sunscreen ingredients that it determined to be "safe and effective and not misbranded" for use in sunscreen, cosmetic and toiletry products. The monograph outlined the rules and regulations over sunscreen labeling, maximum concentrations, testing procedures and allowable combinations of ingredients. Within the testing procedures, the monograph defined the measurements of sun protection factor (SPF) of a sunscreen as well as determination whether a product is water resistant or very water resistant. Not discussed in this monograph was the subject of UVA protection, as the SPF measurement only indicates protection against the erythemogenic UVB wavelengths of UV light (13,14). On August 27th, 2007, the FDA released the proposed rule to amend the 1999 FDA final monograph, addressing the "formulation, labeling and testing requirements for both UVB and UVA radiation protection" (15). On November 28th, 2007, the time period for implementation of the amendment was extended an additional 30 days (16). The proposed changes were to include a cap in the SPF to 50+, new categories for grading UVB SPF, a 4-star rating system for UVB protection and various warning statements and labeling directions for sunscreen products (15). Four years later, on June 17th, 2011, the FDA issued its updated and comprehensive final ruling regarding labeling and testing of approved sunscreens. However, to date, the sunscreen monograph itself remains to be finalized, as three documents published by the FDA are still under review and call for accepting new data submissions. These documents address the unresolved issues of capping the SPF label at 50+ and dosage formulations of various sunscreen product vehicles (such as sprays, wipes, towelettes, powders and body washes). While the FDA did not release a timeline of when these remaining issues are to be resolved, the results of the final ruling were scheduled to take effect and be enforced for all sunscreen manufacturers beginning June 17, 2012 (a 12-month compliance date from release of the final rule) (77). As of May 2012, the FDA again extended the deadline for compliance with new labeling to December 2012, giving larger sunscreen manufacturing companies six additional months to comply.

Considering that SPF has historically remained a measure of protection against UVB, with no universal measurement or indication of the UVA-protective abilities of sunscreens, it is important to understand the attenuation levels of specific sunscreen ingredients that protect in both UVB and UVA wavelengths (Figures 1 & 2). Furthermore, taking into consideration the new FDA ruling, it is important to understand chemical properties of sunscreen ingredients and potential limitations of use of each sunscreen ingredient. By nature of their mechanism of action alone, organic or "chemical" sunscreens have been disputed by many to have risks that potentially outweigh benefits. Being aware of and understanding the risks versus the benefits of organic sunscreen ingredients, whether potential or proven, is important to maintain the highest degree of safety and efficacy of sunscreens.

Jessica L. Borowicz, DO,* Cherise Khani, BS,** Richard A. Miller, DO, FAOCD***

*PGY-4 Dermatology Resident, Largo Medical Center, Largo, FL
**OMSIV, Nova Southeastern University, Fort Lauderdale-Davie, FL
***Program Director, Dermatology Residency, Largo Medical Center, Largo, FL
Figure 1: UVB chemical sunscreens: UV-attenuation spectrum

![UVB Chemical Sunscreens](image)

Figure 2: UVA chemical sunscreens: UV-attenuation spectrum

![UVA Chemical Sunscreens](image)
Overview of FDA 2011 Final Rule “Labeling and Effectiveness Testing: Sunscreen Drug Products for Over-the-Counter Human Use”

The scope of this final rule is to establish guidelines and requirements that will ensure that currently marketed sunscreen products are appropriately labeled and tested for both UVA and UVB protection. This will ultimately improve proper use of these products, as well as increase consumer protection from the harmful effects of UV radiation. The following represents new requirements for Principal Display Panel (PDP) labeling highlighted in the June 2011 FDA ruling (79):

**SPF Statement**

In the 2007 proposed ruling, it was suggested to redefine the acronym “SPF” as the “sunburn protection factor,” recognizing that the end-point of SPF testing is erythema. However, in the final rule, SPF will remain an abbreviation for “sun protection factor,” identical to the 1999 FDA monograph, and will continue to appear on the PDP as it has for several years. This decision stems from efforts to avoid consumer confusion and acknowledge the additional harmful effects of sun exposure, such as skin aging and skin cancer, against which sunscreen protects (77,79).

**Broad Spectrum Statement**

The current rule has abandoned the UVA 4-star rating system, as well as the requirement of a “no UVA protection” statement proposed in the 2007 rule. This decision was again based upon minimizing potential consumer confusion regarding choosing between over-the-counter (OTC) sunscreens with various combinations of SPF values and star ratings (79). The FDA has instead adopted a pass/fail test based on an in vitro critical wavelength (CW) to assess UVA protection and ultimately label a product as “broad spectrum.” The CW is calculated based on UV transmittance tested by applying a fixed irradiation dose to plated sunscreen products. The CW represents the wavelength below which 90% of a sunscreen’s absorption spectra curve resides. It is thus a measurement of the breadth of UV absorbance, requiring the amount of UVA protection to increase as the product’s SPF is increased (77). While there has been some recent criticism relating to the exact numerical CW value (78), the CW at or above which a sunscreen can be labeled “broad spectrum” has been set at 370nm (77).

**Water Resistance Statement**

The terms “sunblock,” “water proof,” and “sweat proof” are no longer permitted on the PDP. Instead, the label can only contain the statements “water resistant (40 minutes),” or “water resistant (80 minutes)” based upon the water resistance test. The revision of these statements aims to make it easier for consumers to purchase products based upon actual time of water resistance (79).

**Drug Facts Labeling: Use Statements and Application Directions**

For the first time, the FDA has adopted a skin cancer and early skin aging indicator for sunscreen products with an SPF of 15 or higher, pending also passing the test for broad spectrum labeling. These new benefit claims do not apply to sunscreens that are not broad spectrum, or are broad spectrum but with an SPF below 15. Such products must instead include a “skin cancer/skin aging alert” message in the product label (77). Of important note, the American Academy of Dermatology still recommends an SPF of at least 30, based upon the assumption that in actual daily use, the majority of consumers will apply significantly less sunscreen than the FDA mandated amount used for testing purposes (77).

The final rule also addresses sunscreen application directions, including a required statement that parents of children younger than 6 months old consult a physician prior to using sunscreens (77). The directions for non-water-resistant products state to apply liberally 15 minutes before sun exposure, use a water-resistant sunscreen if swimming or sweating, and reapply at least every 2 hours. The only difference in directions for water-resistant products is to reapply after 40 (or 80) minutes of swimming or sweating, and immediately after towel drying (79).

**Ongoing FDA Review**

Despite the 2011 final rule having been issued, there remains ongoing FDA review of products to ensure safety and effectiveness. One of the pending issues involves a maximum allowable SPF label of “50+.” Over the years, product manufacturers have continued to increase SPF values, with some OTC sunscreens exceeding an SPF of 100. The FDA has indicated that although a higher SPF may be beneficial, such products can also create a false sense of security and result in consumers spending excessive lengths of time exposed to the sun (77). On the premise that there is insufficient data supporting any increased clinical benefit of products with an SPF above 50, the FDA has proposed this cap on labeling pending sufficient submission of data to support the contrary (80).

Furthermore, the FDA is requesting additional data needed to establish specifications for certain dosage forms of sunscreens. Dosage forms such as wipes, towelettes, powders, body washes, and shampoos are currently considered ineligible for inclusion in the sunscreen monograph. Conversely, eligible dosage forms anticipated to be included in the monograph are oils, lotions, creams, gels, butters, pastes, ointments and sticks. Spray dosage forms are considered potentially eligible yet require additional data to assess their safety and efficacy, specifically relating to amount dispensed, uniform coverage, and possibility of inhalation of aerosolized particles (81).

There exists a number of new organic filters awaiting FDA approval; however, limitations on allowable concentrations of active ingredients and certain combinations pose a formulation challenge. As a result, FDA approval of several organic filters remains pending (77). The following reviews organic UVB and UVA filters that have all received FDA approval for use in sunscreen manufacturing.

**Organic UVB filters**

The UVB spectrum ranges from 290-320nm. While only 5% of UV radiation reaching the earth’s surface is comprised of UVB (9), radiation from this shorter-wavelength light spectrum has significant harmful effects. UVB is primarily absorbed in the epidermis with little dermal penetration. UVB radiation primarily causes acute erythema, sunburn and cellular DNA damage such as thymidine dimers, which are the hallmark of photocarcinogenesis (9,17). Studies have shown that UVB is approximately 1,000 times more erythemogenic than UVA (10). Furthermore, both UVA and UVB radiation can induce immunosuppression (9). In the early 1900s it was found that skin could be protected from sunburn by specifically filtering out these harmful UVB wavelengths, and the first sunscreens consequently appeared on the market (18). FDA-approved organic UVB filters are classified as aminobenzoates (para-aminobenzoic acid [PABA] and PABA derivatives), cinnamates, salicylates, octocrylene or ensulizole (Table 1) (12). The following paragraphs will detail the various organic UVB filters currently available in the United States, including the controversial issues linked to certain ingredients.

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### Table 1: FDA-Approved Organic UVB-Blocking Ingredients

<table>
<thead>
<tr>
<th>Ingredient Type</th>
<th>Example Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABA &amp; derivatives</td>
<td>Padimate A, Padimate O</td>
</tr>
<tr>
<td>Cinnamates</td>
<td>Octinoxate, Cinoxate</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Octisalate, Homosalate, Trolamine salicylate</td>
</tr>
<tr>
<td>Octocrylene</td>
<td></td>
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<tr>
<td>Enulsulizole</td>
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</table>

### Table 2: FDA-Approved Organic UVA-Blocking Ingredients

<table>
<thead>
<tr>
<th>Ingredient Type</th>
<th>Example Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzophenones</td>
<td>Oxybenzone, Sulisobenzone, Dioxybenzone</td>
</tr>
<tr>
<td></td>
<td>Avobenzone/Parsol 1789</td>
</tr>
<tr>
<td></td>
<td>Meradimate</td>
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<tr>
<td></td>
<td>Ecamsule/Mexoryl SX</td>
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<tr>
<td>Non-FDA Approved</td>
<td>Drometrizole/Mexoryl XL</td>
</tr>
<tr>
<td></td>
<td>Tinosorb M/Bisoctrizole</td>
</tr>
<tr>
<td></td>
<td>Tinosorb S/Bemotrizinol</td>
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Aminobenzoates

Para-aminobenzoic acid (PABA) is one of the most commonly found UVB absorbers in sunscreen products (11). PABA absorbs UV wavelengths in the 290-320nm range (19). It represents one of the first organic sunscreens to become widely available, with the formulation patented in 1943 (10,20). PABA is a highly efficient UVB filter at 5% concentration in a 50-60% alcohol-based vehicle (21). Any alteration in the alcohol or water content of the formulation will decrease its protective effects (18).

One of the most advantageous properties of PABA is its chemical composition, consisting of long-chain aliphatic alcohols that make it nearly insoluble. It therefore has the ability to penetrate the skin by attaching to proteins within keratinocytes via hydrogen bonding (10). Approximately 30 minutes after application, the product is able to withstand swimming, perspiration, and the trauma of towel abrasion (10,18).

For several years, PABA was the primarily used organic sunscreen ingredient (20); however, several issues resulted in its limited use over time and the rise of “PABA-free” products beginning in the 1980s (10). Disadvantages of PABA include the staining of clothing (18) and subjective stinging with allergic contact dermatitis (17). The reported photoallergic reaction to PABA likely results in part from its phototoxicity. The reported photoallergic reaction to PABA following sunlight exposure, thus undergoing a transformational change from the standard E (trans)-configuration to the photo-degradation product Z (cis)-configuration, which has decreased UVB filtering efficiency (35). Damiani et al. has studied the ability of cinnamate to induce in vitro lipid peroxidation even in the presence of other molecules thought to photostabilize octinoxate, further supporting the photo-unstable properties of octinoxate (36). Despite being considered photostable, the photoisomerization reaction seen with cinnamates is well characterized and highly predictable (22). Although degradation after brief UV exposure decreases product efficacy, factors such as base formulation, use of preservatives and nanoencapsulation can serve to improve photostability (5,34,37).

Cinnamates

Cinnamates represent the most commonly used UV filter globally (22), with nine cinnamate derivatives approved worldwide (18). Only two cinnamate UV filters are available in the United States: octinoxate (2-ethylhexyl-p-methoxycinnamate, formerly octyl methoxycinnamate), and the rarely used cinoxate (2-ethoxyethyl-p-methoxycinnamate or dietholamine methoxycinnamate). Cinnamates absorb UV in the 290-345nm range with peak absorption at 300-320nm (17). This class of organic sunscreens is the next-most potent UVB absorber after PABA and PABA derivatives (29). Since octinoxate is a less-potent absorber than padimate O, it requires formulation with additional UVB filters to achieve a desirable SPF (21). The physical form of this ingredient is a thin liquid, commonly used to impart UV protection in color cosmetics (10,22). Cinnamates have a high water solubility, leading to potential skin penetration and thus decreasing its sun protective properties (5).

Despite its many desirable physiological properties, there do exist drawbacks to the use of cinnamates in sunscreen products. Because cinnamates are chemically related to cocoa leaves, balsam of Peru and cinnamon oil, they should be avoided in individuals with hypersensitivities to these products due to the risk of cross-reactivity (30,31). Although octinoxate has been reported to elicit a positive reaction during photopatch testing, the incidence is low, with a negligible degree of skin irritation typically seen (22,32,33).

Commercially available sunscreens must be exposed to both natural and artificial UV radiation in order to study and determine photostability. While manufacturers commonly market their products’ protection against UVA and UVB radiation, labels rarely declare photostability. Gonzalez et al. performed a study of seven sunscreen products available in the U.S. to evaluate their photostability. Results demonstrated that octinoxate is photo-unstable and starts to degrade rapidly following UV exposure (34). Octinoxate has been shown by nuclear magnetic resonance spectroscopy to degrade into a configurational isomer following sunlight exposure, thus undergoing a transformational change from the standard E (trans)-configuration to the photodegradation product Z (cis)-configuration, which has decreased UVB filtering efficiency (35). Damiani et al. has studied the ability of octinoxate to induce in vitro lipid peroxidation even in the presence of other molecules thought to photostabilize octinoxate, further supporting the photo-unstable properties of octinoxate (36). Despite being considered photostable, the photoisomerization reaction seen with cinnamates is well characterized and highly predictable (22). Although degradation after brief UV exposure decreases product efficacy, factors such as base formulation, use of preservatives and nanoencapsulation can serve to improve photostability (5,34,37).

New product formulations of cinnamates that aim to decrease allergic or irritant reactions, decrease percutaneous absorption and increase photostability, leading to improved efficacy by micro-encapsulation, are becoming available. The first product to use this technique, Eusolex® UV-pearls, contains roughly 37% octinoxate (38). Micro-encapsulation involves entrapment of the organic sunscreen ingredient within a silica glass shell. These extremely stable spheres have a diameter one-hundredth the width of human hair and form a protective film on the skin. Because the active UV filter is entirely contained
within the spheres, there is no direct contact with skin, and the sunscreen ingredient remains in the outermost layers of the skin. Thus, there is a significantly reduced risk for dermatitis and systemic absorption and improved sun-protective efficacy of the encapsulated sunscreen ingredient (37,38). This encapsulation technique can also be used to solve the problem of incompatibility between ingredients (such as avobenzone and octinoxate) by physical segregation (38).

Salicylates

Salicylates are a group of aromatic compounds, with three agents commercially available in the U.S. Octisalate (formerly octyl salicylate) and homosalate, both water insoluble, are the two most commonly used salicylate sunscreens. Trolamine salicylate is the only water soluble of the compounds, frequently used in hair photoprotective agents (10). Salicylates are well tolerated, with rare reports of skin irritation or photosensitization (22). They are often used in combination with other sunscreen products, such as oxybenzone and avobenzone, to minimize photodegradation (21). Salicylates absorb 290-355nm UV light, with peak absorbance at 310-320nm (17). Because of their weak UVB absorption, salicylates must be used in higher concentrations than most organic sunscreens and are often used in combination with other UVB absorbers. Nonetheless, they all have a favorable safety profile (17,21). The high lipophilicity of salicylates make them capable of accumulating in the lipid phase of the stratum corneum while being unable to significantly permeate the hydrophilic epidermis below and therefore having little systemic penetration. Walters et al. studied the in vitro skin permeation of octisalate from two different vehicles, an oil-in-water emulsion and hydroalcoholic formulation. Results demonstrated less than 1% of the applied dose of octisalate penetrated the epidermis of the skin in 24 hours, regardless of the vehicle (39). These results suggest that the human skin penetration of salicylate sunscreens is relatively low. Another mechanism for the prevention of systemic absorption of the salicylates is their metabolism. Salicylate sunscreens’ breakdown in the stratum corneum results in cleavage of the ester bond, forming salicylic acid and octyl or trimethylcyclohexyl moieties. Any potential systemic toxic effects of the sunscreen would be limited to the almost negligible amount of salicylic acid able to be absorbed and present within the body (21). Overall, salicylates represent a commonly used sunscreen ingredient with several advantageous attributes.

Octocrylene

Octocrylene (2-ethylhexyl-2-cyano-3,3 diphenylacrylate) is an organic sunscreen with a relatively broad UVB absorption spectrum, rendering it less effective at UV filtration (10). It has both UVB and short-wave UVA coverage from 290-370nm, with peak absorbance at 300-320nm. It can be used in combination with other UV absorbers to achieve higher SPF formulas (17). It acts as a photostabilizer and can be combined with other sunscreen ingredients to improve photostability profiles of photolabile products such as avobenzone (21). The number of products containing octocrylene has thus logically increased over the years since the approval of avobenzone (22). Octocrylene is easily incorporated into gel sunscreens and is popular in products labeled as noncomedogenic (10). It has also been shown to have a favorable toxicity profile, with studies showing no evidence of maternal or developmental toxicity after subchronic repeat exposure in mice (40).

Despite the various benefits of octocrylene, it is costly and difficult to manufacture, resulting in limitations to widespread use (10). Of additional concern is emerging data of octocrylene as a photoallergen. It had initially been considered a non-allergenic, non-irritant molecule(41). In 2003, the first cases of patch-test-confirmed photoallergy to octocrylene were reported (42). It was not until three years later that four more cases were reported, with expectations for further occurrences of photoallergy due to the progressively increased use of octocrylene in sunscreens and cosmetics (41,43). Currently, octocrylene is well described in the literature as a photoallergen, with over 50 documented cases of contact dermatitis and/or positive photopatch tests. It has been reported to be a strong allergen, leading to contact dermatitis in children and in adults with a history of photoallergy from ketoprofen (44). It is important for clinicians to be aware of this risk and recommend avoidance of octocrylene-containing products in susceptible patients.

Ensulizole

Ensulizole (2-phenylbenzimidazole-5-sulfonic acid or PBSA) is a water-soluble and aesthetically pleasing sunscreen. It absorbs UVB light in the range of 290-335nm almost exclusively, with peak absorption at 310-320nm. It became available on the U.S. market in 2003, comprising less than 10% of all sunscreens (10). Ensulizole is used in products formulated to feel lighter and less oily, such as daily cosmetic moisturizers (17). It is a photostable ingredient with rare occurrence of skin irritation or photoallergy (10,22). Despite its cosmetic elegance, ensulizole has disadvantages due to its highly selective UVB-attenuating properties, allowing near-complete UVA transmission, as opposed to most other UV blockers, which have a broader absorption spectrum (17). Furthermore, studies have shown that a small amount of ensulizole does penetrate the skin to enter systemic circulation (22). Nonetheless, the available information regarding human safety of ensulizole is not nearly as extensive as that of other sunscreen products, and it remains favorable on the market.

Organic UVA filters

The UVA radiation spectrum ranges from 320-400nm, and is further subdivided into UVA I (340-400nm) and UVA II (320-340nm). The amount of UVA radiation remains nearly constant throughout the day and year, with little temporal flux (30). UVA rays are not filtered by standard window glass, whereas UVB rays are filtered out. Furthermore, UVA rays are relatively unaffected by atmospheric conditions and changes in altitude, while UVB intensity decreases at lower altitudes as the light moving toward Earth is scattered, reflected, or absorbed (13,82,83). The longer UVA wavelengths penetrate deeply into the dermis, affecting skin elasticity and producing prolonged pigmentation, and they have been shown to inhibit enzymes necessary for repairing the cells damaged by UVB rays (10,30). UVA causes immunosuppression by decreasing Langerhans cells and increasing the expression of the tumor suppressor gene p53, thus promoting UVB carcinogenicity and oxidative stress (4,10). These unique characteristics of UVA radiation contribute to its predominant role in photoaging and immunosuppression, as well as a secondary role in photocarcinogenesis. UVA radiation also significantly contributes to most drug-induced photosensitivity reactions, as well as the exacerbation of photodermatoses such as polymorphous light eruption, lupus erythematosus, solar urticaria and actinic prurigo (4,30,45).

Prior to changes set to be implemented by December 2012, the SPF indicated on current product labeling is primarily representative of UVB protection, making it difficult for consumers and physicians to compare the UVA protection afforded by various sunscreens (46). Regardless of such labeling shortcomings, which are soon to change, there are an increasing number of organic UVA filters on the market that serve to broaden the absorption spectra of commercially available products and...
afford protection from damaging UVA rays. The present FDA-approved organic UVA filters on the market are benzophenones, avobenzone, meradimate and examcule. With the 2011 FDA final ruling, these organic UVA filters will represent part of the active ingredients in sunscreens labeled "broad spectrum." Drometrizole trisiloxane, bemotrizinol and bisoctrizole, all available in other countries, are currently at various stages of the FDA approval process (Table 2).

**Benzophenones**

The benzophenones comprise a class of aromatic ketones that provide broad-spectrum UV coverage (10). Benzophenones absorb wavelengths predominantly in the UVB and UVA II range from 270-350nm, with peaks at 288 and 350nm (47). The benzophenone class consists of oxybenzone (benzophenone-3), sulisobenzone (benzophenone-4) and dioxybenzone (benzophenone-8), with oxybenzone being the most popular of the substituted derivatives (22). Oxybenzone is presumably photolabile and rapidly oxidized upon irradiation (21). Schallreuter et al. demonstrated that oxidation of oxybenzone itself inactivates important antioxidant enzymes on the living skin surface. Upon photo-oxidation, oxybenzone is converted to free-radical intermediates with the capacity to inhibit the antioxidant defense system of enzyme thioredoxin reductase and substrate glutathione (48,49). This process is hypothesized to disrupt the homeostasis of the epidermis and potentiate photodamage of the skin. However, Rapp et al. contends that the methods used to determine photostability of oxybenzone were inadequate (50). Thus, the extent of the potential reactive oxidation effect of oxybenzone remains inconclusive.

Ultraviolet filters are frequently added to cosmetic products such as lipstick, moisturizer, foundation and concealer. Addition of the organic sunscreens to cosmetics protects the skin from photoaging, as well as increases the products’ longevity by preventing photodegradation (31). The increase in consumer exposure to UV filters has led to numerous reports of photolergy and allergic contact dermatitis (33). Oxybenzone is the most common sunscreen agent in widespread use to cause photolergic and contact dermatitis to benzenophenone sunscreen agents (52-55). In 2001, Darvey et al. conducted a retrospective analysis of 2,715 patients who underwent photopatch testing at their institution. The results showed an overall low yield of positive photopatch tests. Nonetheless, oxybenzone was shown to be the most common UV-filter photoallergen among those tested. In this study, a photoallergic reaction was diagnosed if irradiated patch-tested sites were positive, while non-irradiated sites remained negative. An allergic contact dermatitis was diagnosed when both irradiated and non-irradiated sites were positive. Furthermore, Darvey et al. found that patients exhibiting an underlying photodermatoses, such as polymorphous light eruption or chronic actinic damage, represent a population at increased risk of photosensitivity to such products. The exact mechanism behind this association is unclear; however, it is hypothesized that repeated application of high concentrations of UV filters is more likely in such individuals, leading to an increased risk of sensitization (33).

In 2010, Chretien et al. reported a novel strategy that aims to reduce some of the adverse effects of oxybenzone via a synthetic preparation known as zeolite encapsulation. Use of zeolites for sunscreen encapsulation creates a supramolecular sunscreen product that retains the protective benefits intrinsic to UV filters while eliminating the associated risk of dermatitis. Supramolecular sunscreens maintain the scattering and absorbing properties of a UV filter while concomitantly eliminating the interaction between multiple sunscreen ingredients. This phenomenon is attributable to restricted diffusion of the zeolite-encapsulated particles. Chretien et al. demonstrated with absorption spectroscopy that zeolite-encapsulated oxybenzone provides in vitro SPFs that are similar to unencapsulated formulations. The researchers further showed that encapsulation significantly decreases the degradation of oxybenzone in the presence of the inorganic sunscreen-agent titanium dioxide, which normally occurs when the combination product is irradiated. Zeolite encapsulation can theoretically eliminate photoallergic reactions by prevention of direct contact between the skin and active organic sunscreen ingredients (56). The concept of supramolecular sunscreens that serve to decrease photoallergic dermatitis as well as product degradation, while maintaining intrinsic UV protective properties, represents a promising strategy for future formulations.

Since oxybenzone has enhanced bioavailability following topical application in comparison to other UV filters, it has gained attention in recent years regarding systemic effects and toxicity (22). One of the major controversies surrounding oxybenzone is its potential to disrupt the endocrine system. In an attempt to solve the debate of whether environmental accumulation of oxybenzone leads to effects on reproduction, there have been several studies examining estrogenic activity of oxybenzone metabolites (47). Nakagawa and Suzuki showed that hydroxylated intermediates of oxybenzone act as a xenosterogen via biotransformation in human breast-cancer cells (57). In a study performed by Coronado et al., it was indicated that oxybenzone alters endocrine or reproductive endpoints in two fish species. However, this conclusion was reached with concentrations of the sunscreen ingredient significantly higher than those observed in typical wastewater (58). Ultimately, oxybenzone most likely poses no significant risk to fish reproduction, presenting a limited contribution to estrogenic activity. Schlumpf et al. evaluated the estrogenic effect of oxybenzone on uterine weight in rats exposed to the ingredient. Although the findings indicated an increase in uterine weight of oxybenzone-exposed rats, the administered supraphysiologic oral dosage that was required to show a statistically significant outcome was exceedingly high (59). Considering the minuscule concentrations of oxybenzone applied topically in sunscreen products, this study did not support the hypothesis that oxybenzone has significant estrogenic activity. In studies done in 2004 and 2007, Janjua et al. demonstrated that oxybenzone was absorbed through the skin and excreted in urine; however, it did not accumulate in plasma and therefore posed no risk to endocrine function (60,61). Reports of potential endocrinologic and metabolic effects of other sunscreen ingredients will be reviewed further in this discussion.

Researchers in India reported a project whereby solid lipid nanoparticles (SLNs) containing oxybenzone were formulated to improve the effectiveness of the sunscreen (62). The product was intended to show slowed drug release and improved SPF. The study showed this cream formulation to exhibit good skin retention and enhanced UV protection. Though the use of SLNs did not address hormonal alterations due to oxybenzone, this innovative drug-delivery system may represent a solution to the issue of systemic toxicity of oxybenzone due to the intrinsic benefit of displaying superior skin retention. If such a formulation can maintain the product at the layer of the stratum corneum, oxybenzone theoretically will not enter systemic circulation, thus reducing the risk of suggested endocrine disruption (62). Although systemic absorption of oxybenzone has gained significant attention from both animal and human studies, sig-
For patients with mild to moderate rosacea,
Deliver a spectrum of benefits with

**Finacea® (azelaic acid) Gel, 15%**

- The first and only gel approved to treat inflammatory papules, pustules, and associated erythema* (See Indication & Usage below)
- 61% of patients achieved treatment success in 12-week clinical studies
- Helps maintain the stratum corneum barrier function
- #1 dermatologist-prescribed topical brand for mild to moderate rosacea

**INDICATION & USAGE**

FINACEA® (azelaic acid) Gel, 15% is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea.

*Although some reduction of erythema was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

**IMPORTANT SAFETY INFORMATION**

FINACEA Gel, 15% is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other components of the formulation. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation. FINACEA and its vehicle caused irritant reactions at the application site in human dermal safety studies. Skin irritation (e.g., pruritus, burning or stinging) may occur during use with FINACEA, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and/or persists during use with FINACEA, discontinue use and institute appropriate therapy.

In clinical trials with FINACEA, the most common local adverse events (AE's) (inclusive of mild, moderate and severe categories) were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/iritation (4%). Contact dermatitis, edema and acne were observed at frequencies of 1% or less.

Rarely reported AE’s included: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and exacerbation of recurrent herpes labialis. Post-marketing safety information: Skin (facial burning and irritation); Eyes (iridocyclitis on accidental exposure with FINACEA to the eyes). To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare at 1-866-463-3634 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

FINACEA is for topical use only. It is not for ophthalmic, oral or intravaginal use. In case of accidental eye exposure, wash eyes with large amounts of water and consult a physician if eye irritation persists. Wash hands following application of FINACEA.

See following page for Brief Summary of full Prescribing Information.

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Model used for illustrative purposes only.

References: 1. FINACEA package insert, Montvale, NJ: Intendis, Inc. 2010 2. Danko ZJ, Effects of azelaic acid 15% gel on skin barrier in rosacea. Cosmet Derm 208(2)(5):259-261. 3. Wolters Kluwer Pharma Solutions, Source® Pharmaceutical Audit Suite, July 2010-December 2011. Based on TBI counts, dermatology specialty, inclusive of labeled products/strains only. Wolters Kluwer Health makes no representations regarding the accuracy of its data for the purpose of substantiating any advertising and promotional claims made by Bayer. Bayer remains solely responsible for full compliance with any and all applicable advertising and marketing laws and regulations. Provision of approval for data release for publication is contingent upon Bayer's acknowledgement of sole responsibility for accuracy of the claim made, as well as for compliance with any and all applicable marketing and advertising laws.

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Borowitz, Khani, Miller 66

For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravitreal Use
Rx only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
FINACEA Gel, 15%, is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema, which was present in patients with papules and pustules of rosacea, occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

CONTRAINDICATIONS
FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS
FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravitreal use. There have been isolated reports of hypoglycemia after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypoglycemia.

PRECAUTIONS
General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of FINACEA Gel led to an increased number of animals with papillomas at the treatment site (see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility). The clinical relevance of the findings in animal studies to humans is not clear.

Information for Patients: Patients using FINACEA Gel, 15%, should receive the following information and instructions:

• FINACEA Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
• Clean affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA Gel, 15%. Avoid alcoholic cleansers, tinctures and astrigent and peeling agents.
• Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucus membranes.
• If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
• The hands should be washed following application of FINACEA Gel, 15%.
• Cosmetics may be applied after FINACEA Gel, 15%, has dried.
• Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician (see ADVERSE REACTIONS).
• Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
• Patients should report abnormal changes in skin color to their physician.
• Avoid the use of cosmetic dressings or wrapping.

Drug Interactions: There have been no formal studies of the interaction of FINACEA Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week oral carcinogenicity study using transgenic (TGAC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female TGAC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male TGAC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males.

This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of in vivo Ames assay, HGPSRT in V79 cells, Chinese hamster lung cell, and chromosomal aberration assay in human lymphocytes and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests. Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B
There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicity studies have not been performed with azelaic acid. 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 63 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through postnatal day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: Equilibrium dialysis was used to assess human milk partitioning in vitro. At an azelaic acid concentration of 25 µg/ml, the milk/plasma distribution coefficient was 0.7 and the milk/serum distribution coefficient was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA Gel, 15%, did not include sufficient numbers of subjects aged ≥65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS
Overall, treatment related adverse events, including burning, stinging/tingling, drying, dryness/blackness, scaling, itching, and erythema/irritation/redness, were 19.4% (214/1241) for FINACEA Gel, 15%, and 17.1% (91/527) for the active comparator gel at 16 weeks.

In two vehicle controlled, and one active controlled U.S. and clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=604), and the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mild (n=112)</th>
<th>Moderate (n=61)</th>
<th>Severe (n=27)</th>
<th>Vehicle (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buring/</td>
<td>71 (67%)</td>
<td>42 (42%)</td>
<td>17 (44%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>stinging/</td>
<td>29 (26%)</td>
<td>18 (17%)</td>
<td>5 (16%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>21 (52%)</td>
<td>5 (12%)</td>
<td>5 (16%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Scaling/dry</td>
<td>27 (24%)</td>
<td>7 (17%)</td>
<td>5 (16%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>skin/erosions</td>
<td>6 (1%)</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Erythema/</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>irritation</td>
<td>4 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Contact</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>dermatitis/</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Subjects may have ≥1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least ≥1 cutaneous adverse event.

FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application sites in human dermal safety studies. FINACEA Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergy were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of acne, vellus hair degradation, small digitated spots, hypertrichosis, reddening (signs of keratoses pilares), and exacerbation of recurrent herpes labialis.

Post-marketing safety: Skin: facial burning and irritation; Eyes: irritation or irritation on accidental exposure with FINACEA Gel, 15%, to the eye (see PRECAUTIONS).

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icient alterations of endocrine function in humans have yet to be indisputably demonstrated. The lack of conclusive evidence of a biologically substantial hormonal disruption establishes the need for future studies in this area.

**Avobenzone**

Avobenzone (trade name Parsol 1789), or butyl methoxydibenzoylmethane, represents a class of substituted diketones. Avobenzone provides superior protection throughout the UVA spectrum, with peak coverage within the UVA I range (10). This ingredient revolutionized UVA protection and provided great benefit to consumers by allowing manufacturers to broaden the spectrum of UV coverage in available sunscreen products. Systemic bioavailability of avobenzone is considered to be low, attributable to the lipophilicity of the molecule. Extensive evaluation via toxicity studies has shown avobenzone to have a favorable profile (22). It is an uncommon photoallergen; however, Collaris et al. reported a case of a delayed-type hypersensitivity reaction after use of sunscreen products containing avobenzone (32).

Photodermatoses represent a group of conditions characterized by a heightened sensitivity and reaction to UV radiation, particularly the longer-wavelength ranges. The management of a photosensitive patient always includes use of sunscreen. Of the currently FDA-approved organic sunscreens, avobenzone is the only active ingredient for which the absorption spectrum extends well into the UVA I range. Avobenzone has thus been shown highly effective in treatment of the photodermatoses such as lupus syndromes, polymorphous light eruption and actinic prurigo (45).

A major disadvantage of avobenzone is its photostability. Gonzalez et al. demonstrated that in three out of six combination sunscreen products studied, avobenzone was degraded following UV irradiation (34). In formulations where avobenzone is not photostable, UV radiation transforms the molecule into one that no longer absorbs UVA wavelengths. Photoprotection therefore decreases with increased duration of sun exposure, and can occur rather rapidly (46). The photoprotective capacity of avobenzone is shown to decrease by 50-60% after only 1 hour of UV exposure (21). In such photostable products, continuous reapplication becomes necessary in order to provide adequate sun protection.

Due to its photostability, avobenzone is frequently combined with other sunscreens or stabilizing agents in order to reduce UV-induced degradation of the final product. Stabilization of avobenzone can be achieved by addition of diethylhexyl 2,6 naphthalate (DEHN). DEHN is a non-UV filter that accepts excess energy absorbed by avobenzone, thus stabilizing it during UVA exposure. Combination of DEHN, avobenzone and oxybenzone is commercially known as Helioplex® (10). Tinosorb S (bemotrizinol) and enzacamene have both been shown to photostabilize avobenzone, although they are not yet approved in the U.S. (14,46). Other agents that photostabilize avobenzone, as well as provide the added benefit of broadening the absorption spectra, are the UBV filters homosalate, octisalate, and octocrylene. The UVA filter oxybenzone and inorganic filters titanium dioxide and zinc oxide can be incorporated into formulations to stabilize avobenzone as well (14).

Avobenzone also has the potential to degrade other sunscreen ingredients when used in combination products. It has specifically been reported to strongly enhance the degradation of octinoxate (63,64). Following rapid photodegradation, avobenzone can react with octinoxate via formation of cycloaddition products. This product has the ability to destabilize the otherwise photostable cinnamonate molecule (63). Sayre et al. demonstrated that the resulting photolysis products exhibit drastically diminished UV protection (64). An encapsulation technique whereby organic sunscreen active ingredients are entrapped within a silica glass shell can be employed to address the problem of product incompatibility. The microsized silica spheres are extremely stable and form a protective film over the skin. Encapsulation of the organic sunscreen ingredient prevents direct contact of the molecule with skin, thus decreasing the risk for allergic contact dermatitis; this technique was first commercially available in a sunscreen product containing octinoxate (38). In addition to diminished contact dermatitis, physical segregation of avobenzone and octinoxate eliminates the chemical interaction between these two UV filters. This encapsulation technique stabilizes avobenzone/octinoxate formulations by preventing any chemical interaction and thus prevents product degradation (38).

**Meradimate**

Meradimate (formerly known as methyl anthranilate) is a weak UV filter that absorbs primarily in the UVA II range (21). It has been available for over 70 years but is rarely used due to its inferior UVA-absorption capacity compared to the benzophenones and avobenzone (10).

**Ecamsule**

Ecamsule (terephthalylidene dicamphor sulphonic acid; Mexoryl SX) was introduced in the U.S. in 2006 after more than 10 years of being available in other regions of the world. In July of that year, ecamsule was approved as an active ingredient in combination products rather than as an individual UV sunscreen drug (14). It is marketed by LaRoche-Posay™ as Anthelios SX™ and is used in combination with avobenzone and octocrylene. Ecamsule is a photostable, broad-spectrum ultraviolet light absorber (51). It is water resistant and has minimal systemic absorption owing to its inability to penetrate the stratum corneum (10). This new agent has been shown to reduce photoaging characteristics such as pigmentation, epidermal hyperplasia, and decreased skin hydration and elasticity (21). It has also been reported to prevent pyrimidine dimer formation, p53 protein accumulation and alterations in Langerhans cell density (65). Ecamsule is additionally effective in treating photodermatoses, owing to its superior UVA-absorption capacity (10,45).

Drometrizole trisiloxane (Mexoryl XL) is a photostable organic sunscreen with mid-range UVA protection. The addition of Mexoryl XL to Mexoryl SX is shown to have a synergistic effect on increasing UVA protection and prevention of pigmentation induction (51). Drometrizole trisiloxane was introduced in Canada in 2006 and is available around the world. However, this active ingredient is not yet approved in the U.S. (46). As of June 2010, drometrizole trisiloxane, in concentrations of up to 15 percent, became eligible to be considered for potential inclusion in the OTC sunscreen drug monograph. It is being considered as both a single active ingredient and in combination with other sunscreen active ingredients generally recognized as safe and effective (66).

**Tinosorb S and Tinosorb M**

Tinosorb S (bemotrizinol; anizotriazine; bis-ethylhexyloxyphenyl methoxyphenol triazine) and Tinosorb M (biscosrtizole; methylene-bis-benzotriazoyl tetramethylbutylphenol) were submitted to the FDA in April 2005 by Ciba Specialty Chemicals Corporation (67,68). They are currently undergoing FDA approval via the Time and Extent Application (TEA) process for inclusion in the OTC sunscreen monograph (14). Both products have been available in Europe since 2000, with Tinosorb S currently sold in 31 countries worldwide (67), while Tinosorb M is available in 39 countries (68). Tinosorb S is a photostable, broad spectrum filter, absorbing UBV as well as UVA rays (14). It is an oil-soluble
filter, intended for oil-phase sunscreen formulations as well as for use in photostabilizing avobenzone and octinoxate. Tinosorb M is intended for use in aqueous formulations, as it consists of microfine organic particles easily dispersed in the aqueous phase of a sunscreen emulsion (51). It is marketed as the first of a new class of sunscreens that combines the benefits of both an organic and inorganic filter in that in can reflect, scatter, and absorb UV radiation (65). The significant photostability profiles of both Tinosorb S and Tinosorb M are due to a unique molecular structure that facilitates the dissipation of energy by intramolecular heat transfer and vibrational relaxation. Consequently, there are no reactive intermediate species or photolytic decomposition products generated in the skin (21). Considering these unique qualities, both Tinosorb M and Tinosorb S possess great potential in the future of sunscreen ingredients.

Other controversies of organic sunscreen agents

Phototoxicity, Skin Absorption and Encapsulation

Hayden et al. studied the penetration and retention of five organic sunscreen agents (padimate O, octinoxate, octocrylene, avobenzone and oxybenzone) in human skin. Results showed that after 24 hours, detectable amounts were present in the stratum corneum and viable epidermis. Cell culture studies further showed these levels to be too low to cause toxicity in keratinocytes after topical application to intact skin, with octinoxate demonstrating the least cytotoxic effect in vitro (69). Taken into consideration with additional studies of epidermal penetration of UV filters, concern was fueled regarding photodegradation leading to incomplete photoprotection as well as the possibility of photogeneration of reactive oxygen species (ROS) among sunscreen molecules (35, 49, 69, 70). Direct imaging of various epidermal depths by fluorescence microscopy allowed for the study of ROS levels after application of octinoxate, octocrylene and oxybenzone. Results of the data showed that if the aforementioned UV filters are able to penetrate the stratum corneum, they can in fact generate ROS within keratinocytes of the epidermis (49). Damiani et al. have done several studies in support of avobenzone's ability to inflict DNA strand breaks and cause oxidative modification of in vitro proteins (71). The mechanism of oxygen free-radical formation and the extent of damage caused by ROS warrants further exploration.

Considering the data stating that epidermal penetration is required for ROS formation (49), it is reasonable to assume that a vehicle or product formulation that limits penetration would also decrease systemic absorption and potential oxidative damage. Thus, new strategies are being developed to minimize penetration of UV filters. Encapsulation of octinoxate with poly-D,L-lactic acid nanoparticles has shown that the product remains at the skin surface and within the stratum corneum at significantly higher concentrations than nonencapsulated octinoxate. Nanoparticles coat the skin surface and are impeded by the stratum corneum, representing an ideal technique for reducing transdermal penetration of UV filters and increasing the efficacy of photoprotection (37).

Systemic Endocrinologic and Metabolic Effects

In 2001, Schlumpf et al. studied in vitro and in vivo estrogenic effects of six organic sunscreens: padimate O, octinoxate, homosalate, oxybenzone, avobenzone, and the non-US FDA approved 3-(4-methylbenzylidene) camphor (4-MBC). In vitro estrogenicity was evaluated by exposure of the UV filters to MCF-7 breast-cancer cells, and five out of the six ingredients displayed dose-dependent estrogenic activity. Oxybenzone demonstrated the most active cell proliferation, while avobenzone remained inactive. However, the authors state that it cannot be determined whether the observed estrogenic effects are attributable to the actual sunscreen ingredients or instead to possible metabolites. Furthermore, the data did not entirely correlate with in vivo studies, in which only three out of the six UV filters displayed estrogenicity. These three sunscreens, octinoxate, oxybenzone, and 4-MBC, were found to elicit dose-dependent increases in uterine weight among immature hairless rats (59). Investigation of the same three sunscreen ingredients was later undertaken by Janjua et al., who examined the plasma and urine of 32 subjects after topical application of each formulation. The aim of the studies was to investigate systemic uptake and effects on endogenous reproductive hormones. The researchers concluded that despite systemic presence of the three sunscreens, there was no apparent influence on the levels of endogenous hormones in men and women (60, 61).

Oxybenzone was further studied by Schlecht et al. in 2004. Their study compared the effects of estradiol to benzophenone-2 (BP2) and benzophenone-3 (BP3) on estrogen and estrogen-like receptors in mice. They sought to determine the physiologic impact of these chemicals on pituitary, thyroid and uterine function, as these organs possess estrogen and estrogen-like receptors. The results suggested that BP2 exerts estrogenic effects similar to those of estradiol on all three organs, but that BP3 lacked any effect (72). These results apparently contradict those of Schlumpf et al., making the physiologic relevance of these studies uncertain and yet-to-be established (59, 72).

Seidlova-Wuttke et al. tested the estrogenicity of orally administered octinoxate and 4-MBC by comparing it to the effects of chronic estradiol treatment in ovariec-tomized female mice. The data showed that octinoxate slightly stimulated uterine weight only at the higher dose, while 4-MBC did so equally at both doses tested. Histologic examination of both uterine and vaginal tissue, as well as quantitative computer tomography of the tibial metaphysis, revealed a very weak estrogenic effect of octinoxate and 4-MBC in the uterus and vagina, and no estrogenicity in bone (73). Considering systemic absorption of topically applied sunscreen ingredients has been shown to be negligible, and this study was done with high doses of orally-administered octinoxate and 4-MBC, it is unlikely that these results would support or prove any risk of metabolic effects from topical sunscreen exposure (60, 61, 73).

Because in vivo estradiol has other metabolic effects besides reproductive, the same team of investigators additionally studied octinoxate and 4-MBC on fat and lipid homeostasis along with thyroid hormone production. Results showed effects that differed from those of estradiol in the measures of weight gain, size of fat deposits, serum leptin, lipid profiles, LH, T4 and TSH levels. Thus, researchers concluded that octinoxate and 4-MBC may affect the endocrine system in ways differing from that of in vivo estrogen, and further studies are warranted (74).

Coronado et al. sought to evaluate oxybenzone's impact on the estrogenic effects and reproduction of juvenile rainbow trout after several studies came out concerning the levels of oxybenzone in wastewater outfalls along the New York and California coasts. The theory was that benzophenones potentially affect estrogen receptors, either by impacting gene expression or by acting as a direct ligand (58, 72). This interaction could lead to developmental and reproductive effects in fish and other aquatic organisms living in waters affected by wastewater outfall. Results showed that oxybenzone did induce vitellogenin, a plasma marker of
estrogenic activity, but the measured concentration of oxybenzone in wastewater is much lower than the concentrations necessary to affect estrogenic activity or reproduction. The researchers concluded that oxybenzone most likely is not a significant risk to fish and other aquatic wildlife (58).

While several experimental models have evaluated systemic absorption and hormonal effects, the precise estrogenic and other metabolic activity of these various UV absorbers is still controversial and unclear (14). Future studies on the possible endocrine effects of organic sunscreens, particularly among human subjects and at actual concentrations in commercially available products, are warranted.

**Conclusion**

Safe sun practices involve a combination of sunscreen, sun-protective clothing and sun-avoidance behaviors such as shade-seeking and abstaining from strong midday sun (75). When choosing a sunscreen, there are numerous options in brand, SPF, properties, and ingredients. Studies on the risks versus benefits of organic (chemical) sunscreen ingredients will continue to be carried out, further fueling the debate, and patients will turn to their physicians and skin-care specialists for advice on sunscreen safety and efficacy in making their product choices. Therefore, it is important for clinicians to be aware of the properties of organic sunscreen ingredients and the controversies surrounding them.

Although not discussed in this review, inorganic (physical) sunscreen ingredients are not excluded from the sunscreen controversy. A host of concerns regarding exposure to titanium dioxide and zinc oxide exists based on studies reporting theoretical risks. The FDA recognizes titanium dioxide and zinc oxide as approved ingredients for OTC sunscreen products. The inclusion of UVA protection in labeling products as "broad spectrum" as well as modifications in product claims and statements represents a large step in the right direction toward improvement in consumer safety and increased protection from harmful effects of UV irradiation. While there remain pending issues to be addressed prior to a release of the final sunscreen monograph, such comprehensive guidance set to be enforced by December 2012 aids in validation of the crucial protective role of sunscreen in halting both skin cancer and photoaging.

**References**

THE IMPORTANCE OF RAPID RECOGNITION AND MANAGEMENT OF STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS IN ADULT PATIENTS

Leah K. Shama, DO,* Vienna Lowenbraun, DO,** Kimball Silverton, DO, FAOCD***

*PGY-2 Family Medicine Resident, NSUCOM/Largo Medical Center, Largo, FL
**2nd-year Dermatology Resident, Genesys Regional Medical Center, Grand Blanc, MI
***Program Director, Department of Dermatology, Genesys Regional Medical Center, Grand Blanc, MI

ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, and potentially fatal adverse cutaneous reactions that must be recognized rapidly in order to minimize morbidity and mortality. Medications are implicated in the majority of cases and initial lesions can vary in morphology. The progression to bullae formation, erythromelalgia, and desquamation leave the patient acutely vulnerable. Mucosal involvement is reported in greater than 90% of patients and, in conjunction with suspicious skin lesions, should alert the clinician for risk of rapid progression to SJS/TEN. Mortality for SJS is estimated to be 1-5% and 25-35% for TEN. Management currently includes immediate withdrawal of the offending drug, and aggressive supportive care in a multidisciplinary approach, ideally in a burn unit. The case described is of a patient that developed SJS, and rapidly progressed to TEN. The goal of this paper is to emphasize the importance of early recognition, biopsy and empiric treatment.

Case Report

A 44-year-old Caucasian male with an extensive past medical history presented to the emergency department with complaints of excessive bleeding from insulin injection sites, oozing from his legs, nausea, and near syncope. His past medical history included B-cell type acute lymphoblastic leukemia (ALL), insulin dependent diabetes type II, obesity, gout, benign prostatic hypertrophy, migraine headaches, gastritis, hypertension, obstructive sleep apnea, and hyperlipidemia. He had no known drug allergies but did admit to an upset stomach with erythromycin ingestion. Family history included breast cancer, hypertension, and fibromyalgia. His social history was negative for tobacco, alcohol, or illicit drug abuse. He was married with three children.

Magnetic resonance imaging (MRI) of the brain performed in the emergency department was negative for acute abnormality. When compared to a study approximately two months prior showing chemotherapy-induced CNS arachnoiditis, there was no change. He was admitted for ALL with acute anemia, acute renal failure, and thrombocytopenia. All other laboratory data were within normal limits. Hematology-oncology was consulted, and a blood transfusion was administered.

Of note, the patient was treated approximately four months prior with cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, and methotrexate (induction hyper-CVAD) for B-cell type ALL. He was also on imatinib for a short time, but it had to be discontinued secondary to protracted nausea and vomiting. He achieved remission approximately 40 days prior to this hospitalization, and chemotherapy was discontinued. Patient deferred any further treatment at that time. Follow-up with hematology/oncology one month later, approximately 10 days prior to his hospitalization, was unremarkable.

Review of systems was positive for lumbar back pain, occasional mild headaches, nausea, fatigue, and near syncope that was made worse with standing.

His home medications included insulin glargine, methotrexate, allopurinol, omeprazole, metoprolol, nifedipine, indomethacin, nortriptyline, lorazepam, isomethetene/dichloralphenazone/acetaminophen (midrib) as needed for headaches, and butalbital/acetaminophen/caffeine (Fioricet) as needed for headaches. He also required the use of a BiPAP for sleep apnea. All home medications were continued, and the patient was started on hyper-CVAD, phase 2 chemotherapy for treatment of his B-cell type ALL.

On physical exam, this 5ft, 10in male weighed 295lbs with a BMI of 42. His heart was regular and rhythmic at 100 beats per minute, and he had petechiae on the lower extremities, as well as several ecchymotic lesions at abdominal injection sites. His baseline labs showed thrombocytopenia at 10,000/mL, and electrocardiogram (ECG) demonstrated normal sinus rhythm at 87 beats per minute.

During the first four days of the patient’s hospital stay, he was given a blood transfusion, chemotherapy (hyper-CVAD phase 2) was initiated, and supportive care was provided. On the fifth day of admission, the patient was evaluated by nephrology for hypernatremia and an elevated creatinine, and by pulmonology/critical care. The patient had become hypotensive, had developed acute renal failure (ARF) with an anion gapped metabolic acidosis, and electrolyte abnormalities, including hypercalcemia and hypophosphatemia. The patient remained pancytopenic. Review of systems was positive for nausea. On physical exam, his blood pressure was 86/48, with a pulse of 79, respiratory rate of 23, and an oxygen saturation of 99% on BiPAP, and his temperature had been down as low as 94.8 degrees F. He was noted to have decreased breath sounds with crackles in the left lower lobe of his lung, non-pitting edema of the upper extremities, and mild pitting edema of the lower extremities. Exam of HEENT was normal, and no skin manifestations were present at this time. Laboratory value abnormalities other than mentioned previously were a lactate dehydrogenase (LDH) elevated at 1689. He was given fluid resuscitation with normal saline, and electrolytes were corrected. Allopurinol was discontinued in light of his ARF. Blood cultures were obtained and empiric antibiotics were started, including ciprofloxacin, ceftazidime and vancomycin. On day seven, posaconazole oral suspension was added for prophylactic prevention of invasive fungal infection, and filgrastim was added to his daily medications for his pancytopenia. On day eight, the patient became diffusely erythrodermic, and vancomycin was discontinued by primary care secondary to the possibility of red man syndrome. The patient developed atrial fibrillation with rapid ventricular rate at 121-211 beats per minute with prolonged QT intervals. The patient was transferred to the intensive care unit and diltiazem titration was initiated. Total parenteral nutrition was started on the tenth day of admission as the patient had intractable nausea, vomiting, mucositis and odynophagia. On physical examination, his temperature was found to be 101.7 degrees F, blood pressure 172/84, heart rate 147 beats/min, respiratory rate 22 and pulse ox 98% on 50% Ventimask. Electrocardiogram again showed atrial fibrillation with a variable ventricular rate range of 129-185 beats/min. His HEENT exam was notable for congested conjunctivae and dry oral mucosa. Skin...
exam was again notable for erythoderma, as well as petechiae on the lower extremities present since admission and a single bulla on the abdomen. An unspecified intertriginous rash was also noted. Blood cultures were still pending, and stool culture and stool for Clostridium difficile were negative. Laboratory values showed pancytopenia, blood urea nitrogen of 34, blood glucose of 300, and serum bicarbonate of 17. SCORTEN was 6 (calculated retrospectively from hospital records). He was diagnosed with neutropenic fever and systemic inflammatory response syndrome (SIRS), with possible sepsis (blood cultures pending). It was felt that the skin findings of erythroderma and the single abdominal bulla were more likely the result of an allergy to vancomycin rather than red man syndrome. It was noted that they doubted Stevens-Johnson syndrome. Linezolid was added along with intravenous metoprolol 5mg every 6 hours, as well IV metronidazole, lorazepam, pantoprazole, diphenhydramine, hydroxyzine, methylprednisolone, and ondansetron. Miconazole powder was prescribed to be applied three times daily, presumably for the unspecified intertriginous rash noted the previous day.

Dermatology was consulted to rule out SJS on the eleventh day of admission. Physical exam revealed diffuse erythroderma of the patient’s face, abdomen and extremities and the majority of his back. Petechiae were present on the upper extremities. Approximately 10% of his back had flaccid bullae, and there were areas of denudation. Multiple tense bullae on erythematous bases, along with ruptured bullae, were located in his intergluteal fold, axilla, antecubital fossae, abdomen (Figure 1), groin, and thigh. The oral mucous membranes had black, eroded crusts (Figure 2).

Perirectal skin had erythema without denudement. Bilateral conjunctivae were erythematous, and yellow crust was adherent to the periorbital skin (Figure 3). His ears were erythematous with yellow exude emerging from the auditory canals. There were bullae on bilateral upper extremities, but there were no bullae on the palms, soles, or dorsal feet at that time. However, petechiae were present on the dorsal aspect of the patient’s feet. Approximate total body surface area (TBSA) with bullae was 15%. Diagnosis of SJS/TEN overlap was made, and STAT ophthalmology and wound care consults were ordered. Initial dermatology recommendation was for the patient to be transferred to a burn unit once stable. Two perilesional 3mm punch biopsies, one for hematoxylin and eosin (H&E) staining and the other for direct immunofluorescence (DIF), were obtained from the patient’s abdomen. His oral cavity was cultured for aerobic, anaerobic, and fungal organisms. A regimen of kanamycin topical, mupirocin, and mineral oil were applied to the body twice daily. SCORTEN was calculated to be 7. Ophthalmology evaluated the patient and agreed he had early ocular involvement secondary to SJS. Conjunctiva had +1 chemosis, subconjunctival hemorrhage, and +1-2 injection. An inferior corneal staining defect was present on second exposure. He was started on AKWA ophthalmic ointment (petroleum jelly, mineral oil, and lanolin), ¼” applied to each eye every 2 hours for aggressive lubrication, and ciprofloxacin ophthalmic 0.3% solution, one drop to each lid margin twice daily for antimicrobial coverage. When reevaluated by dermatology later that morning, bullae were present on approximately half of the patient’s back (Figure 4). The rectum was boggy with yellow crusts and erythema. The scalp also had crusting and denuded areas.

**Figure 1: Abdominal bullae**

**Figure 2: Erosions and crusting of the oral mucosa and labia**

**Figure 3: Erythematous conjunctiva**

**Figure 4: Back and flank with epidermal detachment**

**Figure 5: Left upper extremity with epidermal detachment**

**Figure 6: Massive desquamation of the back**
There were also large areas of epidermal sloughing on bilateral upper extremities with palm involvement (Figure 5). TBSA epidermal detachment was estimated to be 40% (Figure 6). His conjunctiva now showed swelling and injection in addition to previously noted erythema.

The patient subsequently became unresponsive and required cardiopulmonary resuscitation and intubation. At that time, it was obvious that there was sloughing of the esophagus and oral cavity evidenced by the exsanguination during intubation. Transfer to a burn unit would require a greater than one-hour ambulance ride to the facility. Due to a constant need for dialysis for renal failure treatment and unstable atrial fibrillation, transfer to a burn unit was not possible at that time.

On the 13th day of admission, the patient was deemed stable enough for transfer to a burn unit in critical condition. Burn unit hospital records for days 13 and 14 state that the patient required multiple vasoressors to maintain perfusion and that he was started on continuous hemodialysis. He remained severely acidic and poorly perfused, despite aggressive volume resuscitation. He continued to deteriorate, and the family and physicians agreed to withdraw care. The patient expired on day 14.

Histopathology
The two perilesional 3 mm punch biopsies of the abdomen were evaluated by pathology. They showed full-thickness epidermal necrosis with subepidermal clefting consistent with toxic epidermal necrosis. DIF was negative for any immunoglobulin or other protein deposition.

Discussion
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and potentially fatal adverse cutaneous reactions that must be recognized rapidly in order to minimize morbidity and mortality.1 SJS and TEN are currently believed to be diseases in a continuum, based on total body surface area (TBSA) of epidermal detachment.1-5 Clinical symptoms may include a prodromal fever and skin pain, with primary lesions varying in appearance. Distribution of epidermal detachment may be diffuse or localized in addition to mucosal and possibly systemic involvement. Keratinocyte apoptosis leading to epidermal exfoliation is the hallmark of SJS and TEN, and idiosyncratic reactions to medications are implicated in the majority of cases. Several theories describing molecular and immunological mechanisms of this apoptotic process exist, but despite considerable research to identify the precise pathophysiologic mechanism(s) of SJS/TEN, this has yet to be fully elucidated.1,4 A severity-of-illness score, or score-TEN (SCORTEN), based on seven independent prognostic factors of death is used to predict clinical outcome.5 Immediate withdrawal of the offending drug(s), providing supportive care, ideally in a burn unit, and use of a multidisciplinary approach are the mainstays of management.6-8 Additional treatment of SJS/TEN has largely been anecdotal based on case reports in the literature, clinicians’ prior treatment experience, and current understanding of disease mechanisms. Experimental treatments showing variable success are being explored. Some of these experimental therapies may augment supportive care, and a few are aimed at thwarting the proposed disease mechanisms.9-12

Stevens-Johnson syndrome (SJS) was originally described in 1922 as a pediatric mucocutaneous affliction thought to be of infectious etiology.1 SJS later became known as erythema multiforme major (EMM), and the terms were used synonymously from approximately 1983 until more recently.1 Bastuji et al. presented a prospective case-control study on causative factors for severe bullous erythema multiforme (EM), SJS, and TEN, and developed criteria to classify the diseases into five categories. The authors suggested that SJS should be distinguished from EM, but that further investigation was necessary.2 Lyell published a paper in 1956 describing four patient cases characterized by eruptions resembling scalding of the skin and proposing the term toxic epidermal necrolysis.13 But it wasn’t until more cases were described with similar clinical characteristics to those cases presented by Lyell that medications were identified as the primary etiologic agents.1,13 It is now well accepted that SJS and TEN are separate entities and should be distinguished from EM based on different clinical characteristics and etiology, as SJS and TEN are largely associated with medication use and EM is more commonly post-infections.1,16

The incidence of SJS and TEN are estimated to be 1.1 to 7.1 and 0.4 to 1.3 cases per million, per year, respectively.1 The incidence can regionally vary, based on genetics, comorbidities such as immuno-compromised states (malignancy and HIV), and regional differences in medication prescription.1,17 SJS and TEN can occur in patients of any age, and higher average age has been associated with larger percentage of total body surface area (TBSA) of epidermal detachment.1 A study from Germany found individuals of more advanced age (average 63 years) and women to be more at risk for TEN.14 A small retrospective study also found women to be more commonly affected by TEN, but average mean age for development of TEN was younger (22.3 years).15 Mortality rates vary, but an estimated average mortality for TEN is 25-35%, and for SJS is estimated to be 1-5%.6,7,16 Complications and factors leading to high mortality include sepsis, massive transfusional fluid loss, electrolyte imbalances, impaired temperature regulation, and interstitial pneumonitis, which may progress to adult respiratory distress syndrome.7

Medication use strongly correlates with the development of SJS/TEN, and over 200 drugs have been identified.6 Medications are implicated in 72.6% of cases of SJS, an infectious etiology in 10.4% and unknown cause in 17%, according to a review of the literature from 1975 to 2003. This same review established drugs as the causative agents in 76.2% of TEN cases, whereas infection and etiology unknown accounted for 3.2% and 20.6% of cases, respectively.1 Medications observed to have high relative risk based on data from the SCAR study and more recent EuroSCAR study include: sulfonamide antibiotics (especially trimethoprim/sulfamethoxazole), anticonvulsants (carbamazepine, phenobarbital, phenytoin, lamotrigine), non-steroidal anti-inflammatory drugs (NSAIDS) of the oxicam class, allopurinol, and nevirapine.21 Antibiotics are the most commonly blamed medications in the development of both SJS and TEN.1 However, in Europe and Israel, allopurinol was found to be the most common cause of SJS/TEN. This risk was higher for dosages of at least 200 mg daily. Higher risk was also associated with the start of allopurinol in the two months preceding development of SJS/TEN.22 The co-morbid conditions for which our patient was taking an offending medication were diabetes mellitus, gout, migraine headaches, chemotherapy-related nausea and vomiting and ALL. The patient’s medications were analyzed for incidence of SJS/TEN (see Table I20). The importance of rapid recognition of SJS and TEN and identification of possible causes is clear based on the high morbidity and mortality mentioned previously (1-5% of SJS14 and 25-35% of TEN6,16 cases).6,10,14 Typically, SJS and TEN begin four to 28 days after the start of the offending medication, or within the first 2 months for aromatic anticonvulsants, which typically last less than two weeks in the bloodstream. As such, medications providing highly effective anti-epileptic therapy may be contraindicated.3,17,21,22 It is important to note that SJS and TEN are distinct diseases, as the mortality associated with TEN is significantly higher than SJS.16,17 The mortality rate in SJS is 1-5%, whereas that of TEN is 25-35%.16,17 SJS and TEN are separate entities and should be distinguished from EM based on different clinical characteristics and etiology, as SJS and TEN are largely associated with medication use and EM is more commonly post-infections.1,16
Table I: Cutaneous reactions associated with medications that were administered to the patient in the above case report.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half Life</th>
<th>Reported Skin and other relevant reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>1-3 hours</td>
<td>Rash (&gt;10%); SJS (&gt;10%); TEN reported, cutaneous reactions (severe), oral ulcerations, and stomatitis reported</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>0.5-1 hour</td>
<td>Erythoderma reported; pruritus (1-10%); rash (1.5%); SJS (&lt;1%); TEN (&lt;1%)</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Initial: 10-15 minutes</td>
<td>Pruritus (1-10%); rash (&gt;10%); TEN reported; anal ulceration (&gt;10%); oral ulceration (&gt;10%)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.5 hours</td>
<td>Bullous eruptions (&lt;1%); SJS (&lt;1%); TEN (&lt;1%); ulcerative stomatitis (&lt;1%)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3-4 hours</td>
<td>Pruritus (1-5%); exfoliative dermatitis, and TEN reported</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>2-8 hours</td>
<td>SJS (&lt;1%); TEN (&lt;1%); rash (&gt;1%); pruritus (3-9%); stomatitis (&gt;1%)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4 hours</td>
<td>Bullous eruption reported; SJS (&lt;1%); TEN (&lt;1%); pruritus (&lt;1%); vaginitis (&lt;1%)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1-2 hours</td>
<td>SJS (2%); TEN (2%); pruritus (2%)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4-7 hours</td>
<td>Rash (1-10%); TEN (&lt;1%); pruritus and SJS reported</td>
</tr>
<tr>
<td>Vincristine</td>
<td>24 hours</td>
<td>Rash (1-10%); oral mucosal lesions (1-10%); oral ulcerations (1-10%)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>α-phase 0.6 hours; β-phase 16.7 hours</td>
<td>Stomatitis (&gt;10%); mucositis, oral mucosal, and oral ulceration reported</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3-10 hours</td>
<td>Pruritus (1-5%); rash (1-3%); SJS reported; TEN (&lt;1%)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5-11 hours</td>
<td>Bullous eruption, and TEN reported; red man syndrome (1-10%); SJS (&lt;1%)</td>
</tr>
</tbody>
</table>

Table II: Clinical spectrum of SJS, SJS-TEN overlap, and TEN

<table>
<thead>
<tr>
<th>Clinical Entity</th>
<th>SJS</th>
<th>SJS-TEN overlap</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>% TBSA* detachment</td>
<td>&lt;10</td>
<td>10-30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Primary lesions</td>
<td>Dusky red lesions</td>
<td>Dusky red lesions</td>
<td>Poorly delineated erythematous plaques</td>
</tr>
<tr>
<td></td>
<td>Flat atypical targets</td>
<td>Flat atypical targets</td>
<td>Epidermal detachment (spontaneous or by friction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dusky red lesions</td>
<td>Flat atypical targets</td>
<td>Dusky red lesions</td>
</tr>
<tr>
<td></td>
<td>Flat atypical targets</td>
<td></td>
<td>Flat atypical targets</td>
</tr>
<tr>
<td>Distribution</td>
<td>Isolated lesions</td>
<td>Moderate confluence on face and trunk</td>
<td>Much confluence on face, trunk, and elsewhere</td>
</tr>
<tr>
<td></td>
<td>Minimal confluence on face and trunk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td>At least 2 mucosal surfaces involved</td>
<td>At least 2 mucosal surfaces involved</td>
<td>At least 2 mucosal surfaces involved</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Usually</td>
<td>Always</td>
<td>Always</td>
</tr>
</tbody>
</table>

74 THE IMPORTANCE OF RAPID RECOGNITION AND MANAGEMENT OF STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS IN ADULT PATIENTS
It is recommended that all medications be considered suspect regardless of duration of therapy.7

In this case report, the medication causing SJS/TEN in our patient was not clear. Of note, our patient had a past medical history of gout, for which allopurinol was used as treatment. This medication was being taken prior to hospital admission for several years. As mentioned previously, the cause of SJS and TEN may not be identifiable in a significant number of patients.1 Individuals may be on several medications when they develop cutaneous signs worrisome for the development of a drug reaction, and they may be on more than one medication associated with the development of SJS/TEN. Although medications are the most frequent agents to cause SJS/TEN, it is important to keep in mind other less commonly associated causes. Infection, vaccination, systemic disease, physical agents, and foods are associated with the development of SJS. In addition to medications, food additives, fumigants and contact with chemicals have also been reported to cause TEN.1,7

SJS and TEN are considered to represent two ends of a clinical spectrum of cutaneous disease, differing in severity. Histological findings are indistinguishable between SJS/TEN, and the causative drugs are similar. They are differentiated based on extent of TBSA (total body surface area) of detached epithelium, appearance and distribution of primary skin lesions, mucous membrane, and systemic involvement.3 The accepted criteria defines SJS with less than 10% TBSA epidermal detachment, TEN with greater than 30% TBSA detachment, and SJS-TEN overlap with 10%-30% TBSA affected (see Table II). When measuring TBSA, both detached and detachable epidermis should be included.1,3,7

Despite considerable research to identify the precise pathophysiologic mechanism of keratinocyte apoptosis leading to necrosis in SJS/TEN, it has yet to be fully elucidated. It is currently proposed to be an immune-mediated mechanism since, as mentioned previously, re-challenging an individual with a drug can lead to rapid recurrence of SJS/TEN.3 Several theories describing the molecular mechanism of apoptosis in SJS/TEN exist, including the involvement of the death receptor Fas and its ligand, FasL, tumor necrosis factor (TNF)-α, cytotoxic T lymphocytes (CTLs), perforin, and granzym.1,3,17,32 Cell death via apoptosis is an organized process possible through several mechanisms including ligation of cell surface death receptors such as tumor necrosis factor (TNF)-α, Fas, or through receptor-independent mechanisms, primarily through the release of perforin and granzyme B from cytotoxic T cells. The most well accepted theories point to the Fas-FasL interaction or to cytotoxic T cells as the mediators of apoptosis in SJS/TEN.4

Genetic susceptibility has been shown to play a role in the development of SJS/TEN. HLA-B*1502 and carbamazepine in this same population; however, it should be noted that this allele is not an independent population marker for SJS/TEN in patients exposed to carbamazepine, as it has since been associated with exposure to phenytoin and lamotrigine.7 Other HLA alleles shown to be associated with increased susceptibility for the development of SJS/TEN are HLA-B12 and HLA-DQB1*0601.21

Clinically, a prodrome that may include a fever with malaise, cough, stinging eyes, and headache precedes the onset of cutaneous lesions by a few days to two weeks.6,2 Tender cutaneous lesions, described as irregularly shaped, dusky-red or purpuric macules, generally first appear on the trunk, and then spread symmetrically to the neck, face, and upper extremities. The palms and soles are sometimes an early site of involvement.3 Distal upper and lower extremities are infrequently affected, and the scalp is typically spared.1 Progression to a vesiculobullous eruption with variable levels of lesion confluence follows, and full-thickness epidermal necrosis, as a result of keratinocyte apoptosis, can occur rapidly. The bullae are typically flaccid and are the result of fluid filling the spaces where the epidermis has detached. When involved epidermis is subject to any slight trauma, it tends to tear and has been described as resembling “wet cigarette paper.”23 Clinically appearing involved tissue where epidermal detachment has not occurred can be lightly stroked with a finger to induce epidermal separation, a positive Nikolsky sign. It should be noted, however, that

<table>
<thead>
<tr>
<th>Independent Risk Factors</th>
<th>Point score</th>
<th>Total Points</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 years</td>
<td>1</td>
<td>0-1</td>
<td>3.2</td>
</tr>
<tr>
<td>Malignancy present</td>
<td>1</td>
<td>2</td>
<td>12.2</td>
</tr>
<tr>
<td>BSA detached &gt; 10%</td>
<td>1</td>
<td>3</td>
<td>35.3</td>
</tr>
<tr>
<td>Heart rate &gt; 120 beats/min</td>
<td>1</td>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>Serum urea nitrogen &gt; 28 mg/dL</td>
<td>5-7</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Serum glucose &gt; 252 mg/dL</td>
<td>1</td>
<td>SI (Système International) units: Serum urea nitrogen &gt; 10 mmol/L, Serum glucose &gt; 14 mmol/L, Serum bicarbonate &lt; 20 mmol/L</td>
<td>Mortality (%)</td>
</tr>
<tr>
<td>Serum bicarbonate &lt; 20 mEq/L</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SHAMA, LOWENBRAUN, SILVERTON 75
Although used in the diagnosis of SJS/TEN, the Nikolsky sign is not specific. This acute epidermal sloughing phase of TEN lasts for eight to 12 days. Systemically, mucositis can occur on conjunctiva, respiratory tract, gastrointestinal tract, and vaginal and perineal mucosa. Mucous membrane involvement is present in 90-100% of cases, and ocular complications, usually involving the cornea, conjunctiva, and eyelids, has been reported in 60-84% of cases. This mucosal involvement helps to distinguish SJS/TEN from TSS, SSSS, and some immunobullous disorders. Visceral involvement may be overlooked, which contributes to high morbidity and mortality in SJS/TEN. The frequency of visceral involvement (gastrointestinal mucosa, tracheal or bronchial erosions, glomerulonephritis, and hepatitis) is from 8.1% to 61.5%. Depending on how widespread the epidermal necrosis, re-epithelialization may begin within one to three weeks, but could take as long as three to six months to fully heal. The skin generally heals without scarring when no infection is present, but pigmented changes are reported in 88% of patients.

Diagnosis relies not only on the initial high index of suspicion, progressive skin lesions, TBSA, and presence of two or more regions of mucosal involvement as described previously, but also on histological features. Two to three 4mm skin punch biopsy specimens should be taken. One biopsy is sent for immediate frozen section for emergent diagnosis, if available; another for formalin-fixed hematoxylin and eosin staining; and a third biopsy for immunofluorescent studies to exclude immunobullous diseases. Histologically, in early lesions (prior to dermal-epidermal separation) of SJS and TEN, there are scattered apoptotic keratinocytes in basal and suprabasal layers of the epidermis, which can be a warning sign that epidermal necrolysis and detachment are impending. Later lesions (after epidermal detachment) show full-thickness epidermal detachment with splitting above the basement membrane, minimal inflammatory infiltrate, and normal immunofluorescence.

Bastuji et al. in 2000 developed a now widely used severity-of-illness score for TEN (SCORTEN), based on seven independent prognostic factors of death. It is useful for predicting clinical outcomes, where a SCORTEN of 0-1 confers 3.2% mortality, and a score of 5 or greater predicts 90% mortality (Table III). It is recommended that SCORTEN be calculated within the first 24 hours of admission, and then again on day three.5,20 Our patient's initial score was 6. Calculation on day three was 7. In addition to these seven prognostic factors, neutropenia, lymphopenia, and thrombocytopenia in TEN are associated with poor outcome. Factors contributing to higher mortality in general for SJS/TEN are patient age, number of medications, neutropenia, lymphopenia, thrombocytopenia, and extent of exfoliation. As described in the present case, our patient was not only on multiple medications but also had B-cell type ALL and remained pancytopenic throughout his hospitalization.

The differential diagnoses for SJS/TEN include: staphylococcal scalded skin syndrome (SSSS), drug hypersensitivity/DRESS syndrome, linear IgA bullous disease, toxic shock syndrome (TSS), and erythema multiforme (EM). SSSS affects children more commonly than adults, has no mucosal involvement, and histologically the detachment is in the stratum granulosum; in SJS/TEN, mucositis is prominent, and histologically, epidermal separation is at the basement membrane. Erythematous drug eruptions usually lack mucosal involvement and the skin pain common in SJS/TEN. Linear IgA bullous disease less frequently presents with mucous membrane involvement, and it can be further excluded on immunofluorescent study. TSS presents with more prominent involvement of multiple organ systems and is caused by toxin-releasing strains of group A streptococci and Staphylococcus aureus. EM and SJS have primary lesions that appear similar, although rarely, and EM primary lesions are described as “targetoid.” Although red man syndrome is associated with erythroderma, it usually presents on the back of neck, occasionally spreading to upper trunk, face and arms. It is not a diffuse erythroderma and does not continue to form bullae.

Immediate withdrawal of the offending drug (when implicated), aggressive supportive care, ideally in an intensive care or burn unit, and a multidisciplinary approach are the mainstays of management. Acute management of SJS/TEN should also include determination of the severity and prognosis of the disease (Table III) so that further management can be directed. Interestingly, it was found that rapid withdrawal of the offending drug only affected outcome when the drug had a short half-life (T1/2), and there was no difference when drugs with long half-lives were removed early on or late in management. Supportive care includes wound care, fluid and electrolyte management, temperature regulation, nutritional support, ocular care, pain control, and monitoring for infection. Wound care should be treated conservatively with non-adhesive, loosely draped dressings and avoidance of debridement (commonly performed in burn units). Ophthalmology involvement is essential in the care of patients with SJS and TEN. A significant number of patients (60-85%) have ocular involvement, with chronic problems remaining in 35%, a prevalence of ocular morbidity that has remained unchanged for the past 35 years. Additionally, according to a recent retrospective observational case series by Morales et al., SCORTEN is not useful to predict ophthalmic complications, further necessitating ophthalmology participation in the care of these patients. Topical antibiotics and corticosteroids, along with frequent lubrication are commonly provided. Amniotic membrane transplantation has been successfully used for treatment of severe corneal involvement. Therapy used in the treatment of SJS/TEN is largely anecdotal based on case reports describing successful modalities and on our current understanding of molecular mechanisms to date. Corticosteroid treatment of SJS/TEN is not universally accepted. Some authors state that steroids do not alter the course of disease and actually increase risks for complications such as prolonged wound healing and increased risk of infection, and place patients at risk for gastrointestinal bleeding. However, others believe that short-term high-dose steroids, such as prednisone at 2mg/kg/day for a short course of 7-10 days, very early on in the disease may improve survival, and there have been a few cases of TEN treated with dexamethasone pulse therapy early. Our patient was treated with dexamethasone as part of his hyper-CVAD induction chemotherapy for treatment of his ALL.

Although the use of intravenous immunoglobulin (IVIG) and cyclosporine for SJS and TEN have not been fully researched, reports of their benefits in general suggest they should be considered. Serum Fas ligand (FasL), a transmembrane protein responsible for apoptosis, has been found to be increased in patients with SJS/TEN demonstrated rapid clinical improvement using cyclosporine A (Csa)
Interleukin (IL)-2 has been demonstrated in blood samples of patients with TEN and has been found to promote inflammation through its receptor CD25 and the activation and proliferation of lymphocytes in skin lesions. CsA inhibits IL-2, therefore preventing its pro-inflammatory action. CsA was demonstrated to shorten the duration of active disease and time to complete re-epithelialization. Treatment using plasmapheresis and cyclophosphamide have more conflicting levels of effectiveness, and thalidomide was shown to increase mortality in patients with TEN.

Although the mainstay of treatment for SJS/TEN at this time is early recognition and supportive treatment, it is difficult to determine the most effective management of SJS/TEN for several reasons. As SJS/TEN are likely immune-mediated processes, drug re-challenge with a suspected medication is not an option. In addition, our knowledge of treatment options to date is based on retrospective case studies, and these are generally limited by small sample size. Once a therapy is found to be effective, a larger, randomized controlled clinical study will be needed to conduct to confirm its effectiveness. Survivors must be educated of their medical caretakers of their history and avoid medications if found to be the cause of their SJS/TEN and should be counseled to advise their medical caretakers of their history of SJS/TEN. The US FDA currently recommends screening Asian patients for the HLA-B∗1502 allele prior to the initiation of carbamazepine due to the casual association found between carbamazepine use and SJS/TEN in this population.

Literature search and data sources

Medline searches for Stevens-Johnson syndrome, toxic epidermal necrolysis, and Stevens-Johnson syndrome and toxic epidermal necrolysis were performed. Several clinical case reports and reviews of the current literature were provided. Also searched for the previously mentioned topics were Cochrane Database of Systematic Reviews, which produced a single article, and UpToDate. A search of evidence-based guidelines from the National Guidelines Clearinghouse and the United States Preventive Services Task Force did not provide any results. Search date range: March 2011-May 2011.

References

ABSTRACT
We report a case of an 11-month old Caucasian male who presented with a persistent reddish-orange macular discoloration of the central face that bridged multiple papules on bilateral cheeks as well as red, orange and tan papules diffusely scattered over the torso. The clinical features were not typical of either classic juvenile xanthogranuloma or benign cephalic histiocytosis. These non-Langerhans cell histiocytoses have been described as separate pathologic entities. However, based on the history, physical examination, and skin biopsies, we support the theory that these disorders may be a continuous spectrum of disease, as our patient had overlapping features of both juvenile xanthogranuloma and benign cephalic histiocytosis.

Case Report
An 11-month-old boy presented for evaluation of a six-month history of a persistent, reddish-orange macular discoloration of the cheeks. Soon after this eruption appeared, the patient developed a solitary papule on his forehead, with subsequent development and expansion of numerous papules over his arms, legs and torso.

The child was the product of artificial insemination from a sperm donor and a mother on levothyroxine for hypothyroidism. His birth history was significant for being large for gestational age (birth weight 5.3 kg / 11.7 lbs). He had no known drug allergies and took no medications. There was no personal or family history of celiac disease, thyroid cancer, neurofibromatosis or optic pathway gliomas.

Physical examination revealed a well-appearing Caucasian male. Bridging multiple 1-3mm papules on bilateral cheeks was a yellowish-orange macular confluent discoloration of the central face (Figure 1). Diffusely scattered 1-3mm red, orange and tan papules were concentrated over both upper and lower extremities and were scarce on the abdomen, lumbosacral and gluteal regions (Figures 2, 3). The remainder of the physical examination was appropriate for age.

A biopsy of the right cheek, performed by another dermatologist several months earlier, was consistent with juvenile xanthogranuloma, displaying Touton giant cells. The patient was referred for further evaluation and treatment.
cells and mixed inflammatory infiltrate with lymphocytes and eosinophils. Punch biopsies of the distal and proximal forearm of both macular and papular areas were performed. The histopathology revealed a dermal histiocytic infiltrate, containing xanthomatous histiocytes with a few lymphocytes and eosinophils, and an absence of Touton giant cells. CD68 immunoperoxidase stains were positive, whereas CD1a was negative for both lesions. These findings were consistent with benign cephalic histiocytosis.

Biopsies of the upper gastrointestinal tract revealed mild esophagitis and mild chronic gastritis; duodenal biopsy was negative for Langerhans cell histiocytosis. Laboratory tests, including complete blood count, metabolic and lipid profiles, sedimentation rate and serum protein electrophoresis, were all within the normal range. Ophthalmology and oncology were also consulted; their findings revealed no abnormalities.

Because of the intense redness associated with his cheek and extremity lesions, a single treatment with pulsed dye laser (Candela Perfecta, 8.75J/cm²) was given to all of the areas. It was not beneficial.

The clinical features of diffusely scattered red-orange and tan papules with unusual reddish-yellow macules and patches bridging the papules are not typical of either classic juvenile xanthogranuloma (JXG) or benign cephalic histiocytosis (BCH). It has recently been theorized that JXG and BCH may be part of the same clinical spectrum. Based on our patient's findings, we support this theory, as our patient had overlapping features of both JXG and BCH.

**Discussion**

A benign proliferation of histiocytic cells, non-Langerhans cell histiocytoses (non-LCH) arise from a monocyte/macrophage or dermal dendritic cell lineage, recognized immunohistochemically by the expression of factor XIIIa, CD68, CD14, CD11b, lysozyme and vimentin. The absence of Birbeck granules ultrastructurally and lack of CD1a surface antigen and S100 protein expression distinguish non-LCH from Langerhans cell histiocytoses. The main types of non-LCH include benign cephalic histiocytosis, juvenile xanthogranuloma, xanthoma disseminatum, and generalized eruptive histiocytomas. Although they have been described as separate pathologic entities, recent reports indicate that these disorders may rather be a continuous spectrum of disease categorized as non-Langerhans cell histiocytoses.

Juvenile xanthogranuloma (JXG) is the most common histiocytosis of childhood. There is a slight male predominance, and almost 75% appear during the first year of life, although it may be present at birth or appear in adulthood. The micronodular variant presents with widely scattered, asymptomatic, pink-to-red-brown, 2-5mm dome-shaped papules that rapidly turn yellow-orange in color. JXG lesions are most commonly seen on the head and neck, and may extend to the upper torso as well as upper and lower extremities. Extracutaneous sites of involvement may include ocular, pulmonary, hepatosplenic, musculoskeletal and central nervous systems. Unilateral lesions of the iris are rare but may present prior to 2 years of age with potential complications such as heterochromia, hyphema, glaucoma, and rarely blindness. Classic histologic findings are foamy “xanthomatous” histiocytes and Touton giant cells within the papillary dermis. These lesions also stain positively with HAM56, CD68 and factor XIIIa and are generally negative for CD1a and S100. Spontaneous involution with resultant atrophic scars occurs over 3 to 6 years. Although JXG is usually benign and limited to the skin, due to the potential for extracutaneous involvement it is prudent to monitor these patients and refer for ophthalmologic evaluation.

Benign cephalic histiocytosis is a rare histiocytic proliferative disorder, affecting generally healthy young children within the first 3 years of life without pre-dilection. Multiple asymptomatic, 2-5mm red-brown macules and papules initially present on the cheeks, progressing toward the ears and rest of the face. Lesions may then appear on the trunk and extremities, but are infrequently found on the buttocks or thighs. The mucous membranes, acral surfaces and viscera are spared. Histologic and ultrastructural studies reveal a well-circumscribed dermal histiocytic infiltrate with cytoplasmic worm-like bodies and desmosome-like junctions between histiocytes. Touton cells are absent; foamy cells and multinucleate giant cells are rarely observed in early lesions, but xanthomatization can occur with time. Histiocyes express CD11b, CD14, CD68, HAM56 and factor XIIIa but are negative for CD1a and S100. Most children have a self-limited course without internal organ involvement. Resolution with flattening and hyperpigmentation of the papules occurs after a mean of 26 months from onset. An association with diabetes insipidus has been reported, thus clinical monitoring is recommended.

**Conclusion**

Distinction between multinodular JXG and BCH is dependent upon the correlation of clinical and histopathologic findings. Overlap of these two entities has also been reported, suggesting that benign cephalic histiocytosis may in fact be an early variant or aborted phase of juvenile xanthogranuloma. Our patient's findings were most consistent with this overlap of long-standing multinodular JXG and BCH.

**References**

ABSTRACT

Tinea corporis is a common fungal infection of the glabrous skin that classically presents as an erythematous annular plaque with central clearing and an advancing, raised border. We present a case of a highly atypical manifestation of tinea corporis: bullous tinea corporis secondary to Trichophyton tonsurans.

Case Presentation

A 31-year-old African American female presented with an 8-month history of disseminated papules and plaques that would turn into vesicles and fragile bullae within days of their appearance. The lesions were focused mainly over her extremities and upper chest, and tended to follow a 3-week progression. Flat-topped reddish papules and plaques of variable shapes and sizes progressed into fragile vesicles and bullae ranging from nickel- to quarter-size that would rapidly break and drain clear fluid. Scales and crust formation soon developed after that. Post-inflammatory hyperpigmentation patches marked areas of resolution. The patient was asymptomatic with the exception of pruritus during the papular phase of lesion development.

The patient recalled that her symptoms began when she was staying in multiple hotels on a family vacation. Of note, the patient's husband and two male children began exhibiting similar symptoms during the same period. Past medical histories were unremarkable for all members of the family. They did not own any pets. All family members experienced temporary improvement but not complete clearance following a 10-day course of trimethoprim-sulfamethoxazole (prescribed by their primary care provider after aerobic cultures revealed a few Staphylococcus warneri, which were later determined to be contaminants).

Examinations revealed few-to-sporadic, mildly crusted or significantly scaly flat-topped eczematous papules and small plaques asymmetrically distributed on the patient's neck, shoulders, upper extremities, and back. No bullae were visualized, but two lesions had slight vesiculation at borders and a few crusted lesions appeared to be sequelae from preceding small bullae (Fig. 1). Patches of hyperpigmentation were evident at sites of resolved lesions. No scarring was noted.

The initial differential diagnosis included bullous impetigo, eczematosid dermatitis, papular urticaria (attributed to possible arthropod bites from hotel infestation at time of symptom onset), and pityriasis lichenoides. The patient was prescribed a 2-week course of trimethoprim-sulfamethoxazole and a decolonization regimen for her family. She demonstrated no improvement and even developed new lesions while on the medication. Additional bacteriologic cultures of the affected areas and nares were negative.

Fungal cultures were performed on the patient's children, whose inflammatory papules were isolated to their hairline, occiput, and posterior neck. Trichophyton tonsurans (the leading cause of tinea capitis in the United States) was isolated from both children. Further questioning of the family revealed that the patient would frequently use the same clippers to cut her children's and husband's hair at home. Despite the highly atypical appearance, the patient's bullae were cultured for fungus, and a punch biopsy of a new plaque was performed.

Histologic examination showed compact keratosis with focal areas of parakeratosis. The epidermis was mildly spongiotic. Marked papillary dermal edema was noted. The mid-dermis displayed perivascular lymphohistiocytic infiltrates, characterized by rare neutrophils and eosinophils (Fig. 2, 3). Both periodic Acid-Schiff and Grocott methenamine silver stains (Fig. 4, 5) revealed multiple hyphae in the stratum corneum. Fungal culture confirmed Trichophyton tonsurans from the patient, as well.

Treatment of the patient and her family with oral terbinafine 250mg daily for four weeks resulted in rapid improvement and complete resolution of all skin lesions.

Discussion

Tinea corporis is a fungal infection of the face, trunk, or limbs caused by dermatophytes of the Microsporum, Trichophyton,
or Epidermophyton genera. Following an incubation period of 1-3 weeks, the dermatophytes invade, attacking the top layer (stratum corneum) of the skin, hair, and nails, surviving only on dead keratin.\(^2,3\) Invasion typically occurs in a centrifugal pattern, creating the classic presentation of an erythematous annular plaque with central clearing and an advancing, scaly raised border.\(^4\) Although vesicles and pustules may be seen in inflammatory cases, frank bullae are exceedingly rare. Less than 15 cases of bullous tinea corporis have been reported in the literature.\(^2,5,6,7,8\) Our patient represents the second ever reported case of bullous tinea corporis caused by Trichophyton tonsurans (the first case was reported by Azfar et al. in 2009).\(^9\)

Bullous dermatomycoses can be easily misdiagnosed as allergic bullous impetigo, contact dermatitis, herpes simplex, and dishydrotic eczema. In all reported cases (including ours), the correct diagnosis was established only after biopsy and culture of the lesions. Delay of these simple tests can result in a missed diagnosis and prolonged treatment course. A high index of suspicion is necessary to prompt the examining physician to search for fungi in atypical bullous lesions. As demonstrated in all cases of bullous tinea corporis, the value of a fungal culture and biopsy cannot be underestimated when investigating the cause of refractory bullous eruptions.

References
