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With the help of the Education and Evaluation Committee and with the support of the AOCD office, the JAOCSD is making real progress. The AOCD requires that all residents in AOCD-approved programs submit their annual papers for consideration for publication to a scientific journal of their choice. We are very excited that the AOCD residents have, for the most part, chosen to submit their annual manuscripts to the JAOCSD for consideration for publication.

The residents have enjoyed seeing their efforts come to life in the JAOCSD. More medical students, interns and residents are co-authoring great cases and reviews of the literature with members of our college. We would like to encourage all of our members to present interesting cases and dermatologic pearls that seem to have been proven true over the years.

Technology, in the way of electronic health records, employee management, and digital medical transcription, makes for a great topic for discussion in our journal. New innovations, rediscovery of previously discussed topics, and practice-management tips all make for interesting contributions to the JAOCSD. There are so many ways for every member of our college to participate. Don’t put it off any longer; it’s time to get published. It is refreshing and makes you feel younger!

We continue to have the unwavering support of our sponsors. We could have the best material for our journal, but without sponsor support the JAOCSD would remain nothing more than a dream. Our sponsors continue with their commitment to our residents and to our membership by sponsoring the JAOCSD.

We are thankful to have Allergan Skin Care, Global Pathology Laboratory, Medicis-The Dermatology Company and Stiefel Laboratory as sponsors of the JAOCSD. They continue their commitment to the dermatology profession and support the AOCD in all of its endeavors.

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

Stanley E. Skopit, D.O., F.A.O.C.D. (Editor)
James Q. DelRosso, D.O., F.A.O.C.D. (Associate Editor)
Dear Fellow & Resident AOCD members,

There is no question that non-cosmetic dermatology remains an underserved specialty in medicine. The average wait time to see a board-certified dermatologist for a suspicious growth on the skin is about six weeks; the average wait time to have Botox Cosmetic injected by a board-certified dermatologist is about two weeks. As osteopathic dermatologists, we need to remember why we have become such a strong profession. The osteopathic profession has always prided itself on treating the whole patient and not just the presenting disease process. We have always kept the patient’s best interests as our core value. This should never change.

Monetary pressure is increasing on all physicians today. This stems from the increased cost of practicing medicine and decreased reimbursements for services rendered. It should be no surprise that physicians are looking for ways to maintain their revenue stream while practicing the specialty they have chosen, and one way to do so is to offer cosmetic procedures. There is now tremendous competition for the cosmetic dollars spent in this country. We see emergency room physicians, OB-GYN physicians, pediatricians and dentists offering cosmetic services. This includes Botox Cosmetic, facial fillers and lasers and lights. I attended a Contour Thread course (while they were still available) and had a gastroenterologist as my cadaver mate in the anatomy lab!

There is something wrong with this whole picture. We as board-certified osteopathic dermatologists need to stay focused. We need to remember that we are the only specialty that is fully trained to treat the skin, hair and nails, while still remembering that we are treating a patient and not a disease process. In my previous medical career, I was a board-certified facial plastic surgeon. I never knew what I didn’t know about the skin until I had completed a three-year residency in dermatology. I urge our profession to stay focused on what is most important: dermatology, treating our patients, and treating our patients as people who happen to have an issue with their skin, hair or nails. They will know that we care about them, and they will seek our expertise when it comes to their cosmetic concerns also.

The AOCD has come a long way since inception in 1957. Our college was then recognized as a separate specialty within the American Osteopathic Association. There are now more than 450 members and 19 residency programs throughout the United States training 89 residents. The AOCD is the organization responsible for residencies, board certification and continuing medical education for our specialty nationwide. I will be working with the Education and Evaluation Committee to improve our in-training examination process over the next year.

As President of the AOCD, my goals and objectives will revolve around strengthening our college. I will continue to work to make the JAOCD more reflective of our college. I will seek to take actions that will allow our members and our resident members equal status in our local, state and national dermatology organizations. We will continue, though our current diplomatic efforts, to make the American Academy of Dermatology our ally in education, social and economic endeavors. I am looking forward to an exciting and challenging year.

*Jay Gottlieb, DO, FAOCD, FOCOO*
Case Report

A 52-year-old, black female presented to our clinic with the complaint of rough, painful lesions on the palms of both hands and lower extremities for many years (Fig. 1, 2). For the last year, the lesions had become very painful. No treatments had been tried for the condition other than topical moisturizers. A review of her history revealed that the patient had grown up in an area of Florida where the only drinking water came from a well.

Clinical exam demonstrated thick, firm, punctate, brown, keratotic papules on bilateral palms, soles and lower extremities. Lab studies consisting of CBC, CMP, lipid profile and CXR were obtained, all of which were within normal limits. Skin biopsy was performed to confirm the working diagnosis of arsenical keratosis.

The biopsy demonstrated epidermal hyperplasia with hyperkeratosis and underlying dermis with sparse, perivascular, predominantly lymphocytic infiltrate. These histopathologic findings can be seen in arsenical keratosis. There were no atypical cells and no malignancy noted in this specimen.

The patient was initially started on topical keratolytics. On follow-up, the patient reported minimal relief of pain and slight improvement of lesions. Labs were then drawn for liver function, and she was started on acitretin 25 mg qd. She is currently pending follow-up.

Discussion

Arsenic is ranked first in a list of 20 hazardous substances by the Agency for Toxic Substances and Disease Registry and the United States Environmental Protection Agency. It has been classified by the International Agency for Research on Cancer as a human carcinogen. Arsenic is found widely distributed in the earth’s crust and may be introduced into water sources through dissolution. Long-term exposure to contaminated drinking water is the most common cause of chronic arsenic poisoning. Exposure also occurs from industries that use arsenic in the manufacture of goods. This includes mining, smelting, and the manufacture of paint, pesticides, glass, plywood and semiconductors. Exposure also occurs in the sheep industry, which may employ an arsenic-based “sheep dip” as an insecticide/fungicide.

Arsenic is also present in the air due in part to the combustion of fossil fuels. Chronic arsenic poisoning is a growing health problem in regions of India and Taiwan. It is estimated that 200,000 to 250,000 cancer deaths in Bangladesh will be caused by arsenic in drinking water.

Arsenic has been used as a medication for more than 4,000 years and is still used today in Chinese proprietary medications. Historically, arsenic-containing medications such as Fowler’s solution (1% solution of potassium arsenate), Donovan’s solution (arsenic triiodide), de Valagin’s solution (arsenic trichloride), Salvarsan (arsphenamine), Sin Lak Asthma Pill and Bell’s asthma medication were used in the treatment of many ailments including but not limited to rheumatism, arthritis, malaria, trypanosome infections, tuberculosis, diabetes and asthma. Recently, arsenic trioxide (Trisenox) has been approved for the treatment of acute promyelocytic leukemia.

Arsenic has two forms: organic and inorganic. Organic arsenic is found abundantly in seafood but is readily excreted from the body. Inorganic arsenic has two forms: trivalent arsenite (As III) and, less commonly, pentavalent arsenate (As V), both of which are considerably toxic to humans.

As early as 1887, Hutchinson reported the correlation between arsenic intake (via medications containing arsenic) and the development of cancer. Arsenic has been documented to induce lung, kidney, liver, urinary bladder, and skin cancer. It also has noncancerous effects such as diabetes, peripheral neuropathy, cutaneous lesions and cardiovascular diseases. Skin cancers associated with arsenic are Bowen’s disease, basal cell carcinoma, and squamous cell carcinoma. In addition, Merkel cell carcinoma has been reported with chronic arsenicism in endemic regions of Taiwan.

The exact way in which arsenic exerts its toxic effects and clinical manifestations is not completely understood. However, three mechanisms have come to the fore: oxidative stress, chromosomal abnormalities and altered transcription factors. These
Reactive oxygen species, specifically peroxyl radical, superoxide radical and hydroxyl radical, are proposed to occur during the methylation process of inorganic arsenic. In human skin, arsenic can induce oxidative damage in cellular DNA and generate 8-hydroxy 2′-deoxyguanosine (8-OHdG) oxidative DNA adducts. Studies on arsenic-induced Bowen’s disease show that the increased 8-OHdG levels are positively correlated to the lesional arsenic concentration, suggesting the involvement of oxidative stress in arsenical skin carcinogenesis.

Arsenic is reported to increase chromosomal aberrations and sister chromatid exchanges and cause endoreduplication, as well as inhibit the incision step and ligation step of the DNA repair system. This has been shown to interfere with genome stability of the cells. Furthermore, arsenic enhances the mutagenicity of carcinogenic stresses such as UV, X-ray and chemical agents.

Skin lesions, occurring after a few years of exposure, are almost always the first clinical sign of chronic arsenicism. The most common clinical cutaneous manifestations of chronic arsenicism are hypopigmentation, hyperpigmentation, multiple keratoses, basal cell carcinoma, squamous cell carcinoma and Bowen’s disease. Mees’ lines, though rare, have been noted to occur in both chronic and acute arsenicism.

The differential diagnosis for arsenical keratosis is quite extensive, including but not limited to clavus, trichophytosis, pityriasis rubra pilaris, keratoderma climacterium (Hashthausen’s disease), lichen simplex, syphilis, hypothyroidism, leprosy, neoplasms of the breast, multiple myeloma and lymphoma. Also, there are many genetically present that manifest with similar clinical findings, including diffuse tylosis, Howell Evans syndrome, mutilating keratoderma, progressive keratoderma, Mal de Meleda syndrome and Mees’ lines.

The key to clinical management begins with suspicion of chronic arsenic exposure. Management should include a complete history, including where the patient was born and lived as a child. History of exposure to contaminated well water, arsenic containing medications or an industrial setting that routinely uses arsenic needs to be obtained. Medical database should include a CBC, CMP, chest X-ray, urinalysis, EKG, electromyography (if patient has polyneuropathy) and skin biopsy of a sample lesion. Chemical analysis of arsenic levels in tissue, hair or nails may be done, but levels may be normal if exposure is not recent. A point to remember is that if a young patient presents with skin cancer (BCC, SCC or BD) on a non-sun-exposed area, chronic arsenicism should be suspected.

There are few studies in the treatment of chronic arsenicism. Oral retinoids have been the most studied group of agents.

Retinoids have anti-keratinization, antiproliferative, and anti-inflammatory properties and have been effective in near-complete clearing of arsenical keratosis lesions. Topical fluorouracil has also been used successfully. As of yet, there is no set dosing regimen for either agent in regards to chronic arsenicism. The chelating agent dimercaprol, or BAL (British anti Lewisite), is also commonly used for treatment of acute arsenic toxicity. It has been tried in the chronic form, but, as is the case for the other medications, there are no established biologic criteria or measures of effectiveness.

In conclusion, arsenical keratosis is a condition caused by chronic exposure to inorganic arsenic, most commonly from contaminated well water, arsenic containing medications and industrial arsenic use. Physicians should consider this disease in their differential any time a young patient presents with consistent history and clinical findings, especially any non-melanoma skin cancer on non-sun-exposed areas. Physicians should then obtain the necessary lab studies and continue monitoring the patient indefinitely for any signs or symptoms of internal or external malignancies. Also, any ongoing exposure to arsenic should be sought and eliminated. Finally, treatment, although not well studied, has been successful in safely alleviating the clinical lesions.

References

Stiefel Laboratories, Inc. is the largest privately-held pharmaceutical company specializing in dermatology, with a broad scope of products for skincare available around the world. With more than 3,000 employees, our network includes 30 plus subsidiaries, R&D facilities on four continents and products marketed in more than 100 countries. We continue to build on 160 years of success and growth by partnering with dermatologists and patients worldwide to create a lifetime of healthy skin.
Clinical Presentation

A 19-month-old, Caucasian boy presented to our dermatology office with a symmetric, papular eruption localized to his arms, legs, and face for six to seven weeks. The non-pruritic eruption began on the boy’s face and later spread to his arms and legs. Approximately two months prior to the development of the rash, the patient had an upper respiratory infection along with mild axillary and inguinal adenopathy. The respiratory infection resolved without any complications.

Physical Exam

Erythematous papules symmetrically distributed across the face, arms, and legs.

Plan

A skin biopsy was performed that revealed mild epidermal acanthosis, spongiosis, and lymphohistiocytic infiltrate in the dermis. The patient’s mother was educated on the possible etiology of her son’s rash, and a follow-up appointment was made for two weeks later to review the results of the biopsy and to assess the need for symptomatic treatment.

Histopathology

Differential Diagnosis

Drug eruption, papular urticaria, viral exanthem, molluscum contagiosum.

Drug eruptions and papular urticaria can present similarly to Gianotti-Crosti syndrome.

(GCS) in many cases; therefore, an adequate history must be taken and a complete physical exam performed.\(^1\) Viral exanthems must also be considered and ruled out. Most often, viral exanthems of other etiologies present at the same time as the patient is experiencing the viral symptoms, which does not fit the clinical presentation of GCS. Also, viral exanthems may be pruritic, and they generally don’t last as long as the exanthem of GCS. Molluscum contagiosum (MC) is caused by up to four types of pox viruses.\(^2\) Children are most often infected with MCV-1, and the disease is distributed worldwide. The lesions of MC are smooth-surfaced, firm and domeshaped with a central umbilication. This clinical description goes against GCS. Also, MC, unlike GCS, affects all areas of the body and often affects the trunk.

Discussion

Gianotti-Crosti syndrome (GCS) is an infrequently recognized skin disorder that was first described in 1955.\(^3\) It is characterized by a symmetrical distribution of papules localized to the face, extremities, and buttocks.\(^1\) The papular eruption begins abruptly and generally spares the trunk. It presents as monomorphic, skin-colored-to-pink-red papules, which are often edematous. Sometimes the lesions are vesicular, but generally they are non-pruritic in nature. This self-limiting, cutaneous exanthem is often preceded by an upper respiratory infection with mild constitutional symptoms, which is consistent with the history and clinical findings in this patient. Systemic manifestations include a low-grade fever and inguinal and axillary lymphadenopathy. Rarely, hepatomegaly and splenomegaly are seen. The lymphadenopathy may persist for several months.

GCS occurs most commonly in children with a mean age of two years, and it is primarily seen in the spring and early summer. GCS has been associated with a variety of viral agents, such as hepatitis A, B, and C, Epstein-Barr virus (EBV), respiratory syncytial virus, adenovirus, and possibly other agents as well. One clinical case from an Indian pediatrics journal reported GCS in a 9-year-old child with no known previous infection or recent immunizations.\(^2\) Another case reported the syndrome occurring in a boy after he got his routine immunizations.\(^2\) The most frequent etiologic agent reported in the United States is EBV.\(^1\) In the past, GCS was specifically associated with the hepatitis B exanthem, and other causes of the syndrome were placed under a different name; but the two entities are clinically indistinguishable from each other and are now under the same title of GCS.

The diagnostic criteria for GCS were proposed by Chuh in 2001 and include the following:\(^4\)

1. a monomorphic, flat-topped, pink-brown papular eruption or papulovesicular eruption of 1mm to 10mm in diameter
2. any three or all four of the following sites involved: face, buttocks, forearms, and extensor legs
3. symmetrical distribution
4. duration of at least 10 days

Extensive truncal lesions and scaly lesions are considered negative clinical features.\(^4\)

Treatment is mainly supportive after a thorough physical exam is performed.\(^1\) No treatment has been shown to shorten the course of the illness.\(^1\) Evaluation for hepatitis should only be performed if history and symptoms indicate the need to do so. GCS is believed to be under-reported, especially in cases not associated with jaundice and in cases that do not persist beyond two to three weeks in duration.\(^2\)

References


Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood)

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MANAGEMENT OF PERIORAL DERMATITIS

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ABSTRACT

Perioral dermatitis (POD) is a common skin condition characterized by “papules and pustules on an erythematous and sometimes scaling base confined to the chin and nasolabial folds sparing the vermilion border.” It is most common in females aged 16 to 45 years. A variant of POD is granulomatous POD, which is found in children. These often difficult-to-treat skin diseases can be a source of frustration and anxiety for the patients. This article focuses on the nonpharmacological and pharmacological therapies for perioral dermatitis.

Clinical Features

POD is characterized by papules and pustules on an erythematous base about 5 mm from a vermilion border. Initially, the papules are 1 mm to 2 mm in size, but later they become confluent and form satellite lesions. Eczematous lesions and scaling may be present, but comedones are not present. Initially, this skin condition may be present in the perinasal area and then spread to the perioral region and even further into the periorbital location. The glabella and forehead are sometimes involved. Pruritus is uncommon; however, some patients may experience a burning sensation.

Diagnosis

Biopsy is normally not needed, as clinical distribution is often characteristic of the disease. If a biopsy is done, it resembles eczema, with spongiosis changes occurring mostly in the external root sheaths of the follicles. Histology may reveal perifollicular or perivascular lymphohistiocytic infiltration and mononuclear cell exocytosis. Less commonly, plasma cells are present. Telangiectases are usually not seen. A culture can be done to rule out Staphylococcus infection. The differential diagnosis includes rosacea, allergic and irritant contact dermatis, atopic dermatitis, acne vulgaris, seborrheic dermatitis, steroid acne, lip-licking chilblains, xanthomas, eruptive syringomas, xerogranuloma syndrome, papular sarcoïd, and lupus miliaris disseminatus.

Epidemiology

Perioral dermatis is believed to be first described by Frumess and Lewis in 1957, at which time the skin manifestation was referred to as a light-sensitive seborrhoeid. In 1964 it was renamed “perioral dermatis” in an article by Mihan et al. The age of onset is 16 to 45 years of age, and it occurs primarily in females. A variant to peri-oral dermatis, usually found in children, is called granulomatous perioral dermatis. The disorder is characterized by small, monomorphous, skin-colored papules that develop in periorificial areas of the face without erythema or scale.

Etiology

The cause of perioral dermatitis remains elusive. An association of corticosteroids and POD was first described in 1972. Prolonged use of topical corticosteroids has since been cited in many articles as the key culprit of POD. Although there are reports of a small number of patients who deny prior steroid use, one source has illustrated that corticosteroid exposure can be inadvertent and without knowledge. In one case, eruption of POD occurred in a patient after kissing her husband, who used an intraoral corticosteroid. In another patient, leakage of intranasal betamethasone dipropionate nasal spray from her nose caused POD. In two cases, children with asthma developed POD, one after using a budesonide nebulizer, the other after using a spacer with a mask. Another theory, which emerged in the 1980s, was the association of perioral dermatis with occlusive moisturizing creams that led to the proliferation of skin flora. In a study of 133 patients, a combination of moisturizer, foundation and night cream resulted in a 13-fold increase in POD, compared to a 2.9-fold increase resulting from a combination of moisturizer and foundation. No increase was noted for moisturizer use alone. Some articles have hinted at infectious causes of POD. In one study, there were eight patients who had POD, all of whom exhibited fusobacteria (anaerobic, Gram-negative fusiform rods in the oral cavity). Two studies showed the presence of Demodex folliculorum, an ectoparasite, in patients with POD. Candida was found in one case report; however, further studies failed to support any causal connection between Candida and POD. Some studies have indicated contact dermatitis as an etiology. An 11-year-old girl developed perioral lesions after using a flavored lip balm. A 48-year-old patient developed POD after an acrylate-based, temporary crown was inserted. POD has also been found in female patients after orthognathic surgery. Another, often-argued theory is that POD is a subset of rosacea. However, in a study of 275 patients, transepidermal water loss was significantly increased in patients with POD versus patients with rosacea. Also, features of atopic diathesis (history, clinical signs, prick test reactivity and specific IgE antibodies to eight allergens) were more common in patients with POD when compared to those with rosacea and the control group.

Nonpharmacologic Management

New lesions arise over a course of weeks to months. If left untreated, these lesions may even fluctuate for years. Avoiding or decreasing the frequency of occlusive products, especially heavy facial moisturizers (night creams and foundations), may assist in lessening the incidence and recurrences of POD. Moisturizer use alone has not been found to increase the incidence of POD.

Pharmacologic Management

In many instances, topical steroids are prescribed and/or used inappropriately to treat this condition. Initially, lesions will reappear and worsen within a few days. Patients should discontinue the use of all topical steroids, and time must be spent educating patients on how the lesions may get worse before getting better. For patients with a severe form of POD who are using potent steroids, topical 1-2.5% hydrocortisone ointment may be used for up to a week as a tapering measure.
Oral tetracycline is a very effective medication for POD. While used for its antibacterial activity against Propionibacterium acnes in acne vulgaris, its role in fighting POD is thought to be via a direct anti-inflammatory component with inhibition of neutrophil chemotaxis. The dose of tetracycline is 250 mg to 500 mg twice a day for two to three weeks or until clear. Once the lesions have disappeared, tetracycline may be discontinued or slowly tapered over four to six weeks. For severe cases, a long-term maintenance dose may be necessary. Tetracycline and tetracycline derivatives are contraindicated in children eight years of age or younger due to the risk of permanent discoloration in the teeth and enamel. Other side effects may include nausea, vomiting, diarrhea, and photosensitivity. POD has also responded to doxycycline and minocycline at doses of 50 to 200 mg per day. One study of five renal-transplant recipients with POD on long-term corticosteroids and immunosuppressive therapy showed benefit from oral doxycycline. Doxycycline, unlike tetracycline, can be taken with food. Although not studied in patients with POD, a low, subantimicrobial-dose (SD) doxycycline (Periostat or Oracea) may provide another option for patients. SD doxycycline is not an antimicrobial treatment (so there's less chance of developing resistant bacteria); rather, it is believed to down-regulate matrix metalloproteinases and cytokines involved in inflammation. SD doxycycline (20mg BID) has been studied in patients with moderate acne, and there was improvement of their lesions when compared to placebo. Other options for treating POD include oral erythromycin and the combination of trimethoprim and sulfamethoxazole. Isotretinoin has also demonstrated a role in treatment of POD. A study was done on 14 females with a history of irregular menstrual cycles who experienced POD after discontinuing their oral contraceptives. Flare-ups were associated with their cycles, and treatment was refractory to conventional therapy including topical erythromycin, topical tetracycline, topical metronidazole and oral tetracycline. Subsequently, patients were prescribed isotretinoin in the dose of 40 mg/day tapering down to 10 mg/day over six months. Twelve out of the 14 patients remained symptom-free for at least 12 months after therapy.

While oral therapy is most effective, there are topical medications available. Although topical therapy has the benefit of fewer side effects when compared to systemic therapy, response to topical therapy is often less immediate. A case report of a 32-year-old woman with biopsy-confirmed POD benefited from four weeks of a topical application of adapalene 0.1% gel (once a night) without the use of systemic medication. Adapalene works on selective nuclear retinoic acid receptors (RAR-beta and RAR-gamma). It is hypothesized that adapalene interferes with polymorphonuclear leukocyte functions and arachidonic-acid metabolism and has the ability to act as a moderate-to-potent anti-inflammatory medication. In another trial, the topical therapy azelaic acid was tested for its effectiveness. An open clinical study was conducted on 10 POD patients aged 32 to 65 years old. Patients were treated with topical 20% azelaic acid in cream formulation applied twice daily. Response was noted in two to three weeks, and resolution of the lesions occurred in two to six weeks. Azelaic acid is a saturated, straight-chain, nine-carbon-atom, dicarboxylic-acid derivative. Azelaic acid has been shown to have antibacterial activity and inhibit keratinization. In vivo and ex vivo research has also indicated an anti-inflammatory component by which it reduces the generation and/or release of proinflammatory, reactive oxygen species by neutrophils. Adverse effects included erythema, itching and dryness. Topical metronidazole has also shown to be of some therapeutic value. One study in children using metronidazole gel (0.75%) twice daily led to improvement after two months and complete resolution in 14 weeks. However, another study comparing twice daily topical 1% metronidazole cream to twice daily 250mg oral tetracycline revealed that both treatments were effective but that oral tetracycline was significantly more effective. Additionally, the use of topical erythromycin or topical clindamycin may prove beneficial, and one article discussed the benefit of using tacrolium ointment for the relief of steroid-induced rosacea and perioral dermatitis. Another case report describes a 22-year-old man who had complete POD clearance in two weeks using pimecrolimus (Eldel) twice daily. Finally, a comparison study between photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) and PDT with topical clindamycin revealed a mean POD clearance of 92.1% and 80.9%, respectively.

In sum, patients with POD may be frustrated with their condition, especially if it is not diagnosed early or appropriately treated. While its etiology remains elusive, it is important to explain to patients that POD is a commonly treatable skin condition that reoccurs infrequently. Tetracycline and its derivatives appear to be the most effective treatment, but other therapies are available when their use is not appropriate or if patients are non-responsive.

References:
Skin of Color

Different races of our species, *Homo sapiens*, were originally categorized based on the skin color and skin reactions to environmental factors such as sunlight. Anthropologists believe that racial variation is the result of a natural selection process – a process that caused different biologic traits to develop in different races to facilitate adaptation to a particular environment. This might explain darkly pigmented skin evolving closer to the equator. On the other hand, people living north of the equator probably have lighter skin to promote adequate UV absorption for vitamin D synthesis.1 We know today that molecular analysis has identified genetic differences between different ethnic groups and races. Our species has been divided into a number of races that include Caucasoid (e.g. Europeans); Mongoloid (e.g. Asians); Negroid (e.g. Africans, African Americans and African Caribbeans); Capoid (e.g. The Kung San African tribe); and Australoid (e.g. Australian aborigines).2 This data clearly indicates that most races consist of people with skin of color.

The skin phenotype system initially developed by Fitzpatrick correlates the color of skin with its ability to respond to ultraviolet radiation (Table I). This system is used by dermatologists to categorize all people. For the purposes of this article, we will define “skin of color” or “ethnic” skin as skin types IV-VI. This article briefly (1) summarizes the structure and physiology of ethnic skin; (2) describes some common dermatologic conditions in people with skin of color; and (3) reviews the cultural practices of individuals with pigmented skin. It is hoped that this article will help prepare today’s dermatology community to better evaluate, diagnose and treat skin conditions unique to this segment of our population.

Table I. CLASSIFICATION OF SKIN PHOTOTYPES (SPT)

<table>
<thead>
<tr>
<th>SPT</th>
<th>Basic Skin Color</th>
<th>Response to Sun Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pale white</td>
<td>Does not tan; burns easily</td>
</tr>
<tr>
<td>II</td>
<td>White</td>
<td>Tans with difficulty; burns easily</td>
</tr>
<tr>
<td>III</td>
<td>White</td>
<td>Tans after initial sunburn</td>
</tr>
<tr>
<td>IV</td>
<td>Light brown</td>
<td>Tans easily</td>
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<tr>
<td>V</td>
<td>Brown</td>
<td>Tans easily</td>
</tr>
<tr>
<td>VI</td>
<td>Black</td>
<td>Becomes darker</td>
</tr>
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Melanin is synthesized by melanosomes present within the melanocyte. The melanocytes reside in the basal layer of the epidermis and the matrix of the hair bulb.6,7 During embryonic development, neural crest melanoblasts migrate to the epidermis and differentiate into melanocytes. More melanocytes are found on the face and genitalia than on other parts of the body. The density of melanocytes is the same in all races - about one melanocyte per 10 keratinocytes in the basal layer. The difference in skin color is due to the distribution and the size of melanosomes. The melanosomes in dark skin are large and singly distributed, whereas the melanosomes in light skin are small and grouped.8 Each melanocyte is associated with its dendrites.

There are 36 keratinocytes in the malpighian layer of the epidermis.9,10 Melanocytes express E-cadherin, which allows them to adhere to adjacent keratinocytes. Two types of mammalian melanin, namely eumelanin and pheomelanin, are produced in the melanocytes by the involvement of the enzyme tyrosinase. Melanosomes progress from stage I (round, no melanin) to stage IV (oval, dense melanin).

The unique biologic feature of ethnic skin is the amount and epidermal distribution of melanin. Though it is well established that no racial differences exist in the number of melanocytes, the actual number of melanocytes may differ from individual to individual and from one anatomic part of the body to another. Research done by Toda et al.11 and Olsen et al.12 has demonstrated that melanosomes tend to be large and non-aggregated in subjects with skin of color, and melanosomes larger than 0.3 x 0.8 ?m are unable to be structurally grouped together in membrane-bound units. There are, however, variations in each racial group. Melanocyte cultures14 have demonstrated that total melanin content is higher in individuals with darker skin types, e.g. Fitzpatrick skin type VI as compared to Fitzpatrick skin types I and II.

The photoprotective effects of melanin are well documented.1 Melanin acts as a filter of UV radiation, reducing all wavelengths of light equally. Kaidbey et al.15 determined that the main site of UV filtration in Caucasian skin is the stratum corneum, whereas in black skin it is the...
stratum malpighi. Despite the photoprotection conferred by melanin, pigmented skin can also experience photodamage, dermal collagen and elastin damage and, most noticeably, hyperpigmentation. The stratum corneum is equally thick in black and white skin. However, structural differences do exist between black and white skin as demonstrated by increased resistance to stripping, increased lipid content, increased electrical resistance and decreased number of ceramides in black skin. Assessment of skin irritability in skin of color as compared to Caucasian skin is a controversial subject, and studies have shown conflicting data.

**Cutaneous Disease and its Implications in Skin of Color**

The terms "ethnic skin" and "skin of color" have often sparked a difference of opinion as to usage in dermatology. Some authors feel that neither term is appropriate, because "ethnic" refers to nationality and "skin of color" refers solely to pigmentation. The initial use of these terms could be related to the fact that traditional dermatology has had a Caucasian frame of reference. The terms "ethnic skin" and "skin of color" have been used interchangeably in this article. It is believed that these terms may undergo a revision in the future; but at this time, they are accepted by the majority of members in the dermatology community.

The following represents some common dermatologic diagnoses in patients with skin of color and also addresses some disease implications in this patient population.

**Acne**

Acne represents one of the most common problems in ethnic skin. Although the clinical disease tends to be milder in darker skin types, marked inflammation is present histologically. This may explain the postinflammatory hyperpigmentation seen in acne in darker skin. The PIH itself is a common reason for dermatologic consultation. The incidence of nodulocystic acne is lower in the population but accounts for 50% to 70% of melanomas in the Caucasian population but accounts for 5% of all melanomas in the Caucasian population but accounts for 5% of all melanomas in the dark-skinned population. Furthermore, the prognosis of melanoma is less favorable in people with skin of color. This could be related to delayed in diagnosis and treatment in conjunction with the more aggressive nature of the tumor.

**Melasma**

Melasma is a benign pigmentary disorder seen frequently in people with skin of color. Its onset is often related to hormonal factors and ultraviolet radiation. Melasma is often challenging to treat, although combination therapy and lasers have shown promise. Normal variants of pigmentation more commonly seen in African Americans, Asians and Hispanics include pigmented bands on nails (melanonychia) and pigmented lines of demarcation (Voigt’s lines or Butcher’s lines). Pigmentation of the oral mucosa may be seen in more than 75 percent of black patients. Dermatologists today need to be aware of these pigmented disorders and counsel patients accordingly.

**Hair Disorders**

Four types of hair are recognized - straight, wavy, helical and spiral. The vast majority of African Americans have spiral hair, whereas Asian hair tends to be straight. Studies have shown that Western European subjects have hair with the smallest cross-sectional area, whereas people of Chinese descent have hair with the largest cross-sectional area. Montagna and Carlisle looked at hair ultra-structurally and found fewer elastic fibers anchoring hair follicles to the dermis in African American subjects. This might explain the incidence of certain types of alopecia, both scarring and non-scarring, in African Americans. Alopecia is more common in African American women than in African American men. Traction alopecia has been attributed to the cultural practices of tight braids, braid extensions and hair weaves. Centrifugal-scarring alopecia, follicular-degeneration syndrome, and hot-comb alopecia, to name a few, also affect African American women more commonly and cause significant psychological trauma.

**Pigmentary Conditions**

Postinflammatory reactions and dyschromia tend to be more common and noticeable in patients with skin of color. Inflammatory diseases that can result in hyperpigmentation include acne, drug eruptions, eczema, lichen planus and trauma (burns, surgery), to name a few. Postinflammatory hyperpigmentation, although not as common as postinflammatory hyperpigmentation, can be more noticeable in ethnic skin and may include conditions like P. alba, hypopigmented mycosis fungoides, atopic dermatitis and post cryotherapy. Halder et al. found pigmentation disorders to be a very common problem among African American patients. The cosmetic disfigurement impacts patients both physically and psychologically and thus requires early intervention.

**Melanoma**

Melanoma appears to be more prevalent in the Caucasian population compared to Asian, Hispanic and African American subjects. Melanoma in ethnic skin appears to arise most often on non-sun-exposed sites such as palms, soles and subungual areas. Plantar melanoma accounts for only 5% of all melanomas in the Caucasian population but accounts for 50% to 70% of melanomas in the dark-skinned population. Furthermore, the prognosis of melanoma is less favorable in people with skin of color. This could be related to delayed in diagnosis and treatment in conjunction with the more aggressive nature of the tumor.

Cutaneous T-cell lymphoma is also found more commonly in dark skin. A correlation between cutaneous T-cell lymphoma and either industrial exposure or viruses as possible etiologic agents for CTCL has not been proven.
growth factor? is over-expressed in keloid fibroblasts. Fibroblast hyperactivity along with a decrease in the activity of the collagenease enzyme and interaction with cytokine and mast cells seem to be intimately involved in keloid formation.

**Cultural Dermatology and its Impact on Cutaneous Disease**

A detailed discussion of the cultural practices of various ethnic groups is beyond the scope of this article. However, a brief summary is presented. Lighter skin is considered more desirable in many ethnic communities including Chinese, Indian, Pakistani, and some Afro–Caribbean communities. There has been a marked increase in the sale of skin-lightening agents in the United States alone. Some of these products are available over the counter in beauty supply stores throughout the country that cater to certain ethnic populations. Some of the imported facial-lightening products contain topical corticosteroids and/or mercuric compounds. Dermatologists must be aware of the availability of these products and educate their patients about the risks of using these products.

Products that contain hydroquinone (2–4%) are the most common bleaching agents used in the United States. However, higher-strength hydroquinone products imported from other countries can be purchased by distributors nationally. Overuse of hydroquinone is well known to cause ochronosis.

Many women from the Indian subcontinent adorn their central foreheads with a "bindi" - a brightly colored spot. Bindis come in different shapes and sizes and can vary from powder applications to stickers. Allergic contact dermatitis caused by pigments (lead, mercury or turmeric) and PHR are some common problems caused by the application of a bindi.

Betal-nut chewing is a common practice seen from Pakistan to Micronesia. Betel nut is the fruit of the areca palm (Areca catechu) and is chewed usually mixed with "pan" (pepper leaf) and lime (calcium hydroxide or calcium carbonate). Many immigrants from Asia and the Pacific Islands continue this practice in the United States. Betel and pepper-leaf chewing stains the oral mucosa, teeth and gingiva. The staining ranges from a red to reddish black and has been linked to the development of squamous cell carcinoma of the oral cavity.

Many Asians engage in the traditional healing practices of coining (cao gio), moxi-bustion and cupping. Coining is used to treat various illnesses and involves the application of warm oil on the skin of the back and chest followed by firm rubbing with a coin. The linear ecchymoses that develop are temporary and should not be confused with physical abuse. Moxibustion is an ancient oriental medical practice of igniting medicinal herbs on the skin. The circular burn scars are usually seen on the trunk, wrists and ankles. Cupping is another healing practice seen in Asians that involves the application of a suction device to the skin. Circular ecchymoses are produced. This practice is thought to restore balance to the body. Some African societies perform "scarification," which leaves small parallel scars on the face.

Application of henna to the skin and hair has been practiced in the Middle East, Africa and the Indian subcontinent for centuries. Henna is a natural dye derived from the leaves of the shrub Lawsonia alba. The application of henna on the palms, soles, fingers, toes and hair of women mainly centers on religious and social occasions such as Eid ul-Fitr (the end of Ramadan fasting in Islam) and weddings. Its use is integral in religious and decorative purposes in women, children and some men. Though not as common, contact dermatitis to henna has been reported at the sites of its application. "Black henna," adulterated with paraphenylenediamine (PPD), is a cause of contact dermatitis and angioneurotic edema.

The cultural significance of hair and hair products bears similarities and differences across many ethnic populations. As mentioned earlier, hair styles popular in the African American community, combined with the use of hair pomades and conditioners, can lead to temporary and permanent traction alopecia, pomade acne and exacerbation of seborrhoeic dermatitis.

Hair and hairstyles have religious significance as well. Shaven or short hair has been considered a symbol of bodily dedication to the gods. Buddhists, Jains and Hindu widows traditionally have shaven heads. Hair sacrifice is still practiced in certain ethnic and religious communities. In South India, the temple of Tirupati has thousands of hair offerings every year. Many people from the Indian subcontinents shave the heads of infants because of religious and cultural reasons.

Uncret hair is considered a sign of withdrawal from materialistic, worldly concerns by certain ethnic groups, as seen in the Sikh religion, Hindu sadhus (priests) and the Rastafarians. The dermatologic community must be aware of the social and religious practices of various ethnic groups.

**Conclusion**

The majority of the world's population consists of people with skin of color, and the changing demographics in the United States point toward a rapid increase in the non-Caucasian population. Racial and ethnic groups that constitute people with skin of color include Africans, African Americans, Asians, Hispanics and Native Americans. Data on the structure and function of the skin and incidence of skin diseases are not equally available for each individual ethnic/racial group. The literature does support ethnic differences in epidermal melanin content, fibroblast structure and hair structure in dark-skinned individuals compared to fair-skinned individuals. Understanding racial differences in skin function is important in order to prevent and treat skin diseases across various ethnicities. The physical differences among various skin types can be attributed to both genetic and environmental factors. Finally, cultural practices differ in various racial/ethnic groups, and today’s dermatologist must be aware of some of these practices and their cutaneous manifestations. More data is needed to properly understand the dermatological needs of the dark-skinned people who will shortly comprise a very large segment of the U.S. population.

**References**

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However, in IP, without NEMO, this protective pathway is not present and apoptosis occurs in cells with the active mutated X chromosome.

### Case Report

An inpatient consult was received for a six-day-old female with adjusted gestational age of 36 weeks, born in respiratory distress, who developed an erythematous vesiculopustular rash on the right arm and leg at birth. The mother was GBS+ and was given prophylactic ceftriaxone before delivery. Prior to consultation, ampicillin and gentamicin were administered to the newborn because of the high index of suspicion of possible sepsis, however blood cultures were ultimately negative. Topical nystatin was also applied to the affected areas, however the eruption continued to spread to the face and trunk.

Upon examination, multiple plaques with intense erythema, widespread vesicle formation, and honey colored crusts were noted on the right extremities, buttock, and abdomen (Fig 1a & 1b). Differential diagnosis included bullous impetigo, herpes zoster, eczema herpeticum, erythema toxicum neonatorum, incontinentia pigmenti, epidermolysis bullosa and diffuse cutaneous mastocytosis. The work-up included shave biopsies obtained from the right forearm and back which were sent for H&E, PAS, and Gram staining. In addition, bacterial C+S and viral cultures for HSV/VZV were performed on expressed vesicular fluid. Furthermore, chlorhexidine bathings b.i.d. and mupirocin applications t.i.d. were initiated to prevent secondary infection.

Biopsies revealed no bacteria or fungi on Gram and PAS stains, respectively. Multiple level sections were negative for characteristic viral cytopathic changes seen in herpetic dermatitis. Viral and bacterial cultures also returned negative. However, the H&E showed an intraepidermal vesicle containing numerous eosinophils with scattered neutrophils. Furthermore, apoptotic keratinocytes were noted in the adjacent epidermis, as well as spongiotic areas of epidermis with aggregates of eosinophils consistent with eosinophilic spongiosis.

Numerous eosinophils were also seen in the underlying dermis. These histological findings are most consistent with stage 1 lesions of incontinentia pigmenti (Fig 2).

### Genetics

Garrod first described a case of incontinentia pigmenti in 1906. Since which point the intricacies of inheritance and wide variability in its multisystem pathologies have been extensively logged and researched. IP is an X-linked dominant neurocutaneous syndrome characterized by abnormalities of the tissues derived from ectoderm and neuroectoderm. Usually IP is a male lethal syndrome due to a male's XY genotype. However, males with Klinefelter syndrome (XXY), somatic mosaics, and those with less deleterious mutations have conferred compatibility with life. Nonetheless, the ratio of females to males affected with IP is 37:1. In females with IP, lyonization occurs (inactivation of one of the X chromosomes) which leads to functional mosaicism of X-linked genes. This is exemplified phenotypically through blaschkoid distribution of cutaneous lesions. Those cells with an active mutated X chromosome become selectively eliminated perinatally through apoptosis, thus leading to the typical vesicles seen at birth or shortly thereafter. Cells with a normal active X chromosome are represented phenotypically in unaffected skin.

Incontinentia pigmenti is caused by mutations in the gene for NEMO, located on Xp28. NEMO, or nuclear factor kappa B essential modulator, is a regulating subunit of the inhibitor kappa kinase (IKK) complex. In NEMO’s absence, the IKK complex cannot activate the transcription factor NF-kappa B whose activity is central to multiple inflammatory, immune and apoptotic pathways. The activation of NF-kappa B prevents apoptosis in response to TNF-alpha. However, in IP, without NEMO, this protective pathway is not present and apoptosis occurs in cells with the active mutated X chromosome.
Clinical Manifestations

Stage 1 (vesicular) is marked by development of linear vesicles, pustules, and bullae on an erythematous base located along the lines of Blaschko (Fig. 1a & 1b). Lesions are typically present at birth (>90%) as in our patient, or will appear in the first few weeks. Resolution of vesicles occurs within the first few months, however a rare recurrence of this stage can occur later in affected children during a febrile illness.15

Stage 2 ( verrucous) occurs usually between 2-8 weeks of age. It is characterized by warty, hyperkeratotic papules and plaques on an erythematous base distributed in a linear and whorled pattern following the lines of Blaschko. In general, they will begin to form on the distal extremities as the vesicles begin to clear. The lesions are noted to clear by 6 months in 80% of cases.

Stage 3 (hyperpigmentation) is characterized by the appearance of the namesake lesions of IP and begins between 12 and 40 weeks of age. Hyperpigmented macules in a whorled “marble cake” pattern along the lines of Blaschko typify this stage. In some cases the new lesions correspond to the vesicular or verrucous stage distributions; in others, the relationship is not obvious. Resolution of the hyperpigmentation occurs slowly during the second decade.

Stage 4 (atrophic/hypopigmented) lesions are hypopigmented streaks and patches usually involving the lower extremities. Atrophic lesions have been noted to occur in 30-75% of IP patients, with persistence into adulthood. Commencement usually begins in adolescence; however, stage 4 lesions can present from infancy through adulthood.

Multiple hair and nail changes are also prevalent in IP. Absence or hypoplasia of the eyebrows and eyelashes are common manifestations. Hair can be sparse during early childhood, gradually becoming wiry, course, and lacking. Scarring alopecia is also noted to occur in 28-38% of IP patients. Nail abnormalities include nail dysplasia ranging from mild pitting or ridging to hyperkeratosis and onycholysis, which may be noted by atrophic epidermis, loss of normal rete ridge pattern and ecrine structures, scarring, and occasional colloid bodies.

Discussion

There is no specific curative treatment for incontinentia pigmenti. Timely diagnosis is very important to patient care because of the potential treatable morbidities that can occur soon after birth. Seizures are common within the first week of life; therefore, a neurologist should be consulted to perform an initial evaluation, including imaging and EEG, and provide anticonvulsant therapy for patients who seize. Neurologic prognoses is usually very good if there are no complications in the first months of life. In addition, ophthalmologic anomalies may also become evident within the first few weeks and rapidly progress to permanent visual deficits. Ophthalmologic exams should be performed as soon as possible after birth and on a routine monthly basis for the first 3-4 months. At which point the schedule changes to: every three months until the end of the first year, twice a year until age 3, and then once a year for life.16

Management of cutaneous lesions includes preventing secondary infection of the perianal vesicles. In later stages, the skin may become dry due to loss of eccrine appendages and require the use of emollients. A general dentist should be able to provide the dental care needed in most cases, including screening for dental anomalies, and restorative dental work. A geneticist should also be sought to determine the mode of inheritance if it cannot be elicited through family history, and to provide counseling to the family regarding future affected offspring.

Though the skin manifestations in IP are extensive and numerous, few treatments are required. However, the dermatologist’s role in diagnosing IP is most important. Delays in treatment can lead to significant morbidity and can have medico-legal repercussions. Thus, when consulted to diagnose an erythematous vesiculopustular rash in a neonate it is imperative to biopsy if the diagnosis cannot be illicitly clinically. Once the diagnosis is established, coordination of care should be conferred with the pediatrician and appropriate specialists.

References

RAPIDLY PROGRESSING ANGIOSARCOMA IN THE CHRONICALLY LYMPHEDEMATOUS LEG OF A 60-YEAR-OLD FEMALE

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ABSTRACT

Angiosarcoma is an aggressive, endothelially derived tumor that can present as several distinct clinical syndromes, all of which are characterized by local recurrence and poor long-term prognosis. Despite advances with chemotherapy, surgery continues to provide the best chance for survival. We present the case of a 60-year-old woman with a high-grade angiosarcoma arising in her chronically lymphedematous leg. She underwent four cycles of chemotherapy with gemcitabine and docetaxel and then received an above-the-knee amputation. This case is unusual in that there are few reported cases of angiosarcoma that arise in the setting of chronic lymphedema not related to previous malignancy.

History and Clinical Presentation

A 60-year-old, white female was referred to our office because of a fungating mass on her right lower extremity that had been present for approximately two weeks. The patient had a history of morbid obesity with longstanding lymphedema of both lower extremities. Other past medical history included well-controlled ulcerative colitis diagnosed 14 years prior with no recent flares; asthma; and osteoarthritis. She had noticed bilateral shin erythema one month prior to presentation. Soon after, she developed increased pain along with blistering of her right anterior shin and was treated by her primary physician for shingles without relief of symptoms (Figure 1). She was then treated as in inpatient for cellulitis at a local hospital, where an initial biopsy was thought to represent erythema nodosum; she was treated with a course of steroids with no response. Shortly after, she noticed progressive worsening with the development of a large, ulcerating mass involving the right lower extremity (Figure 2) and was referred to our office for the initial consultation.

Physical Exam

The patient was well nourished, in no distress and appeared her stated age. Vital signs were stable with a weight of 308 pounds. The left lower extremity showed 2mm pitting edema extending to her distal knee with venous stasis changes. The right lower extremity showed 3mm pitting edema to her distal knee as well as a fungating, ulcerated lesion, 9 cm in diameter, along the anterior aspect of her distal calf with evidence of serous drainage and surrounding erythema. There were also numerous red satellite lesions extending both distally and proximally up to the level of her knee. There was no obvious inguinal lymphadenopathy, although this was difficult to assess due to body habitus.

Laboratory Studies

Abnormal laboratory findings

Wound cultures showed heavy growth of Pseudomonas aeruginosa and light growth of Enterococcus faecalis.

Normal laboratory findings

Comprehensive metabolic panel and CBC were essentially normal. Helical CT of the chest, abdomen, and pelvis with contrast failed to show any evidence of lymphadenopathy or metastasis. Chest X-ray was also negative for metastasis.

Dermatohistopathology

Dermatopathology showed a poorly differentiated, malignant neoplasm. Medium-sized tumor cells with scant cytoplasm and large, hyperchromatic, irregular nuclei, some with prominent nucleoli, were throughout the dermis, between collagen bundles, and around vessels. In some areas, there were malignant cells lining vascular spaces (Figures 3, 4). Immunohistochemical stains were positive for Vimentin, CD31, and CD34 and were negative for Factor XIIIa Cytokeratin, CD68, Mart-1, S100, and Factor VIII (Figure 5).

Therapy and Course

The patient was sent to a tertiary care center, where the diagnosis of a high-grade angiosarcoma with advanced disease was re-confirmed. She had been started on amoxicillin/clavulanate (Augmentin) following her wound cultures, which did alleviate some of the surrounding erythema. There was some questionable, right inguinal adenopathy at the initial visit. The staging CT, chest X-ray, as well as initial labs were re-ordered at that time, all of which were unremarkable. On subsequent visits, the questionable inguinal adenopathy had resolved, and it was felt that this was most likely reactive due to the extent of the ulcerated lesion. It was believed that because there was not any evidence of metastasis, her best treatment option would be six cycles of chemotherapy with Gemzar (gemcitabine) and Taxotere (docetaxel), each lasting 21 days, followed by a possible above-the-knee amputation. It was emphasized to her that given her body habitus, an above-the-knee amputation would likely result in great morbidity with little chance of a successful prosthesis. She received a total of four cycles of chemotherapy with an excellent response, including shrinkage...
considered included lipodermatosclerosis, elephantiasis nostrum, pyoderma gangrenosum with a history of ulcerative colitis, and angiosarcoma. Also included were angiosarcoma-like tumors such as epithelioid hemangioendothelioma, Dabska tumor, and retiform hemangioendothelioma. Kaposi sarcoma can also be confused with angiosarcoma both clinically and histologically. Immunohistochemical stains and histological appearance will differentiate angiosarcoma from other, similar lesions.

Discussion

Angiosarcoma is an uncommon malignancy accounting for less than 1% of all malignancies diagnosed in the United States and less than 2% of all soft-tissue sarcomas. They tend to be multifocal, to recur, and to metastasize early. The diagnosis is often delayed because of a lack of clinical suspicion, as most appear insidiously as a bruise with indistinct borders. They most often show one of three clinical patterns. The most common is on the scalp or face of an elderly person. Second in frequency is cutaneous angiosarcoma following chronic lymphedema resulting from mastectomy, trauma, infection or other malignancies; rarely, they can be idiopathic. Last and least common is angiosarcoma developing as a sequela of previous radiation therapy. Factors that have been considered in the pathogenesis of this tumor include radiation, lymphedema, ulceration, and chemicals such as vinyl chloride, arsenic, and thorium dioxide. It is believed to be of endothelial cell origin.

Angiosarcoma arising in an area of chronic lymphedema is referred to as Stewart-Treves syndrome. Stewart and Treves first described lymphangiosarcoma occurring in postmastectomy lymphedema in the arm in 1948; since then, several authors have reported this postmastectomy complication. The incidence of Stewart-Treves syndrome of the breast is low, with a prevalence estimated between 0.07% and 0.45% of patients treated for early carcinoma of the breast, but it makes up 90% of the reported cases of angiosarcoma associated with lymphedema. Stewart-Treves syndrome in a lower extremity is much less common and is reported only occasionally. The average duration of the lymphedema before the tumor occurs is 10 years and 3 months (the full range is one to 26 years). Lymphedema from causes other than a mastectomy has a relatively longer duration before angiosarcoma is discovered: 19 years and 10 months on average (with a full range of 6 months to 46 years). The prognosis in Stewart-Treves is poor, with reported five-year survival rates of less than 40%. The most common sites of metastasis, in descending order, include lymph nodes, lung, liver, and bone.

Histopathologic findings are variable in angiosarcomas, ranging from tumors containing deceptively benign-appearing vascular channels to tumors with sheets of pleomorphic cells with ill-defined or virtually absent vascular spaces to numerous mitoses. The main diagnostic clue for cutaneous angiosarcoma is the presence of anastomosing, dermal vascular channels lined by atypical cells, many of which have hyperchromatic and pleomorphic nuclei. Papillary endothelial proliferations may project into the vascular lumen.

Special stains are useful to help confirm the vascular nature of the neoplasm and exclude other tumors, although no single marker is ideally sensitive and specific. Thirty-five percent of angiosarcomas will stain positive for cytokeratin. Factor VIII-related antigen and Ulex europaeus I lectin (UEA1) stain endothelium and are often positive in angiosarcoma, although not all the time. UEA1 is more sensitive but less specific than Factor VIII. Vimentin intermediate filaments are found in almost all angiosarcomas because they are mesenchymal neoplasms, so this stain is extremely nonspecific. Endothelial cell membrane markers CD31 and CD34 are sensitive markers for angiosarcoma. CD34 is the most sensitive vascular marker, while CD31 is the most specific. Epithelial membrane antigen, S100, and HMB45 are not expressed in angiosarcoma.

Local recurrence and metastases are very frequent regardless of treatment modality. Most metastases occur in the first 24 months, either by lymphatic or hematogenous spread. There is presently no generally accepted method of staining. The greatest prognostic factor appears to be the success of obtaining wide surgical margins. There is a correlation between survival and primary tumor size. Patients with lesions less than 5 cm have a significant survival advantage compared with those with lesions greater than 10 cm. There is no evident statistical prognostic relationship with age, sex, or clinical appearance of the tumor. Extremity involvement from lymphedema appears to have a slightly better prognosis than head and neck or visceral involvement.

Standard therapy continues to be primary excision, especially if the tumor is less than 5 cm. Frequently, subclinical and multifocal disease is present, and adjuvant therapy with chemotherapy, radiation, or both is reasonable and has shown benefit in select studies. Surgical therapy offers no benefit in the presence of metastatic disease. Chemotherapy alone has been reported to have a poor response in trials using metho-
tretax, 5-fluorouracil, doxorubicin with dacarbazine, and actinomycin D. New chemotherapeutic options now being tried include liposomal doxorubicin, safingol, thalidomide, docetaxel, paclitaxel, interferon alpha, and retinoids.

Summary

In summary, angiosarcoma is an endothelially derived tumor that presents as several distinct clinical syndromes, all of which are characterized by local recurrence and poor long-term prognosis. We need to further understand the biology of this tumor as well as continue to explore new treatment strategies if progress is to be made in the treatment of this disease.

References

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CRYPTORCHIDISM IN A PATIENT WITH X-LINKED RECESSIVE ICHTHYOSIS

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ABSTRACT

X-linked recessive ichthyosis, also known as steroid sulfatase deficiency, is an uncommon skin condition presenting early in life with hyperkeratotic, adherent scales predominately on the trunk, neck, and extensors with typical sparing of the flexural regions, palms, and soles. One of the key features of this disease, the presence of cryptorchidism, requires screening due to an increased risk of testicular cancer. We present the case of a 47-year-old male previously diagnosed with X-linked recessive ichthyosis and an un-descended testicle that had yet to be identified.

Case Presentation

A 44-year-old, white male presented to our office for evaluation of his “ichthyosis,” which presented shortly following his caesarian section birth. He had been evaluated by a dermatologist as a young adult but had not been treated for this skin condition for more than 20 years. He admitted to a significant sloughing of his skin that waxed and waned throughout the years. The condition noticeably worsened in the winter, while markedly improving during the summer months in Michigan. On review of systems, there was no history of atopy, visual impairment, weight loss, or anosmia. Upon query, he admitted to having only one testicle and denied any previous genitourinary surgery as a child.

On physical exam, the patient had large, polygonal, brown and tan, firmly adherent scales, which were translucent upon removal, on the extensors, trunk, and neck with relative sparing of the flexural regions of his arms, palms, and soles. The scalp and face were spared with exception of the retroauricular region. He had one non-tender, appropriately sized, palpable testicle.

The patient was started on mild emollients and was referred to urology for surgical evaluation of his cryptorchidism. On one-month follow-up, the patient had markedly improved with liberal application of urea 40% twice daily and gentle scrubbing of the affected area while bathing. He had yet to be evaluated by urology.

Discussion

X-linked ichthyosis is an uncommon dermatosis occurring in one out of 2,000 to one out of 9,500 males. The condition is due to an X-linked recessive gene deletion of the steroid sulfatase (STS) gene, located on chromosome Xp22.32, resulting in a deficiency of steroid sulfatase (aryl sulfatase C). The depletion of steroid sulfatase activity in the stratum corneum results in impaired hydrolysis of cholesterol-3-sulfate and dehydroepiandrosterone sulfate (DHEAS). Subsequent accumulation of cholesterol-3-sulfate, a serine protease inhibitor released by Odland bodies, results in hyperkeratotic retention and reduced desquamation from persistent cellular adhesion due to delayed dissolution of desmosomes in the stratum corneum. Males are typically born via caesarian section due to a failure of progression of labor resulting from placental sulfatase deficiency. Inadequate conjugation of DHEAS precipitates a state of low estrogen, resulting in insufficient progression of cervical dilation.

Ocular findings include asymptomatic corneal opacities and deuteranopia (green-color blindness). There is up to a 20-fold increased incidence of cryptorchidism, resulting in an increased risk of testicular cancer. Other associated features include subsequent development of acute lymphoblastic leukemia, congenital defects of the abdominal wall, and epileptic seizures.

X-linked ichthyosis should be differentiated from ichthyosis vulgaris, an autosomal-dominant, hyperkeratotic retention genodermatosis that is due to a defect in profilagrin synthesis. Ichthyosis vulgaris typically spares the neck, has hyperlinear palms and soles, keratosis pilaris, and other findings suggestive of atopy. Ichthyosis vulgaris commonly improves with age, a characteristic not typically seen in X-linked recessive ichthyosis. Similar skin findings, in addition to anosmia, can be seen in Kallman’s Syndrome. X-linked recessive chondrodysplasia punctata, a genodermatosis in a contiguous gene syndrome with X-linked recessive ichthyosis and Kallman’s Syndrome, also may present with similar skin findings in conjunction with hypogonadism, anosmia, facial hypoplasia, mental retardation, and hypoplasia of the distal phalanges.

On histopathology, hyperkeratosis and/or parakeratosis with hypergranulosis is seen, often in conjunction with follicular hyper
Diagnostically, elevated levels of cholesterol sulfate can be measured indirectly via serum lipoprotein electrophoresis, while direct measurements may be obtained by spectrophotometry using epidermal scale, placenta, or amniotic fluid. Southern Blot, FISH, and PCR of chorionic villi or amniotic fluid may be used for prenatal diagnosis, although non-invasive measurements of decreased estrogen levels and nonhydrolyzed sulfated steroids in maternal urine may be more appropriate initially.

Treatment for these patients typically involves emollient skin hydration, particularly in the winter months and in cooler environments. Alpha-hydroxy acids such as lactic acid often serve as useful keratolytics. Patients should be counseled regarding future pregnancies, receive regular ophthalmology screenings and be evaluated by urology if indicated. Although there is an association with acute lymphoblastic leukemia, there are no current recommendations for screening patients with X-linked recessive ichthyosis other than routine physicals and blood work if indicated.

Summary

Up to 20 percent of patients with X-linked recessive ichthyosis may present with cryptorchidism, a condition associated with a markedly increased incidence of testicular cancer. Although cryptorchidism is typically screened in neonates and infants, clinicians should never make assumptions regarding what another physician may or may not have done in previous examinations. In all patients with an ichthyotic skin dermatosis, it is essential for the dermatologist to identify the specific disease in order to appropriately screen for associated findings that may increase the mortality rate in their patients.

References

CREST SYNDROME: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Scleroderma is a clinical entity defined by the presence of thickened, sclerotic collagen. It encompasses a heterogenous group of diseases commonly broken down into diffuse and localized forms. CREST syndrome is a localized, cutaneous form of the larger entity scleroderma. CREST syndrome displays five cardinal features, each delineated by the letters of its name: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Unlike the diffuse counterpart, CREST syndrome has a benign course and better overall survival. In this report, we present a case of CREST syndrome and review the literature with emphasis on therapeutic modalities.

Case Presentation

A 56-year-old, Caucasian female presented to the dermatology clinic with a chief complaint of painful lesions on her upper back. The patient first noted the lesions approximately four years ago; however, recently they had become progressively tender and had begun to drain a copious, yellow liquid. She also admitted to "tightening" of her skin, which was first noted approximately one-and-a-half years prior to this appointment. The patient’s medical history was significant for hypertension and GERD. Her family history was non-contributory.

On physical examination, there were multiple, 3-5 mm, white-to-cream-colored papules and nodules coalescing into a 20cm x 35cm, indurated plaque on the patient’s upper back. Multiple ulcerations were present within the plaque. Many of the ulcerations demonstrated an overlying, yellow-colored crust. Extrusion of a white, chalky material could also be noted amongst the ulcerations.

Examination of the patient's extremities revealed taut, indurated, shiny skin, with loss of hair, on the extensor surface of the arms and legs. Mild induration of the hands and fingers was noted as well.

Scattered telangiectasias were noted on the face and upper chest. Examination of the cuticles revealed enlarged, tortuous capillaries with sporadic absence. Upon questioning, the patient admitted to pain and color change in her fingers related to cold exposure. The patient also admitted to symptoms of dysphagia to liquids.

A biopsy from a nodule on the upper back and right extensor forearm was performed. The nodule on the upper back revealed a central ulceration overlying a fibrotic dermis with sparse inflammation. Basophilic calcification was noted within the fibrotic stroma of the dermis.

The biopsy from the patient's right forearm revealed an atrophic epidermis overlying marked fibrosis which extended into the deep reticular dermis. Sparse perivascular and interstitial lymphocytic inflammation was present.

Laboratory investigation revealed an antinuclear antibody titer of 1:320, a positive anti-centromere antibody, and a negative anti-Scl70 antibody titer. The complete blood cell count and blood chemistry profile were found to be within normal limits, including the BUN and creatinine. Serum calcium and phosphorus levels were also found to be within normal limits.

Given the constellation of cutaneous, laboratory, and histopathological findings, a diagnosis of CREST syndrome was rendered.

Discussion

Scleroderma is a clinical entity defined by the presence of thickened, sclerotic collagen. Scleroderma encompasses a heterogeneous group of diseases that are commonly broken down into systemic and localized forms. The systemic forms are further categorized into limited and diffuse subtypes. CREST syndrome is the limited, systemic form of the larger entity scleroderma. First described by Thibierge and Weissenbach in 1910, it is a slowly progressive disease that commonly occurs in individuals aged 30 to 65 years. Women are affected more commonly than men in a 4.6:1 ratio. Moreover, the incidence tends to be greater during the female childbearing years. As well, the incidence of disease tends to be greater amongst African American individuals, and it has been found that African Americans are more likely to experience a worse prognosis.

CREST syndrome displays five cardinal features, each delineated by the letters that compose its name: calcinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Fulfillment of three or more of these criteria indicates the presence of CREST syndrome with a sensitivity and specificity of 99% and 100%, respectively.

Calcinosis cutis is caused by the pathologic deposition of calcium into the dermis of the skin. These deposits present as hard plaques or nodules in the skin, which are typically tender and painful. Ulceration of these nodules may occur with subsequent drainage of a white, chalky substance. The lesions of calcinosis cutis are predominately found on the extremities, around the joints, and around bony prominences. Calcinosis typically results despite normal levels of serum calcium and phosphorus, a phenomenon referred to as “dystrophic calcification.”

Raynaud’s phenomenon, first described by Maurice Raynaud in 1862, is characterized by episodic and reversible vasospasms of the extremities manifesting as a triphasic color change of pallor (white), cyanosis (blue), and rubor (red).

Each color represents the phases of vasoconstriction, slow blood flow, and reperfusion, respectively. Involvement of fingers and hands is most common. Toe, foot, nose, and ear involvement is rare. The episodes
of Raynaud’s phenomenon typically last from minutes to hours. Pain and paresthesias are commonly experienced during these episodes. Raynaud’s phenomenon is the presenting sign of CREST syndrome in 70% of patients.

Esophageal dysmotility, which occurs in 75% to 86% of CREST syndrome patients, affects the smooth muscle of the distal 2/3 of the esophagus. It typically presents as a decepted peristalsis, with resultant difficulty in swallowing foods, and/or reduced lower esophageal sphincter pressure. The risk of Barrett esophagitis, esophageal adenocarcinoma, and aspiration pneumonia have subsequently increased.

Sclerodactyly is the thickening of the digital skin distal to the elbow and knees. The skin appears shiny and tight, with loss of the skin creases. The change in skin appearance and texture occurs progressively in three phases. First, the digits swell and demonstrate symptoms of early morning stiffness or arthralgias. Over a period of months, these digits become shiny and tight with subsequent loss of skin creases. In late stages, the skin is fragile and atrophic.

Finally, telangiectasias are flat and non-pulsatile collections of dilated blood vessels with predilection for the face, upper trunk, and hands. Mucosal surfaces and the gastrointestinal tract may be involved in some cases. Involvement of the gastrointestinal tract may lead to episodes of bleeding with resultant anemia.

Individuals suspected of having CREST syndrome may be screened for this disease through anti-nuclear and anti-centromere antibody testing. The anti-nuclear antibody is a predictive screening test with a sensitivity of 85% and a specificity of 54%. It commonly displays a speckled or homogenous pattern. Also, 82% to 96% of patients with CREST syndrome display a positive anti-centromere antibody. The specificity of this antibody test is estimated to be approximately 95%. Unlike the patients with diffuse scleroderma, who display the anti-Scl70 antibody, the presence of the anti-centromere body indicates more localized disease and a better overall survival.

Treatment for CREST syndrome is multifaceted and specific to each of the cardinal features that comprise the CREST syndrome.

For calcinosis cutis, intralesional steroids have achieved the most improvement. Several case reports using low-dose warfarin to treat calcinosis have shown efficacy in treating calcinosis, as well; however many of these successes were limited to cases of early or mild disease. Probenecid, edathamil, and diltiazem have been tried, anecdotally, with varied response. Surgical removal of the calcium deposits and extracorporeal shock wave lithotripsy may be performed if medications fail.

Calcium channel blockers, such as nifedipine, are the mainstay of therapy in the treatment of Raynaud’s phenomenon. In fact, in a study conducted by the Raynaud’s Treatment Study Investigators, nifedipine was found to decrease the frequency of episodes by 60%. Prostaglandin E1, prosta-cyclin I2, and iloprost (a prostacyclin-I2 analogue) were found to be successful in reducing the frequency and duration of attacks in several small studies. Anti-platelet medications, however, have been found to be ineffective. As an adjunct to medical therapy, patients must be educated to avoid the risk factors that may induce episodes of Raynaud’s phenomenon, such as smoking and the use of beta-blockers. As well, patients must be taught hand-and-body warming activities.

Behavioral changes are also essential to the treatment of esophageal dysmotility. Patients must be advised to elevate the head during recumbency, reduce the amount of caffeine, tobacco, alcohol, and chocolate intake before bedtime, and exercise to induce weight loss. H2 blockers and motility-promoting agents have been shown to help mild symptoms. The use of proton-pump inhibitors is necessary if erosive esophagitis is present.

Sclerodactyly has proven to be very resistant to treatment. Although proposed to undergo softening naturally after a period of four to five years, this process occurs very slowly and may not occur in all individuals. Many studies on the treatment of sclerodactyly have been performed; however, little success has been found. D-penicillamine in either high-dose (750-1000 mg/d) or low-dose (125 mg qod) has been proposed to be the most effective for this cardinal feature of CREST syndrome. However, such improvement was only seen after treatment periods of two years or greater in many studies.

Finally, studies for the treatment of telangiectasias have shown desmopressin, laser ablation and sclerotherapy to be beneficial.

Because of the recalcitrance of many of the cardinal features of the CREST syndrome, the estimated 10-year survival rate for patients with this syndrome is 60% to 70%. As such, these patients are known to have a mortality rate two-fold higher than the general population. Although touted as a localized, cutaneous form of scleroderma, patients with CREST syndrome may rarely display visceral complications. In such cases, the GI tract (other than the esophagus), heart, lung, and kidney are the organs most commonly involved. Visceral involvement, when present, is associated with increased mortality.

References:
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PSEUDOXANTHOMA ELASTICUM AND PREGNANCY: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Pseudoxanthoma elasticum is a rare disorder of the connective tissue that affects the elastic fibers of the skin, eyes, and cardiovascular system. We present a case of pseudoxanthoma elasticum diagnosed during the first pregnancy of a 32-year-old woman. The diagnosis was made based on clinical and histological findings discovered after an exacerbation of the skin lesions. The effects of this condition on pregnancy are poorly understood. We present our findings and discuss the impact of pseudoxanthoma elasticum on pregnancy, including appropriate counseling and treatment options for these patients.

CASE REPORT

A 32-year-old, Caucasian female at six weeks gestation of her first pregnancy presented with papules on her posterior-lateral neck. The papules were of recent onset and asymptomatic. She reported an onset of hypertension and epistaxis beginning three weeks before her initial office visit. Her medical history was otherwise unremarkable. The patient’s family history was significant for a grandparent with “eye changes” of unknown etiology.

On physical exam, the patient had multiple tan-to-yellow papules that were present only on her posterior-lateral neck (Figure 1). A punch biopsy of a single lesion revealed thick, coarse and basophilic elastic fibers in the lower reticular dermis in an irregular pattern (Figure 2). These alterations in the elastic fibers were highlighted by a Verhoeff-van Gieson stain (Figure 3). A von Kossa stain demonstrated calcification of these fibers (Figure 4).

The patient was referred to an ophthalmologist and a cardiologist for a baseline examination and follow-up. She will be closely supervised by an obstetrician for the remainder of her pregnancy. The patient received dietary counseling that included avoidance of excessive calcium intake and encouragement of a heart-healthy diet with antioxidant supplements. She was also advised to avoid tobacco and any activity that might increase her chances of head trauma.

DISCUSSION

Pseudoxanthoma elasticum (PXE) is an inherited disorder of the connective tissue. Abnormal calcification and fragmentation of elastic fibers affect the skin, eyes, and cardiovascular system. The molecular defect in PXE has been identified as the ABCC6 gene, located on chromosome 16p13, that encodes for the protein adenosine triphosphate binding cassette MRP6. This gene is also responsible for encoding a transmembrane transporter protein related to the defective proteins in cystic fibrosis. PXE was initially believed to develop in a sporadic fashion, but the identification of the PXE gene as a member of this transmembrane family has further classified this condition as a genetic metabolic disorder. Both autosomal-dominant and autosomal-recessive modes of inheritance have been reported. Currently, the largest body of evidence suggests that an autosomal-recessive inheritance pattern is the most frequent. Sporadic cases without ocular findings may be seen with D-penicillamine therapy, exposure to salt peter, or in end-stage renal disease.

PXE is predominantly seen in the female gender, with an estimated prevalence of 1:70,000 to 1:100,000 live births world-wide. The prevalence is thought to be a gross underestimation due to many factors. PXE has a variable expression and penetrance and thus has a very heterogeneous clinical presentation. In addition, the rarity and lack of awareness of PXE in both the general public and the medical field contribute to underdiagnosis. The diagnosis of PXE based on skin abnormalities is usually made in the second or third decade of life. However, case reports of individuals as young as six years of age have been documented. The average time from the onset of symptoms to diagnosis can range anywhere from nine to 23 years. This large gap in time can be attributed to either early eye involvement or the asymptomatic nature of the skin lesions. The average patient with PXE does not seek medical attention until he or she experiences a symptomatic ocular lesion, which usually takes many years to develop.

Individuals with PXE exhibit a marked heterogeneity in terms of clinical presentation, age of onset, and severity of organ involvement. The skin lesions of
Although not exclusive to PXE, angioid streaks develop in about 85% of patients by the age of 30. These are a consequence of breaks in the elastic lamina of Bruch’s membrane in the eye. This is seen as a reddish-brown band around the optic disk with glistening streaks radiating away. Angioid streaks are initially asymptomatic, but they are the site of choroidal neovascularization and may result in subretinal hemorrhages and scarring that can lead to a loss of visual acuity.  

Cardiovascular complications and symptoms are typically late presentations of PXE. Accelerated atherosclerotic disease is a particularly worrisome complication. Involvement of the mid-sized arteries leads to calcification of the elastic media and intima, resulting in atherosclerotic plaques and a reduction of the vessel lumen. This can manifest as intermittent claudication, peripheral artery disease, mitral valve prolapse, epistaxis and hypertension with subsequent premature coronary artery disease. Gastric hemorrhage resulting from calcified elastic fibers in the thin-walled blood vessels of the gastric mucosa can occur in 10% of patients.

PREGNANCY

The impact of pregnancy on PXE and vice versa is unclear in the medical literature. Case reports have emphasized the risk that PXE poses to both the mother and fetus. Warnings of detrimental consequences have had an impact on reproductive decisions made by women with PXE. In a recent study of 407 women with PXE, 366 of them reported a history of pregnancy. Of these, 12% reported an increase in the severity of skin symptoms during pregnancy. In addition, the 101 nulliparous women were questioned why they never became pregnant. Four percent of these nulliparous women reported being warned by a medical professional to avoid pregnancy based on the diagnosis of PXE. Three percent elected to avoid pregnancy based on their own concern regarding the potential side effects of being pregnant with PXE. A more extensive understanding of the true risks women with PXE face concerning reproduction will allow medical professionals to better inform them of the potential risks and avoid giving unsupported information.

Maternal complications during pregnancy are vast and include, but are not limited to, exacerbations of current skin lesions, an advancement of ophthalmologic pathology, hemorrhage, arterial hypertension, ischemic arteriopathy of the lower limbs, cardiac failure with arrhythmia and thromboembolic events. One of the most severe and potentially life-threatening maternal complications reported is gastrointestinal hemorrhage. Past medical literature reported that up to one-third of PXE pregnancies were complicated by hemorrhage, while more recent literature suggests that this complication is seen in less than one percent of pregnancies. Although it remains to be seen whether the incidence of hemorrhage is more frequent when compared to nonpregnant, age-matched women with PXE, affected women who are pregnant should still be followed closely.

The consequence of labor and delivery on ocular manifestations may deserve more attention. Labor and delivery increase the pressure in the superior vena cava, which may theoretically increase the severity of existing angioid streaks in the retina. If subretinal neovascularization is present at the time of delivery, the Valsalva maneuver may cause subretinal bleeding. The literature suggests that the presence of angioid streaks is a reasonable cause to recommend elective cesarean section. Therefore, pregnant women should have an ophthalmologic examination of the retina. In the presence of angioid streaks, the regular use of an Amsler grid is advised in order to detect the presence of neovascularization or hemorrhage.

Fetal complications reported include a slightly increased risk of first trimester abortion, intrauterine growth retardation, and prematurity. Intrauterine growth retardation is a consequence of hypoplasia and atrophy caused by diffuse calcification of the placenta. The increased risk of abortion is currently under debate, as recent literature suggests that there is not a dramatic increase in the risk of first trimester spontaneous abortions in women with PXE. Placentas have significantly more necrotic changes and mineralization in the setting of PXE. Mineral precipitates and matrix-type fibrinoid are found on the maternal side of the placenta. Problems during gestation with birth weight and with growth and development are similar in women with and without PXE. Therefore, the increased mineralization does not seem to affect the function of the placenta or fetal health.

TREATMENT

There is currently no cure for patients with PXE. The most logical and effective treatment they can be given is in the form of anticipatory guidance and preventative care. Patients should be advised to reduce cardiac risk factors through an appropriate diet and control of hypertension and cholesterol, if necessary. Avoidance of platelet inhibitors to reduce the risk of gastrointestinal bleeding and of activities that may increase the risk of retinal bleeding is also encouraged. These activities include heavy straining, head trauma, and smoking. Patients should also be examined regularly by an ophthalmologist, who may also recommend regular use of sunglasses and a diet rich in antioxidants.
A greater understanding of PXE may help to develop effective treatments in the future. Research has demonstrated that idiopathic hyperphosphatemia is associated with PXE. In addition, it has been reported that patients with PXE who have a history of low calcium intake as children seem to have a less severe clinical presentation later in life. A recent study employed this information in an attempt to identify an effective therapy. The research was based on the idea that using aluminum hydroxide would theoretically lower serum phosphate levels in patients, resulting in phosphorus depletion that would draw calcium out of the pathologic tissues. Fifty percent of patients participating in the six-person study experienced an improvement in their clinical disease involving the skin and vasculature. Individual serum levels of calcium and phosphorous were inconsistent with clinical results. There was also no evidence of ophthalmologic improvement. Hopefully these findings will allow further understanding of this condition and lead to established treatment options where none are currently available.

References:
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of treatment, the possibility for permanent sequelae such as visual loss that may be permanent or severe. Patients should be advised to discontinue therapy prior to initiation of treatment with tetracyclines and should be routinely checked for papilloma while on treatment. Continuous therapy with tetracyclines should be avoided because tetracycline is not known to be avoided because tetracycline is not known to cause pseudomembranous enterocolitis.

Photosensitivity

Photosensitivity manifested by an exacerbation sunburn and upon prolonged use of tetracyclines. This has been reported rarely with minocycline. Patients should minimize or avoid exposure to natural or artificial light during treatment with tetracyclines. If necessary, they should use sunscreen that will protect skin from sun exposure and discuss other sun protection measures with their physician.

PRECAUTIONS

General

Safety of SOLODYN™ beyond 12 weeks of use has not been established.

As with other antibacterial preparations, use of SOLODYN™ may result in overgrowth of nonsusceptible organisms, including fungi. Superinfection or pseudomembranous enterocolitis may be caused by the growth of resistant organisms or spores of fungi. If such an infection occurs, the patient should discontinue therapy with SOLODYN™ and receive appropriate therapy.

Autoimmune Syndromes

Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis, and endocrinopathies. Specific cases of serum sickness have been reported shortly after minocycline use. Symptoms may be severe or life-threatening and are frequently fatal. In symptomatic patients, liver function tests, ARIA, CBC, and serologic tests for autoimmunity should be performed to evaluate the use of all tetracycline-class drugs should be discontinue immediately.

Serious Skin Reactions

Postmarketing cases of anaphylaxis and serious skin reactions such as Stevens–Johnson syndrome and erythema multiforme have been reported with minocycline use in treatment of acne. Tissue Hypersensitivity

In rare instances, patients who are allergic to antibiotics are known to cause hyperepigmentation. Tetracycline therapy may induce hyperepigmentation in many patients, especially those with acne, skin, eyes, teeth, visceral tissue, oral cavity (teeth, mucosa), bone, cartilage, bone, and skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue changes have been reported upon prolonged administration. Skin pigmentation includes diffuse hyperpigmentation as well as over sites of scars or injury. Information for Patients

(See Patient Package Insert that accompanies this product for additional information to give patients)

Phototoxicity manifested by an exaggerated sunburn reaction has been reported with tetracyclines, including minocycline. Patients should minimize or avoid exposure to natural or artificial light during treatment with tetracyclines. If necessary, they should use sunscreen that will protect skin from sun exposure and discuss other sun protection measures with their physician.

Leukopenia

Leukopenia has been observed in premature human infants given tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissue, and can cause retardation of skeletal development on the developing fetus. Evidence of tetracycline accumulation in the animal literature and the human experience in premature infants treated in pregnancy (see PRECAUTIONS: Pregnancy section).

Gastro-intestinal effects

1. Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening. Therefore, it is important to consider the diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Tetracyclines are absorbed from the small intestine and alter the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxoid produced by Clostridium difficile is a principal cause of “colitis” associated with tetracyclines. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. Under such conditions, fewer than usual total doses are indicated, and if therapy is necessary, use of the tetracyclines for the treatment of acne may be advisable.

2. Hepatotoxicity – Postmarketing cases of serious liver injury, including reversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with minocycline use in treatment of acne. Renal effects

The metabolic effect on the tetracyclines may cause an increase in BUN. While this is a normal response in patients with normal renal function, in patients with impaired renal function, higher serum levels of tetracycline-class antibiotics may accumulate. Therefore, dosage should be reduced in patients with renal impairment. It is not known whether or not tetracyclines cross the placenta. Signs and symptoms of pseudomembranous colitis resolve after discontinu-
A 65-year-old female with a history of well-controlled hypertension, hypothyroidism, and urge urinary incontinence presented to our continuity clinic with a chief complaint of “excess scalp sweating” that occurred almost daily for “many years.” She admitted to associated facial flushing, with onset of both symptoms prior to menopause. She also noted that her symptoms lasted longer than the “hot flashes” of peri-menopause, often for many hours. She denied relation of symptoms to emotion, exercise or foods; associated palpitations, abdominal cramping, nausea, vomiting or diarrhea; shortness of breath; headache; visual change; lethargy; weight loss; or weakness. She had no concurrent axillary, palmar or plantar hyperhidrosis. She had stopped styling her hair because it was “too wet to curl” and had used topical aluminum chloride 10% (Xerac-AC®) and various herbal remedies without resolution of or improvement in her symptoms. When she started on oxybutynin (Ditropan XL®) for urge urinary incontinence, she noted no decrease in perspiration.

On physical examination, the patient was a well-appearing, mildly overweight female with obvious hyperhidrosis involving the scalp and forehead. Other than incidental solar lentigines and seborrheic keratoses, the rest of her physical exam was unremarkable. Laboratory evaluation to rule out pheochromocytoma was also unexceptional (Table I).

Since the patient had already failed topical aluminum chloride 10% solution, her treatment options included simple avoidance of triggers, oral or topical anticholinergics, or sympathectomy. Avoidance of triggering factors had not been successful for the patient in the past, and the side effects of additional oral anticholinergics or sympathectomy were unacceptable to the patient. The patient had read an article about the treatment of excess perspiration of the axillae with Botox® and asked if that would be effective for her scalp. Botulinum toxin type A has been used with success in axillary, palmo-plantar, gustatory and even frontal hyperhidrosis, but to our knowledge had never been used for primary scalp hyperhidrosis. Theoretically, botulinum toxin type A should be an effective therapy for hyperhidrosis regardless of the location.

As botulinum toxin type A has been used safely and effectively via intramuscular injections of the temporal and occipital scalp in the treatment of migraine and tension headache, it was felt to be safe to use for intradermal injection for scalp hyperhidrosis in those locations. After proper patient consent was obtained, 20 units of botulinum toxin type A (dilution of 100 units with 3 cc normal saline) was injected in a scattered pattern in the superficial dermis of the right temporal scalp as a test-patch over an area of 20 cm² via a 30-gauge hypodermic needle.  

At two-week follow-up, the patient still had positive Minor’s starch-iodine test on both the right and left temporal scalp. No further treatment was offered at that office visit, as response times to botulinum toxin type A have been reported to take up to three to four weeks after initial treatment of frontal hyperhidrosis and headache disorders. The patient was rescheduled for follow-up one week later. At that time, the patient had noticed decreased sweating on the right frontal scalp compared to her left and had noted no adverse side effects. Minor’s starch-iodine test confirmed the patient’s observations with a roughly 50 percent decrease in sweating on the right frontal scalp compared to the left frontal scalp (Figures 1 and 2). The patient wished...
to proceed with treatment of the rest of her scalp. Again, proper consent was obtained, and 100 units of botulinum toxin type A (dilution with 3 cc normal saline) was then injected intradermally via a 30-gauge needle in a scattered pattern over the frontal, temporal, parietal and upper occipital scalp. At three-week follow-up, the patient stated that she had only “two percent improvement” in her symptoms. Clinical examination, however, demonstrated her frontal, temporal and parietal scalp hair to be dry to the touch with over 90 percent improvement of hyperhidrosis (Figures 3 and 4). However, there was some moderate, residual hyperhidrosis of the lower occipital scalp. Minor’s starch-iodine test confirmed the clinical observations. Upon questioning, the patient felt she had not had significant symptom resolution because her neck and upper anterior chest were still perspiring. With reassurance that those areas not treated (the neck and upper chest) would still exhibit normal sweat function and were not expected to resolve with treatment of the scalp, the patient agreed she had much more significant improvement. After proper consent, 20 additional units of botulinum toxin type A, again at 3 cc dilution, were injected, following the prior treatment technique, in the lower occipital scalp.

At the time of preparation of this article, 12 weeks from initial injection, the patient continued to have improved quality of life (she again started to style her hair), decreased symptoms of scalp hyperhidrosis and acceptable clinical outcome (greater than 90 percent reduction in sweat production as evidenced with Minor’s sweat-iodine test) without any noticeable side effects.

Discussion

There are three major sweat glands in humans: eccrine, apocrine and apoeccrine glands. They have a generalized distribution and are under emotional, thermal and neural influence. Innervation of the eccrine glands is provided by post-ganglionic sympathetic fibers that have acetylcholine as their principal terminal neurotransmitter; these fibers are controlled by the hypothalamic sweat center. Continuous secretion of sweat provides a mechanism for thermoregulation and maintenance of electrolyte balance and keeps the thick stratum corneum moist to ensure fine tactile skills and pliability of the skin.

Hyperhidrosis is the excess function of eccrine sweat glands and may be generalized or focal. Hyperhidrosis may be primary or secondary to neural dysfunction, local heat, drugs, or changes in blood flow to sweat glands. The prevalence in the United States is 2.8 percent, affecting roughly 7.8 million individuals. The pathophysiology of hyperhidrosis is believed to be associated with over-stimulation via an autonomic pathway, either through thermal or cortical stimuli, but is poorly understood.

Primary focal hyperhidrosis is a disorder of excessive, bilateral perspiration occurring on the palms, soles, axillae and, less frequently, the craniofacial region. The disorder is characterized by visible, excessive sweating of at least six months’ duration without apparent cause and with at least two of the following features: bilateral and relatively symmetric perspiration, impairment of daily activities, frequency of at least once per week, age at onset of younger than 25 years, positive family history and cessation of focal sweating during sleep. It is a disorder with significant psychological and social impairment.

Intradermal botulinum toxin type A is a relatively new option in the treatment of primary focal hyperhidrosis, with significant data supporting its efficacy and safety. Botulinum neurotoxins are derived from the bacterium Clostridium botulinum and include seven distinct serotypes, identified as A, B, C1, D, E, F, and G. There are two commercially available subtypes, botulinum toxin type A (Botox®) and botulinum toxin type B (Myobloc®). They both block neuromuscular motor transmission by binding to receptor sites on motor nerve terminals and inhibiting the release of acetylcholine. However, botulinum toxin type A has been more extensively evaluated in the treatment of hyperhidrosis.

The light chain of botulinum toxin type A cleaves to a 25-kd synaptosome-associated protein (SNAP-25), a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. Botulinum toxin, when injected intradermally, produces temporary chemodenervation of both muscle and eccrine sweat glands, thereby reducing sweat output. Repeat injections may be required to maintain anhidrosis, as there is continuous turnover of neuromuscular junctions. Reports of adverse reactions to botulinum toxin type A injection include cutaneous eruptions; local, reversible muscle weakness; development of anti-botulinum toxin antibodies with resulting immunoresistance to treatment; and even anaphylaxis. Properly used, however, the incidence of complications is low, and their severity is mild.

While there is strong evidence supporting botulinum toxin type A treatments for axillary and palmo-plantar hyperhidrosis, there has been limited study in the management of craniofacial disease. Injection of botulinum toxin safely and effectively produces relative anhidrosis in the cranial region as the above case suggests.

References:

An 88-year-old female presented with a long history of right alar ulceration adjacent to a sclerotic white plaque of the right nasolabial fold. She had a history of trigeminal neuralgia of many years. She had undergone two attempts at Gasserian ganglion ablation without success.

She admits to parasthesias and rubbing the area when it is painful. An initial biopsy was done in 2002, which showed hypertrophic squamous epithelium with overlying scale crust consistent with an ulcerated seborrheic keratosis but no obvious malignancy. The patient reported a second biopsy of the area with a different dermatologist, which only showed "scar tissue."

At the time of presentation, she admitted to an enlarging ulceration of the ala. Another biopsy was performed, which revealed an ulcerated actinic keratosis. She was sent for Mohs micrographic surgery for a clinical basal cell carcinoma where the histology revealed morphea-like features but no malignancy. The scar was excised and a cheek rotation flap performed. A second area of ulceration was noted in the area of the scalp innervated by V1 of the trigeminal nerve. A biopsy was performed, and malignancy was not observed. The patient also admitted to manipulating this area due to paresthesias.

At follow-up, the patient had manipulated the sutures and scar and had developed ulceration due to chronic manipulation of the wound. After multiple treatments, topical preparations and advising the patient to stop manipulating the wound, the area finally healed. The trials of topical medications prescribed included: mupirocin, triamcinolone, vigilon, intralesional triamcinolone, and topical etanercept in a 25 mg/ml dilution. In spite of surgical intervention, multiple topical medications, and patient education about self mutilation, occlusion with vigilon was the only treatment that allowed complete healing. We believe that a bulky dressing that provided protection and did not allow further manipulation of the wound was the key to healing.
neuritis and herpes have been reported in the literature as well. Syringobulbia, postencephalitic parkinsonism, trauma, and idiopathic causes completes the list of implicated causes of trigeminal trophic syndrome.1,3,6

There is often a latent period before the ulceration begins, which can range from a few weeks to many years.1,2,3,4,9,11,12,17,22 It is more common in elderly women, although it has been reported in both sexes.1,2,5,9,10

Classically, the patient reports a slowly enlarging ulcer with a crescentic shape. It frequently involves the ala nasi but can involve the lip, cheek, eyelid, scalp, or brow.1,2 The ulcer is often mistaken for a basal cell carcinoma or squamous cell carcinoma by a health-care practitioner. Reports of paresthesia, hypo- or hyperesthesia, or pain in the trigeminal dermatome(s) are often described by the patient.1,3,9,12,17,20

Once the ulcers appear, they are persistent and heal very poorly.1,3,7,11,19,21

Self-mutilation due to the dysesthesias and parasesthesias results in iatrogenic ulcers. Typically, the first and second branches of the trigeminal nerve are affected, but a key to the diagnosis is the sparing of the tip of the nose. The tip of the nose is innervated by the medial nasal branch of the anteroethmoidal nerve.1,2,7,22

The differential diagnosis includes any condition with a chronic ulcerative lesion of the face. Basal cell and squamous cell carcinomas are often the first diagnoses to come to mind, with many patients being subsequently referred for Mohs micrographic surgery. Chronic infections such as herpes simplex virus, leishmania, fungi, syphilis, leprosy, blastomycosis, and paracoccidiomyces are also on the list.1,2,3,7,19,20 Other inflammatory or vasculitic diseases should be considered. Wegener’s granulomatosis, temporal arteritis, and pyoderma gangrenosum are frequently added to the list of ulcerative wounds.1,3,11,19,20

Multiple treatments have been tried without great success in any one area. Perhaps the most important factor in healing is educating the patient about avoidance of manipulation of the area.1,7,18,20 Due to the rarity of this disorder, most treatment options have been anecdotaly described. Pharmacologic therapies include pimozide, carbamazepine, chlorpromazine, amitriptyline, diazepam, vitamin B, and clonazepam.1,5 Immunosuppressive agents have been used with little or no benefit.

Surgical intervention has been described also and tends to be unsuccessful. Transcutaneous electrical stimulation, iontophoresis, nerve blockade, radiation, cervical sympathectomy, and stellate ganglionectomy have all been attempted with minimal success.1,3,4 Reconstruction with innervated skin flaps has been reported with variable success.1,3,4,7,17,20,22

Trigeminal trophic syndrome is a very rare disorder that requires appropriate recognition, work-up and management. The management of this persistent disorder requires patient education and a multifactorial approach to the healing of the ulcer. It is also important to obtain a good history, as this may give the practitioner a clue about the diagnosis. The work-up to exclude infectious, malignant, and vasculitic etiology is quite extensive; a good history may direct the practitioner to the appropriate work-up. It is imperative that practitioners recognize this condition, as it is becoming more commonly reported in the literature.

References:

Case Report

A 68-year-old, Caucasian female presented to the dermatology clinic for evaluation of an enlarging lesion on her left buttock. It had been present for approximately five months. The lesion was noted to be asymptomatic, without associated pruritis, tenderness, or burning. Past medical history was significant for mantle cell lymphoma, basal cell carcinoma, hypothyroidism, coronary artery disease, and diabetes mellitus type II. Her family history was negative for skin cancer.

On physical examination, a 3cm x 2.5cm, firm, bluish-red, shiny dermal nodule could be palpated on the patient’s left buttock (Figure I). The patient also appeared to have shotty lymphadenopathy of the bilateral axilla. Other systems were unremarkable.

A punch biopsy was taken from the lesion and revealed islands of small, blue cells extending from the upper papillary dermis to the deep reticular dermis. Closer examination of these blue cells revealed scanty cytoplasm, large, hyperchromatic nuclei, and numerous mitotic figures. Immunohistochemical staining was subsequently performed on the specimen. The tumor stained positive for cytokeratin AE1, AE3 and 20 was performed. The biopsy was seen when staining for cytokeratin AE1, A peri-nuclear, dot-like staining pattern was found for neuron-specific enolase, synaptophysin and chromogranin. The tumor stained positive for neuron-specific enolase, synaptophysin and chromogranin. Metastasis to the bilateral axillary lymph nodes was confirmed. No visceral organ involvement was detected, however. The patient was diagnosed with stage II Merkel cell carcinoma. The patient underwent radical lymph node dissection and radiotherapy. She is currently in remission.

Discussion

Merkel cell carcinoma is a rare, aggressive skin cancer accounting for less than 1% of cutaneous malignancies nationwide.1 This tumor is commonly referred to as a primary neuroendocrine carcinoma of the skin because it is known to arise from neuroendocrine cells. The actual origin of these cells is debatable. Although once thought to originate from the Merkel cell, a mechanoreceptor cell mediating touch and hair movement found in the basal layer of the epidermis, most Merkel cell carcinomas are actually found in the dermis, not the epidermis. Therefore, more recently, it has been postulated that Merkel cell carcinomas may actually originate from immature pluripotent stem cells that acquire neuroendocrine features during malignant transformation.2

Many hypotheses as to the etiology of Merkel cell carcinoma have been proposed, including deletion or translocation of the 1p36 domain on chromosome 1; loss of heterozygosity in the 3p21 domain of chromosome 1; arsenic exposure; and predisposition secondary to erythema ab igne, congenital ectodermal dysplasia, and Cowden’s syndrome.3 However, chronic ultraviolet radiation and immunosuppression are the two etiologies given most credence in the literature.1,2,3

Merkel cell carcinomas typically present in the late sixth to seventh decade of life, with a median age of 68 years.4 Only 50% of cases occur before the age of 50, typically appearing in those with congenital ectodermal dysplasia and Cowden’s syndrome. A slight male predominance exists, with men affected more than women in a 1.5:1 ratio.5 Additionally, the carcinoma tends to show a predilection for Caucasians, with prevalence rates of 0.23 cases per 100,000 persons in Caucasians versus 0.01 cases per 100,000 persons in African Americans.5 In fact, in a study performed by Agelli and Clegg that looked at the incidence and survival data collected from the Surveillance, Epidemiology, and End Results (SEER) program, it was found that the incidence rate of Merkel cell carcinoma in Caucasians was 11.3 times higher than in African Americans and 2.2 times higher than in all other ethnic groups combined.6

Immunocompromised patients, particularly those with solid organ transplants or HIV infection, are particularly prone to development of Merkel cell carcinoma. It has been estimated that individuals diagnosed with HIV have a relative risk of 13.7 for development of this tumor.3

Merkel cell carcinoma typically presents as a rapidly growing, solitary, dome-shaped nodule or a firm, indurated plaque smaller than 2 cm in diameter. The lesion is commonly red, violaceous, or purple in color. The epidermal surface is smooth and shiny with telangiectasias. As seen in our patient, the tumor tends to be asymptomatic. Ulceration and bleeding may occur; however, this finding is rare and generally signals advanced disease.4 Merkel cell carcinomas show predilection for actinically damaged areas, with 53% of cases occurring on the head and neck and 35% of cases occurring on the extremities. The most common location, however, is the periorbital area, where 46% of Merkel cell carcinomas are located.4

Figure 2 - Common locations for Merkel cell carcinoma on head/neck
Because the histology of Merkel cell carcinoma can easily be confused with that of undifferentiated small cell carcinomas, a combination of light microscopy in addition to immunohistochemistry or electron microscopy is often required to make a definitive diagnosis of Merkel cell carcinoma. On light microscopy, Merkel cell carcinoma appears as an intraepidermal tumor, oftentimes extending into the subcutaneous fat layer. The tumor is composed of diffuse, atypical, small, blue, ovoid–appearing cells arranged in clusters, rosettes, and cords. Upon close examination of the individual cells, one will see the characteristic triad of vesicular nuclei with small nucleoli, abundant mitoses, and apoptosis. These features, although typical of Merkel cell carcinoma, are not pathognomonic and can be seen in many undifferentiated small cell neoplasms, as well. Therefore, further studies using immunohistochemical stains or electron microscopy are typically performed before an accurate diagnosis of Merkel cell carcinoma can be rendered. Of these two methods, immunohistochemistry is most commonly utilized in clinical practice today.

Two stains, neuron-specific enolase and cytokeratin 20, are considered to be the most specific markers for Merkel cell carcinoma. These markers are present in 100% of Merkel cell tumors. Characteristically, staining with cytokeratin 20 produces a peri-nuclear, dot staining pattern that helps to distinguish Merkel cell carcinoma from oat cell carcinoma. Staining with neurofilament protein is commonly performed to further distinguish between these two entities as well. Other stains that may be used to make a diagnosis of Merkel cell carcinoma are chromogranin, synaptophysin, vasoactive intestinal peptide (VIP), calcitonin, adrenocorticotropic hormone (ACTH), somatostatin, and cytokeratin 8, 18 and 19. Staining with S-100 and leukocyte-common antigen is also typically performed in order to rule out other malignant entities such as melanoma and lymphoma, respectively.

Electron microscopy is another adjunctive test that can be utilized to make a diagnosis of Merkel cell carcinoma. Here, membrane-bound, dense-core granules and perinuclear whorls of intermediate filaments are characteristic of Merkel cell carcinoma.

Once a diagnosis of Merkel cell carcinoma is made, it is advised that patients undergo a complete history and physical examination to assess for satellite lesions and dermal seeding. Additionally, the presence of peripheral lymphadenopathy should be assessed. A baseline CBC, chemistry profile, and liver-function tests should be done. Chest radiography should be performed to rule out oat cell carcinoma, a tumor that closely mimics Merkel cell carcinoma. Also, a CT of the chest, abdomen, pelvis, and relevant nodal regions should be performed to exclude metastasis. Sentinel lymph node biopsy may be called for, as well.

Recently, the idea of including sentinel lymph node biopsy (SLNB) in the routine workup of patients with Merkel cell carcinoma has been introduced. Multiple studies have been performed to determine the efficacy of sentinel lymph node biopsy versus CT scans in screening for visceral and lymph node metastasis. These studies have found that imaging studies, including CT and PET scans, oftentimes fail to detect nodal disease until clinically apparent nodal involvement is present. In one such study performed by Gupta et al. at the Dana-Farber/Harvard Cancer Center in Boston, 122 patients with biopsy-proven Merkel cell carcinoma were evaluated for metastases by CT scans, PET scans, and sentinel lymph node biopsy. Results showed that scans of the lymph node basin had a low sensitivity (20%) and high specificity (87%) for the detection of nodal disease. In addition, imaging studies failed to detect nodal disease in 20% of patients who later had positive sentinel lymph node biopsies. Most important, results of sentinel lymph node biopsy caused a change in the stage designation in 39 of 122 patients initially presumed to have stage I disease. As a result, these patients went on to receive adjunctive radiotherapy, which was found to increase their relapse-free survival rate from 0% to 60%. Additionally, this study showed that results of sentinel lymph node biopsy may actually be predictive of disease-free survival.

In this study, patients with negative SLNB studies were found to have a higher rate of disease-specific survival at five years (97%) compared to patients with a positive SLNB (52%). Sentinel lymph node biopsy not only improved surveillance of nodal metastasis, but it also resulted in better therapeutic treatment and therefore improved overall relapse-free survival.

There are three stages of Merkel cell carcinoma: Stage I/A, II, and III. Stage I is indicative of local disease differentiated only by the size of the primary tumor. Stage II disease signifies regional lymph node involvement. A designation of stage III is given when systemic metastases beyond the regional lymph nodes, or into viscera, is apparent. Although it is estimated that 76% to 89% of cases at initial presentation exhibit stage I disease, studies show that between 50% and 75% of patients will develop regional lymph node metastasis at some point during the course of their disease. As well, distant metastases to the liver, bone, brain, and skin will eventually occur in up to 34% of patients. Because of the aggressive nature of the Merkel cell carcinoma, prognosis for most patients is oftentimes grim. Despite efforts to locally excise the lesion, studies show that local cutaneous recurrence is seen in 44% of patients, and relapse in nodal regions is estimated to occur in 76% of cases. Additionally, 55% of patients eventually develop lymph node metastasis, and 34% develop distant visceral metastasis. Studies show that positive involvement of the lymph nodes is the strongest predictor of distant spread and overall survival. In fact, a study performed at New York’s Memorial Sloan-Kettering Cancer Center that looked at survival patterns of 251 Merkel cell carcinoma patients over 46 months revealed a survival rate of 97% in those individuals with no involvement of their lymph nodes compared to 52% in individuals with pathologically positive nodes. Tumor stage at the time of initial diagnosis was another factor found to be predictive of patient survival: Patients with stage I disease often have five-year survival rates of 64%; stage II patients have an average five-year survival rate of 47%; and those with a diagnosis of stage III disease confer the worst prognosis, with five-year survival rates of only nine months. Female gender, tumor location on the limbs, localized disease, and younger age at initial presentation are thought to be positive predictors of survival.

Wide local excision is the treatment of choice for all stages of Merkel cell carcinoma. Typically, this is performed with 2.5cm to 3.0cm margins of normal–appearing skin. Because Merkel cell carcinoma is known to be a radiosensitive tumor, radiotherapy and chemotherapy are oftentimes used as adjunctive measures in treatment. This combination of therapies...
has been shown to reduce the risk of local recurrence and increase survival rates in many studies.\textsuperscript{6}

For stage I disease, wide local excision is oftentimes the mainstay of therapy. However, because of the high propensity for Merkel cell carcinoma to recur and to metastasize to local lymph nodes and distant visceral organs, most clinicians advocate adding radiation therapy in cases where negative marginal status after standard excision is not attained.\textsuperscript{4} A study performed by Allen et al. at Memorial Sloan-Kettering Cancer Center supports this reasoning, showing an 8% local recurrence rate for those with margin-negative excision compared with an 18% local recurrence rate when positive histologic margins were found.\textsuperscript{4} Further support is given in a study conducted by Lewis et al. that also looked at the disease recurrence and survival rates of Merkel cell carcinoma patients. This study showed that patients treated with surgery alone were 2.9 times more likely to develop a regional recurrence than those individuals who underwent combination therapy.\textsuperscript{4} Rates of distant metastasis were also found to be affected. Of those who underwent surgery alone, 87% of patients at one year and 69% of patients at five years were found to be free of distant metastasis. Comparatively, 87% of patients at one year and 79% of patients at five years were found to be free of distant metastasis when combination therapy was rendered.\textsuperscript{4} Also, higher survival rates were found in those who underwent combination therapy. Patients treated with surgery alone were reported to have a survival rate of 86% at one year and 50% at five years, compared to 89% and 57%, respectively, in those who underwent combination therapy.\textsuperscript{4}

Stage II Merkel cell carcinoma is treated with wide local excision and radiation therapy in most instances. As in stage I disease, the addition of radiation therapy has been shown to decrease nodal recurrence after treatment and to improve overall survival rates.

Because of the grave prognosis in those diagnosed with stage III Merkel cell carcinoma, treatment in this subset of patients is oftentimes purely palliative. Doxorubicin and cyclophosphamide are the most commonly used agents. Other agents such as cisplatin, etoposide, methotrexate, bleomycin, 5-fluorouracil, and vincristine have also been tried with some success.\textsuperscript{4}

Once treatment has been rendered, patients with Merkel cell carcinoma should be followed monthly for six months then every three months for the next two years. Biannual clinic visits are recommended thereafter.\textsuperscript{4} At each follow-up visit, a total-body skin exam should be performed, with specific attention to lymph node enlargement.\textsuperscript{2} A routine chest X-ray should also be performed periodically during the follow-up period.\textsuperscript{2} For early detection of recurrence, measurement of neuron-specific enolase has been found to be beneficial.\textsuperscript{2}

Although Merkel cell carcinoma is known to be a highly aggressive, cutaneous tumor with increased propensity for local recurrence and both regional-lymph-node and distant visceral metastasis, early detection and treatment may help to increase patient survival.

References:

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Hansen’s Disease: A Case Report and Review

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ABSTRACT

Leprosy, a debilitating and stigmatizing disease, is a mycobacterial infection caused by the acid-fast bacillus Mycobacterium leprae. Although there has been a decline in the prevalence of leprosy due to multi-drug therapy (MDT), this chronic, infectious condition is seeing a slight rise in incidence subsequent to the emergence of resistant strains and to an increase in the number of immunocompromised hosts. Leprosy is typically found in the tropics and subtropics; however, it is seen worldwide secondary to global travel and immigration. We present a case of leprosy, or Hansen’s disease, in an East Asian immigrant. Leprosy is a public health concern because of its potential to cause disabilities and the subsequent social consequences. However, when diagnosed early and treated promptly, leprosy has a good prognosis and an excellent survival rate. Through this case report and review of the literature, we hope to shed light on the pathogenesis, diagnostic criteria, current classification systems, reactions, histopathology, and treatment of leprosy.

Case Report

A 32-year-old, Asian, female immigrant presented with a one-year history of a progressively worsening rash. This pruritic, nontender rash began on her chest and spread to involve her face, ears, back, abdomen, and bilateral upper and lower extremities. The only remarkable systemic symptom was chest tightness. The patient had no significant medical history. No close contacts had a similar rash. On physical examination, the patient was noted to have indurated, erythematous-to-violaceous papules, plaques and nodules involving the forehead, nose, cheeks, ears, chest, back, abdomen, and bilateral upper and lower extremities (Figures 1, 2, and 3). No abnormalities were noted in her bloodwork. Histopathologic examination of one of her skin lesions depicted, on H&E staining, a Grenz zone (uninvolved papillary dermis) overlying foamy histiocytic and mononuclear cells (Figure 4). A Fite stain revealed red, rod-shaped organisms against a blue background of inflammatory cells (Figure 5). The subsequent diagnosis of lepromatous leprosy, or Hansen’s disease, was made.

Introduction

In the Old Testament, leprosy was depicted as a divine curse for sin; and in Buddhism, it was thought to be related to karma. The term “leprosy” originates from the Latin word leprous, which means defilement. During the medieval times, leprosy was endemic in Western Europe (Figure 63). Today, it is seen in developing countries of the tropics and subtropics, mainly India and Brazil, due to poor socioeconomic conditions. The deformities and disabilities associated with leprosy, and the notion that leprosy is incurable, have led to much suffering by its victims, both from the disease itself and from public discrimination.

The organism causing leprosy, Mycobacterium leprae, was first identified in armadillos, monkeys, and mice. The main modes of transmission occur via nasal secretions and open skin lesions. Key factors for spread of the disease include the degree of infectivity of the contagious person, the susceptibility of the healthy individual, and close contact between the two.

Diagnostic Criteria

Diagnosis of leprosy is made when at least one of the following cardinal features is present and the person is without proper treatment:
• Hypopigmented or erythematous skin lesions (macules and plaques) with definite sensory deficits
• Peripheral nerve thickening and/or tenderness +/- dysfunction
• Demonstration of bacilli in slit skin smear

If the two cardinal cutaneous features are absent and there is strong clinical suspicion, then skin smears to detect the acid-fast bacilli should be taken from both ear lobes and from one of the skin lesions.

Classification

There have been several different classification systems developed for leprosy. Two commonly used systems include the Ridley and Jopling classification and the World Health Organization (WHO) classification. Ridley and Jopling created a spectral classification based on the patient’s immune status. This system is divided into five main groups plus the indeterminate
**Table 1** - Classification of leprosy and characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full lepromatous (LL)</th>
<th>Borderline lepromatous (BL)</th>
<th>Borderline borderline (BB)</th>
<th>Borderline tuberculoid (BT)</th>
<th>Full tuberculoid (TT)</th>
<th>Indeterminate (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of lesion</td>
<td>Macules, papules, nodules, diffuse infiltration</td>
<td>Macules, plaques, papules, infiltration</td>
<td>Plaques and dome-shaped, punched-out lesions</td>
<td>Infiltrated plaques</td>
<td>Infiltrated plaques</td>
<td>Macules</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>Numerous</td>
<td>Many</td>
<td>Many</td>
<td>Unique, usually with satellite lesions or more than 5 lesions</td>
<td>One or a few (up to 5)</td>
<td>Variable</td>
</tr>
<tr>
<td>Distribution of lesions</td>
<td>Symmetrical</td>
<td>Tendency to symmetry</td>
<td>Evident asymmetry</td>
<td>Not diffuse; asymmetrical</td>
<td>Localized; asymmetrical</td>
<td>Not always defined</td>
</tr>
<tr>
<td>Definition of lesions</td>
<td>Vague; hard to define healthy and ill-affected skin</td>
<td>Vague; ill-defined external border</td>
<td>Vague; ill-defined external border</td>
<td>Well-defined</td>
<td>Well-defined</td>
<td>Impaired</td>
</tr>
<tr>
<td>Sensation</td>
<td>Not affected</td>
<td>Diminished</td>
<td>Diminished</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Bacilli in skin lesions</td>
<td>Many (globi)</td>
<td>Many</td>
<td>Many</td>
<td>Negative or weakly positive</td>
<td>Negative</td>
<td>Usually negative</td>
</tr>
</tbody>
</table>

And the papules and plaques may have punched-out centers. Sensation may also be diminished. Finally, lepromatous leprosy has a poor cell-mediated immune response and presents as numerous macules, papules, plaques, and nodules that are bilateral and symmetrical. It is often difficult to delineate between healthy and affected skin. The classic leonine facies (Figure 8), infiltration of the forehead skin, and maderosis, loss of the eyebrows, may be seen. Some peripheral nerves may be thickened.

**Reactions**

There are two main types of reactions that can occur in leprosy as complications of treatment. However, untreated patients have presented with these reactions as well. Patients with type I reaction (reversal lepra reaction) present with tender, erythematous, and edematous lesions; neuritis; edema of the hands, feet, and face; and sometimes fever.

This reaction is an example of a Type IV hypersensitivity reaction, where activation of the cell-mediated immune system by an unknown stimulus is the proposed mechanism.

Type I reaction is commonly seen in the borderline forms of leprosy (BT, BB, BL).

Patients with type II reaction (erythema nodosum leprosum reaction) present with several small, tender nodules with or without ulcers on the upper and lower extremities; neuritis; fever; iritis; and arthritis. This reaction is an example of a Type III hypersensitivity reaction and is considered to be a vasculitis resulting from immune complex deposition triggered by an increase in the humoral immunity.

Type II reaction is commonly seen in the lepromatous forms of leprosy (both BL and LL).

A third type of reaction rarely seen in leprosy is known as the Lucio phenomenon. Clinically, it manifests as symmetrical,
erythematous-to-black, necrotic lesions occurring on the extremities and occasionally the face. Fever and generalized lymphadenopathy may be present. This reaction is usually seen in untreated, specifically lepromatous leprosy patients.

**Histopathology**

There are three basic histologic patterns of leprosy: lepromatous, tuberculoid, and borderline. The lepromatous pattern has a Grenz zone, which is a band that delineates normal epidermis from the lymphoplasmocytic dermal infiltrate. Macrophages with engulfed bacilli and lipid droplets have a foamy appearance and are known as Virchow cells. Bacilli can be found alone or in globi in the dermis and are detected by the Ziehl-Neelsen stain. The tuberculoid pattern has a dermal infiltrate that appears as nodules (granulomas) of epithelioid cells that abut the epidermis. There are lymphocytes at the edges and Langhans giant cells at the center of these granulomas. Nerves are involved and can appear edematous. Finally, the borderline pattern of leprosy shows features of both the lepromatous and tuberculoid patterns, including Virchow cells (lepromatous) and epithelioid granulomas (tuberculoid). Predominance of one feature over the other depends on the borderline form (BL, BB, or BT). The indeterminate form of leprosy shows a nonspecific infiltrate of lymphocytes and histiocytes present around blood vessels, nerves, and adnexa. A few bacilli may be present in dermal nerve tissue when visualized with acid-fast stains.

**Laboratory Diagnosis**

The diagnosis of leprosy can be confirmed by detecting bacilli in nasal secretions, skin scrapings, and lymph nodes. As mentioned earlier, staining tissue with the Ziehl-Neelsen stain can detect bacilli; detection occurs in 100% of the lepromatous form of leprosy, 75% of the borderline form, and rarely in the tuberculoid form. Other tests utilized include neurological exam evaluating sensation, pain, and temperature; pilocarpine test to assess the parasympathetic system; and the Mitsuda test to obtain prognostic (not diagnostic) information about the form of leprosy. The Mitsuda test is a delayed-type hypersensitivity test that is administered and read similarly to the PPD skin test, which is used to detect tuberculosis. This test is positive in the tuberculoid forms of leprosy and negative in the lepromatous forms. Other, less-utilized tests include the fluorescent leprosy antibody (FLA)-abs to detect for the *M. leprae* organism; DNA amplification using polymerase chain reaction (PCR); and phenolic glycolipid-I (PGL-I), which is a marker for *M. leprae*.

**Treatment**

There are three important goals of treating leprosy: (1) early detection, (2) appropriate therapy, and (3) care and prevention of disabilities. Once the diagnosis is confirmed, early antibiotic therapy is crucial. There are several chemotherapeutic medications used against *M. leprae*. In 1942, sulfones were found to be effective against *M. leprae* and were the mainstay of therapy. After decades of monotherapy use of dapsone, resistant strains of *M. leprae* developed, which led to the implementation of the multi-drug therapy (MDT) recommended by the World Health Organization (WHO). The standard regimen is comprised of three drugs: rifampicin (rifampin), clofazimine, and dapsone. Other medications also utilized include ofloxacin, minocycline, levofloxacin, sparfloxacin, and clarithromycin. The duration (six months vs. 12 months) and dosage is dependent on the form of leprosy (paucibacillary single-lesion [SLPB], paucibacillary, or multibacillary). SLPB can be treated with a single,
therapeutic dose as opposed to a six-month regimen with similar results.1 (See Table 2 for the treatment regimen recommended by WHO.3)

There are a few main points regarding the key drugs of the multi-drug therapy worth noting here. Dapsone is a bacteriostatic -- or weakly bactericidal -- drug that is found to have occasional skin eruptions.1 Other side effects, including anemia, hemolysis, and methemoglobinemia, are more serious and are generally found in patients with a deficiency in glucose-6-phosphate-dihydropyridine (G6PD). 1,3 Rifampicin is bactericidal against M. leprae and kills 99.9% of viable organisms; this drug is enhanced by subsequent doses. Patients should be forewarned of the potential for reddish discoloration of the urine early in the treatment.1,3 Rifampicin is given monthly in a supervised setting to prevent drug resistance. Clofazimine preferentially binds to mycobacterial DNA, thereby inhibiting mycobacterial growth, and is slowly bactericidal.1,15 This drug is given in a loading monthly dose in a supervised setting to ensure adequate tissue levels in case an occasional daily dose is missed. A disturbing side effect is a brownish-black discoloration and dryness of the skin that resolves within a few months after discontinuing the drug.1,3

Essentially, the key to effective treatment of leprosy is strict adherence to the multi-drug therapy regimen. Leprosy rehabilitation is extremely important to prevent disability and sustain an active lifestyle.

**Conclusion**

This case report serves as a reminder to consider such conditions as leprosy in an era of global travel. A high index of suspicion coupled with a thorough history and physical examination, appropriate pathology and laboratory evaluation, early diagnosis, and prompt administration of therapy can lead to a good prognosis and an excellent survival rate. Having reviewed the current literature on leprosy, we have shed light on its pathogenesis, diagnostic criteria, common classification systems, reactions, histopathology, and the appropriate treatment regimen in hopes of de-stigmatizing this chronic, infectious yet treatable condition.

**References:**

Erythema dyschromicum perstans (EDP), or ashy dermatosis, is a peculiar, slowly progressive, macular hyperpigmentation that leaves a permanent discoloration. It is an acquired dermatosis that occurs most frequently in Central and South America, although cases have been described from many different parts of the world. At present, the etiology of EDP remains unclear, and there is no single, well-established therapy. This is a report of a 36-year-old, Hispanic female with extensive patches of EDP. In addition, clinical and histologic features of EDP are reviewed.

Case Presentation

The patient is a 36-year-old, Hispanic female with a one-year history of progressive, cutaneous pigmentary changes. These dark patches began on the patient's bilateral breasts and slowly spread to her upper back and the nape of her neck (Figures 1 and 2). The patient's medical history and review of systems was typical, and her family history was noncontributory.

Physical examination revealed a well-developed, well-nourished Hispanic female in no acute distress. Comprehensive cutaneous examination revealed multiple, hyperpigmented patches on the patient's breasts, upper back, and nape of neck. These patches on the nape of her neck had a minimally erythematous border with no evidence of scale.

The clinical differential diagnosis of these hyperpigmented patches included confluent and reticulate papillomatosis, Addison disease, post-inflammatory hyperpigmentation, hemochromatosis, drug eruption, macular amyloidosis, and figurate erythemas.

Histopathology of a representative biopsy of a hyperpigmented patch demonstrated a superficial, perivascular lymphocytic infiltrate with vacuolar interface change and pigment incontinence in the papillary dermis with macrophages (Figures 3 and 4).

Discussion

Erythema dyschromicum perstans (EDP), or ashy dermatosis, was first described by Ramirez in 1957, seen in Salvadorans as a peculiar, asymptomatic, ash-colored, macular hyperpigmentation that is slowly progressive and leaves a permanent discoloration. EDP is an acquired dermatosis occurring most frequently in South and Central America and the south-central United States, although it may occur in other areas. Some authors report this entity to be more common in females; however, there is no clear sexual predilection. Differential diagnoses include Addison disease, fixed drug eruption, arsenism, hemochromatosis, lichen planus, argyria, macular cerulae of pediculosis, pinta, leprosy, urticaria pigmentosa, figurate erythema, and other post-inflammatory conditions that produce pigmentation.

Histopathology of an early, active border may demonstrate a lichenoid dermatitis with basal vacuolar change and occasional Civatte bodies. The upper dermis shows a mild-to-moderate perivascular lymphohistiocytic infiltrate intermingled with melanophages. Often, exocytosis of the infiltrate into the epidermis occurs. In older areas, prominent melanin incontinence is evident, but the melanophages may extend deeper, perhaps because of appendageal structures. The inflammatory infiltrate often diminishes as the disease progresses, and there is a gradual loss of the rete ridge pattern.

Various causes of EDP have been reported but are not conclusive. EDP has occurred following ingestion of ammonium nitrate and treatment for hookworm infestation, as well as immediately after an X-ray contrast study. EDP has been reported in patients with HIV infection, as well as in patients with vitiligo. Speculation exists that EDP is a variant of lichen planus (LP) because EDP has accompanied, preceded, and followed lesions of LP and has similar histopathologic and DIF patterns.

Keratolytics, dapsone, oral and topical steroids, antibiotics, griseofulvin, ascorbic acid, chloroquine, estrogen, chemical peels, antihistamines, laser therapy, hydroquinone,
psychotherapy, placebo, and avoidance of sun and sun-blocking agents have been claimed to be at least partially successful as treatment options.\textsuperscript{2,3,11} Clofazimine has been used with some success apparently due to its immunomodulatory and anti-inflammatory effects.\textsuperscript{12,13} It is not clear if clofazimine produces improvement by masking the lesions with its characteristic yellow discoloration of the skin or by reducing the inflammatory infiltrate and, therefore, the post-inflammatory inflammation.\textsuperscript{4}

In summary, our patient’s case exemplifies EDP with the classically described macular hyperpigmentation. The patient reports to have noted minimal improvement thus far with topical retinoids in combination with topical hydroquinone. For many patients, EDP can be a chronically disfiguring and disconcerting problem that is resistant to treatment. Clinicians should suspect this entity whenever a large pigmented process presents so that therapy can be initiated as soon as possible. More research is needed to better our understanding of the pathophysiology of this condition and determine more effective treatment regimens.

References:
Case Report

A 45-year-old, Caucasian female presented with an erythematous nodule occurring along a cicatrix from an abdominoplasty performed several months prior. She had repeated, transsepidermal elimination of subcutaneous sutures, which were removed by the plastic surgeon without incident. The latest nodule, however, was markedly more erythematous and possessed cystic qualities on palpation. No other lesion was noted. Patient did report mild discomfort with no pruritis. Punch excision was performed with a 3mm punch (Figure 1).

Differential diagnosis included suture granuloma, foreign body reaction, contact dermatitis, perforating disorders, and traumatic cyst.

Routine histology revealed a cystic structure with transsepidermal elimination (Figure 2). Upon closer examination, architectural resemblance to a synovial cyst was seen (Figure 3, 5). Individual cells examined had large intracellular spaces with polygonal shapes. They were also noted to have marked metaplasia (Figure 4). A tentative diagnosis of cutaneous metaplastic synovial cyst was made.

Immunohistochemistry was performed to help confirm the diagnosis. Synovial cysts are characterized by positivity for CD68 and vimentin. These were both vividly positive (Figure 6 and 7).

The lesion was completely removed with the punch excision, and the surrounding tissue erythema resolved. To date, no recurrence has occurred, and no new lesions have arisen.

Discussion

Cutaneous metaplastic synovial cyst is a very rare, reactive process seen mainly in areas of previous trauma. This entity was first termed in 1987 by Gonzalez et al. as a phenomenon seen months to years following surgical procedures. There are only 19 other reported cases of this, all occurring in sites of previous trauma, including myocardial pacemaker implantation, laparotomy, joint prostheses, silicone breast implants and testicular implants. One non-surgical case occurred with previous rupture of a flexor tendon. One case in a patient with Ehlers-Danlos was also observed, but no direct correlation was made. It was felt that this patient's underlying fragile skin and abnormal healing led to the cyst. Connection with underlying articular spaces was not observed in any of the cases.

Cutaneous metaplastic synovial cysts often appear clinically, as in our case, as an erythematous, painful nodule in areas of previous trauma. There seems to be no predilection for age or sex. One reported case of multiple cysts occurring simultaneously has been reported. Recently, the first reported case of recurrent cutaneous metaplastic synovial cysts was described in England in a 34-year-old male following excision of an epidermal cyst.

Diagnosis is usually made histologically with a combination of architectural and immunohistological findings. Histological description includes a cystic cavity partially lined by a row of polygonal cells with extensive eosinophilic cytoplasm. Rounded metaplastic nuclei are occasionally located at the periphery of the cell. The cystic cavity is lined by fibrinous, amorphous material (Figures 3-5). This lining has a villus appearance with occasional projections into the cavity. One case described recently reported markedly elongated, villus projections that, to the clinician, gave the appearance of a “bag of worms.” Immunohistochemistry, as in our case, is generally positive for vimentin and CD68. These two markers are commonly positive in entities of mesenchymal origin and in normal synovium, respectively.

No definite theory of genesis exists; however, Goiriz et al. proposed a theory. During wound repair, foreign material...
resists penetration by fibroblasts, resulting in formation of a synovial-like membrane. In a surgical wound, air, fluid spaces or suture materials could remain trapped, leading to the large polygonal cells. Ultimately, this would form a structure which resembles a synovial cyst with metaplastic cells. Overall, trauma seems to be the only correlating agent; and until recently, the literature reported only single lesions.

Treatment for this entity is simple and usually curative – excision. One caveat is that a new cutaneous metaplastic synovial cyst could arise from this treatment, even up to several months after excision.1,2 Therefore, patient education must include the possibility of new lesions arising, even several years after the initial cause of trauma.

Conclusion

Cutaneous metaplastic synovial cyst is a very rare entity which usually occurs as a tender, erythematous, cystic lesion in areas of trauma. This should be included in a clinician's differential for new erythematous nodules and papules in previous lines of trauma, especially if suture granuloma is suspected. Awareness of this phenomenon should become part of the clinician's and dermatopathologist's knowledge base.

References:
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Case Report:

A 28-year-old man presented to our office for evaluation of a rash on his right forearm that had been expanding during the previous eight weeks. He complained of tenderness, itch, and yellow, pus-like discharge. He denied any antecedent trauma or insect bites. In addition, he denied systemic symptoms such as fever, chills, myalgia or arthralgia.

Three weeks prior to presentation, he had seen his primary physician, who had given him topical halobetasol 0.05% (Ultravate), oral prednisone, and ciprofloxacin for a blistering eruption on the arm, thought to be an allergic contact dermatitis. He was unsure of the dosage of the medications, but reported worsening of the condition and stopped using the prescribed therapy against the advice of his physician. He denied any cardiovascular, pulmonary, gastrointestinal or endocrine illnesses. He had no known drug allergies. His family history was significant for diabetes mellitus type II in his father. He drank alcohol socially and did not smoke. Interestingly, he worked as a sandblaster!

Initial examination was documented as "an irregular, erythematous, annular patch with a raised border and overlying scale and crust" located on the right medial forearm. The complete examination of the skin, oral mucosa, hair and nails revealed early androgenetic alopecia. There was neither cervical nor axillary lymphadenopathy. No additional studies (i.e. KOH, bacterial, fungal cultures) were performed, and no image was obtained.

The patient was presumptively diagnosed with tinea corporis and treated with oral ketoconazole tablets, 200mg daily, and betamethasone 0.05%/ clotrimazole 1% (Lotrisone) cream. He called three days later to report that "his infection was getting out of control" and that he was "very worried." He was told to return to the office immediately.

Follow-up examination of the right, dorsal forearm revealed a discrete, well-demarcated, 4.2cm x 5.6cm, erythematous, violaceous, ulcerating plaque with an irregular, serpiginous, raised border. The lesion had associated blue-black, hemorrhagic bullae as well as friable, pustular areas (Images 1, 2). Further physical examination was non-contributory.

The patient was questioned further about his medical history, and he revealed that he had been diagnosed with ulcerative colitis three years earlier. This had required treatment with balsalazide (Colazal), mesalamine (Asacol), and azathioprine (Imuran), as well as prednisone as needed for a flare-up of symptoms. He explained that he went off his prior treatment regimen against the advice of his physician because he felt no symptoms of his disease.

A 4mm punch-biopsy specimen was obtained from the advancing edge of the lesion and sent for dermatohistopathology. A PAS stain was requested, but no cultures were obtained. The epidermis exhibited parakeratosis and irregular acanthosis with spongiosis and exocytosis (Image 3). Within the dermis, there was a massive inflammatory infiltrate composed of lymphocytes, numerous sheets of neutrophils, histiocytes and rare eosinophils (Images 4, 5). Hemorrhage was extensive. The PAS stain failed to reveal fungal elements (Images 6, 7). The findings were those of intense
inflammation with ulceration that could have been quite compatible with pyoderma gangrenosum or other forms of pyoderma. There was no evidence of dermatophyte infection or malignancy.

Our differential diagnosis included pyoderma gangrenosum, insect/spider bite reaction, Sweet's syndrome, primary bacterial cellulitis/panniculitis, bullous tinea corporis, exogenous tissue injury (“outside job” from occupational sandblasting), vasculitis, necrobiosis lipoidica (NLD), atypical mycobacterial infection, and possibly an aggressive neoplasm.

Following the biopsy, his dermatitis was empirically treated with cephalexin (Keflex) 500mg TID and mupirocin 2% ointment to the affected area TID. We declined to prescribe an oral corticosteroid due to the phenomenon in which cutaneous trauma initiates the development of PG. The ulcerative or classical type usually presents on the upper extremities, dorsal hands, or face. It is most often encountered in the setting of hematological malignancies such as acute myelogenous leukemia and myeloproliferative disorders such as IgA monoclonal gammopathy. It can be severely hemorrhagic, and patients may have systemic symptoms of fever, myalgia and arthralgia.

Pustular PG occurs as multiple, small pustules that may or may not progress to a classical lesion of PG. Inflammatory bowel disease or Behcet’s disease may be associated conditions.

The superficial, granulomatous type of PG usually follows major trauma or surgery, and acute myelogenous leukemia or hairy cell leukemia, monoclonal gammopathies (IgA paraproteinemias/myelomas), hepatitis, SLE, Sjogren’s syndrome, Sweet’s syndrome, Behcet’s, and other autoimmune diseases. PG can arise before, during or after diagnosis of any of the associated systemic conditions. Its pathophysiology is often idiopathic and poorly understood, but altered neutrophil chemotaxis is thought to play a major role in this highly inflammatory, neutrophilic dermatosis.

PG is encountered worldwide, with diagnosis most commonly occurring during the third to sixth decades of life. Women are more often affected than men, and childhood involvement is rare (4%). Pathergy, the phenomenon in which cutaneous trauma initiates the development of the disease, occurs in approximately 30% of all cases.

There are several recognized variants of PG. The ulcerative or classical type usually begins as a small, tender papule or pustule on an erythematous base, which rapidly expands outward. A common misdiagnosis is that of a spider bite, due to the pain and clinical presentation. The area becomes purulent and ulcerates with necrotic, undermined borders that have a gun-metal gray color. The classical type most often presents on the pretibial legs. Lesions typically heal as an atrophic, cribriform, pigmented scar. Healing may occur spontaneously or only after treatment of an underlying systemic condition, most commonly inflammatory bowel disease.

Atypical or vesicobullous PG most often presents on the upper extremities, dorsal hands, or face. It is most often encountered in the setting of hematological malignancies such as acute myelogenous leukemia and myeloproliferative disorders such as IgA monoclonal gammopathy. It can be severely hemorrhagic, and patients may have systemic symptoms of fever, myalgia and arthralgia.

We diagnosed this patient with atypical pyoderma gangrenosum based on clinical and histopathological findings as well as the history of ulcerative colitis and non-compliance with medical treatment. The hypothesis is that his occupation as a sandblaster placed him at risk for superficial injury to unprotected skin. He reported that he often wore little protection on the job, and small dust particles were always bombarding his skin. These injuries most likely resulted in pathergy of the involved extremity and initiation of the inflammatory process. A detailed discussion stressed the need for compliance with therapy and protection of his skin while working as a sandblaster. Clobetasol 0.05% (Temovate) cream was prescribed BID, and he was told to follow up in two weeks. The patient is assumed to have resolved completely as he has not kept any subsequent appointments.
to the skin. There is less neutrophilic inflammation compared to the other variants, and it is not aggressive. This type favors the trunk and may be related to Wegener’s granulomatosis.

Pyostomatitis vegetans is PG occurring on the oral mucous membranes. It is encountered in the setting of inflammatory bowel disease. Other potentially involved sites include peristomal, labial, vulvar, scrotal, and perianal areas.

With all of the above types of pyoderma gangrenosum, neutrophilic inflammation may occur extracutaneously. Neutrophilic infiltrates may affect the lungs (most common), heart, bones, eyes (peripheral ulcerative keratitis), GI tract, liver, pancreas, spleen, kidneys, lymph nodes and central nervous system.

The differential diagnosis is broad and includes vascular occlusive disease, vasculitis, carcinoma, infection, exogenous tissue injury, insect bite, eczema, sporotrichosis, Sweet’s syndrome, Churg-Strauss syndrome, Wegener’s granulomatosis, tuberculosis gumma, syphilitic gumma, deep fungal infection, factitial disease and other conditions. In order to accurately diagnose PG, it is imperative to rule out other diseases via a comprehensive history, physical examination and medication review. A biopsy should be obtained from an advancing edge of the lesion, and special stains should be employed. Histopathological findings in PG are non-specific but usually include massive neutrophilic inflammation, hemorrhage, and necrosis. It is necessary to culture for bacterial, viral, fungal, and mycobacterial organisms. Basic laboratory evaluation includes a CBC with differential, comprehensive metabolic panel with liver function tests, hepatitis panel and urinalysis. If PG is considered, obtain serum and urine protein electrophoresis, ANA, ANCA, antiphospholipid antibody, and an RPR. A CXR and GI tract studies may be recommended as well.

Treatment of PG is usually directed at the underlying systemic illness, if present. In those cases in which no underlying systemic illness can be found, there are many treatments available. In addition to topical therapies, including superpotent steroids, cromolyn sodium 2%, tacrolimus, pimecrolimus and topical and oral antibiotics, the standard treatment of choice is either oral systemic corticosteroids at a dosage of 1 to 2 mg/kg/day or pulsed IV methylprednisolone until resolution. In steroid-unresponsive cases, other immunosuppressants may be used. These include cyclosporine, azathioprine, mycophenolate mofetil, cyclophosphamide, chlorambucil, tacrolimus, intravenous immunoglobulin (IVIg), thalidomide, etanercept, infliximab, adalimumab, clofazimine, dapsone, metronidazole, colchicine, methotrexate, SSKI, and nicotine. In a recent study published in the journal Gut, 69% of patients treated with infliximab at an infusion dose of 5 mg/kg improved clinically whether they had associated inflammatory bowel disease or not.

In addition to pharmacologic treatment, local wound care should be employed to prevent secondary bacterial contamination and sepsis. Hyperbaric oxygen may be used to assist in the healing of refractory cases. Finally, surgical debridement should be avoided due to the risk of pathergy. Recurrence and chronicity is not uncommon.

References:

Male with Multiple Pigmented Eccrine Hidrocystomas

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ABSTRACT

Eccrine hidrocystoma is generally regarded as a rare tumor of the eccrine sweat glands and is typically confined to the cheeks and periorbital areas. We report a case of a 53-year-old male with multiple, darkly pigmented lesions on his malar cheeks and temple areas. Histopathology revealed a cystic space lined by one to two layers of cuboidal cells, consistent with eccrine hidrocystoma. In addition, the interior of these cysts were filled with pigmented material. These lesions were treated by simple incision using a comedone extractor, with resolution of the majority of the lesions at six months.

Introduction

Robinson1 first described eccrine hidrocystomas in 1893. Ninety percent of his patients were women who worked in hot humid conditions (cooks and washer-women) and had multiple lesions. Their lesions were characterized as multiple, small papules affecting the periorbital and malar areas. In 1973, Smith and Chernosky2 described their group of patients, who most commonly had a single lesion. In contrast to Robinson, 40% of their patients were men. These two clinical presentations have become known as the “classic Robinson” and the “Smith and Chernosky” types of hidrocystoma. Although men commonly have one or two lesions, there have been few reports of men with multiple lesions.3,4 We describe a man with multiple, pigmented, eccrine hidrocystomas of the cheeks and temples.

Case Report

In October 2005, a 53-year-old, white male presented complaining of dark spots on his temples. He said that these spots had been present for a number of years. He felt that these spots were “black-heads,” and he occasionally poked them with a needle and expressed black material. The lesions had not changed in size with seasonal variation or environmental temperature, and there was no family history of similar lesions. The patient generally worked indoors and had not experienced any other trauma to these areas. He denied any consumption of silver salts or minocycline. Examination revealed multiple, deep-seated, black-to-blue pigmented lesions, measuring 0.5 to 1.0 mm in diameter, located on his temples bilaterally (Fig. 1) and on his malar cheeks. No abnormalities of hair, nails, or teeth were noted. The differential diagnosis included deep-seated comedones, exogenous pigment, and pigmented milia.

A biopsy specimen revealed a solitary, dilated cystic structure in the dermis lined by one to a few layers of short, cuboidal epithelium (Fig. 2). The cystic structure was surrounded by a flattened layer of cells. Pigment was noted within the lumen of the cyst. These features indicated a diagnosis of pigmented eccrine hidrocystoma.

These cysts were incised with a comedone extractor, and a black-currant-jelly-like material was expressed. This was repeated two months later to the remaining lesions. The patient was seen six months later, and a majority of his lesions had resolved.

Discussion

Eccrine hidrocystomas can appear as solitary (most common) or multiple lesions, ranging in size from 0.5 cm to 1 cm. Multiple lesions are observed as small papulonodules having a prominent surface with a translucent, intensely bluish dome, and they may be frequently confused with comedo. Although cheeks and eyelids are the commonly involved sites,1 the head, trunk and popliteal fossa have been reported.5 Lesions are cystic, and the diagnosis can be confirmed by piercing with a pin to exude a translucent fluid. Frequently, there is a history of increase in both number and size of lesions on exposure to heat.

The cause of multiple eccrine hidrocystomas is unknown. In his original article, Robinson1 surmised that the cause was an abnormality in the sweat duct or in the surrounding connective tissue, causing obstruction to the outflow of sweat. He emphasized the importance of a hot environment as a common factor in all of his patients. However, in our patient, a hot environment, exercise, or excessive sweating did not seem to play a role. Others, including Murayama6 et al., have suggested that eccrine hidrocystomas are a hamartoma-like disorder that becomes prominent as a result of retention of perspiration.

Apocrine hidrocystomas pose a problem in clinical and histopathologic differentiation with eccrine hidrocystomas. Smith and Chernosky2 stated that apocrine hidrocystomas are often larger, a darker blue in color, and are less likely to be periorbital.

In addition, unlike eccrine hidrocystomas, apocrine hidrocystomas generally do not present with multiple lesions and do not change or become symptomatic in hot weather. Histopathologically, eccrine hidrocystomas, which are lined by two layers of cuboidal epithelial cells, differ from apocrine hidrocystomas by the absence of decapitation secretion, PAS-positive granules, and myoepithelial cells. Eccrine hidrocystomas are usually unilocular, with eccrine-duct remnants close to the cyst in the dermis, whereas apocrine hidrocystomas are multilocular.11

From a histopathological point of view, most authors consider multiple hidrocystomas to be cystic structures arising from the excretory portion of eccrine glands.11,12
However, some authors believe that multiple hidrocystomas of the face are apocrine hidrocystomas in which the characteristic “decapitation” secretion has been effaced by the pressure of the cyst contents against the lining epithelium, and that only after serial sections is it possible to identify some areas of the cyst lining showing apocrine secretion in the luminal border of columnar cells.13

To help distinguish apocrine from eccrine hidrocystomas, S-100 staining may be useful. Eccrine hidrocystomas are usually positive, although the “Robinson type,” as in our patient, has been reported as negative.14 Some authors stress the importance of electron microscopy in differentiating between eccrine and apocrine hidrocystomas; however, this is often not clinically feasible.15 Additionally, apocrine hidrocystoma and eccrine hidrocystoma have been proven to be distinct tumors defined by the expression of keratins and human milk-fat globulin 1.16

The treatment regimen of multiple eccrine hidrocystomas is difficult. Surgical incision,17 excision or aggressive destructive procedures may be effective, but the risk of scarring, ectropion, and postinflammatory hyperpigmentation may limit these options.18 Atropine has been reported to be useful,19 but systemic side effects may occur even if it is used topically,19 and the improvement is only transitory. Topical scopolamine has been reported to be effective by some investigators20 but not others.19 Other novel treatment options reported with success include the use of botulinum toxin and pulse dye laser.21,22

Conclusions

Herein we have presented an unusual case of multiple pigmented eccrine hidrocystomas arising on the face of a 53-year-old male. We have reviewed the literature in regard to history, presentation, etiology, and histopathology of eccrine hidrocystoma. This case is unique due to the paucity of reports of pigmented eccrine hidrocystomas in males.7 We treated our patient with simple incision of his lesions. In this paper, we also reviewed other treatment modalities.

References:

**ABSTRACT**

Xanthochromia striata palmaris (XSP) is a rare skin disease consisting of yellow-orange macules exclusively along palmar creases. It is of great consequence because it is a cutaneous manifestation of an underlying type III hyperlipidemia, in which there is an elevation of total plasma cholesterol and triglycerides. We present a case of a 48-year-old female with a four-year history of this disorder, and we review the five different types of hyperlipoproteinemias (HLPs).

**History**

A 48-year-old, Caucasian female presented to the office with the complaint of “orange palms.” For four years, she had had asymptomatic, “orange” areas in both her palm creases bilaterally (Figure 1). She had shown this to several other physicians in the past, but no diagnosis had ever been made. She had not used any topical medications or over-the-counter hand creams to treat this.

Past medical history revealed only migraine headaches and herniated discs in her cervical and lumbar spines secondary to a motor vehicle accident four years ago. She denied any coronary artery disease, hypertension, diabetes, hypercholesterolemia or hypertriglyceridemia.

Past surgical history was significant for subsequent herniated-disc repair as well as neck fusion. She was allergic to propoxyphene. She had been taking amitriptyline for three years to alleviate her migraine headaches, but she discontinued this therapy one year ago. She revealed that she smoked one pack of cigarettes a day for more than 20 years. Family history was unhelpful since she was adopted. She did admit, however, that her 24-year-old son, who runs 6 miles a day, has a past medical history significant for hypercholesterolemia.

**Physical**

On physical examination, there were yellow macules distributed along all of her palm creases bilaterally. Her soles were spared. No lesions were noted anywhere else on her body, including the rest of her hands, knees, elbows, flexures and sclerae.

A skin biopsy was taken from her left palm, and a complete cholesterol panel was ordered along with a complete blood count, complete metabolic panel and thyroid-function tests.

**Histology and Blood Work**

The skin biopsy revealed a dermal interstitial infiltrate with foamy histiocytes containing cholesterol, consistent with xanthochromia striata palmaris (Figure 2).

Blood work was all within normal limits except for the cholesterol panel, which showed a total cholesterol of 523 (140-200), triglycerides of 684 (<150), low-density lipoprotein (LDL) of 72 (<100) and high-density lipoprotein (HDL) of 50 (>50).

**Treatment**

The patient was referred for therapy to her primary care physician, who placed her on atorvastatin and ezetimibe for cholesterol and triglyceride control. EKG and stress tests were normal. She is to have regular follow-up with her primary care physician in the future. Within two weeks of being on therapy, her cutaneous disease was 40% improved.

**Review of the Literature**

In “Hamlet,” Shakespeare referred to hands as “pickers and stealers,” since these are two of their more notorious functions. Hands may also be the first clue to internal disease. Examples include the Gottron’s papules on the interphalangeal joints as a marker for dermatomyositis; telangiecstasias on the palms as an indicator of hereditary hemorrhagic telangiectasia; and petechiae on the palms as a sign of Rocky Mountain spotted fever.

Our patient presented with yellow macules that followed the distribution of the creases of the palms. This is known as xanthochromia striata palmaris (XSP), which is a very rare type of cutaneous xanthoma. Xanthomas are cutaneous infiltrates of histiocytic foam cells containing lipids, clinically presenting as yellow macules, papules or nodules on the skin. Cutaneous xanthomas are usually markers for underlying hyperlipoproteinemia (HLP).

While the term “hyperlipidemia” refers to an elevation of lipids in the blood, “hyperlipoproteinemia” is more specific because these lipids, which are insoluble in water, are transported in the blood attached to specialized proteins. These lipoproteins may be classified based on density. The five main lipoproteins, from lowest to highest density, are as follows: 1) chylomicrons; 2) very low density lipoproteins (VLDLs); 3) intermediate density lipoproteins (IDLs); 4) low density lipoproteins (LDLs); and 5) high density lipoproteins (HDLs). These plasma lipoproteins contain varying degrees...
of cholesterol, triglycerides, phospholipids and specialized proteins called apoproteins. The formation of lipoproteins may be of exogenous or endogenous origin.

In the exogenous cascade, chylomicrons, which are a major source of triglycerides, are formed in the intestine in response to ingestion of dietary triglycerides. These chylomicrons also contain cholesterol (from the diet); apoproteins B48 (required for chylomicron secretion into the lymphatics); apoproteins A, E, and C; and phospholipids. It is apoprotein CII within the chylomicron that activates lipoprotein lipase in the capillary walls. This enzyme hydrolyzes the triglycerides from the chylomicron to liberate fatty acids, which are then transported into the cells of the body. As more of the triglyceride is removed, the chemical composition and size of the chylomicron changes; it then becomes a chylomicron remnant. This chyloremnant, which retains apoprotein E at the surface, attaches to the apoprotein E receptors in the liver and becomes catabolized by these hepatic cells.

In the endogenous cascade, VLDLs containing abundant amounts of triglycerides are synthesized in the liver. Stimuli for this pathway include obesity, high-carbohydrate diet, and alcohol consumption. VLDL contains apoprotein B-100, which is secreted by the liver. VLDL also contains apoprotein CII, which activates lipoprotein lipase in the capillary wall. This allows for continued hydrolysis of the triglyceride within the VLDL, which subsequently becomes an IDL.

LDLs are metabolized after binding to specific liver and extrahepatic tissue-cell receptors that recognize the apoprotein B-100 component of the LDL. Some of the IDLs attach to the apoprotein-E receptors in the liver and are subsequently catabolized there. The IDLs that escape hepatic uptake are transformed into cholesterol-rich apoprotein B-100 LDLs. LDL is then subsequently internalized and degraded, thus increasing the cellular content of cholesterol and phospholipids.

Genetic mutations of lipoproteins may alter their metabolism, leading to their subsequent elevation in the plasma. The most widely used classification of hyperlipoproteinemias (HLPs) is that of Fredrickson's, in which there are five main types: I, IIa, IIb, III, IV, V.

XSP as seen in our patient is almost pathognomonic for type III HLP. In this condition, a genetic mutation of apoprotein E, known as APOE2, is present on the lipoproteins. This APOE2 has a decreased ability to bind to hepatic receptors, resulting in impaired clearance of chylomicron remnants and IDLs. This results in hypertriglyceridemia and hypercholesterolemia, as seen in our case. These patients are at risk for developing premature atherosclerosis and subsequent myocardial infarctions (MI) and cerebral vascular attacks (CVA). There is also an increased risk of multiple myeloma and biliary cirrhosis. Cutaneous lesions in type III HLP include plane xanthomas, tuberous xanthomas and eruptive xanthomas. Plane xanthomas are soft, yellow macules or plaques containing cholesterol that can occur on any site but are most commonly seen on the eyelids and hands. Tuberous xanthomas are firm, yellow-to-red nodules containing cholesterol that occur in areas of pressure such as the knees, elbows, knuckles and buttocks. Eruptive xanthomas are small, red-to-yellow papules containing triglycerides, and they have an erythematous halo around the base. They may be pruritic and tender, and they may appear in crops over pressure points such as the extensor surfaces, buttocks and shoulders.

In type I HLP, there is a deficiency of the enzyme lipoprotein lipase. This leads to an impaired clearance of chylomicrons and, thus, hypertriglyceridemia. The most characteristic skin manifestations are eruptive xanthomas. Systemically, abdominal pain, hepatosplenomegaly and pancreatitis may occur. Ophthalmic examination may reveal lipemia retinallis, which consists of a milky appearance of retinal vessels and is a marker for this disease.

In type II HLP, there is a deficiency of LDL receptors. Since the LDL cannot be internalized, there is an increase in plasma LDL and consequent hypercholesterolemia. Sometimes, triglycerides are also increased from slightly elevated VLDL. Cutaneous manifestations of this disease include intertriginous plane xanthomas, xanthelasma, tuberous xanthomas and tendinous xanthomas. Xanthelasma are yellow plaques containing cholesterol on the eyelids. They are not diagnostic of hypercholesterolemia because they may also be seen in patients with normal plasma-cholesterol levels. Tendinous xanthomas are clinically similar to tuberous xanthomas but occur over tendons, such as the Achilles' tendon. Patients with type II HLP are at significant risk for developing premature coronary artery disease.

In type IV HLP, there is an increase in VLDL, which leads to elevated plasma-triglyceride levels. It is not clear what the molecular defect is. Patients are usually obese and have glucose intolerance and hyperinsulinemia, which further increases VLDL synthesis in the liver. Clinically, eruptive and plane xanthomas occur. Systemically, premature cardiovascular disease and pancreatitis are common.

Finally, in type V HLP there is a defect in the apolipoprotein C-II gene, which results in a deficiency of lipoprotein lipase activator and subsequent inactivity of lipoprotein lipase. This results in an increase in chylomicrons and VLDL, leading to hypertriglyceridemia. The main cutaneous manifestations are eruptive xanthomas. Abdominal pain, hepatosplenomegaly, pancreatitis, hypertension and polynuropathy may also occur in these patients.

Diagnosis of a primary HLP begins with a detailed history and physical examination. This is followed by a measurement of both plasma cholesterol and triglycerides in the fasting state. Other medical diseases that may increase triglycerides and cholesterol must be ruled out, as well; these include myxedema, obstructive liver disease, chronic renal failure and diabetes mellitus.

Treatment of primary HLP is based upon dietary restriction of fat and cholesterol, exercise, and maintaining ideal body weight. Medications can also be helpful if diet and exercise are not sufficient; these include HMG-CoA reductase inhibitors, bile acid-binding resins, nicoitonic acid and fibric-acid derivatives.

Dermatologists are often in a unique position to first diagnose an occult internal disease because the skin may be a window to internal problems. Our patient had been seen by other physicians who were unable to make the proper diagnosis because they were not familiar with XSP. It is important, then, that dermatologists be aware of this and other rare, cutaneous manifestations of internal disease, and it is for this reason that we have presented this case. By making the correct diagnosis and promptly instituting therapy, this patient may have been saved from developing an MI or CVA later in life.

References:

Follicular degeneration syndrome (FDS) refers to a form of common scarring alopecia occurring mainly in African-American females. Historically, it was referred to as “hot comb alopecia” because of the common hair styling techniques used at the time of initial description. FDS is a subtype of central, centrifugal scarring alopecia with characteristic clinical and histological findings. The disease usually begins in the crown and slowly spreads peripherally, revealing smooth, shiny scalp. Alopecia is incomplete, with some normal hair remaining in the areas of involvement. The necessary histological feature is premature desquamation of the inner root sheath. Later disease shows typical histological features of this disorder. The pathogenesis of the condition and proposed mechanism for clinical appearance is fairly commonly seen in practices with a high percentage of ethnic-skinned patients, very few articles in the literature have been published, with the last comprehensive review by Sperling LC in 1992. A search on PubMed under keywords “follicular degeneration syndrome” reveals only eight reference articles, only two of them containing the syndrome name in their title. This article describes the syndrome as well some of the common issues and controversies accompanying it.

**Background**

The first description of this clinical entity dates back to 1968 by Lopresti et al., who had numerous other titles, including “hot comb alopecia” and “central centrifugal scarring alopecia” (CCSA), as well as “ethnic variant of cicatricial alopecia.” Even though the condition is fairly commonly seen in practices with a high percentage of ethnic-skinned patients, very few articles in the literature have been published, with the last comprehensive review by Sperling LC in 1992. A search on PubMed under keywords “follicular degeneration syndrome” reveals only eight reference articles, only two of them containing the syndrome name in their title. This article describes the syndrome as well some of the common issues and controversies accompanying it.

**ABSTRACT**

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curliness of black hair, several techniques have been used to increase the manageability and the ability to style it. Pomades, hot combing, and chemical relaxers have all been utilized to achieve desired hair styles.

Pomades function as straighteners by plastering hair into position once it has been dampened and stretched. Although the use of pomades as straighteners has been superseded by other techniques, pomades are still used by many as lubricants to decrease dryness and increase manageability.1

Hot combing has been largely replaced by the use of chemical hair straighteners, but is still used occasionally. This technique entails applying oil to washed and dried hair, which serves as a heat-transferring agent and lubricant. A heated metal comb (148° to 260° F) is then applied to the hair, causing rearrangement of cortical hydrogen and disulfide bonds and "straightening." In addition to causing structural damage and hair breakage, this technique could also lead to traction alopecia.

The use of chemical relaxers is the most common method of achieving straight hair by African Americans. This method involves reduction and reformation of the cortical disulfide bonds using alkali-containing compounds. Most agents contain sodium hydroxide, guanidine hydroxide, sulfites or thioglycolates. Sodium hydroxide is most effective in straightening kinky or extremely curly hair and is the most commonly used relaxer in the United States.4 Inappropiate use of these agents by an inexperienced person can result in significant hair damage.

Clinical Presentation

Follicular degeneration syndrome has a classic clinical presentation. The disease is most commonly seen in African American women, usually beginning in their 20s and 40s, with an average age of onset reported at 37.2 Although most of the patients presenting with this disorder are black females, this condition has been described in both black males and Caucasians. Hair loss begins in the crown, almost at the geometric center of the head. As the disease progresses, the alopecia spreads peripherally to form a large circle of hair loss, occasionally reaching as far as the frontal hair line. The hair loss is incomplete, with some normal hairs remaining in the area of involvement.1 The hair loss is usually diffuse and not patchy. The scalp surface is usually shiny, and the skin oftentimes feels thinner. Contrasting the scarring nature of the disease, inflammatory changes are usually absent, although occasionally there is presence of visible erythema. The skin does not have the quality of the usual types of scarring alopecia, and there are no pigment changes. Closer examination shows an obvious decrease in the density of follicular orifices. Most of the patients report that the condition is slowly progressive over several years. Hot comb use has been described as the primary hair-styling technique; however, most patients with the disease report using a variety of techniques. Some patients deny the use of hot combs altogether. In our experience, most patients with follicular degenerative syndrome report using chemical relaxers and spending anywhere from 30 to 45 minutes under the hair dryer.

Histopathology

Just as there are specific clinical features, this condition also demonstrates some typical findings under the microscope. Performing a punch biopsy not only confirms the diagnosis but also rules out other conditions. One of the features necessary for the diagnosis of follicular degeneration syndrome is premature desquamation of the inner root sheath. Some consider this to be the earliest observable finding and the primary event in the pathophysiology, while others think of it as a secondary phenomenon.4 This finding is evident in the inner root sheath of follicles scattered among histologically normal hair. In patients with FDS, follices lose their inner root sheath below the follicular isthmus. More advanced disease shows features of other scarring alopecias, including mononuclear infiltrate and lamellar fibroplasias, disintegration of follicular epithelium, and replacement of the entire follicle by thick, fibrous tracts.5 Histopathology is very helpful in confirming the diagnosis of alopecia due to FDS and in ruling out other possible causes.

Figure 3. Perifollicular fibrosis with ragged inner root sheath

Figure 4. High power: Scarred fibrous tract of an extinct hair follicle

Treatment

Even though FDS has been very well described both clinically and histologically, treatment options remain few. There are no published clinical, placebo-controlled trials to date addressing treatment of this disorder. Since exact etiology remains unknown, most of the treatments target possible inflammation and avoidance of further physical damage to the hair follicles. Most authors advocate discontinuation of aggressive hair-styling techniques, including the use of chemical relaxers and hair dryers that apply intense heat to the top of the crown. Intranasal and high-potency topical corticosteroids may be used to reduce inflammation and hair loss. In unpublished reports, hydroxychloroquine has been used because of its anti-inflammatory properties.4

Discussion

Follicular degeneration syndrome is a fairly common, well-described subtype of scarring alopecia with distinctive clinical and histological features. Even though this condition is common amongst the African American population, very little research has been done into elucidating the cause and identifying possibly effective treatments. Most authors believe that the primary etiological agent is trauma to the hair follicle due to aggressive hair-styling techniques. With time, these techniques have shifted from hot combs with petrolatum to chemical relaxing agents. Another observation is that even when aggressive hair-styling techniques are abandoned, hair loss continues to progress in most patients. Ackerman BA et al., in their recent publication, stated that follicular degeneration syndrome is simply a form of traction alopecia. It is easy to blame the pathogenesis of this disease on patients’ hair-styling practices, but there are several inconsistencies that indicate there is something besides trauma causing FDS. Women who discontinue using all traumatic grooming practices continue to experience progression of hair loss. The condition has even been reported in males, most of whom have never used chemical relaxers.11 Since a lot of patients use this technique and only a small portion develop the disease, there is the question of whether there could be a genetic predisposition for the development of FDS. This and many other questions remain unanswered currently. A change in hair-styling techniques is hard to implement, especially as a preventive measure in patients who are not showing clinical signs and symptoms of the disease. Further clinical and basic scientific research should illuminate the true cause and effective treatments.
References:
EXTINA® (ketoconazole) Foam, 2%, is indicated for the topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older.

Important Safety Information
Safety and efficacy of EXTINA Foam for treatment of fungal infections have not been established. The most common adverse reactions to EXTINA Foam observed in clinical trials (incidence >1%) were application site burning (10%) and application site reaction (6%). EXTINA Foam may result in contact sensitization, including photoallergenicity. Please see Brief Summary of Prescribing Information for EXTINA on the following page.

Referenced: 1. Stiefel Laboratories Inc. Data on file. 2. Stiefel Laboratories Inc. Data on file. Post-study questionnaires. StiefelCare is a service mark; VersaFoam-HF is a trademark; and EXTINA, the V logo, and Stiefel are registered trademarks of Stiefel Laboratories, Inc. www.stiefel.com
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INTRODUCING EXTINA®—THE FIRST AND ONLY
KETOCONAZOLE FOAM FOR SCALP, BODY, AND FACE.*

Now you can give your patients the proven efficacy of ketoconazole, a well-established treatment for seborrheic dermatitis, in a foam formulation that patients prefer.1,2

• Applies easily on multiple body areas2
• Cosmetically elegant2
• Vehicle dissolves quickly2
• Suitable for a wide range of patients

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For topical use only
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INDICATIONS AND USAGE
Extina® (ketoconazole) Foam, 2% is indicated for the topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older. Safety and efficacy of Extina Foam for treatment of fungal infections have not been established.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS

Contact Sensitization
Extina Foam may result in contact sensitization, including photoallergenicity. [See Adverse Reactions, Dermal Safety Studies]

Flammable Contents
The contents of Extina Foam include alcohol and propane/butane, which are flammable. Avoid fire, flame and/or smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).

Systemic Effects
Hepatitis has been seen with orally administered ketoconazole (1:10,000 reported incidence). Lowered testosterone and corticosteroid serum levels have been seen with high doses of orally administered ketoconazole. These effects have not been seen with topical ketoconazole.

ADVERSE REACTIONS
Adverse Reactions in Clinical Trials
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use and for approximating rates.

The safety data presented in Table 1 (below) reflect exposure to Extina Foam in 672 subjects, 12 years and older with seborrheic dermatitis. Subjects applied Extina Foam or vehicle foam twice daily for 4 weeks to affected areas on the face, scalp, and/or chest. Adverse reactions occurring in >1% of subjects are presented in Table 1.

Table 1: Adverse Reactions Reported by >1% Subjects in Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Extina Foam N = 672 n (%)</th>
<th>Vehicle Foam N = 497 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with an</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>188 (28%)</td>
<td>122 (25%)</td>
</tr>
<tr>
<td>Application site burning</td>
<td>67 (10%)</td>
<td>40 (10%)</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>41 (6%)</td>
<td>24 (5%)</td>
</tr>
</tbody>
</table>

Application site reactions that were reported in ≤1% of subjects were dryness, erythema, irritation, pruritus, rash and warmth.

Dermal Safety Studies
In a photoallergenicity study, 9 of 53 subjects (17%) had reactions during the challenge period at both the irradiated and non-irradiated sites treated with Extina Foam. Extina Foam may cause contact sensitization.

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects, Pregnancy Category C:
Ketoconazole has been shown to be teratogenic (syndactyly and oligodactyly) in the rat when given orally in the diet at 80 mg/kg/day (4.8 times the maximum expected human topical dose based on a mg/m² comparison, assuming 100% absorption from 8 g of foam). However, these effects may be partly related to maternal toxicity, which was also observed at this dose level. [See Pharmacokinetics]

No reproductive studies in animals have been performed with Extina Foam. There are no adequate and well-controlled studies of Extina Foam in pregnant women.

Extina Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether Extina Foam administered topically could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Extina Foam is administered to women who are breastfeeding.

Pediatric Use
The safety and effectiveness of Extina Foam in pediatric patients less than 12 years of age have not been established.

Of the 672 subjects treated with Extina Foam in the clinical trials, 44 (7%) were from 12 to 17 years of age. [See Clinical Studies]

Geriatric Use
Of the 672 subjects treated with Extina Foam in the clinical trials, 107 (16%) were 65 years and over.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic or photo-carcinogenic potential of Extina Foam.

In oral carcinogenicity studies in mice (18-months) and rats (24-months) at dose levels of 5, 20 and 80 mg/kg/day ketoconazole was not carcinogenic. The high dose in these studies was approximately 2.4 to 4.8 times the expected topical dose in humans based on a mg/m² comparison. In a bacterial reverse mutation assay, ketoconazole did not express any mutagenic potential. In three in vivo assays (sister chromatid exchange in humans, dominant lethal and micronucleus tests in mice), ketoconazole did not exhibit any genotoxic potential.

At oral dose levels of 75 mg/kg/day (4.5 times the expected topical dose in mg/m²), ketoconazole impaired reproductive performance and fertility when administered to male rats (increased abnormal sperm, decreased sperm mobility and decreased pregnancy in mated females).

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802650-0707
Case Report

A 70-year-old, Caucasian man presented to the ED in August 2006 complaining of fatigue, low blood pressure and a low-grade fever. He also complained of pain in his right first toe, present since February 2006, which he described as sharp, intermittent and 10 out of 10 on the pain scale. He stated that he had a history of gout, although this pain seemed to be far worse than that felt during any of his previous attacks. During this episode, he had undergone treatment for gout unsuccessfully with both indomethacin (Indocin) and colchicine. Medical history also revealed recent diagnosis of a poorly differentiated, stage IV, non-small-cell lung cancer, with metastasis to the brain and adrenal gland, for which he was on a chemotherapy regimen. He also had a history of prostate cancer.

On physical exam, the first toe of the right foot appeared erythematous and edematous. It was warm to the touch and exquisitely tender, with no palpable nodules or masses. The patient denied any weakness or paresthesias of the toe; however, the exam was complicated by the presence of a deep-vein thrombosis of the right lower extremity. A working diagnosis of gout was made. An X-ray of his right foot showed dissolution of the bony matrix of the proximal phalanx of the right great toe, with findings suggestive of osteomyelitis. A podiatry consult was obtained, and I&D and bone biopsy with cultures were performed. Infectious Diseases was consulted and concurred with the diagnosis of osteomyelitis, suggesting piperacillin/tazobactam (Zosyn) treatment. All cultures were negative at 72 hours. Bone and tissue biopsies were submitted to pathology for histologic examination.

Microscopic Examination and Histology

Biopsy showed a well-to-moderately differentiated, papillary, glandular neoplasm, extensively involving the submitted tissue, which was histologically consistent with aggressive digital papillary adenocarcinoma (Figures 1 and 2). Because of our patient’s extensive cancer history, several immunoperoxidase reactions were run on the specimen in order to confirm the diagnosis of aggressive digital papillary adenocarcinoma and to rule out metastasis from the lung. The streptavidin-biotin-peroxidase method, which uses layers of proteins with affinity for each other and a secondary antibody to link the primary antibody to the rest of the detection molecule, was used to run the immunoperoxidase reactions. The Ventana Benchmark XT automated immunostainer was used to run the immunohistochemistry assays. The Ventana Benchmark XT is a barcode-driven, modular, microprocessor-controlled system that performs immunohistochemistry assays. Tests performed included carcinoembryonic antigen (CEA), S-100, thyroid transcription factor-1 (TTF-1), CK7 and CK20. CEA was strongly positive, consistent with adenocarcinoma (Figure 3). S-100 was weakly positive, a feature consistent with eccrine origin (Figure 4). TTF-1 was negative, supporting a primary eccrine tumor over a lung metastasis (Figure 5). CK7 was strongly positive (Figure 6) and CK20 was negative (Figure 7), a pattern not consistent with prostatic adenocarcinoma. This CK7/CK20 pattern might be seen in cancer of the lung, breast, ovary, endometrium, or a mesothelioma. However, a mesothelioma would be CEA negative; patient gender rules out ovarian and endometrial cancers; and TTF-1 was negative, making lung metastasis unlikely.

At a later date, the patient had a staged amputation of the right great toe and metatarsal, which showed extensive residual...
tumor, without evidence of lymphatic or perineural involvement. Grossly, the tumor and bone at the site were soft and gelatinous. The final resection margins were negative for tumor, and no definite evidence of further metastasis was identified (Figures 8 and 9).

**Discussion**

Aggressive digital papillary adenocarcinoma (ADPaca) is a rare tumor of the sweat or eccrine glands, first described by Helwig in 1979. The classic patient is usually a Caucasian male between the ages of 50 and 70. These lesions typically present as a mass on the finger, toe, or adjacent skin of the palms and soles. Lesions are usually freely moveable and asymptomatic, but they may be tender, bleeding or ulcerated. Range of motion and neurovascular status is usually in tact. The classic histologic description of ADPaca is multinodular, solid and cystic, with papillary projections present in the cystic spaces. The solid portion contains a pattern of fused, back-to-back glands lined by cuboidal to low-columnar cells. The cystic regions are likely formed by central degeneration/necrosis of a solid area, and the papillations are either pseudo-papillae or true papillae. The differential diagnosis includes ganglion cyst, giant cell tumor, pyogenic granuloma, glomus tumor, foreign body granuloma, soft-tissue infection, osteomyelitis, gout, hemangioma, and metastatic neoplasm. The risk of local recurrence is estimated to be about 28% to 45%, and it’s even greater if the lesion is not adequately excised. In fact, in the study conducted by Duke et al., local recurrence occurred in 50% of the patients who were not treated by re-excision after the initial biopsy. That study also concluded that re-excision or amputation does not absolutely protect against metastatic disease. The risk of metastasis is between 12% and 14%, and the most common site is the lung.

Helwig initially divided the lesion into two variants, aggressive digital papillary adenoma, thought to be the benign variant, and aggressive digital papillary adenocarcinoma (ADPaca). In 1986, Kao et al. studied 57 cases of ADPaca from the Armed Forces Institute of Pathology, using specific histological criteria to separate the adenoma from the adencarcinoma, including degree of glandular differentiation, nuclear atypia, pleomorphism, necrosis and vascular or bone invasion. However, a more recent retrospective study found that clinical and histologic criteria did not correlate with tumor recurrence or rate of metastasis. In fact, the study concluded that a distinction between aggressive digital papillary adenocarcinoma and adenoma cannot be made on the basis of histologic characteristics. The study went further to state that those lesions previously diagnosed as adenomas were actually malignant neoplasms. Furthermore, the paper went on to note that of the 30 cases originally diagnosed by the Armed Forces Institute of Pathology as aggressive digital papillary adenoma, nine cases recurred and three cases metastasized. In 2001, another case report from the University of Pennsylvania supported the conclusion that all aggressive digital papillary lesions should be classified as adenocarcinomas. They also found that lesions described as ADPA have metastasized. Additionally, they illustrated that even if all the original criteria used to diagnose ADPA are met, the lesion can still really be an adenocarcinoma. Therefore, all lesions diagnosed as ADPaca should be treated with wide excision with clear surgical margins, followed by close clinical observation and annual chest radiographs to screen for metastatic foci.

The usefulness of sentinel lymph node biopsy in the treatment of aggressive digital papillary adenocarcinoma has recently been explored. Although most metastases from ADPaca affect the lung, regional lymph nodes are the second most common site for metastasis. Therefore, sentinel node biopsy may be a beneficial technique to rule out metastasis in these patients. Sentinel lymph node mapping and biopsy have replaced regional lymphadenectomy as the initial treatment option for malignancies that are prone to lymphatic spread, like ADPaca. The advantages of sentinel node biopsy include a reduced morbidity and fewer complications such as lymph-
The early detection of a metastatic eccrine carcinoma is very important because theoretically, tumor recurrence at the draining node can be prevented. One study, entitled Sentinel Node Biopsy for Staging of Aggressive Digital Papillary Adenocarcinoma, published in 2000 in the Journal of Dermatologic Surgery, suggested that the technique of lymphatic mapping with sentinel node biopsy allows for early detection of regional lymph node metastasis with minimal morbidity. Furthermore, sentinel lymph node biopsy may be of benefit in detecting subclinical or occult metastases of eccrine tumors. The authors of this study believe that lymph node metastasis may affect the prognosis of aggressive digital papillary adenocarcinoma much in the way that it affects the prognosis of patients with melanoma.

Earlier reports in the literature claim that patients with aggressive digital papillary adenocarcinoma had no benefit from chemotherapy. Malafa et al. postulates that by using sentinel lymph node biopsy, possible occult malignancy could be uncovered and therefore detected earlier in patients with less tumor burden. In this case, it is possible that adjuvant chemotherapy could be more beneficial. Furthermore, early treatment of lymph node metastasis may improve local control of the tumor and improve patients’ disease-free survival rate.

Conclusion

Aggressive digital papillary adenocarcinoma is a rare tumor of eccrine origin, most often found on the fingers or toes. Historically divided into aggressive digital papillary adenoma and aggressive digital papillary adenocarcinoma, these tumors are now all considered to be malignant with a high potential for metastasis. Though our patient presented with a complicated history, the initial biopsy findings were consistent with aggressive digital papillary adenocarcinoma. Because of his extensive cancer history, several tests were completed to ensure that this was a primary cancer and not metastasis from a distant organ. Based on our findings and an extensive review of the literature, we support the more recent data suggesting that all forms of aggressive digital papillary adenocarcinoma are malignant tumors, and therefore the term “aggressive digital papillary adenoma” should no longer be used to describe the pathology. Furthermore, to use the term “aggressive” to describe the lesion is redundant because these tumors are malignant and therefore should always be considered aggressive, treated with wide excision and close clinical follow-up. Sentinel node biopsy may be useful for evaluating the need for initiation of early adjuvant treatment.

References:
The use of botulinum toxin for facial aesthetics and rejuvenation has revolutionized the treatment of facial rhytids over the past 15 years. This non-surgical, minimally invasive procedure causes paralysis of facial musculature by stopping the release of acetylcholine into the neuromuscular junction, virtually eliminating dynamic rhytids. The botulinum toxin is administered through percutaneous injection into facial musculature.

Pain is a common complaint of botulinum toxin injections, and patients typically describe this pain as “crunching” and achy. Currently, many physicians use multiple techniques to reduce the discomfort of the injections. They may use topical anesthetic, pre- and post-injection icing, changing needles every fourth to sixth injection to prevent dulling of the needle, and using saline with preservatives. While these techniques have lowered patient pain perception, patients still experience moderate discomfort while going through this procedure. These techniques are only minimally effective since they mostly affect skin puncture pain and do not reach the deeper, achy, “crunchy” pain beneath the skin. The majority of pain from botulinum toxin injections is occurring in the muscle and deeper soft tissues.

We are introducing a new technique that significantly reduces patient pain. This technique is called manual tissue stabilization, or the "no crunch" technique. This simple technique is employed using any two digits of the non-injecting hand and applying very firm pressure and stabilization to the underlying tissues. To use this technique, the patient’s body part being injected must be firmly rested on an object that provides resistance. For instance, if injecting into the facial musculature, we recommend having the patient lie down on a table without a pillow. To begin the technique, firmly place pressure with one digit of the non-injecting hand on the location you wish to inject (Figure 1). Then, with the other hand, place the needle adjacent to the first digit, applying pressure (Figure 2). Next, place another digit of the non-injecting hand between the first digit and the needle and hold firm pressure (Figure 3). This technique ensures proper placement of the needle and avoids auto-injections. The needle then swiftly punctures the skin until the periosteum is reached. The needle is then slightly drawn back and the contents injected into the muscle belly. While injecting into the muscle belly, the practitioner can feel the fluid expansion of botulinum toxin beneath their digits. The needle is then pulled back out of the puncture site while still maintaining manual tissue stabilization.

In our experience, this technique has proven effective with 100% of our patients being treated with botulinum toxin. Patients regularly report that it accounts for a 70% to 90% reduction in pain. Patients describe the difference as dramatically less painful and consistently say that the method eliminates the “crunchy,” achy sensation. This is a dramatic breakthrough in pain control and is by far the most effective method of pain control in this area to date. In fact, most patients need no other form of pain control, such as topical anesthetics or post injection icing, when utilizing manual tissue stabilization, or “no crunch.”

The mechanism of manual tissue stabilization is currently being investigated, but it is thought to act by three different processes. The first involves the stabilization of the microstructure of the muscle while the botulinum toxin is injected. According to this theory, the diffusion of the botulinum toxin is not causing as much soft-tissue tearing. This is why the patient experiences “no crunch.” The second mechanism is the avoidance of separating the skin from bone by affixing the periosteum with firm manual pressure. The third mechanism is a type of pain-gating. Patients normally perceive pain from nociceptors responding to tissue injury from the needle and injection. In manual tissue stabilization, mechanoreceptors are activated via manual pressure of the skin and sub-dermal tissues, effectively gating or suppressing painful information before it projects to the spinal cord. By these three mechanisms, patients experience an overwhelming reduction in general pain and, specifically, “no crunch.” Current investigations and research are underway to find the exact mechanism of manual tissue stabilization.

References:
TAZORAC® Cream 0.1% is indicated for acne vulgaris. TAZORAC® Gel 0.1% is indicated for mild to moderate facial acne vulgaris.

Important Safety Information

Contraindications

Retinoids may cause fetal harm when administered to a pregnant woman. TAZORAC® Cream and Gel 0.1% are contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus.

Warnings

Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream or Gel 0.1% is used.

Precautions

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

TAZORAC® Cream or Gel 0.1% should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Adverse Events

The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne occurring in 10% to 30% of patients, in descending order, included desquamation, dry skin, erythema, and burning sensation.

The most frequent adverse events reported with TAZORAC® Gel 0.1% in the treatment of acne occurring in 10% to 30% of patients, in descending order, included desquamation, burning/stinging, dry skin, erythema, and pruritus.

Please see adjacent pages for brief summary of prescribing information.
TAZORAC®
(tazarotene) Gel 0.1%

BRIEF SUMMARY
(For full prescribing information, see package insert)

INDICATIONS AND USAGE:
TAZORAC® (tazarotene) Gel 0.1% is indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity.

The efficacy of TAZORAC® Gel in the treatment of acne previously treated with other retinoids or resistant to oral antibiotics has not been established.

CONTRAINDICATIONS:
Retinoids may cause fatal harm when administered to a pregnant woman.

Rabbits dosed topically with 0.25 mg/kg/day (2.75 mg/m² total body surface area/day) tazarotene gel during gestation days 5 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydro- cephalus, and extraocular lenses; these effects at 0.25 mg/kg/day were not seen at 0.05 mg/kg/day. Tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits represented 0.78 and 0.84 times, respectively, the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

As with other retinoids, when tazarotene was given orally to experimental animals, developmental delays were seen in rats, and teratogenic effects and post-implantation loss were observed in rats and rabbits at AUC(0-24h) values that were 0.68 and 16.4 times, respectively, the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights, all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/day from 15 days before mating through gestation day 7. A low incidence of retinoid-related malformations at that dose was reported to be related to treatment. This dose produced an AUC(0-24h) that was 2.1 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

SYSTEMIC EXPOSURE TO TAZAROTENIC ACID IS DEPENDENT UPON THE EXTENT OF THE BODY SURFACE AREA TREATED. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODY SURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THOSE ORALLY TREATED ANIMALS. ALTHOUGH THERE MAY BE LESS SYSTEMIC EXPOSURE IN THE TREATMENT OF ACNE OF THE FACE ALONE DUE TO LESS SURFACE AREA FOR APPLICATION, TAZAROTENE IS A TERATOGENIC SUBSTANCE, AND IT IS NOT KNOWN WHAT LEVEL OF EXPOSURE IS REQUIRED FOR TERATOGENICITY IN HUMANS.

There were thirteen reported pregnancies in patients who participated in clinical trials for topical tazarotene. Nine of the patients were found to have been treated with topical tazarotene, and the other four had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy for non-medical reasons unrelated to treatment. The other eight pregnant women who were inadvertently exposed to topical tazarotene during clinical trials subsequently delivered apparently healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.

TAZORAC® Gel is contraindicated in women who are or may be pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient appraised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Gel is used. A positive result of pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Gel therapy, which should begin during a normal menstrual period (see also PRECAUTIONS; Pregnancy; Teratogenic Effects).

TAZORAC® Gel is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS:

PRECAUTIONS:

General:
TAZORAC® Gel should be applied only to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water. The safety of use of TAZORAC® Gel over more than 20% of body surface area has not been established in acne.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC® Gel is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to yield a systemic exposure (AUC(0-24h)) in the rat equivalent to 0.35 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

In evaluation of photo-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with concurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks. A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.35 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untrated control animals were not completely evaluated. Systemic exposure (AUC(0-24h)) at the highest dose was 2.5 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

Tazarotene was found to be non-mutagenic in the Ames assay using Salmonella and E. coli and did not produce structural chromosomal alterations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-carcinogenic in the in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure (AUC(0-24h)) in the rat would be equivalent to 0.38 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at 2.0 mg/kg/day (see CONTRAINDICATIONS). This dose produced an AUC(0-24h) which was 2.1 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure (AUC(0-24h)) in the rat would be equivalent to 0.38 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm² of tazarotene gel 0.1% over 15% (targeted) body surface area.

Pregnancy: Teratogenic Effects: Pregnancy Category C. See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Gel is used. The possibility that a woman of childbearing potential is pregnant at the time of initiation of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Gel therapy, which should begin during a normal menstrual period (see also PRECAUTIONS; Pregnancy; Teratogenic Effects).

TAZORAC® Gel is contraindicated in individuals who have shown hypersensitivity to any of its components.

Pediatric Use:
The safety and efficacy of tazarotene have not been established in pediatric patients under the age of 12 years.

Geriatric Use: Tazarotene gel for the treatment of acne has not been clinically evaluated in persons over the age of 65.

ADVERSE REACTIONS:
The most frequent adverse events reported with TAZORAC® Gel 0.1% in the treatment of acne occurring in 10 to 30% of patients, in descending order, included desquamation, burning/stinging, dry skin, erythema and pruritus. Events occurring in 1 to 10% of patients included irritation, skin pain, fissuring, localized edema and skin discoloration.

OVERDOSAGE:
Excessive topical use of TAZORAC® Gel may lead to marked redness, peeling, or discomfort (see PRECAUTIONS; General).

TAZORAC® Gel 0.1% is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary.

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BRIEF SUMMARY (For full prescribing information, see package insert)

INDICATIONS AND USAGE: TAZORAC® (tazarotene) Cream 0.1% is indicated for the topical treatment of patients with acne vulgaris.

CONTRAINDICATIONS:
- Retinoids may cause fetal harm when administered to a pregnant woman.
- Tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenic effects in humans.
- Tazarotene has not been clinically tested in persons 65 years of age or older. The safety and efficacy of tazarotene cream have not been established in patients under 18 years of age.

WARNINGS:
- Pregnancy Category X. See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period (see also PRECAUTIONS: Pregnancy: Teratogenic Effects).
- TAZORAC® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

PRECAUTIONS:
- General: TAZORAC® Cream should be applied only to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.
- Retinoids should not be used on eczematous skin, as they may cause severe irritation.
- Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the treatment period. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy for non-medical reasons unrelated to treatment. The other eight pregnant women who were inadvertently exposed to topical tazarotene during clinical trials subsequently delivered apparently healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.
- TAZORAC® Cream is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period (see also PRECAUTIONS: Pregnancy: Teratogenic Effects).
- TAZORAC® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

ADVERSE REACTIONS:
- In human dermal safety studies, tazarotene 0.1% cream did not induce allergic contact sensitization, phototoxicity, or phototagging. The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne, occurring in 10-30% of patients, in descending order included desquamation, dry skin, erythema, and burning sensation. Events occurring in 1 to 5% of patients included pruritus, irritation, face pain, and stinging.

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TAZORAC® Cream for the treatment of acne has not been clinically tested in persons 65 years of age or older.

Drug Interactions: Concomitant dermatologic medications and cosmetics that have a strong drying effect should not be used. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC® Cream is begun.

In evaluation of photo-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intermittent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks. A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.025 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Untreated control animals were not completely evaluated. Systemic exposure (AUC_{0-24h}) at the highest dose was 13 times the maximum AUC_{0-24h} in acrinen patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

Tazarotene was found to be non-mutagenic in the Ames assays using Salmonella and E. coli and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the in vivo mouse micronucleus test. No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum AUC_{0-24h} in acrinen patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

No effect on parameters of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene. That dose produced an AUC_{0-24h} that was 6.3 times the maximum AUC_{0-24h} in acrinen patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

No effect on parameters of mating performance or fertility was observed in male rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrus stages and an increase in developmental effects at that dose (see CONTRAINDICATIONS). That dose produced an AUC_{0-24h} that was 11 times the maximum AUC_{0-24h} observed in acrinen patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum AUC_{0-24h} in acrinen patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

Pregnancy: Teratogenic Effects: Pregnancy Category X: See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, there is a potential risk and use adequate birth-control measures when TAZORAC® Cream is used.

Nursing mothers: Administration of topical doses of "C-tazarotene gel to the skin of lactating rats, radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

Pediatric Use: The safety and efficacy of tazarotene cream have not been established in patients with acne under the age of 12 years.

Geriatric Use: Tazarotene cream is used for the treatment of acne has not been clinically tested in persons 65 years of age or older.

OVERDOSAGE: Excessive topical use of TAZORAC® Cream 0.1% can lead to marked redness, peeling, or discomfort (see PRECAUTIONS: General). TAZORAC® Cream 0.1% is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be warned of the potential risk and use adequate birth-control measures should be administered as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids.

CONTRAINDICATIONS: See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period.

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It is easy to forget about some of the more esoteric findings in dermatology. Beau’s lines seem to be a disease process that is not encountered too frequently.

Beau’s lines are transverse lines of depression that occur at the base of the lunula weeks after a stressful event. These events can be either physical or emotional in nature. The traumatic event causes a temporary interruption in the nail formation. The process is self-limiting in nature.

The photographs in this case presentation are from a five-year-old, Hispanic male who had a viral illness about two months prior to presentation to our office. The child was perfectly healthy at the time of presentation, and the only action needed was reassurance for the parents.

Beau’s lines can be associated with many diseases, including syphilis, uncontrolled diabetes, peripheral vascular disease, myocarditis, zinc deficiency and, as seen in this case presentation, viral illnesses.
Members of the AOCD may advertise "position available"

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

- Black and White - 1/4 page-$125, 1/2 page-$200, full page-$350
- Full 4 color ad - 1/4 page-$275, 1/2 page-$350, full page-$500

Resident members may run a 3" column black and white ad stating their desired professional position.

These ads must be submitted as an e-mail attachment and sent to jaocd@aol.com. Any photos to be included in an active member's ad, must be in a .pdf format.
Case Report

A 73-year-old, Caucasian woman presented with a four-year history of a putrid-smelling, pedunculated, bleeding, fungating, ulcerated, necrotic mass of her right forearm. It was initially discovered when she came to the emergency room for cough, incontinence, anorexia, dehydration and weakness. The patient had at that time rejected seeing a physician to evaluate the growth on her forearm. The mass was neither pruritic nor painful, but it did limit the use of her extremity. The patient said the mass started as a small brown spot that had enlarged over the past four years. The patient would cover the mass in cotton balls and sanitary pads and wear a long-sleeve shirt to conceal the mass from family members who would infrequently visit her. The patient had a past medical history of uterine and cervical cancer, which was treated by hysterectomy when she was 30. On further examination, the patient had a 10 cm mass of her right axilla with a blue-colored infiltrate of the skin over the mass.

A CT scan of the right forearm was performed, and the patient was taken to the operating room to have the mass surgically debulked by means of electrodessication. A chest radiograph, chest CT, abdominal CT and bone scan were also part of the work-up to look for metastatic lesions.

On gross examination, the tumor was nodular, ulcerated, necrotic, and hemorrhagic, measuring 11.0 x 7.5 x 4.0 cm. Histologically, melanocytes were seen in a multinodular growth pattern, with both spindle-cell and epithelial-cell characteristics and ghost cells. The melanocytes were found deep into the subcutaneous adipose tissue, and angiolymphatic invasion was present. Immunohistochemical stains of HMB 45 and S100 were positive, aiding in the diagnosis of invasive nodular melanoma. Chest radiograph, CT and abdominal CT revealed a 10 cm axillary mass; a 4.5 cm right infrarhilar mass; more than 20 pulmonary masses; bilateral adrenal masses; and a 5.0 cm mass in the spleen. Bone scan did not delineate any metastatic lesions. The oncologist did not feel the patient was a candidate for interferon-α or any other chemotherapeutic (Dartmouth) regimen because the patient had such an advanced presentation and multiple metastatic lesions. The oncologist recommended palliative care and discharge to a nursing home.

Discussion

Malignant melanoma presenting as a giant mass is rare in the medical literature.\(^1\,^2\,^3\) Malignant melanomas of this size are infrequently seen because most patients seek earlier treatment, and physicians are aware of the potential catastrophic sequela of neglecting a malignant melanoma at earlier stages.\(^7\) The author could find only seven other instances of giant melanoma reported in the literature,\(^1\,^7\) with this case being the second and the largest amelanotic, nodular melanoma ever reported.

Malignant melanoma is the sixth most common cancer in the United States, with an incidence of 18.3 new cases per 100,000.\(^4\) In 2006, an estimated 62,190 people were expected to develop malignant melanoma.\(^7\) The lifetime risk of developing invasive melanoma is 2.04 percent for Caucasian men and 1.45 percent for Caucasian women; about one in 74 Americans will be diagnosed with melanoma.\(^7\)

The incidence of amelanotic melanoma is between 2 percent and 8 percent, and the incidence of nodular melanoma is
between 15 percent and 30 percent. The term amelanotic implies a tumor lacking any pigment, but it is often used to describe tumors that are only partially devoid of pigment. The prognosis for amelanotic melanoma is the same as its pigmented counterpart and is based largely on Breslow thickness, ulceration, number of metastatic lymph nodes, tumor burden, satellite lesions and in-transit metastases, site of distant metastases, and lactate dehydrogenase.

Since 1981, the incidence of melanoma has been increasing by 3 percent per year, faster than any other malignancy. Since 1973, the mortality rate for melanoma has increased by 50 percent. About 8,110 people in the United States are expected to die of melanomas during 2007. Because melanoma is among the cancers with the fastest increasing incidence and because of its potential for mortality, early detection and treatment is the key to reducing the mortality rate of this disease. Unfortunately, the patient presented here refused to seek medical treatment when she first noticed a change with one of her moles, not knowing the potential consequences of her actions.

**Histology**

All histology pictures presented were taken by Joseph E. Huth M.D. University Hospitals Health System Richmond Heights Hospital.

**References:**

Histology I: lymphocytic response to melanoma.

Histology J: HMB 45 immunohistochemical stain.

Histology K: S100 immunohistochemical stain.
It is with deep regret that we acknowledge the passing of Dr. Daniel Koprince. Dr. Koprince died peacefully after a short illness on Tuesday, October 16, 2007. He was born on November 3, 1921 in Detroit, Michigan. He will be missed by his daughters Janet and Diane Koprince, his wife Helen, 5 grandchildren, 2 sisters and many relatives, friends and patients.

The family has requested that memorials be sent to the Foundation for Osteopathic Dermatology, c/o the AOCD national office.
AOCD Mid Year Meeting in Monterey, California
Hyatt Regency Monterey
March 12-15, 2008
Program Chair- Leslie Kramer, DO

Golf, Wine and Dine! Great Venue for a Family Get Away