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The editors of the JAOCD want to take this opportunity to wish the entire AOCD a very happy and healthy New Year. We hope that your holiday season was exciting and spent with your family.

The JAOCD continues to grow, and we are expanding our editorial board. The expanded board will ensure that we are able to review manuscripts in a timely and efficient way. The manuscripts continue to improve in both content and writing style. All residents are required by the EEC to have their annual papers reviewed, proofed and approved by their program directors. This has made the review process on our end much more efficient.

Because of professional and personal obligations, Andrew Racette, D.O., has decided to step down as a co-editor of the JAOCD. We would like to thank Dr. Racette for his time and effort in helping the JAOCD grow.

The JAOCD has hired our proofreader, Julia Layton, to become the copy editor of the journal. She will be in direct contact with the authors to make sure that their manuscripts are complete and in the proper format to be published in the JAOCD. We are very excited about having Julia step up into this new position. We are confident that this will serve to improve the quality of our journal and also make the journal more uniform and consistent in format and content.

As always, we would like to increase the number of members that sit on our editorial board. Beginning with the next issue, all editorial-board members will have their photos in the front of the journal.

We extend our thanks to all of the members of the AOCD who help to improve the quality of our journal.

Special thanks are in order for Global Pathology, Galderma Pharmaceuticals, Medicis-The Dermatology Company and Ranbaxy Pharmaceuticals for their sponsorship of the JAOCD. The JAOCD would remain just an idea and a dream if we did not have their support.

Sincerely,

Jay Gottlieb, DO, FAOCD
Senior Editor

Jon Keeling, DO, FAOCD
Co-Editor

Help the JAOCD to grow...
The JAOCD staff is small and the budget is limited for the production of the JAOCD. The AOCD Education and Evaluating Committee (EEC) has made it a requirement, that every resident in the AOCD must submit their annual paper for consideration for publication to a scientific journal each year of their residency. We appreciate the number of residents that elect to submit their annual papers to the JAOCD for consideration to be published.

The EEC has also made it mandatory that every resident’s annual paper must be reviewed, proofed and approved by their residency program director. Each manuscript must be co-authored by the resident’s program director.

The JAOCD provides the best possible peer review based on the number of AOCD members that are able to review these manuscripts. The JAOCD recently has employed a Copy Editor to assure that our journal is proofed for grammar, spelling and format.

If any reader has questions or issues with any of the manuscript that appears in this issue, they should contact the author and/or their program chairman directly. The staff of the JAOCD will continue to do our best to keep the quality of the JAOCD at the highest level possible based on the resources at our disposal.

Jay S. Gottlieb, DO, FAOCD, FOCOO
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Irritant Contact Vasculitis with Systemic Symptoms After Exposure to the Agave Americana Plant

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ABSTRACT

Agave Americana, also known as the Century plant, is a low-growing plant that is prevalent in tropical, subtropical, and temperate climates and is mostly an ornamental plant in the United States; however, in Mexico it is fermented into a “pulque,” an alcoholic beverage. The sap of this plant consists of calcium oxalate crystals, acrid oils, saponins, and other compounds. Previous case reports have demonstrated a contact reaction to this plant sap with both skin and systemic symptoms. A vesiculopapular and purpuric variant has been described with and without systemic manifestations. Clinical purpuric lesions were also shown to have a leukocytoclastic vasculitis upon histologic exam. A toxin within the A. americana causes an immediate irritant reaction to the skin, but the cause of a systemic reaction has yet to be elucidated. This case report provides clinical demonstration of a purpuric variant with concomitant systemic symptoms soon after exposure to the sap of this plant.

Key words: agave americana; century plant; vasculitis; contact dermatitis; irritant contact dermatitis; systemic symptoms

Case Report

A 63-year-old male presented with a three-day history of a pruritic rash on his legs and arms that was unresponsive to self treatment with topical hydrocortisone and Eucerin calming moisturizer. He also complained of concomitant mild shortness of breath, subtle blurry vision, decreased appetite, myalgia, eyelid swelling, and an overall feeling of malaise. Severe burning and itching of the skin started 10 to 20 minutes after cutting down a Century plant (Agave Americana) with a chainsaw. Soon afterward, the patient went into his pool and then took a shower with soap in an attempt to alleviate the discomfort, without success. No lesions were immediately present. The next day, red papules and vesicles began to appear, and then excoriations began to appear secondary to scratching. A review of his symptoms was negative for gastrointestinal involvement, renal involvement, connective-tissue disease, hematological disorders, and malignancy.

The patient’s only other health issue was high cholesterol, controlled with Zetia and Crestor. He had no known drug allergies. He related a past systemic reaction after eating eggplant. His surgical and social history was insignificant.

Physical exam revealed excoriated erythematous papules and vesicles on both legs and arms sparing the clothing-covered area. There were scattered, bright red, petechial papules with some purpura (Figure 1 & 2). There were neither vision-acuity impairments nor eyelid-swelling present on examination. Vital signs were stable. No biopsy was performed.

Our clinical diagnosis was a vasculitic type of contact dermatitis. The patient was treated with 10mg of prednisone twice a day along with a topical clobetasol spray. The patient returned two days later with dramatic relief of symptoms and a visual fading of lesions. A follow-up visit at seven days revealed a complete resolution of the lesions with only a slight superficial scaling with desquamation remaining.

Discussion

Agave Americana, also known as the Century plant, is a low-growing plant that is prevalent in tropical, subtropical, and temperate climates (Figure 3). It is a member of the Agavaceae family that forms rosettes of tough, sword-shaped leaves with thorny margins. It gets the name “Century plant” from its infrequent, exuberant flowering, consisting of a spike with a cyme of big yellow flowers that arises from a central stem that may reach up to 8 meters in height. It was once believed to flower every 25 years and then dies. Therefore, the name Century plant is a misnomer. Agavaceae plants are used for a variety of commercial (rope, fibers, mescal, tequila), medicinal (steroid extraction, pre-Columbian antibacterial salves), and ornamental purposes.1,2 A. americana is mostly an ornamental plant in the U.S., but in Mexico it is fermented into a “pulque,” an alcoholic beverage.2,3

The sap of this plant consists of calcium oxalate crystals, acrid oils, saponins, and other compounds. It has been presumed by various authors that the calcium oxalate crystals and saponins (precursors of synthetic steroidal hormones) are the source of the marked pruritus and stinging associated with exposure to the sap of the Agave plant.3,5 Oxalic acid poisoning may lead to acidosis, vascular damage, and obstruction of renal tubules.6 Systemic manifestations, such as fever and leukocytosis, have been reported in cases of contact with Ruta chalepensis, attributed to herbal chemicals (sapogenins) or mediators of inflammation released from the damaged skin.7

There have been previous reports that describe a vesiculopapular eruption upon exposure to the sap of the plant.6 In addition, a purpuric variant, with evidence of leukocytoclastic vasculitis and a lack of systemic symptoms, has demonstrated a localized cutaneous vasculitis on histologic exam.5 In another purpuric variant with systemic symptoms, it has been speculated that the oxalic acid crystals lead to localized and systemic vascular damage.8 Systemic toxicities along with lab abnormalities were apparent in 10 of 12 patients found to have a contact dermatitis provoked by Agave americana.9

This case represents another vesiculopapular vasculitic variant with systemic symptoms. A toxin within the A. americana causes an immediate irritant reaction to the skin; however, the systemic reaction has yet to be elucidated. As in the purpuric variants described, a chainsaw was used in this case, which appears to either cause deeper penetration into the skin or to cause more of the toxin to be transmitted to the skin. This author agrees that the oxalic acid crystals may be a culprit in causing localized and the systemic manifestation in the form of a transient vasculitis.

References

Figure 1: Excoriated erythematous petechial papules with purpura sparing clothing-covered areas.

Figure 2: Close-up of lesions showing bright-red petechial papules with purpura.

Figure 3: Agave americana, also known as the Century plant, in non-flowering state.

Figure 4: Agave Americana: Example of exuberant flowering that consists of a spike with cyme of big yellow flowers that arises from a central stem. It may reach up to 8 meters in height.
Muir-Torre syndrome (MTS) is a rare genodermatosis characterized by sebaceous-gland neoplasm and at least one internal malignancy caused by germline mutations within two DNA mismatch repair (MMR) genes, MSH1 (8% of cases) and MLH1 (92% of cases). We present a unique case of Mui-Torre syndrome with angiosarcoma in addition to colon and renal carcinoma.

Case Report

A 62-year-old Russian man presented to the dermatology office for evaluation of a few flesh-colored papules in the head and back region (Fig. 1). Biopsy result returned as sebaceous epithelioma (Fig. 2). The patient had been treated numerous times in the past for similar lesions. In 2004, the biopsy diagnosis was BCC with sebaceous differentiation (Fig. 3). The patient was treated with Moh's surgery. Later in 2004, another lesion along the right nasolabial crease was biopsied and revealed sebaceous carcinoma. This was also treated with Moh's surgery. In 2005, he returned with yet another lesion, for which biopsy diagnosis was sebaceous adenoma. He was referred to a GI specialist for colonoscopy, which revealed transverse colon cancer proximal to the splenic flexure, and he was treated with colon resection. He later developed left-sided renal carcinoma, which was treated by nephrectomy. When the patient returned to the dermatology office in 2009, he was being treated for left-sided renal carcinoma, which was treated with colon resection. He later developed left-sided renal carcinoma, which was treated by nephrectomy. When the patient returned to the dermatology office in 2009, he was being treated for angiosarcoma of the right gluteal region.

Discussion

Muir-Torre syndrome (MTS) is a rare genodermatosis consisting of sebaceous neoplasms (sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma or BCC with sebaceous differentiation) and at least one low-grade keratoacanthoma or BCC with sebaceous neoplasms (sebaceous adenoma, sebaceous carcinoma). Cystic sebaceous neoplasms have only been observed in patients with MTS, strongly suggesting they are highly specific markers for MTS.

Sebaceous epitheliomas (SEs) are benign, sebaceous proliferations clinically described as solitary, yellowish papules with rolled borders and measuring <1 cm in diameter, but larger lesions have been reported.

Sebaceous carcinomas (SCs) are rare, malignant neoplasms associated with MTS. SCs most commonly occur on the eyelids, where they generally arise from the meibomian glands and the glands of Zeiss. They may also appear on the ears, the feet, the penis, and the labia. Unlike SAS, SCs are aggressive in nature, with the tendency for angiolymphatic invasion and subsequent metastatic disease.

A keratoacanthoma (KA) may also be a valid marker for MTS if it shows sebaceous differentiation histologically or if the patient fulfills the following three criteria: multiple keratoacanthomas present, history of two or more low-grade visceral malignancies, and a family history of MTS. Common sites of involvement include the face and the dorsum of the hands, but KAs can occur anywhere on the body.

Sebaceous hyperplasia is not included in the diagnostic criteria of MTS, but there have been reports of patients with sebaceous hyperplasia exhibiting microsatellite instability and a visceral malignancy, warranting an investigation for cancer in the family history for a patient with sebaceous hyperplasia.

SAs and SEs can be excised or treated with cryosurgery. SCs should be excised with wide margin of resection along with removal of involved lymph nodes. Radiotherapy may also be effective. Excision is adequate therapy for a single KA, but cryosurgery can be tried for multiple KAs. Oral isoretinoin may prevent the cutaneous neoplasms in this syndrome. Furthermore, all patients with established diagnosis of sebaceous tumors should undergo a thorough evaluation for the presence of underlying MTS. This recommendation is based on retrospective review of sebaceous neoplasms from the Mayo Clinic Department of Dermatology from 1923 to 1983. This study revealed that 42 percent of patients with one or more sebaceous neoplasms had at least one associated visceral malignancy, consistent with diagnostic criteria for MTS. Skin manifestations of MTS appear to precede the diagnosis of visceral malignancy in 22 percent of cases, to present concurrently in 6 percent of cases, and to present afterwards in 56 percent of cases. Hence, the skin lesion might be a harbinger for an internal malignancy.

Much is being discovered about MTS and its associated causes and health risks. MTS is thought to be a phenotypic subset of the more commonly known hereditary nonpolyposis colorectal cancer syndrome (HNPCC). A high percentage of MTS patients have germline mutations within two DNA mismatch repair (MMR) genes, MSH1 (8% of cases) and MLH1 (92% of cases). These two MMR genes are also a characteristic feature of HNPCC. This may explain why gastrointestinal cancers develop in 61% of those with MTS and tend to be proximal to the splenic flexure. In contrast, the majority of individuals without MTS who develop colorectal cancer have distal lesions. The second most common site is the urogenital tract, representing 22% of cases. A wide variety of other cases have been reported, including breast cancer, lymphoma, leukemia, salivary gland tumors, lower and upper respiratory tract tumors and chondrosarcoma. There have been a few reported cases of the carcinoma of the ampulla of Vater in association of MTS. Recently, there has been one unique reported case of pancreas and colon cancer in MTS. Surprisingly, the internal malignancies associated with MTS generally metastasize but are less aggressive than their sporadic counterparts. The median survival even in the setting of metastatic disease appears to be significantly longer for those patients with malignancies associated with MTS.

Immunohistochemistry (IHC) analysis of tumor specimens for expression of MMR genes is a useful screening/diagnostic method. Studies have shown that IHC staining using antibodies against MSH2 and MLH1 proteins in MTS-associated skin tumors is an extremely practical approach to diagnosis of the MMR-defective subtype of MTS.
2007, MSH1 and MSH2 were thought to be the only MMR genes associated with MTS, but recent cases of MTS caused by MSH6 have also been reported. MSH6 is a germline mutation also found in HNPCC. Therefore, it is recommended to include MSH6 along with MLH1 and MLH2 in IHC screening.

One disadvantage of IHC analysis is that the presence of MSH2 and MSH1 proteins does not exclude the possibility of an underlying DNA repair defect, such as a missense mutation, which may lead to an altered amino acid sequence and a false-negative result. Therefore, it might be helpful to confirm an MTS diagnosis by performing microsatellite instability (MSI) testing.

Testing sebaceous lesions for MSI is another way of evaluating a patient for MTS. Microsatellites are repeated sequences of DNA found in everyone’s genome. They may vary in size but are typically the same length within individuals. Microsatellites are susceptible to mutations, and when the mutations are not repaired they can become abnormally short or long. This variation in length is termed MSI and is a marker for defects in DNA MMR. Many of these studies, however, included a smaller number of patients, and the accuracy of MSI testing is still controversial. Some studies have shown that MSI testing over IHC analysis remains more sensitive at detecting patients with germline MMR defects than IHC.19,20 However, most of these studies were done using fewer antibodies (MLH1 and MSH2). Two studies done with four antibodies (MLH1, MSH2, MSH6 and PMS2) showed sensitivity equal to or greater than MSI, and are more specific in detecting patients with germline MMR defects than IHC.19,20 However, most of those studies were done using fewer antibodies (MLH1 and MSH2). Two studies done with four antibodies (MLH1, MSH2, MSH6 and PMS2) showed sensitivity equal to or greater than MSI, although these included a smaller number of patients.19,20 MSI testing is only available in specialized laboratories and is more costly than IHC. Because IHC analysis is less time-consuming and less expensive, many recent studies are recommending the use of IHC screening for MTS in all diagnosed sebaceous neoplasms. However, it must be noted that a 2%–3% of spontaneous sebaceous lesions tested with IHC have been negative for MSI protein gene expression. This may suggest another subset of MTS not diagnosed by MSI or IHC, associated with a different genetic or pathological mechanism yet to be discovered.21

Summary

The unique feature of our case is the presence of angiosarcoma in addition to colon and renal cancers in a patient with Muir-Torre syndrome. There have been no documented cases of angiosarcoma associated with MTS published yet in the literature. Unfortunately, a family history, which would have been helpful in early diagnosis and treatment, was unobtainable. Genetic testing may be useful in this case to identify a new, unknown MMR germline mutation responsible for angiosarcoma in MTS.

Patients with suspicious cutaneous lesions should undergo screening for any internal malignancy. It has been thought that the strong association of colorectal cancer with MTS mandates annual colonoscopy beginning between the ages of 20 and 25 (or five years younger than the earliest age at diagnosis in the family, whichever is earlier). Periodic upper endoscopy, yearly urinalysis and dermatologic screening at least once a year are also recommended screening tools. Furthermore, screening for women between the ages of 25 and 30 should include a yearly pelvic examination, pap smear, transvaginal ultrasound and endometrial biopsy. All patients with typical cutaneous lesions of MTS and positive family history should be referred for genetic risk assessment and consideration of genetic testing.

Evaluation of an extended pedigree to identify other affected family members is also recommended.

References


Figure 1

Figure 2

Figure 3
A CASE REPORT: ADULT-ONSET STILL’S DISEASE


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ABSTRACT

Adult-onset Still’s disease (AOSD) is a systemic inflammatory condition originally described by Bywaters in 1971.1,2,3 The disease is difficult to diagnose, and other conditions, including infections, malignancies, and vasculitides, must be ruled out before making the diagnosis.2,3,4 Typical presenting symptoms include a triad of spiking fever (often accompanied by pharyngitis), salmon-colored macular rash, and arthralgias.1,3,5 Characteristic lab findings include markedly elevated serum ferritin levels, leukocytosis, and increases in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase, and liver function tests.1,3,5 Rheumatoid factor (RF) and antinuclear antibody (ANA) tests are typically negative.2,5 Finding an effective treatment option can be challenging due to the infrequency of the condition, unknown etiology, and lack of large-scale studies assessing the therapeutic efficacy.2,5 We are reporting a case of AOSD resistant to treatment and exhibiting a chronic arthritic course.

Case Report

A 19-year-old Caucasian female presented to the clinic with a three-month history of a recurrent rash and fever. Her rash was more pronounced with fever spikes that reached 103°F. The fevers occurred almost daily and most often in the evening. She also complained of sore throat, wrist pain, abdominal pain with nausea and vomiting, and fatigue. On multiple visits to the emergency department, she had received intramuscular triamcinolone, with relief of symptoms lasting approximately one week at a time. Previous workup had not revealed any infectious process.

Her past medical history included post-partum depression (P 1G1) and contact dermatitis one year prior. She had no previous surgeries and reported no medication allergies. Her family history included type 2 diabetes mellitus, heart disease, and cancer. She admitted to smoking 3-4 cigarettes per day. She was currently taking fluoxetine for depression and naproxen as needed for pain.

On exam, she was febrile with a temperature of 103°F. She was in mild distress, but otherwise appeared to be in good health. She had a generalized, macular and papular rash showing koebnerization on the abdomen and legs (Figures 1 and 2). She displayed palpable cervical lymphadenopathy and synovitis of the wrists bilaterally. The differential diagnosis included rheumatic fever, rheumatomatoid arthritis, adult-onset Still’s disease, lymphoma, subacute bacterial endocarditis, systemic lupus erythematosus, hepatitis, syphilis, familial Mediterranean fever, and TNF-receptor-associated periodic syndrome, or TRAPS.

A punch biopsy was taken from the upper extremity (Figure 3) and showed interstitial and perivascular neutrophilic-dominant infiltrate without any vasculitis (Figure 4). She tested negative for hepatitis B and C, RPR, RF, and ANA. Her other lab values included: WBC 12.6, Hgb 10.5, Hct 32.1, ESR 118, ferritin 1571, total iron 16, TIBC 216, albumin 2.1, and LDH 26.8. She also had negative blood and strep cultures. She was positive for DNase and had an ASO titer of 115. Her chest X-ray, EKG, and echocardiogram were normal. At this point, a diagnosis of adult-onset Still’s disease was made, and she was admitted to the inpatient medical service.

Discussion

Adult-onset Still’s disease (AOSD) is a rare systemic disorder of unknown etiology.1 AOSD has been speculated to be caused by multiple environmental and genetic factors.6 Studies have shown it to be associated with multiple HLA antigens. The condition mimics infectious (viral or bacterial) diseases and rheumatological conditions, and may present similar to malignancies such as leukemia and lymphoma.2,3 It is considered by many as a reactive arthritis exhibiting a Th1-dominant immune response.2,5,6 This is evident with increased levels of pro-inflammatory cytokines such as IL-1, IL-6, IL-18, and TNF α.2,3,5 Increases in the erythrocyte sedimentation rate, C-reactive protein, and serum ferritin levels have also been found.2

AOSD most commonly occurs in the 3rd and 4th decades of life.2 Three different disease courses have been identified.3,5 First, it may be self-limited, with remission in less than a year.3,5 Second, it may be intermittent or recurrent, which can be with or without joint complaints.3,5 Last, it may exhibit a chronic arthritic pattern with more severe joint involvement including ankylosis.1,3,5 Most common findings include spiking fever, typical rash, and arthralgias.1 The patient’s fever may be greater than 104°F with spikes once or twice a day, particularly in the late afternoon and early evening.1,3 The rash is usually macular, salmon pink, and intensifies with fever spikes.1,5 The rash is most commonly found on the trunk but can appear anywhere, including the palms and soles.1 It may present at sites of pressure and has been shown to exhibit the Koebner phenomenon.1,5 Arthralgias are symmetrical in nature and most commonly affect the knees, wrists, and ankles.1,5

Arthritis with wrist involvement may evolve into carpal ankylosis, which begins around six months after onset of the disease.3 It may reach its full intensity at 1.5-3 years, leading to a marked decrease in carpal range of motion.1,3 Ankylosis has also been reported with the proximal and distal interphalangeal joints, metacarpophalangeal and metatarsophalangeal joints, temporomandibular joints, hips, and cervical spine.1 Other signs and symptoms include myalgias, sore throat, lymphadenopathy, splenomegaly, pleuritis, pericarditis, and abdominal pain (maybe due to mesenteric lymphadenitis).1,5

As mentioned above, the condition has been associated with increased levels of acute phase reactants. This is evident with elevations in ESR and CRP, along with a marked increase in ferritin levels.3,4,5 Furthermore, ferritin levels may be used to monitor disease activity and assess treatment efficacy (levels fall as symptoms are relieved).3 There is also a decreased percentage of glycosylated serum ferritin.5 The glycosylation mechanisms become saturated due to the high serum ferritin levels.3 Glycosylated ferritin is considered a more specific marker for AOSD than ferritin levels alone, but its use is limited by availability and cannot be used to monitor disease activity.5 Other labs include leucocytosis, increased hepatic enzymes, increased LDH, and hypergammaglobulinemia, and some patients show a reactive thrombocytosis.1,2,5 Patients are reported negative for antinuclear antibodies and rheumatoid factor.4 Histological examination of
the rash shows interstitial, dermal, and perivascular infiltrate with a predominance of neutrophils.¹,⁴ These findings are usually present without any associated vasculitis.¹

Before a diagnosis of AOSD can be made, other more common infections, rheumatological diseases, and malignancies must be ruled out.⁵ Most viral infections can be ruled out if symptoms persist for more than three months.³,⁵ Use of hematological studies can help differentiate AOSD from malignancies such as leukemia and lymphoma, but a bone marrow and/or lymph node biopsy may be needed in difficult cases.⁵ Negative ANA and rheumatoid factor can help rule out autoimmune disease.³,⁵

Several physicians have formulated diagnostic criteria that may aid in a more confident diagnosis.³ The most frequently used, published by Yamaguchi et al., yields a sensitivity as high as 96.2%.³ The major criteria include a temperature greater than 39°C for greater than one week, leukocytosis, typical rash, and arthralgias for greater than two weeks. The minor criteria include sore throat, lymph node enlargement, splenomegaly, liver dysfunction, and a negative ANA and RF.²,⁵ Not included in the Yamaguchi criteria are ferritin and glycosylated ferritin.³,⁵ These values are included in more recent criteria by Fautrel, which increases the specificity of making a diagnosis to as high as 98.5% but decreases the sensitivity.³,⁵

Treatment for AOSD is usually empiric and based on small-scale retrospective studies and case reports.⁵ High doses of salicylates/NSAIDs are the mainstay of treatment for mild disease, but systemic steroids may be needed as well.¹,⁶ In fact, some sources say that most patients are given systemic steroids at some point in their treatment.³ Steroids are required in more severe disease or when there is internal organ involvement.³,⁵ It is recommended, with NSAID-resistant disease, that large doses of steroids be limited to six months duration.⁵

For patients who are resistant to both NSAIDs and steroids, disease-modifying anti-rheumatic drugs (DMARDs) and biologics have been used.³,⁶ DMARDs that have been used with some success include methotrexate and sulfasalazine.⁶ Biologics used with success include TNF antagonists and IL-1 antagonists.⁶ IVIG has been used, and an experimental IL-6 antagonist may prove to be beneficial in the future.⁵

In our case, the patient originally responded to high-dose aspirin and was discharged. However, within two months, prednisone was required to control her symptoms. Her disease has now progressed, and she has required treatment with methotrexate and adalimumab (Humira). Her disease course is consistent with the chronic articular pattern described above. Her response to the current treatment regimen will be monitored with the hope to control her symptoms, slow progression, and prevent joint destruction and other complications of the disease.

References
BEHÇET’S DISEASE WITH MAGIC SYNDROME IN A CAUCASIAN FEMALE: A CASE REPORT AND CLINICAL UPDATE

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ABSTRACT
Adult-onset Still’s disease (AOSD) is a systemic inflammatory condition originally described by Bywaters in 1971.1,2,3 The disease is difficult to diagnose, and other conditions, including infections, malignancies, and vasculitides, must be ruled out before making the diagnosis.2,3,5 Characteristic lab findings include markedly elevated serum ferritin levels, leukocytosis, and increases in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase, and liver function tests.1,3,5 Rheumatoid factor (RF) and antinuclear antibody (ANA) tests are typically negative.2 Finding an effective treatment option can be challenging due to the infrequency of the condition, unknown etiology, and lack of large-scale studies assessing the therapeutic efficacy.3 We are reporting a case of AOSD resistant to treatment and exhibiting a chronic articular course.

Case Report
A 43-year-old Caucasian female was admitted to the hospital for severe abdominal pain associated with anorexia, constipation, and bloating of one-month duration. She also complained of swelling and pain in her ankles, hands, and lower back. The patient is well known to us, with numerous hospital admissions in the past six months for similar GI and arthritis complaints. She reported having flares of her typically abdominal symptoms several times a year for the past 13 years. In addition to the pain and bloating, she also sometimes experienced severe odynophagia, oral and genital ulcers, arthritis in her ankles, and various skin lesions. She was first seen eight months prior with severe left ear pain initially diagnosed as cellulitis. The patient reported the development of multiple irritating lesions on various areas of her skin with no particular distribution and genital ulcers that flare with her other symptoms. Since first becoming a patient of ours, she has had an extensive work-up including two EGDS, a colonoscopy, and extensive blood work.

Her past medical history includes esophageal and gastric ulcers, anorexia nervosa, anxiety, partial liver gangrene, and chronic joint pain and swelling. Her past surgical history includes liver biopsy with partial resection, cholecystectomy, lymph node biopsy, three cesarean sections, lysis of pelvic and abdominal adhesions, colonoscopy, and esophageal gastroduodenoscopy. Her father is deceased at age 53 secondary to leukemia. Her mother is alive and well at age 68. She has three children who are all alive and well. The patient is allergic to cephalaxin and penicillin, and she has an adverse reaction to prednisone. She is of American Indian and Irish decent and has smoked a pack and a half a day for the past 12 years. Her home medications include Protonix 40 mg BID, methotrexate 6 mg IM weekly, and Percocet 10/650 mg Q 6 prn.

Physical exam was significant for punched-out, white, oral, and genital ulcerations located in the posterior pharynx. Her abdomen was tender to palpation in the mid-epigastric region. No abdominal distention was appreciated. She had synovitis in the ankles and bilateral swelling of the hands with joint enlargement. Multiple papillary lesions with scabs less than 1 centimeter were noted on her chin, and hypopigmented macules were present on her left deltoid. Laboratory results were significant for an elevated erythrocyte sedimentation rate of 77, C-reactive protein of 11.5, and positivity for HLA-B27. CBC revealed a normocytic, normochromic anemia with a hemoglobin level of 9.0. CT imaging of the abdomen showed mild mesenteric lymphadenopathy and periaortic lymphadenopathy with mild hepatomegaly. ANA, rheumatoid factor, and dsDNA were within normal range.

An EGD with esophageal biopsies and gastric biopsies from a prior admission revealed linear, mid and distal ulcer of the esophagus approximately 2 mm × 15 mm. Examination of the stomach revealed proximal gastric inflammation with erosions and erosions of the distal stomach. There were three discrete ulcers of the antrum, two of which were circular, measuring 3 to 4 mm in diameter, and one that was linear, measuring 2 mm × 4 mm. The duodenum showed mild inflammation, but no ulceration. The second and third portions of the duodenum as well as papilla were otherwise normal.

Histological examination of the esophageal biopsies revealed fragments of squamous epithelium with some erosion and acute inflammation and what appeared to be some collections of bacteria, thought to be cocci. The PAS stain was negative for fungal spores or hyphae, but some of the nuclei in the stratified squamous epithelium were markedly enlarged and suspicious, although not diagnostic for herpes inclusions. The CDX-2 marker was negative. Specimen 2 sections of the stomach demonstrated epithelial hyperplasia, mild intestinal metaplasia, and focal mild inflammation, but no Helicobacter were seen by immunocytochemistry.

A colonoscopy with biopsies had been performed six months earlier. The left colon was significant for numerous isolated ulcerations with areas of inflammation with edema, and multiple ulcerations were noted as the scope was advanced (Images). The ileocecal valve appeared to be normal. The clinical impression was universal patchy colitis with multiple ulcerations that may represent gastrointestinal manifestations of Behçet’s syndrome.

Colon-biopsy reports revealed multiple fragments of colonic mucosa and muscularis mucosa with focal, discrete, well-demarcated areas of acute inflammation with surface erosion and with eosinophils and neutrophils. In one area there appeared to be some changes in the small vessels suggestive of vasculitis. There were no granulomas. No features of ulcerative colitis, Crohn’s disease, dysplasia or malignancy were noted.

The patient was originally treated with prednisone and then colchicine for the joint pain and inflammation, both of which she claimed to have adverse reactions to. She was then started on 1M methotrexate of 6 mg weekly, which controlled the ulcers and joint pain; however, the patient discontinued the medication secondary to financial difficulties three months prior to her most recent admission. Upon discontinuation of the methotrexate, the patient experienced a severe flare with abdominal pain, bloating, oral ulcers, various skin lesions and swelling in her ankles. While an inpatient she re-started the methotrexate at 6 mg intramuscular injection.

Discussion
Behçet’s disease is a chronic, relapsing, multi-vessel vasculitis that can affect many organ systems. Behçet’s was first described by Turkish dermatologist Hulusi Behçet in 1937 as a clinical triad of recurrent buccal aphthosis, genital ulcer, and uveitis with hypopyon. Since the original description,
other systemic features, including skin lesions, arthritis, and neurological and gastrointestinal complications, have become associated with this disease. While relatively rare in the United States and among northern Europeans, it has a higher prevalence along the ancient Silk Road, extending from eastern Asia to the Mediterranean basin. Turkey has the highest prevalence, with 80 to 370 cases per 100,000. Turkish men and Japanese women have the highest prevalence worldwide. In the United States, the prevalence of Behçet’s disease is 0.12 to 0.33 per 100,000. Interestingly, the United States, the prevalence of Behcet’s disease is among the highest worldwide. In Turkey, the prevalence is 0.12 to 0.33 per 100,000. While relatively rare in the United States among white patients who live in Western countries, it has been implicated as an initiating factor in developing Behçet’s disease. Herpes simplex, hepatitis C virus, parvovirus B19, and Streptococcus sanguis have all been implicated; however, research has failed to prove any specific infectious agent. In fact, the results of a series of studies led to the hypothesis that ubiquitous antigens, including heat shock protein of microorganisms, may trigger cross-reactive autoimmune responses in patients with Behçet’s disease. It has been noted that herpes simplex virus DNA and serum antibodies against the virus have been found in a higher proportion of patients with Behçet’s disease than in controls.

Patients present with a variety of symptoms, and diagnosis is one of exclusion based on clinical signs and symptoms. The International Study Group for Behçet’s disease proposed diagnostic criteria in 1990 (Table 1). According to the criteria, recurrent oral ulceration must be present along with at least two of the following: recurrent genital ulceration, eye lesions, skin lesions or a positive pathergy test. While oral ulcers are one of the earliest and most common manifestations of Behçet’s disease, extensive gastrointestinal ulcerations are rare and found in less than 1% of patients. Clinically, GI manifestations of Behçet’s are characterized by crampy abdominal pain, nausea, anorexia, odynophagia, dysphagia, diarrhea, melena, and perforation. Esophageal ulcers may be linear, oval or round lesions primarily found in the mid to distal portion of the esophagus. Unfortunately, gastric ulcers may be complicated by perforation. Small and large intestines may be involved, and lesions include mucosal inflammation, ulcerations, and ischemia secondary to vasculitis. The ileocecal region is reported to be the most commonly involved area. Intestinal ulcers can be classified into three groups based on appearance: volcano, geographic, and aphthous ulcers. Volcano ulcers are deep with discrete margins and may extend into the serosa, with perforation as a major concern. They may be difficult to distinguish from Crohn’s disease, but are typically deeper ulcers with more distinct borders. Aphthous ulcers are small and usually found in clusters near the ileocecal region with surrounding erythema. Skin lesions are common, occurring in over 75% of patients with Behçet’s. The skin manifestations vary significantly from patient to patient, ranging from acneiform lesions to erythema nodosum. Acneiform lesions may be more common in association with arthritis. Arthritis tends to be non-erosive and asymmetric, occurs in about one-half of patients, and is especially severe during exacerbations.

Another interesting association with this disease spectrum is that of polychondritis. MAGIC syndrome was first described in 1985 by Firestein et al. MAGIC is an acronym that stands for Mouth and Genital ulcers with Inflamed Cartilage. Inflamed cartilage is a rare manifestation of Behçet’s and is considered an overlap of Behçet’s disease with relapsing polychondritis. Very few cases have been reported in the literature. A literature search revealed only nine. The inflammation can be destructive at times and is best controlled with immunosuppression therapy.

The lesions of Behçet’s disease are characterized histologically by leukocytoclastic and lymphocytic vasculitis. Neutrophils from patients with Behçet’s have increased superoxide production, enhanced chemotaxis, and excessive production of lysosomal enzymes, indicating that the neutrophils are overactive, leading to increased tissue injury. Elevated levels of cytokines, including IL-8, TNF-alpha, and IL-1B, have been recorded in lesions, which are known to recruit neutrophils. Lymphocyte function is abnormal in patients with Behçet’s, resulting in an expansion of autoreactive T cells.

The differential diagnosis includes chronic oral aphthosis, herpes simplex, Crohn’s disease, rheumatoid arthritis, and Sweet’s syndrome. Because the disease has such diverse clinical presentations, and a pathognomonic laboratory test is lacking, it can be a challenging diagnosis to make. While there is no cure for Behçet’s disease, there are many treatment options for the various manifestations. The focus of treatment is on reduction of symptoms and prevention of the progression of the disease. For severe disease, corticosteroids are used most often. Colchicine is used for mucocutaneous lesions, erythema

<table>
<thead>
<tr>
<th>Table 1. Criteria for the Diagnosis of Behçet’s Disease*</th>
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<tbody>
<tr>
<td><strong>Finding</strong></td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
</tr>
<tr>
<td>Recurrent genital ulceration</td>
</tr>
<tr>
<td>Eye lesions</td>
</tr>
<tr>
<td>Skin lesions</td>
</tr>
<tr>
<td>Positive pathergy test</td>
</tr>
</tbody>
</table>

*The criteria were drawn up by the International Study Group for Behçet’s Disease.*

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nodosum, genital ulcers, and arthritis. Thalidomide is utilized mainly in men due to its teratogenic side effects when used in women. Studies are proving it to be effective for mucocutaneous lesions.

Immunosuppressants such as cyclophosphamide, cyclosporine, azathioprine, and methotrexate are effective and the cornerstone of treatment for MAGIC syndrome. However, the use of these drugs is limited by their side effects, including risk of infection, hypertension, decreased blood counts, and liver and kidney disease. Azathioprine improves prognosis and helps prevent ulcerations and ocular disease when started early. Cyclophosphamide has limited proven effects but is used in neurologic and vascular manifestations. Methotrexate works as a DNA synthesis inhibitor and is S-phase specific. Methotrexate is a folate antimitobolite, irreversibly binding to dihydrofolate reductase.8 It is thought that this is not the mechanism of action responsible for its efficacy in the treatment of Behçet’s and other diseases such as rheumatoid arthritis, Crohn’s disease, and psoriasis. Instead, there are two other effects of low-dose methotrexate treatment: It inhibits the enzymes of purine metabolism and causes adenosine to accumulate; and it inhibits T-cell activation and suppresses T-cell expression of intracellular adhesion molecules. The anti-inflammatory effect of methotrexate was found to be a direct result of these actions.7

Immunomodulators are on the forefront of research for treating systemic disease. Interferon alpha-2a treats mucocutaneous, ocular, articular, and neurologic manifestations. Anti-TNF agents such as infliximab and etanercept are being used for ocular disease and mucocutaneous lesions.3

Conclusion

Our patient presented with abdominal pain and bloating for 13 years and with the recent development of arthritis, mouth and genital ulcers and polychondritis of the pinna. Her diagnosis was delayed for multiple reasons, including possibly the dramatic nature of the patient. However, it is important to constantly review patient complaints and validate their concerns and continue to search for answers. Due to the rare occurrence of Behçet’s disease and MAGIC syndrome, there are no specific treatment guidelines. Therefore, clinical judgment and patient involvement are necessary to choose the right treatment option for each individual. Our patient will continue to take methotrexate to control her symptoms and will be followed clinically.

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BILATERAL IDIOPATHIC AURICULAR OSSIFICANS: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Petrified auricles are an uncommon phenomenon. Of the over 160 cases in the literature to date only 19 demonstrate histologically proven auricular ossification. This review exemplifies the etiologies of auricular petrifaction with an emphasis on true ossification of the auricles. The case discussed is one of bilateral idiopathic auricular ossificans, noted by the incidental finding of asymptomatic stone hard, immalleable pinnae. Under consideration is whether this is a truly rare condition or just rarely reported. It also emphasizes the importance of auricular evaluation beyond visual inspection.

Case Report

A 45-year-old white male presented to the clinic for an annual skin cancer screen with complaint of a lesion to the scaphoid fossa of the left auricle. The tender lesion was clinically suspicious for non-melanoma skin cancer. However, on closer examination, both auricles were stone hard and immalleable, each moving painlessly as a solid unit and unable to fold over as expected. Palpation of the auricles demonstrated more extensive hardening of the left auricular cartilage (Figure 1) than the right (Figure 2), without involvement of the lobules. Visually, both auricles appeared normal with the exception of the chief complaint. Other than actinic damage to the patient’s head, arms and torso, the remainder of his cutaneous examination was unremarkable. The lesion on the left scaphoid fossa was biopsied and found to be a squamous cell carcinoma, which was subsequently successfully treated with Mohs micrographic surgery. The patient’s skin cancer did not appear to contribute to the incidental finding of inflexible auricles.

On follow-up, the patient was re-evaluated regarding his ears. The patient denied otalgia, hearing loss, tinnitus or other auditory symptoms related to his auricles. He reported “stiffening” of his ears as a teenager with progressive rigidity ever since. He denied prior injury or trauma to the auricles including frostbite, persistent cold exposure, wrestling, or boxing. At the time of initial exam, he noted no use of prescription medications and reported no allergies to medications. He denied any history of hypertension, diabetes mellitus, thyroid disease, Addison’s disease, scleroderma or other collagen vascular disease. His family history was unremarkable, and neither his parents nor his siblings reported stone hard ears. He is a native of Arizona, reporting the rare occurrence of alcohol and denying use of tobacco products and illicit substances.

On auditory physical exam, the Weber test showed no lateralization, and the Rinne test was positive bilaterally. As such, audiometry was not performed. Laboratory evaluation demonstrated normal indices for complete blood count, electrolytes, calcium, phosphorus, and glucose as well as hepatic and renal function panels. Thyroid stimulating hormone was in the normal range, and an antinuclear antibody screen was negative. Cortisol, parathyroid hormone, ionized calcium and vitamin D levels were not evaluated. Radiography of the left auricle demonstrated increased parallel opacities in the shape of the auricular cartilage consistent with auricular petrifaction (Figure 3).

The patient consented to another ear biopsy to further evaluate his petrified pinnae. A disposable 3 mm punch biopsy of the antihelix of the left auricle provided a small but full-thickness specimen for evaluation. However, during the procedure, a second 3 mm punch was required to obtain the specimen because the first punch became imbedded in the stone hard auricle, and while attempting to remove the stuck instrument, the plastic handle slid off the back end of the circular punch blade. The blade was extracted with forceps, and a second 3 mm punch successfully completed the procedure. Histologic evaluation of the specimen at low magnification demonstrated trabecular bone formation (Figure 4). On higher magnification, osteocytes in lacunae with Haversian canals and cement lines had replaced the normal auricular cartilage (Figure 5).

Discussion

Bilateral or unilateral petrifaction of the auricles is an uncommon phenomenon. In 1866, Bochdalek, a professor of anatomy in Prague, documented the first case of bilaterally petrified pinnae in a 65- or 70-year-old male cadaver.1 Wassmund described the radiographic characteristics of this process in 1899.2 In the early 1930s, both Higbee and Childrey referred to hardening of the auricles as “calcerous metaplasia,” which does not differentiate between ossification and calcification.3,4 Finally, in 1983, DiBartolomeo coined the term “petrified auricle,” referring to auricular cartilage that has become stone hard and inflexible on palpation, moves as a solid, fixed unit if at all, and clinically appears normal.5 The patient is most commonly asymptomatic but may experience otalgia, ulceration, aural fullness, stenosis of the external auditory canal, hearing loss, and pain with pressure with insomnia secondary to pain.6,7

Petrified auricles due to calcification are more common than those due to ossification, the former defined as deposition of insoluble calcium salts into cartilaginous auricular tissue.6,8 This ectopic calcification is due to either dystrophic (primary) or metastatic (secondary) processes.5,9,10 Dystrophic calcification occurs with normal calcium and phosphorus levels. Calcium deposition is due to the increased alkalinity of nonviable tissue.5,9 The most common causes of dystrophic calcification are Frostbite and mechanical trauma (e.g. wrestling or boxing).5,9 Systemic conditions associated with dystrophic calcification include hypothyroidism,5,6,9,11,12 hypoparathyroidism,13,14 hyperparathyroidism,15,16,17 hypercalcemia,18,19 hypomagnesemia,20,21 hypokalemia,22,23 and sarcoidosis.24

Sherratt attempted epidemiologic evaluation of petrified auricles in 1932. He examined 800 auricular pairs in an outpatient setting during routine ear, nose and throat exams and was unable to find any hardness or immobility.25 However, in a specific population with Addison’s disease, Jarvis found six out of 120 cases with auricular calcification based on radiographic findings.18 And in 1964, Gordon examined 300 patients for nodularity, thickness, or inflexibility of the auricle without regard to diagnosis. He found 11 patients (3%) with auricular calcification based upon radiographic evidence, as well as 12 patients (25%) without the aforementioned clinical criteria but with a history of primary disease associated with ectopic calcification/ossification.8 To date, more than 160 cases of petrified auricular cartilage have been reported in the literature.5,8,10

Lister asserted in 1969 that histologic evaluation of the tissue is “irrefutable proof” of the transformation of the elastic cartilage of the ear into bone.26 DiBartolomeo concurred, stating that ossification of auricular cartilage can only be substantiated by histologic evaluation.27 The histology of auricular ossification includes the presence of osteocytes within lacunae, Haversian canals, and trabeculae within a narrow space. In cases of histologically proven auricular ossification, the pattern of radiographic defraction is identical to that of...
of normal bone.26,27 As such, of the more than 160 cases of petrified auricles in the literature, 19 (inclusive of the current case) include histologic confirmation of auricular ossification (Table 1).4,28,29-32,37-39 The current case is the sixth case of idiopathic bilateral auricular ossications.5,6

Ossification is defined as formation of true bone with deposition of calcium and phosphorus in the form of hydroxyapatite, a matrix of which has also been noted in other cartilage calcification/ossification processes,28,29,30 including hydroxyapatite crystals concomitant to osteoblastic activity.6 Ectopic ossification may be considered either primary (de novo) or secondary when developing within a pre-existing lesion. Reports of primary ectopic ossification include fibrosplasias ossificantes progressiva, congenital plaque-like osteomatoses, Albright hereditary osteodysplasia, and osteomatosis, Albright hereditary osteodysplasia, or secondary when developing within other comorbid conditions such as frostbite/recurrent cold injury.5,6,31,32,35,36 In the patient with acromegaly, the increased circulating growth hormone and acromegalic reduction improved the deformity satisfactorily.30 Similarly, Sterneberg-Vos et al. report a case in which decreased pain while sleeping was noted after excisional biopsy.30 They recommend a wedge excision rather than a punch biopsy in those patients with complaints of discomfort.30 Manni et al. reported the surgical removal of the ossified external ear canal, medical control of the antitragus, the isthmus, and tragus with return of hearing and the ability to visualize the tympanic membrane.31 A patient with complaint of auricular fullness and conductive hearing loss due to stenosis of the external auditory canal experienced improvement of his hearing loss after meatoplasty.32 With the exception of the aforementioned case reports and due to the rarely symptomatic nature of this condition, minimal information is available pertaining to treatment.6

Conclusion

The petrified auricle is an uncommonly encountered entity. However, considering the often asymptomatic nature of this condition, it is likely that it is underreported. Gordon asserted that the low number of occurrences is due to a failure to seek the lesion rather than to its extreme rarity.8 Clinicians are encouraged to examine the pinnae by palpation and visualization, because evaluation of the auricles may lead to the discovery of an undiagnosed systemic condition that is amenable to treatment.

Acknowledgement

Keliegh Culpepper, M.D.

References

Figure 1. The left auricle appears normal but moves as a unit and does not flex forward with pressure from a cotton-tipped applicator. A scar is notable in the scaphoid fossa from resection of the squamous-cell carcinoma by Mohs microscopic surgery.

Figure 2. The right auricle appears normal but moves as a solid, fixed unit with pressure from a cotton-tipped applicator.

Figure 3. Radiography of the left auricle demonstrates parallel densities in the shape of the auricular cartilage consistent with a petrified auricle.

Figure 4. Low-power (2X) view of the biopsy from the left auricle demonstrates trabecular bone formation.

Figure 5. High-power (40X) view of the biopsy from the left auricle demonstrates osteocytes in lacunae with Haversian canals and cement lines.

Table I. Data for 19 documented cases of histologically proven ossification within a petrified auricle

<table>
<thead>
<tr>
<th>No.</th>
<th>Author (year)</th>
<th>Age (years)/Sex*</th>
<th>Unilateral/Bilateral</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td>Carfrae and Foyt (2008)</td>
<td>49/M</td>
<td>Left</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>16.</td>
<td>Sterneberg-Vos et al. (2007)</td>
<td>70/M</td>
<td>Unilateral</td>
<td>Frostbite</td>
</tr>
<tr>
<td>15.</td>
<td>Gonzalez-Sixton et al. (2006)</td>
<td>65/M</td>
<td>Bilateral</td>
<td>Hypothermia</td>
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<tr>
<td>14.</td>
<td>Manni et al. (2005)</td>
<td>63/F</td>
<td>Bilateral</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>13.</td>
<td>High et al. (2004)</td>
<td>60/M</td>
<td>Bilateral</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>12.</td>
<td>Stites et al. (2003)</td>
<td>65/M</td>
<td>Left</td>
<td>Cold injury</td>
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<tr>
<td>11.</td>
<td>Yeatman and Varigos (1998)</td>
<td>66/M</td>
<td>Right</td>
<td>Cold injury</td>
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<tr>
<td>10.</td>
<td>Lautenschlager et al. (1994)</td>
<td>66/M</td>
<td>Bilateral</td>
<td>Recurrent cold injury</td>
</tr>
<tr>
<td>8.</td>
<td>Lari et al. (1989)</td>
<td>17/M</td>
<td>Bilateral</td>
<td>Trauma</td>
</tr>
<tr>
<td>7.</td>
<td>Cohen et al. (1989)</td>
<td>70/M</td>
<td>Bilateral</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>6.</td>
<td>DiBartolomeo (1985)</td>
<td>77/M</td>
<td>Bilateral</td>
<td>Cold injury</td>
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<td>5.</td>
<td>DiBartolomeo (1985)</td>
<td>72/M</td>
<td>Bilateral</td>
<td>Cold injury</td>
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<tr>
<td>4.</td>
<td>Lister (1969)</td>
<td>58/M</td>
<td>Bilateral</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>3.</td>
<td>Gordon (1964)</td>
<td>34/F</td>
<td>Bilateral</td>
<td>Perichondritis</td>
</tr>
<tr>
<td>2.</td>
<td>Scherrer (1932)</td>
<td>53/F</td>
<td>Bilateral</td>
<td>Toxic adenitis</td>
</tr>
<tr>
<td>1.</td>
<td>Knapp (1890)</td>
<td>24/M</td>
<td>Unilateral</td>
<td>Perichondritis</td>
</tr>
</tbody>
</table>

*M: Male, F: Female
Keratitis-ichthyosis-deafness syndrome is a rare, autosomal-dominant ectodermal dysplasia. Mutations in a component of the gap junction connexin-26 are responsible for the clinical aspect of this disorder. KID syndrome is characterized by localized, erythematous, hyperkeratotic plaques, progressive keratitis and sensorineural deafness. This paper presents a young boy with skin involvement at birth and later development of hearing loss as well as severe myopia.

Case Report

A six-month-old Hispanic boy presented to the dermatology office with a complaint of itchy ears, scalp and forehead that had not been treated with medication. The patient also had complete hearing loss in his right ear and 90% hearing loss in his left ear. He was initially evaluated in the NICU shortly after birth for rough, red skin, near-absent finger and toe nails, and absence of hair. The pregnancy was complicated with maternal depression, hypothyroidism and group B strep infection that were treated with Zoloft, Synthroid and clindamycin, respectively. He was born via spontaneous vaginal delivery with APGAR scores of 6 and 6, with delayed breathing that initially required bag mask ventilation; however, he subsequently recovered with no sequelae. The patient had been seen by an ophthalmologist shortly after birth and was found to have no ocular abnormalities. No developmental delays had been noted by the mother or the pediatrician. There had been no genetic evaluation of the patient.

On physical exam, there was widespread, generalized, rough, reddish-colored skin. Dermoscopy of the extremities, trunk and head showed 2mm perifollicular, flat-topped papules with mild scaling. Lichenification and fissuring was seen on both ears. There was fine, patchy hair on the scalp. His eyebrows consisted of sparse, vertically oriented hairs. His eyelashes were intact. On the palms and soles there were 1mm coalescent, hyperkeratotic, flat-topped papules.

The patient was given triamcinolone 0.1% ointment to be applied twice a day to the body. He was also given hydrocortisone 2.5% ointment for his face and advised to occlude with Vaseline twice a day. After one month, there was minimal improvement of his presenting skin condition. The patient’s cheeks and left antecubital fossa showed small, scaling, reddish-brown papules coalescing into plaques. He continued to have a diffuse follicular prominence of his skin. In addition, he now had bilateral hearing aids in his ears.

The patient returned for follow-up in another two months. There was still near-complete absence of hair on his scalp and complete absence of body hair. The bilateral cheeks still had scaling and erythema. The patient’s mother was advised to continue the topical steroids as previously prescribed as well as Protopic 0.1% twice a day to his face and antecubital fossae.

At 11 months of age, the patient was hospitalized for multiple MRSA-positive abscesses. He was later confirmed to have a connexin-26 mutation after evaluation by a geneticist. At two years of age, he was diagnosed with severe myopia requiring eye glasses and mild keratitis that was treated with eye drops by the ophthalmologist. He did not have photophobia. At two years of age he also developed difficulty sweating.

Discussion

Keratitis-ichthyosis-deafness (KID) syndrome was first described in 1915 and was finally named in 1981, although most agree that the ichthyosis is actually an erythrokeratodermia. KID syndrome is representative of an overlap between disorders of cornification and ectodermal dysplasias. It is very rare, with only 100 cases reported. KID is autosomal-dominant, but around 90% of the cases are sporadic. The disease is caused by mutations in two connexin genes on chromosome 13q12.11, and a majority of patients have mutations in gap-junction protein GJB2, which encodes for connexin-26 (Cx26). Cx26 is part of gap junctions in the epidermis, the anterior portion of the cornea, and the stria vascularis in the cochlea. So far, all mutations recognized for KID have been heterozygous missense mutations.

Patients with KID typically present with a transient erythrokeratoderma at birth or during infancy. Later on, well-demarcated, hyperkeratotic plaques with erythematous bases develop symmetrically. These plaques are commonly seen on the knees, elbows, face, outer ears, and scalp. Prominent follicular keratosis and perlèche are common. Patients’ nails can be dystrophic and can also show leukonychia. Lusterless hair and alopecia of scalp, eyebrows and eyelashes have been described in patients with KID. Dental abnormalities can include small or absent teeth. Rarely, heat intolerance has been noted.

All patients have congenital sensorineural hearing impairment, which is generally severe and bilateral, although unilateral or moderate hearing loss has been noted. Deafness is usually apparent by age seven. In 95% of patients, there have been ocular symptoms that are progressive, including photophobia and chronic blepharitis. Vascularizing keratitis and conjunctivitis occurs, with scarring and neovascularization that eventually leads to blindness.
derived from ectoderm, which explains the corneal involvement. KID patients also have susceptibility to bacterial, viral and fungal infections, especially C. albicans, S. aureus, E. coli, P. aeruginosa, and T. rubrum. Squamous cell carcinoma of the skin and oral mucosa has been observed in 11% of patients and is a serious morbidity that can shorten life expectancy. Malignant proliferative pilar tumors of the scalp have been reported in two patients with KID syndrome. Otherwise, patients have a normal life span.

Treatment is usually limited to supportive care. Basic skin care consists of emollients and keratolytics for hyperkeratosis. Topical retinoids have also been used with some benefit. Oral retinoids, on the other hand, can actually aggravate the keratitis and have only shown mixed success for the skin lesions. Topical cyclosporine has been shown to help the keratitis. Corneal transplants are the only known treatment for improving vision, but these are generally not successful because of revascularization. Hearing aids and cochlear implants are used successfully for hearing loss.

**Conclusion**

Keratitis-ichthyosis-deafness syndrome results from a mutation in connexin-26, a gap-junction protein. This mutation leads to erythematous, hyperkeratotic plaques, keratitis and sensorineural deafness. The patient presented here had all three of these main findings along with the often reported bacterial infection. The patient’s skin lesions have been managed with topical steroids and Protopic for supportive care. Topical retinoids have not been tried yet. His eye manifestations are currently managed simply with eye glasses, and his hearing deficit is addressed with hearing aids. He will continue to be managed at the outpatient dermatology clinic.

**Questions:**

What is the most common type of skin cancer associated with KID syndrome?

a. BCC  

b. SCC  

c. Cutaneous lymphoma  

d. Kaposi’s sarcoma

See reference #6  
Correct answer: B

Which connexin is affected in KID syndrome?

a. 21  

b. 26  

c. 31  

d. 32

See reference #2  
Correct answer: B

**References**

**ABSTRACT**

Lobular capillary hemangioma (pyogenic granuloma) is a benign, vascular lesion, appearing as a protuberant red papule on cutaneous or mucosal surfaces. They are rapidly growing and can bleed spontaneously or with minor trauma. We report the case of a 38 year old Caucasian female who presented with an impressively large mass on the pad of her finger. The lesion was surgically removed and sent to histology which revealed a lobular capillary hemangioma. Three months after excision, the lesion has not recurred.

**Case Report**

A 38-year-old Caucasian female presented with an enlarging mass on her right finger. She reported the mass had begun as a small red dot two months prior to her presentation. She complained of mild discomfort and reported recurrent bleeding both spontaneously and with mild trauma. There was no preceding trauma or incident event she could recall. Her past medical history, including medications, was unremarkable.

Physical exam was significant for a large, protuberant polyloid mass emanating from the pad of her right fourth digit (Figures 1 and 2). The lesion had an erythematous base and some mild to moderate tenderness with manipulation. A tourniquet was applied, and the mass was removed with simple scissor dissection. The base of the lesion was cutaneous; however, this failed to provide adequate hemostasis. The defect was subsequently closed with simple interrupted 4.0 nylon sutures.

Histopathology showed a lobular proliferation of capillaries surrounded by an epithelial collarette (Figures 3 and 4). Bands of connective tissue separated the lobules. Three months after removal, there was no recurrence of the lesion.

**Lobular Capillary Hemangioma**

Lobular capillary hemangioma (pyogenic granuloma) is an acquired, benign vascular lesion occurring on both cutaneous and mucosal surfaces. It is most common in young children and adolescents but can manifest in all age groups. Its prevalence is likely equal in men and women; however, mucosal lesions are more common in women. Lobular capillary hemangiomas are rapidly growing and appear as a protuberant red papule or nodule with a moist to scaly surface, often surrounded by a collarette of scale. They are friable and can bleed spontaneously or with minor trauma, frequently leading to ulceration. They are usually small (less than 1 cm) and solitary, but multiple satellite lesions and giant-sized lesions have been reported.

They can occur on any skin surface but are most common on the head, neck, upper trunk, and extremities.

Lobular capillary hemangiomas are characterized as a reactive, hyperproliferative vascular response to a variety of stimuli, including a history of trauma or irritation, preceding the onset of the lesion. They may also develop in patients being treated with antiretroviral therapies and chemotherapeutic agents. Additionally, they have been reported in two cases of acne patients within two to three weeks of topical tretinoin application. There is also one report of a lobular capillary hemangioma that developed secondarily on an inflamed dermatofibroma following application of topical tretinoin.

There is another form of pyogenic granuloma (granuloma gravidarum or epulis gravidarum) that occurs in pregnant women, found primarily in the mucosa and gingiva, and is associated with exposure to estrogen and other hormones.

This lesion can usually be diagnosed based on clinical presentation and history, but histopathological examination may be indicated to distinguish it from similar pigmented and vascular-like growths that may have malignant potential. Mimicking lesions include hemangiomas, amelanotic melanoma, irritated nevi and warts.

In immunosuppressed patients, bacillary angiomatosis and Kaposi’s sarcoma can also appear similar.

The histopathological pattern of pyogenic granuloma appears as active endothelial proliferation resulting in masses or lobules of capillaries separated by fibrous connective tissue. There is a collarette of epidermis demarcating the lesion, and a sparse or prominent inflammatory infiltrate may be noted. They are also surrounded by myxoid stroma containing scattered spindle-and stellate-shaped connective-tissue cells and occasional mast cells.

Treatment of pyogenic granulomas includes removal of the lesion by shave or curettage followed by destruction of the base by electrocautery or chemical means. Smaller pyogenic granulomas are usually treated with electrosurgery or lasers. Surgical excision is usually preferred for larger lesions. For recurrent giant pyogenic granulomas, one case reported adequate response to systemic steroid treatment. Imiquimod may prove an alternative to surgical or destructive removal.

References

Figure 1

Figure 2

Figure 3

Figure 4
Cutaneous Metastatic Breast Carcinoma: Case Report and Review of the Literature

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ABSTRACT

Breast carcinoma has been known to metastasize. This is a devastating condition that may present years or decades after suspected remission. Although the incidence of cutaneous manifestations is low, the morbidity is quite high. We report a case of cutaneous metastases found to be of breast carcinoma origin.

Introduction

Cutaneous metastases arising from malignant tumors are rare but can herald a previously undiagnosed primary internal malignancy or a recurrence of a previously known malignancy. Following the final step in the therapeutic process in the treatment of the original primary malignancy, patients have a sense of completion. The diagnosis of cutaneous metastases can be unexpected and discouraging for patients. This cutaneous manifestation can change treatment plans. Most internal malignancies are not outwardly visible to the patient. Cutaneous metastases add a visible dimension of cancer that can be psychologically disturbing for these patients. The discovery of an acute onset of firm, painless, possibly pruritic papulonodules on the chest of a female with a history of breast carcinoma should raise the suspicion of cutaneous metastases.

Case Report

An 80-year-old female presented with a rash on her chest and abdomen for several months. It was described as non-painful, raised, red bumps with irritation and occasional pruritus. Her past medical and surgical history was significant for a basal cell carcinoma of the scalp diagnosed in 2005 and treated with Mohs surgery in 2006, left breast carcinoma 20 years prior treated with mastectomy and lymph node dissection, and right breast carcinoma seven years prior treated with breast conserving surgery and lymph node dissection and radiation therapy. Medications included alendronate, atenolol, paroxetine, and topical tretinoin. The patient denied having allergies or using tobacco or alcohol. Physical exam of the right breast and chest showed a diffuse distribution of oval-round, pink-red and flesh-colored, erythematous plaques and nodules from the right mid axillary line to the right side of her chest and abdomen (Figure 1). Several lesions on the right breast and nipple were crusted (Figure 2). Dermatopathology of the 4mm punch biopsies revealed metastatic carcinoma of the chest and abdomen consistent with metastatic breast carcinoma (Figures 3-5). The CK7 immunoperoxidase stain was positive (Figure 6).

Epidemiology

Cutaneous involvement is seen in approximately 30% of metastatic breast carcinoma patients. Reports of delayed cutaneous metastases beyond a decade or more after treatment of the primary tumor have been cited in the literature. Cutaneous metastases were an initial presenting sign in 7.6% of patients with prior breast carcinoma. Cancer can involve cutaneous surfaces by direct extension from the primary tumor or by either local or distant metastases. The incidence of cutaneous metastases is 0.7% to 9% of all cancer patients. Although cutaneous metastases can be the first sign of visceral cancer, it is often a sign of recurrence in patients with previously treated breast cancer. In one study, breast cancer was the most common primary malignancy with skin metastases in women, found in 69% of patients. In the same study, 2% of men with skin metastases were found to have breast cancer as the primary malignancy. In a retrospective study performed by Lookingbill et al., 23.9% of 4,020 total patients with breast cancer were found to have cutaneous metastases. The same authors in a different study looking at 7,319 total patients found 6.3% of patients with breast cancer having skin involvement at the time of diagnosis, with 3.5% of patients having skin involvement as the presenting clinical sign.

One study reviewing 78 biopsies found the most frequent anatomical location for cutaneous metastases, without differentiating the type of primary carcinoma, was the abdomen. Lookingbill et al. found that breast carcinoma was the most common cancer to invade the skin at the time of diagnosis. The study, reviewing 4,020 patients, found the most common anatomic location for cutaneous metastatic breast carcinoma was the back, followed by the scalp, upper extremities, abdomen, neck, shoulders, lower extremities, flank, contralateral chest without ipsilateral involvement, buttocks, and face, in descending order of frequency.

Clinical Features

There are traditionally eight distinct patterns of cutaneous involvement, with a ninth type displaying unusual presentations of cutaneous manifestations of breast cancer. These are inflammatory metastatic carcinoma, en cuirasse metastatic carcinoma, telangiectatic metastatic carcinoma, nodular metastatic carcinoma, alopecia neoplastica, Paget’s disease of the breast (considered direct extension of breast cancer to the skin), breast carcinoma of the infra-mammary crease, metastatic mammary carcinoma of the eyelid with histiocytoid histology, and the nose. Cutaneous metastases can be a presenting manifestation of internal malignancy and may present acutely with firm, painless papulonodules.

The clinical appearance of inflammatory metastatic carcinoma is due to capillary congestion and tumor cells inside ectatic lymphatic channels. This gives rise to the characteristic erythematous plaque or patch with an active spreading border. Several case reports noted that inflammatory metastatic carcinoma can resemble eczematoid or erythema annulare centrifugum.

Diffuse induration of the skin, described as encasement in armor, is characteristic of en cuirasse metastatic carcinoma. Clinical manifestations include firm, scattered lenticular papules and nodules on a smooth, red-blue surface or an erythematous surface. Sclerodermatous changes of en cuirasse metastatic carcinoma can occur when papules coalesce into a sclerodermoid plaque without inflammation and are termed carcin eburnée or scirrhous carcinoma with morphea-like induration. One study divided carcinoma en cuirasse into primary and secondary types. Symptoms such as pruritus, foul-smelling discharge, edema, bleeding and pain are due to local disease and are not usually associated with internal organ spread in primary carcinoma en cuirasse. The secondary type is more common than the primary type and presents following initial therapy for primary breast carcinoma including mastectomy, chemotherapy or radiotherapy.

Both primary and metastatic prostate carcinomas can produce prostatic acid phosphatase and prostate specific antigen in the skin. Both contain the same proteinase inhibitors. Prostatic acid phosphatase can be found in prostate tissue and can cause prostatic acid phosphatase positivity.

Cutaneous Metastatic Breast Carcinoma: Case Report and Review of the Literature
Multiple, firm papulonodules or nodules, which may be solitary, ulcerated, pigmented or, less commonly, bullous, are characteristic of nodular metastatic carcinoma. Pigmented basal-cell carcinoma and keratoacanthoma have been suggested when, rarely, pigmented nodules with irregular borders or a dome-shaped nodule with a central core have been clinical findings in cutaneous metastatic carcinoma. Reports of cutaneous metastases from breast carcinoma described as bullous in a zosteriform pattern of distribution have been described in the literature. Circular to oval, painless, nonpruritic, well-demarcated areas of alopecia with or without red-pink, smooth plaques characterize alopecia neoplastica. One study describes scalp erythema without alopecia as a rare variant of alopecia neoplastica. Areas of alopecia without plaques can be mistaken for alopecia areata, whereas cicatricial scalp plaques may resemble discoid lupus erythematosus, morpheaform basal-cell carcinoma, lichen planopilaris, or pseudopelade.

Paget’s disease of the breast commonly occurs on the nipple or areola as a sharply demarcated plaque or patch of erythema and scale, first described by Paget in 1874. Paget’s disease can occur simultaneously with other types of cutaneous metastases from breast cancer. Paget described this entity clinically as a “long—persistent eczema” in women aged 40 to 60 years.

An exophytic nodule in the inframammary crease in women with pendulous breasts appearing clinically similar to squamous-cell carcinoma, basal-cell carcinoma, or intertriginous dermatitis is characteristic for breast carcinoma of the inframammary crease.

Unusual presentations and locations of metastatic mammary carcinoma have been described on the eyelid, known as carcinomatous blepharitis, and as a red nodular nasal tip, known as pseudocarcinomatous hyperplasia with a central core have been clinical findings in cutaneous metastatic carcinoma. One case report describes cutaneous metastatic breast cancer on the right ear and right palm after three years of chemotherapy.

Metastases can be as small as a single milia cyst to as large as a “hen’s egg.” Most cutaneous metastases appear as multiple nodules.

Histologic features of breast carcinoma include glandular formation, Indian filing, intraductal and intralobular proliferation, and fibrotic and epidermotropic patterns. One study divided the histologic classification of breast metastases into ductal origin, lobular origin, mucinous and scirrhous, showing metastatic ductal adenocarcinoma of the breast to be the most common type.

Several immunohistochemical markers used to identify neoplasms of mammary origin are estrogen receptor (ER), progesterone receptor (PR), and BRST-2 (a monoclonal antibody to gross cystic disease fluid protein-15) in surgical pathology to help determine invasive ductal breast carcinoma and invasive lobular breast carcinoma. One study found that BRST-2 can enhance diagnostic sensitivity for ductal and lobular origins of breast cancer when used in conjunction with hormone receptor status but is unable to distinguish primary cutaneous lesions from metastatic cutaneous breast carcinoma.

An aspartic protease known as cathepsin D is an immunohistochemical marker for metastatic breast carcinoma. Podoplanin, or D2-40 antibody, stains completely negative in cutaneous breast carcinomas and is therefore useful to distinguish primary cutaneous adenocarcinomas from adnenocarcinomas metastatic to skin by labeling lymphatic endothelium, vascular tumors, and myoepithelial cells of the breast.

A non-invasive method of detection of cutaneous metastases from breast carcinoma was reported using F-18 FDG PET/CT imaging. Multiple lesions were found as cutaneous and subcutaneous nodules on the posterior neck, bilateral arms, anterior chest wall and trunk in a 73-year-old female with metastatic left breast carcinoma.

Biopsies revealed invasive ductal carcinoma involving the deep dermis.

**Diagnostic Techniques**

Histologic features of breast carcinoma include glandular formation, Indian filling, intraductal and intralobular proliferation, and fibrotic and epidermotropic patterns. One study divided the histologic classification of breast metastases into ductal origin, lobular origin, mucinous and scirrhous, showing metastatic ductal adenocarcinoma of the breast to be the most common type.

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**Prognosis**

Cutaneous metastasis arising from any primary carcinoma is a grave prognostic sign. Survival time of patients with cutaneous metastases from breast cancer is expected to be less than one year at the time of diagnosis; however, the prognosis also depends on the type and behavior of the primary tumor.

Lookingbill et al. found that the mean survival, defined as the average time from diagnosis of skin metastasis to death, for 707 patients with breast carcinoma was 31 months. Another study found the five-year survival and 10-year survival rates for patients with a single cutaneous lesion was 42% and 22%, respectively. However, the same study found that for patients with metastases in multiple organs and cutaneous metastases, the five-year survival and 10-year survival rates dropped to 10% and 0%, respectively.

**Treatment**

The principle goal of treatment is to improve the quality of life. Metastatic skin cancer has been found to respond to systemic anticancer treatment, intralesional chemotherapy, surgical excision, and radiotherapy.

There are currently clinical trials underway examining the use of retinoids against mammary carcinogenesis. Allitretinoin and bexarotene have been found to inhibit growth of premalignant mammary epithelial cells, preventing the progression of invasive breast cancer.

Oncologists are not the only physicians with the ability to use new therapeutic modalities for the treatment of cutaneous metastases from breast cancer. Dermatologists can utilize photodynamic therapy in the palliation of metastatic breast carcinoma to the skin. Photodynamic therapy was found to decrease wound care difficulties and aid in palliation of pain by using IV Photofrin and 630nm diode laser, showing an excellent clinical response.

There have been several promising studies in the literature using topical chemotherapeutic treatments for cutaneous metastases from breast cancer. Topical 6% miltefosine as monotherapy or as adjuvant therapy is well tolerated and can be used effectively in temporarily controlling breast cancer skin metastases in patients pretreated systemically or for use in postponing aggressive chemotherapy.

Other clinical trials have tested the cytostatic topical treatment miltefosine, showing similar results. Topical 6% miltefosine is well tolerated and can be used effectively as monotherapy or as adjuvant therapy in palliative treatment for cutaneous metastases from breast cancer.

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by those cancer cells. One of the original uses of rostaporf in was in the photodynamic treatment of cutaneous metastatic breast cancer; however, the manufacturers announced in 1998 that they were not going to pursue cutaneous metastatic breast cancer so their efforts could be focused on the treatment of age-related macular degeneration. Photodynamic therapy targets dysplastic cells in specific tumor destruction while leaving the surrounding tissue intact, thereby maintaining the cosmosis and leaving the function of the skin undisrupted.

Conclusion

The acute onset of firm, painless nodules in a patient with a history of breast carcinoma should arouse suspicion of the presence of cutaneous metastases from a previously treated carcinoma. The threshold to perform a biopsy on these lesions should be low. The prognosis is extremely poor when cutaneous metastases are present. Nonetheless, cutaneous metastatic breast carcinoma requires a multidisciplinary approach to care in order to maximize a patient’s quality of life.

References

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- Indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
- Systemic absorption of topical corticosteroids has produced reversible, hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients. (See the Precautions section in Full Prescribing Information)
- Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio.

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

Information for the Patient
Patients using topical corticosteroids should receive the following information and instructions:

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

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

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

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

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

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

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

HPA axis suppression, Cushing’s syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed onset of puberty, poor weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headache, and binocular papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

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

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

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

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

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted. Store at room temperature; avoid excessive heat.

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November 2007

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Kenalog® Sprays: triamcinolone acetonide spray
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Sebulex®: salicylic acid and sulfur shampoo
Balnetar®: therapeutic tar bath
Introduction

Dermatofibroma, also known as benign fibrous histiocytoma, is a constituent of the heterogeneous conglomeration known as fibrohistiocytic tumors of the skin. Dermatofibromas are the most common fibrohistiocytic tumor, and these indolent tumors form classically on the lower extremities of young adults. The affected patient age distribution is typically 20-60 years of age, but 20 percent of presentations are in patients younger than 17 years old. The etiology of this proliferation is unknown; however, there is some association with trauma and arthropod bites. Dermatofibromas are usually histologically characterized by a proliferation of fibroblast-like spindle cells, histiocytes, blood vessels, and potentially other mesenchymal components in the dermis depending on the subtype described. Many subtypes have been previously reported (see Table 1), and the presentation of most dermatofibromas as asymptomatic, ≤ 5mm growths with indolent clinical character can be quite dissimilar from some of the more unusual dermatofibroma subtypes, including the case described herein. This case presents an eight-year-old boy with a large polyoid pedunculated dermatofibroma.

Case Report

An eight-year-old boy from Port-au-Prince was seen at a mobile clinic following the tragic earthquake that struck Haiti on January 12, 2010, with a complaint of an enlarging mass on the right arm for the previous few months (Figure 1). Neither the patient nor his mother was able to provide any inciting event or trauma to the area, and the nodule had been asymptomatic apart from its fairly rapid increase in size. He had no medical history apart from occasional asthma, and he had a negative review of systems. He was developmentally normal and did not have any family history of note.

On exam, the patient had a 2 cm pedunculated flesh-colored nodule, which was non-tender and firm to palpation without any palpable signs of infiltration of the deeper tissues. He had no associated adenopathy, and the remainder of his exam was unremarkable. Due to the lack of available specialty physician follow-up and the deficiency of referable medical facilities, it was felt the most beneficial course of action was excision with a subcuticular closure. The patient tolerated the procedure well, and the pathologic specimen was returned to the United States for interpretation.

Table 1: Dermatofibroma Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
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<tbody>
<tr>
<td>Atrophic dermatofibroma</td>
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<tr>
<td>Atypical polypoid dermatofibroma</td>
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<tr>
<td>Balloon cell</td>
</tr>
<tr>
<td>Clear cell</td>
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<tr>
<td>Erosive dermatofibroma</td>
</tr>
<tr>
<td>Generalized eruptive histiocytoma</td>
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<tr>
<td>Giant dermatofibroma</td>
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<tr>
<td>Granular cell</td>
</tr>
<tr>
<td>Intracytoplasmic eosinophilic globules</td>
</tr>
<tr>
<td>Keloidal</td>
</tr>
<tr>
<td>Lichenoid</td>
</tr>
<tr>
<td>Lipidized (ankle-type)</td>
</tr>
<tr>
<td>Multiple clustered dermatofibroma</td>
</tr>
<tr>
<td>Multiple palmoplantar histiocytoma</td>
</tr>
<tr>
<td>Multinodular hemosiderotic dermatofibroma</td>
</tr>
<tr>
<td>Myxoid</td>
</tr>
<tr>
<td>Osteoclast-like giant cells</td>
</tr>
<tr>
<td>Palisading</td>
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<tr>
<td>Polypoid</td>
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<tr>
<td>Prominent myofibroblastic proliferation</td>
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<tr>
<td>Signet-ring cell</td>
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<tr>
<td>Smooth-muscle proliferation</td>
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<tr>
<td>Subcutaneous fibrous histiocytoma</td>
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<tr>
<td>Subungual pleomorphic dermatofibroma</td>
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<td>Ulcerated dermatofibroma</td>
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Table 2: Differential Diagnosis

<table>
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<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Acrochordon</td>
</tr>
<tr>
<td>Acral fibrokeratoma</td>
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<tr>
<td>Atypical polypoid dermatofibroma</td>
</tr>
<tr>
<td>Basal-cell carcinoma</td>
</tr>
<tr>
<td>Dermatofibroma sarcoma protuberans (DFSP)</td>
</tr>
<tr>
<td>Dermatomyofibroma</td>
</tr>
<tr>
<td>Epidermal nevus</td>
</tr>
<tr>
<td>Giant dermatofibroma</td>
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<tr>
<td>Keloid</td>
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<tr>
<td>Lipidized dermatofibroma</td>
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<tr>
<td>Malignant melanoma</td>
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<tr>
<td>Neurofibroma</td>
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<tr>
<td>Pleomorphic fibroma</td>
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<tr>
<td>Polyoid dermatofibroma</td>
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<tr>
<td>Spitz nevus</td>
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</tbody>
</table>

Histopathology

Grossly, the specimen was an irregular pedunculated polyoid portion of skin measuring 2.0 x 1.2 x 1.7 cm in size. The epidermis showed mild acanthosis and widened rete ridges. A dermal spindle-cell proliferation with peripheral collagen trapping and focal storiform morphology was present (Figures 2 and 3). No atypia or mitotic figures were seen. There was a mild mixed infiltrate. Immunohistochemical staining for CD34 expression was negative.
Diagnosis

Polypoid dermatofibroma with myofibroblastic differentiation

Discussion and Comment

Dermatofibroma is a frequently encountered dermatologic entity, the diagnosis of which is usually apparent clinically. However, due to the many types of dermatofibroma, there remains a subset of rare variants that are often clinically misdiagnosed due to their atypical size, location or clinical history. The typical presentation of dermatofibroma is as a red-brown or yellow-brown papule on the leg measuring a few millimeters in diameter. Patients not uncommonly will have complaints of pruritus or tenderness. Clinically, dermatofibromas can usually be recognized by their firm character on palpation and tendency to show the central "dimple sign" when compressed laterally. Larger and more infiltrative subtypes lacking typical superficial changes are more difficult to diagnose clinically and need to be approached more cautiously. Most patients that are affected fall into a broad age range from 20-60 years of age; however, approximately 17% are under the age of 20 when they present. Women are more prone to the development of these lesions, for uncertain reasons.

The etiology of these lesions remains unknown, although they are thought to arise from a reactive dermal process or response to injury. Typical inciting events have been reported and include arthropod assault, folliculitis, and local infections, although cases of eruptive dermatofibromas have been reported with underlying inflammatory diseases such as lupus, HIV, and leukemia. Some consider dermatofibromas to be a neoplastic or clonal proliferation, but many think dermatofibroma to be an initially reactive process with later autonomous growth and customarily benign character. Histologic findings in most cases demonstrate an acanthotic epidermis with elongated rete ridges. Often accompanying this finding is hyperpigmentation of the basal keratinocytes. As this is a mesenchymal process, the papillary dermis is typically not involved, and a tumor-free area (Grenz zone) can be seen. The dermal component consists of spindle cells, some of which are histoid, and other mesenchymally derived cell types depending on the subtype of dermatofibroma being characterized. In this case, smooth-muscle actin staining was indicative of a myofibroblastic differentiation.

Dermatofibromas often have spindle cells that form short, intersecting fascicles, occasionally forming well-formed storiform pattern in focal areas. As a lesion matures, stromal capillary proliferation often increases with time. Hemosiderin deposition in macrophages as well as multinucleated giant cells can be seen. Peripherally, tumor cells can encircle preexisting collagen fibers and cause characteristic "entrapment." The many variants of dermatofibroma can make an accurate clinical diagnosis less feasible; correct diagnosis relies on the lesion’s histopathologic makeup.

Polypoid dermatofibroma is a very rare variant. In a review by Black et al., 810 dermatofibromas from 579 patients were evaluated, and the most common lesion morphology was a slightly elevated, round nodule. In this series, polypoid lesions were much less common at 3%. In another series, Katsumata analyzed 190 dermatofibromas, none of which were polypoid. Oshima et al. studied a series of 101 patients with dermatofibromas and found 16 cases of nodular polypoid lesions.

Few reports of polypoid dermatofibroma exist in the literature, and a series by Hueso et al. presents 21 cases of giant dermatofibroma characterized by a size greater than 5 centimeters in diameter, polypoid/pedunculated appearance, benign biological behavior despite their size, and the same histopathologic characteristics as conventional dermatofibroma. Our case does not fit the 5 cm diameter criteria for giant dermatofibroma, although the original report by Danckaert did not either. We suspect that due to our patient’s young age and the lesion’s rapid growth, the area would likely have continued to enlarge without intervention. This case is also unusual in that most giant dermatofibromas occur on the lower legs or, more rarely, the back. In the review by Hueso et al., 20/21 patients had lower leg or, more rarely, trunk locations, with one patient presenting with a shoulder lesion. Akagi et al. reported a case of polypoid dermatofibroma 2 centimeters in diameter also located on the lower leg. Finally, a 1.5 x 1.4 centimeter case of polypoid dermatofibroma reported by Sogabe et al. was present on the patient’s wrist. They theorized that the lesion’s polypoid morphology was a result of atypical storiform pattern of spindle-cell growth was not seen in our case. In order to distinguish between DFSP and benign dermatofibroma, several reports have suggested using the immunohistochemical staining characteristics of CD34 and factor 13a. These stains are neither perfectly specific nor sensitive, as focal CD34 positivity can be seen in some dermatofibromas, and some DFSPs uncharacteristically express factor 13a. In our case, benign dermatofibroma was confirmed by immunohistochemical staining with CD34 negativity and factor 13a positivity. Other investigators are now considering the use of other immunohistochemical stains such as stromelysin, tenascin, and D2-40 as possible methods of differentiating dermatofibroma from DFSP.

Treatment of large or giant polypoid dermatofibroma is complete excision, which is curative. Despite the large size and sometimes rapid growth of these lesions, many partially resected cases also had no recurrences.
that certain subtypes of dermatofibroma do not have such benign behavior, and a more aggressive clinical approach should be undertaken in those cases.12,13 For multiple or diffuse lesions, some have advocated laser treatment as well.14 In summary, this young patient had the very unusual presentation of a large polypoid pedunculated dermatofibroma on the arm. Although this lesion's presentation was of concern to the patient and clinician alike, the histopathologic diagnosis was reassuring for a benign clinical course.

Acknowledgements

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References


GRELCK, ALLENBY 31
**Lichen Planus Pigmentosus-Inversus**

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**ABSTRACT**

Lichen planus pigmentosus (LPP) is a rare disease process, possibly a clinical variant of lichen planus (LP), that presents as slate gray, brownish-black or brown macules, papules, patches, or reticulated hyperpigmentation classically found on areas of the face and neck and occasionally flexural folds. We present the case of a man with a variant of LPP, lichen planus pigmentosus-inversus, distinguished only by lesional anatomic location.

**Case Report**

A 73-year-old man presented with asymptomatic, dark brown patches in the axillae for three months duration. There was no history of prolonged sun exposure or trauma in the area of investigation. The patient denied any symptoms of pain or pruritus. Past medical history was remarkable for hypertension controlled with atenolol.

On physical examination, there were well-demarcated, brown mottled patches in both axillae (Figure 1). There was no involvement of the extremities, nails, or oral mucosa. Autoantibodies and complete blood workup was performed, resulting in negative or within-normal-limits outcomes.

Several biopsies were performed, showing focal atrophy in the epidermis, a band-like lymphocytic infiltrate associated with pigmented macrophages, and interface vacuolar change (Figure 2). A PAS stain was negative for fungal elements.

**Discussion**

In 1974, Bhutani et al. first reported LPP in Indian patients, describing a pigmentary disorder similar to erythema dyschromicum perstans (EDP), or ashy dermatosis. It differs from classic LP in that it exhibits dark brown macules and or papules and has a longer clinical course without pruritus or scalp, nail, and mucosal involvement. The lesions may be cosmetically unappealing to the patient but are otherwise clinically asymptomatic. Occasionally, LPP occurs on the intertriginous areas of the body, and in such cases has been dubbed lichen planus pigmentosus-inversus, a variant of LP. There have also been a few cases presenting as mottled hyperpigmentation, zosteriform, arcuate and linear patterns. The cause of LPP is currently unknown. It has been strongly suggested that lichen planus may be associated with hepatitis C virus (HCV). In a 2009 study, Al-Mutairi et al. evaluated 33 LPP patients in Kuwait. Of the patients, 20 (60%) were seropositive for HCV, with significantly higher liver enzymes (AST and ALT). Since LPP is considered to be in the spectrum of lichenoid disorders and may be a variant of LP, it is not surprising that this study supports a possible association between LPP and HCV. Therefore, when a diagnosis of LPP is suspected or confirmed, conservative laboratory workup may include serological testing for HCV.

The differential diagnosis of LPP includes EDP, CTCL, granular parakeratosis, drug-induced dermatoses, and contact and occupational dermatoses with hyperpigmentation. LPP can be distinguished from other disease processes clinically and histologically. Clinically, it is essential to distinguish LPP from EDP. EDP has active borders and does not involve mucosal surfaces, whereas LPP does not have active borders and can involve the mucosal surfaces. Histopathological studies reveal similarities between LPP and EDP, making it difficult to distinguish between the two based on histopathology alone. LPP shows atrophy of the epidermis with basal vacuolar changes and the presence of a lymphohistiocytic or lichenoid infiltrate at the dermoepidermal junction. The dermis shows melanophages with pigment incontinence.

There are no specific standard treatments for LPP. Topical steroids, keratolytics, prednisone, griseofulvin and chloroquine have been used with inconsistent results. Tacrolimus ointment showed promising results in one study, with improvement in seven out of 13 patients (53.8%) with LPP. Since LPP is rare, many ongoing treatments are still being tested for their ability to achieve some clearance. We began a new approach with our patient, using a trial of 10% hydroquinone cream with 1% hydrocortisone cream (1:1 ratio, 100gm jar) applied to the axillae twice daily for three months. We report mild success in decreasing the brown pigmentation in our patient’s axillae (Figure 3). Currently, he is on an every-other-day regimen.

**References**

Figure 1 - Right armpit before.

Figure 2 - LPP-40X

Figure 3
MULTINUCLEATE-CELL ANGIOHISTIOCYTOMA: A UNIQUE CASE AND LITERATURE REVIEW

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ABSTRACT
We present the clinical, histologic, and immunologic features of one case of multinucleate-cell angiohistiocytoma (MCAH) on the face. Of the approximately 70 cases reported in the last 24 years, this is the first one documented on the cheek. MCAH typically occurs in middle-aged women and consists of reddish-purple, dome-shaped papules on the extremities. We summarize the significant findings of previous cases, present a table of immunohistochemical staining particular to MCAH, and make recommendations for documentation in future publications.

Case Report
A 72-year-old female presented with progressive development of a small pre-auricular lesion that had been present for three years. The lesion had gradually grown in size and appeared to spread down her cheek. She also had more recently developed a bump within the lesion. The patient denied any other complaints. She denied pruritus or pain. She denied history of travel, trauma, or insect bites prior to the lesion onset. A topical steroid had been applied to the lesions with little to no change in the presentation. The patient did not demonstrate any sun sensitivity. Her dermatologic history was benign except for a distant basal-cell carcinoma that had been excised previously. She was under concurrent medical management for hypertension.

Physical examination revealed scattered violaceous patches and slightly indurated plaques on the left pre-auricular face, with involvement inferior to the mandible (Figure 1). The patches had superficial scale haphazardly arranged within the plaques and outside the borders of the lesion. The lesions were negative for fungal elements via potassium hydroxide preparation. The plaques were blanchable on diascopy. Full body exam revealed no other vascular lesions or lymphadenopathy. The hair, nails, and mucous membranes were unaffected.

The site was biopsied with a 4 mm punch. Differential diagnosis at the time was vascular malformation, discoid lupus erythematosus, Kaposi’s sarcoma, histiocytoma, sarcoidosis, and lymphocytoma cutis. Histopathologic examination revealed sections with increased numbers of thin, ectatic blood vessels in the mid to upper dermis (Figure 2). Annotated multinucleate cells surrounded the vessels (Figures 3 and 4). Patchy lymphocytic inflammation and solar elastosis were seen. CD31 immunohistochemical stain was performed to highlight the vessels in the dermis. An HHV6 immunohistochemical stain was negative. These findings are consistent with a diagnosis of multinucleate-cell angiohistiocytoma. The patient was given treatment options of wide excision, laser treatment, or observation. She chose observation and declined further excision.

Discussion
Multinucleate-cell angiohistiocytoma (MCAH) is a rare, benign soft-tissue lesion with diagnostic histologic, immunohistochemical, and ultrastructural features that was first described by Smith and Wilson-Jones in 1985.1,2 MCAH is an acquired disorder of unknown cause. It is uncertain if these lesions represent a benign fibrohistiocytic vascular neoplasm or a reactive/inflammatory process. It occurs predominantly on the extremities of middle-aged and elderly women. So far there have been no reported cases of mortality or significant morbidity associated with this disorder.

The differential diagnosis of MCAH may include but is not limited to angiofibroma, annular sarcoid granuloma, dermatofibroma, epithelioid angiomatosis, giant-cell fibroblastoma, Kaposi’s sarcoma, lichen planus, planar, progressive lymphangioma, pseudo-Kaposi’s sarcoma, spindle-cell hemangioma, and granuloma annulare.1-4 It is important to differentiate MCAH from Kaposi’s sarcoma and other conditions that require treatment.5

A search of the English and Spanish language literature revealed 63 documented cases of MCAH. Tables 1, 2 and 3 summarize the clinical characteristics of the 63 documented cases of MCAH, plus our case presented above.6-25 The data suggests that most cases occur in middle-aged and elderly women. The lesions develop more frequently in women than in men (M:F 3.85:1). The age range of these patients is 24 to 86 years old (mean 56.92, median 56). The lesions tend to range from 1 to 120 mm in size, with 85% of the cases being 1 to 10 mm in size. The lesions on the limbs were found on the arm/forearm,11,12 dorsal parts of the hands or wrists and fingers,3-9,13,14,16,20,21,23,24 thighs,5,7-10,12,14,16,19,21 knees,5,23,24 and lower extremities.5,23,24 Other, less common lesions have been reported on the face,1,8,20,21 eyelids,22 upper lip,17 temple,26 oral mucosa,7 forehead,18 and trunk.5,12,15,20,24 Lesions usually are unilateral, but bilateral cases5,7-9,16,20,21,23,24 and a generalized case21 have also been reported. MCAH presents as red/pink to violet or brown lesions. Lesions are typically domed or flat-topped papules that are smooth and firm. Lesions often develop on acral surfaces and persist indefinitely without intervention. There may be solitary lesions or multiple groups of papules. Multiple lesions are more common and can coalesce linearly, annularly, or randomly to form patches or plaques. MCAH seems to be a benign condition that progresses slowly over years without associated disease. MCAH typically doesn’t regress, but there have been cases of spontaneous regression reported in the literature.5,21 None of the cases described to date have shown association with either malignancy or systemic symptoms. Lesions tend to be asymptomatic, but some cases have been reported to be pruritic.11,21 The occurrence of MCAH in non-Caucasian races has only been reported in a few cases.3-6,11,17

Pathophysiology

The pathogenesis of MCAH is uncertain. It has been proposed that there exists a relationship between mast cells and factor XIIIa-positive fibrohistiocytic cells. The release of various pro-angiogenic cytokines, such as IL-4, may add to the vascular proliferation.20 Another theory is that the condition may be associated with trauma, because it tends to occur on the dorsal aspects of the hands and around the knees.3 Most available evidence strongly suggests that MCAH is reactive, not neoplastic. The lesions typically do not show an expansive growth pattern, and MCAH has not been correlated with other comorbidities. There have been no reported cases of familial history, malignant degeneration, or association with cancer.
Histopathology

The principle histopathologic findings in MCAH are the presence of multinucleate cells and vascular proliferation. Multinucleate cells found in MCAH are characteristic but not pathognomonic. The multinucleate cells can also be seen in other inflammatory, neoplastic, or reactive processes. The multinucleate cells resemble cells that are in stages midway between activated fibroblasts and fully developed multinucleated giant cells.

The multinucleated giant cells have hyperchromatic nuclei that are closely aggregated or arranged in the center of the cytoplasm.\(^{1,2,3,17,20,22}\) along the cytoplasmic membrane in a ring-like fashion.\(^{3,6,9,20,21}\) The multinucleate cells appear to have a scalloped or angulated cytoplasm and are scattered evenly throughout the lesion. The multinucleate cells usually show an abundant, rough endoplasmic reticulum, nuclear membrane reinforcement (zonula nucleus oclusden), pinocytic vesicles, and cytoplasmic protrusions. Numerous lysosomes have also been reported, suggesting differentiation to a fibroblast/histiocytic phenotype.\(^{3,4,9,20}\)

The vascular proliferation consists of capillaries, venules, and small arterioles,\(^{1,5,23}\) which may be narrowed or dilated.\(^{6}\) The region surrounding the vessels often contains a sparse inflammatory infiltrate containing mostly lymphocytes, plasma cells,\(^{10,22,23}\) and, in some cases, an increased number of mast cells.\(^{10,17,23}\) The vascular proliferation is embedded in a fibrous stroma rich in fibrohistiocytic cells. The endothelial cells lining these vessels have been described as plump, prominent, and luminally protruding.\(^{4,10,17}\)

Other histopathologic characteristics seen in MCAH include collagen bundles that seem to be thickened, coarse, and arranged haphazardly or slightly parallel to the skin surface.\(^{17}\) The overlying epidermis is hyperplastic.\(^{8,24,13,9}\) Closer examination reveals the presence of loosely spaced dendritic cells throughout the lesion.\(^{4,9}\) An abundance of mononuclear cells in the interstitium has also been seen.\(^{28}\) The diagnosis of MCAH is based on histopathologic findings, although immunohistochemical studies may be useful in confirming the diagnosis.

Immunohistochemistry

Table 4 is a summary of the immunohistochemical studies of MCAH reported in the literature. The multinucleated cells were positive for vimentin,\(^{5,6,17,20,21,23,24}\) and more variably positive for factor XIIIa,\(^{3,5,5,15,23}\) CD68,\(^{12,22}\) and factor VIII.\(^{5,18}\) but were negative for CD34,\(^{18}\) MAC 387,\(^{20,23}\) BMA 120,\(^{18}\) S100,\(^{20,21}\) CD31,\(^{20}\) and BCL-2.\(^{9}\) The endothelial cells stained positive for vimentin,\(^{20}\) CD31,\(^{24}\) CD34,\(^{24}\) factor VIII,\(^{6,20,23}\) BMA 120,\(^{9}\) and occasionally factor XIIIa,\(^{5,17}\) but were negative for lysozyme.\(^{23}\) Mononuclear interstitial cells were positive for factor XIIIa,\(^{20}\) vimentin,\(^{20,24}\) CD68,\(^{24}\) and MAC 387,\(^{20}\) but were negative for S100.\(^{20}\)

Dendritic cells were positive for factor XIIIa, characteristic of fibrohistiocytic cells.\(^{20}\)

Treatment

Due to the seemingly benign nature of MCAH, a conservative approach to the treatment and management is recommended. For cosmetic reasons, surgical excision may be recommended, and it appears to be curative.\(^{1,2,5,17,20,23}\) As shown in Table 3, cryosurgery,\(^{21}\) argon laser,\(^{5,18}\) and CO2 laser\(^{24}\) have shown clinical resolution of the lesions. Successful treatments reported include radiotherapy,\(^{2}\) topical steroids,\(^{16}\) and nitrogen mustard.\(^{11}\) MCAH is not known to be associated with any systemic diseases and is thought to be benign, with no cases of morbidity or mortality. Therefore, further follow-up care is not necessarily indicated unless the lesion grows or the patient desires its removal.

Summary

We believe that multinucleate-cell angiohistiocytoma shows enough clinical, histopathologic, and ultrastructural findings to be considered an independent entity. Due to the benign nature of MCAH, it most likely is under-recognized and under-reported. We recommend that future reported cases comment on the demographics and clinical findings to be considered an independent entity. Due to the seemingly benign nature of MCAH, a conservative approach to the treatment and management is recommended. For cosmetic reasons, surgical excision may be recommended, and it appears to be curative.\(^{1,2,5,17,20,23}\) As shown in Table 3, cryosurgery,\(^{21}\) argon laser,\(^{5,18}\) and CO2 laser\(^{24}\) have shown clinical resolution of the lesions. Successful treatments reported include radiotherapy,\(^{2}\) topical steroids,\(^{16}\) and nitrogen mustard.\(^{11}\) MCAH is not known to be associated with any systemic diseases and is thought to be benign, with no cases of morbidity or mortality. Therefore, further follow-up care is not necessarily indicated unless the lesion grows or the patient desires its removal.

References

Table 1. Reported Location of Individual Lesions (n=83) % of Total

Lower Extremity (n=39) 46.99
- Thigh (n=16) 19.28
- Knee (n=11) 13.25
- Calf/leg (n=12) 14.46

Upper Extremity (n=28) 33.73
- Arm/forearm (n=2) 2.41
- Hands/wrists (n=26) 31.32

Head (n=10) 12.05
- Face (n=5) 6.02
- Eyelid (n=2) 2.41
- Upper lip (n=1) 1.20
- Orbit (n=1) 1.20
- Oral mucosa (n=1) 1.20

Trunk (n=5) 6.02
Generalized (n=1) 1.20

Table 2. Reported Lesion Characteristics % of Group Total

Size (n=54)
- 1-10 mm (n=46) 85.19
- 11-40 mm (n=5) 9.26
- 40-120 mm (n=3) 5.55

# of Lesions per Patient (n=45)
- Solitary (n=5) 11.11
- Multiple (n=40) 88.89

Symmetry (n=43)
- Unilateral (n=26) 60.46
- Bilateral (n=16) 37.21
- Central (n=1) 2.33

Symptoms (n=27)
- Asymptomatic (n=22) 81.48
- Pruritic (n=5) 18.51

Table 3. Resolution by Treatment Modality (n=24) % of treated group

- Excision (5/5) 100
- CO2 Laser (2/2) 100
- Cryosurgery (1/1) 100
- Argon Laser (2/3) 66.67
- Observation (1/11) 9.09
- Nitrogen Mustard (0/1) 0
- Radiotherapy (0/1) 0
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We present a case of calciphylaxis cutis and review the literature pertaining to the pathogenesis, diagnostic features, and treatment options for the condition.

Calciphylaxis is an uncommon condition of systemic calcification that often results in death secondary to wound infection, sepsis, and resultant multiorgan failure. It has been purported that an elevated calcium-phosphorus product in the circulation leads to aberrant deposition of calcium in the vasculature, resulting in severe cutaneous manifestations. Most often, patients with end-stage renal disease have a propensity for developing the disease. Much has been written about the effects of obesity, diabetes mellitus, and anticoagulant usage on increasing the risk of being diagnosed with calciphylaxis. In the presence of these conditions, cutaneous abnormalities should be viewed with a high degree of suspicion.

Lesions of calciphylaxis are usually described as painful, rapidly progressive, ischemic plaques on the distal extremities. It is not uncommon for the lesions to evolve into ulcerative and gangrenous wounds over time. The diagnosis is made based on clinical suspicion, histopathologic evaluation of affected tissue, and correlation with laboratory and radiographic findings. The prognosis for patients diagnosed with calciphylaxis is generally poor, notwithstanding aggressive medical and surgical management.

Case Report

A 59-year-old African American woman presented with a three-week history of a non-healing, painful “bruise” on her right calf. The pain was intensely sharp and remained localized to the area of the “bruise.” The patient denied any previous trauma to the area. A venous ultrasound of the leg, taken one day prior in the emergency room, was negative for venous thromboembolism. Her past medical history was significant for primary hyperparathyroidism, secondary hyperparathyroidism, and osteopenia. She was taking two tablets of acetaminophen/hydrocodone 500/5 mg every 2 hours and doxycycline 100 mg twice daily, both of which were given to her at the time of the visit.

Physical examination revealed a 2.3 cm, exquisitely tender stellate ulcer with a surrounding purpuric rim on the right posterior calf (Figure 1). Several painful, indurated nodules were palpated both proximal and distal to this ulceration. There was no evidence of eczematous or infectious changes on either lower extremity. An incisional biopsy was performed, and bacterial cultures were obtained at the time of the visit.

The incisional biopsy revealed epidermal ulceration with mild interstitial dermal inflammation and focal deposition of calcium in the subcutaneous adipose tissue as well as around small vessels (Figures 2-4). The bacterial culture was positive for aerobic growth of normal skin flora but excluded staphylococcus, streptococcus, and pseudomonal agents.

The constellation of clinical and pathological features confirmed the diagnosis of calciphylaxis. The patient was initially instructed to continue antibiotic and pain management as prescribed by the emergency room. In addition, we started the patient on a compound of topical mometasone 0.1% ointment, Garamycin ointment, and Biafine topical emulsion to be used twice daily. The patient was instructed to apply topical lidocaine 5% ointment nightly as needed for break-through pain, and to hold vitamin D and calcium supplementation. Renal and wound-care consultations were requested.

Discussion

Although the clinical symptoms of calciphylaxis have been reported since the late 1800s, the pathogenesis of the disorder remains elusive.1-3 Selye and colleagues utilized a rodent model to illustrate the cutaneous manifestations of calciphylaxis in 1962. They described a systemic hyperparathyroidism process in which calciphylaxis was the primary outcome. Rodents were injected with parathyroid hormone or vitamin D in order to induce systemic hypercalcemia and were then exposed to certain challenging agents including egg albumin, metallic salt, or tissue trauma. The rats subsequently experienced extravascular calcification, inflammatory sequela, and sclerosis.4 It was later postulated that the phenomenon observed in rodents approximates systemic calcification in human disease. Salient features of calciphylaxis in human patients consist of arteriolar calcification, vascular stenosis, thrombosis, and consequent ischemic cutaneous necrosis.5 Calcific uremic arteriopathy is considered the preferred nomenclature for calciphylaxis that occurs in individuals with a history of chronic renal failure, renal transplantation, or secondary hyperparathyroidism.6 8 One accepted theory maintains that in such patients, the dysregulation of calcium homeostasis results in an elevated calcium-phosphorus product, leading to microvascular occlusive phenomena and target organ damage. A calcium-phosphorus product >70 mg2/dL2 is considered highly predictive of metastatic calcification. 8 As many as 1% to 4% of patients with a history of peritoneal or hemodialysis are affected by calcific uremic arteriopathy owing to intravascular microcalcification and other less-understood mechanisms.10-12 A number of studies have been published in recent years that emphasize the prevalence of non-uremic calciphylaxis.13 14 Patients in this subgroup often have a medical history significant for primary hyperparathyroidism, connective-tissue disease, liver cirrhosis, or malignancy.15 As many as 61% report corticosteroid use.16 The measured calcium-phosphorous product in this patient population is within normal limits, and the individuals do not show signs of deteriorating renal function. However, the cutaneous manifestations are equivalent to those noted in calcific uremic arteriopathy.

A multitude of medical conditions are known to increase the risk of developing calciphylaxis, including obesity, diabetes mellitus, malignancy, liver disease, hyperphosphatemia, hypercalcemia, and hyperparathyroidism.2 17-19 Warfarin anticoagulation and immunosuppressant-agent usage have also been implicated in the pathogenesis of calciphylaxis.20 It is also hypothesized that protein C and S deficiencies, which elicit thrombosis, play a role in the pathogenesis of the condition.21-22 In most cases, increased risk is noted in patients with circulatory disease or coagulopathy.

Compelling evidence for increased risk of calcification by molecular mechanisms exists in the literature. The transcription factor NFκB, the receptor activator of NFκB (RANK), RANK-ligand, and osteoprotegerin are critical regulatory factors in bone mineralization and reab-
sorption. Additionally, activity of these essential mediators can result in systemic vascular calcification. Additionally, fetuin-A has been recognized as an inhibitor of systemic calcification, and patients with chronic inflammatory disease or a history of dialysis have markedly decreased circulating levels of the protein. This could lead one to believe that in the absence of functional fetuin-A, the risk of developing calciphylaxis may be elevated.23-25

It is likely that calciphylaxis is the result of a multifactorial process in predisposed individuals in which cumulative insults lead to clinical manifestations. Although any age group may be affected, the median age at presentation is 48 years, and the disease has a 3:1 prevalence in women.2-6 Caucasia represent the majority of individuals affected by the disease.

Patients with calciphylaxis typically present with intensely painful, rapidly progressive ischemic lesions in areas of elevated fat distribution, including the breasts, buttocks, thighs, and lower abdomen.27 The distal extremities are most commonly affected.28 Early-stage calciphylaxis appears as indurated, indolent plaques, with violaceous lesions resembling livedo reticularis. Plaques and firm nodules in an area of surrounding reftirm reftirm purpura are common.29 Mature disease states reveal induration, necrosis, ulceration, and eschar formation.30 Infrequently, bilea and subcutaneous nodules develop during the disease course.

Complications of severe and disseminated disease include necrotizing gangrene, septic wound infections, and multisystem organ failure. Unfortunately, patients with calciphylaxis are typically afflicted with a number of comorbid medical conditions that factor into the degree of extracutaneous systemic manifestations and overall morbidity. Systemic calcification involving soft-tissue calcification of the lungs, heart, and kidneys has been described in the setting of cirrhosis, with exceedingly poor prognostic outcomes.11,12

Histopathologic evaluation of punch and incisional biopsy specimens of affected tissue reveals several hallmark features of calciphylaxis and found that medial-vessel necrosis and vascular calcification, and patients with chronic renal failure. Arch Intern Med 1976;136:1273-80.

39. Brooks, miner, saitta, grekin 39
ZIANA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

**Important Safety Information for ZIANA Gel**

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

See reverse side for a Brief Summary of the Full Prescribing Information.
**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

Colitis

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

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

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpfully diagnostic.

**ADVERSE REACTIONS**

Clinical Studies Experience

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

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

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>ZIANA® Gel</th>
<th>Clindamycin</th>
<th>Tretinoin</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENTS WITH AT LEAST ONE AP</td>
<td>797 (12)</td>
<td>497 (27)</td>
<td>742 (10)</td>
<td>742 (10)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>19 (1)</td>
<td>29 (2)</td>
<td>19 (1)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>86 (5)</td>
<td>165 (12)</td>
<td>103 (13)</td>
<td>103 (13)</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (1)</td>
<td>21 (2)</td>
<td>18 (1)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (1)</td>
<td>21 (2)</td>
<td>18 (1)</td>
<td>15 (1)</td>
</tr>
</tbody>
</table>

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

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

**DRUG INTERACTIONS**

Concomitant Topical Medication

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

Erythromycin

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

Neuromuscular Blocking Agents

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

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

Clindamycin

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

Tretinoin

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

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

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

Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of ZIANA® Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIANA® Gel is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of ZIANA® Gel in pediatric patients under the age of 12 have not been established. Clinical trials of ZIANA® Gel included patients 12–17 years of age.

**Geriatric Use**

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

**Manufactured by:**

Medicis, The Dermatology Company
Scottsdale, AZ 85256

U.S. Patent 6,387,383

ZIANA is a registered trademark of Medicis Pharmaceutical Corporation.

Prescribing Information as of October 2008.

300-138
MULTIPLE JUVENILE XANTHOGRANULOMA: AN UNCOMMON PRESENTATION OF THE MOST COMMON HISTIOCYTOSIS

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ABSTRACT

The histiocytes are a rare group of poorly understood proliferative disorders. After many classification schemes developed over the years, today they are most commonly divided into the Langerhan cell histiocytosis and the non-Langerhan cell histiocytosis, so named for their discovered cell of origin. The following case report is concerning the most common non-Langerhan cell histiocyte proliferation: Juvenile Xanthogranuloma (JXG). Herein we present an uncommon case of multiple JXG in a five month old female. Following the case report we will discuss the histology of the disorder, its pathophysiology with clinical manifestations and discuss the possible extracutaneous involvement that can occur and how to properly screen for these potential problems. Lastly, we will discuss the histology, differential diagnosis and treatment options when necessary as most cases of JXG are self-resolving.

Case Report

We report a case of a five-month-old female, AL, referred to the pediatric dermatologist for the presumed diagnosis of molluscum contagiosum. AL had no significant past medical or surgical history. She lived in Brooklyn, NY, and was born full-term to parents of Italian descent, with no reported prenatal, antenatal or postnatal complications. Her immunizations were up to date. She had no known drug allergies and was not taking any medications. Her parents reported that the lesions began to erupt approximately two months prior to her presenting to us. The first one was noted on the upper back, and then gradually she developed more on the back, scalp and flanks. Her parents said she did not appear to be disturbed by the eruption. She was not observed scratching the lesions and did not appear to be bothered in any way. AL seemed happy and was eating, sleeping and eliminating without difficulty. She had no fever, chills, weight loss or other constitutional symptoms. On physical exam in our office, in general AL was awake, alert and playful. She appeared well-developed and well-nourished. Her skin exam revealed multiple discreet, pink-to-brown papules and nodules distributed over her posterior scalp, back and flanks. The lesions had a firm, rubbery consistency and were non-tender (Figures 1 & 2). The decision was made to do a shave biopsy to confirm our suspected diagnosis of juvenile xanthogranuloma (JXG). The pathology was indeed consistent with JXG and demonstrated a diffuse dermal infiltrate of lipid-laden histiocytes, Touton giant cells and an inflammatory infiltrate consisting mainly of lymphocytes and occasional eosinophils. Immunohistochemistry revealed histiocytes that stained positively for CD68 and factor XIIIa and were CD1a negative (Figures 3 & 4). This pattern confirmed the diagnosis of a non-Langerhans cell histiocytosis and in combination with the clinical scenario confirmed the diagnosis of JXG. The patient was referred for an ophthalmologic exam, and a letter was sent to her pediatrician recommending an evaluation for leukemia.

Introduction

The proliferative disorders known as the histiocytes are a group of well-known but poorly understood disorders. The variety of names given to these disorders over the years reflects the lack of understanding regarding their origin. Today it is clear that all the histiocytes are closely related entities, with Langerhans cell histiocytosis (LCH) representing one group and non-Langerhans cell histiocytosis (non-LCH) representing another. LCH is now synonymous with histiocytosis X and comprises the formerly known Letterer-Siwe disease, Hand-Schuller-Christian disease, eosinophilic granuloma and congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease). Non-LCH histiocytosis is synonymous with non-X histiocytosis and the primarily cutaneous and usually self-resolving entities including juvenile xanthogranuloma (JXG), benign cephalic histiocytosis (BCH), gigant-cell reticulohistiocytoma, generalized eruptive histiocytoma, and indeterminate cell histiocytosis. There are three histiocytes of cutaneous importance: the Langerhans cell, the mononuclear cell (aka macrophage) and the dermal dendrocyte. All three function as antigen-presenting cells (APCs) and/or have phagocytic capabilities. These cells are hypothesized to arise from a common CD34+ progenitor cell within the bone marrow and, depending upon the cytokine milieu, differentiate along two major pathways: CD14+ cells, which can differentiate further into tissue macrophages or dermal dendritic cells, and CD14- cells, which become Langerhans cells.

Pathophysiology, History and Clinical Manifestations

JXG represents an abnormal proliferation of the dermal dendrocyte. It is the most common histiocytosis and is fairly common among the non-LCH.1,11,14 It most often presents in infants and children, is prognostically favorable, and is mostly cutaneous and self-limiting except for the very rare systemic JXG.1,8,14 The prevalence of JXG in normal, healthy children is between 1% and 2%.7 One review by Janssen et al. revealed that the median age at diagnosis is five months.7 The first description of JXG was in 1905 by Adamson, who coined the term congenital xanthoma multiplex.1,7,14 McDonagh was the first to hypothesize on the cellular origin of JXG in 1912 and suggested that the endothelial cell was the source of this lesion.9 The term JXG was offered by Helwig and Hackney in 1954 after discovering the histology of the lesion to be xanthomatous histiocytes and giant cells.1,9,11 Since then, it has been determined that JXG is a macrophage disorder with factor XIIIa + dermal dendrocytes.10 JXG has a male predominance in childhood of 1.5:1 and has no sex predilection in adulthood.1,9 The male-to-female ratio is higher in those with multiple cutaneous lesions.1 The majority of cases occur in Caucasians, with 75% presenting in the first year of life.1,9,12 JXG is rare in adults, but when it does occur the peak incidence is in the late 20s to early 30s, and adult JXG is less likely to resolve spontaneously.1,11,14 It is not known what causes proliferation of a dermal dendrocyte to form a JXG; however, some authors believe it to be a histiocytic reactive process to an infectious or traumatic stimulus. There are two variants of JXG: the small and large nodular forms. The small nodular form is also known as micronodular and is the least common of the two variants. It presents with multiple pink-to-red-to-brown, dome-shaped papules measuring 2-5 mm in diameter that eventually turn yellow. The large nodular form has only one to a few nodules, but they measure 1-2 cm in diameter. Some sources cite a third variant, termed giant xanthogranuloma, which refers to JXG greater than 20mm.11 One review of 129 patients with JXG revealed that nearly 90% of those patients presented with a solitary lesion, whereas multiple cutaneous lesions were present in only 1.9% of cases.2 Multiple JXG is extremely rare in adults, and those reported have been associated with a hematological malignancy such as...
leukemia or a monochonal gammopathy.\textsuperscript{11} JXG is found on the head, neck and trunk more often than on the extremities.\textsuperscript{1} Very rarely, JXG can be found in the mouth, typically on the hard palate or lateral aspect of the tongue.\textsuperscript{1} Lesions of cutaneous JXG may arise at any anatomic site.\textsuperscript{3}

**Extracutaneous JXG**

The most common site of extracutaneous involvement of JXG is the eye.\textsuperscript{1,4,14} Ocular JXG is seen in only 0.4% to 0.5% of patients with cutaneous JXG, while 40% of patients with ocular JXG will have multiple cutaneous lesions.\textsuperscript{14} The iris is the most common site of involvement and can lead to hemorrhage into the anterior chamber (termed a hyphema), glaucoma and ultimately blindness.\textsuperscript{14} Occasionally, involvement of the iris is subtle and may not be easily noted unless a slit-lamp examination is performed.\textsuperscript{4} Determining whether or not ocular involvement will occur is difficult, but the number of lesions appears to be an important risk factor, as all patients reported to have ocular involvement have also had multiple cutaneous lesions.\textsuperscript{11} The second most important risk factor is age, as 92% of patients reported in the literature as having ocular involvement with JXG were less than or equal to two years of age.\textsuperscript{4} Some authors believe that ocular involvement occurs only with the micronodular form of JXG, while other involved viscera is seen more commonly with the macronodular form.\textsuperscript{4,14} The lung is the second most common site of extracutaneous disease, followed by liver, CNS, pericardium, testes, ovaries, colon and bone, but according to the literature almost any organ can be involved.\textsuperscript{10,14} Of the reported cases of systemic JXG, spontaneous regression occurred in most, and only two deaths have been reported to date.\textsuperscript{4,12} Both reported deaths due to systemic JXG had CNS and hepatic involvement.\textsuperscript{14}

**Associated Diseases**

If patients with JXG also display six or more café-au-lait macules (CAM) more than 5mm in diameter, it should be determined whether they have a family history of neurofibromatosis type 1 (NF1) or if they display other stigmata that fulfill criteria for NF1.\textsuperscript{2,4} CAMs may occur independently of NF1; however, the presence of JXG and multiple CAMs is considered significant for NF1.\textsuperscript{3} The association between JXG and NF1 is well known.\textsuperscript{3} The earliest mention in the literature of an association between these two entities was in 1937.\textsuperscript{12} It is also known that patients with NF1 have a much higher risk of developing juvenile myelomonocytic leukemia (JMML), and a so-called “triple association” consisting of JXG, NF1 and JMML has been reported in several patients.\textsuperscript{14} Patients with JXG and NF1 should be observed closely for the development of JMML as they are known to have a 20- to 32-fold increased risk of developing this type of leukemia compared to patients with NF1 who do not have JXG.\textsuperscript{11} JMML makes up 2% of childhood hematologic malignancies and has a poor prognosis, with a median survival of four years.\textsuperscript{16} Suggestive features of JMML include lymphadenopathy, hepatosplenomegaly, pallor and skin rash.\textsuperscript{2} The cutaneous signs of JMML may include JXG, a leukemic infiltrate, urticaria, petechiae and purpura reflecting the underlying thrombocytopenia, or, less commonly, a toxic exanthema consisting of erythematous macules.\textsuperscript{2,3,15} The incidence of JMML in patients with NF1 is exceedingly rare and reported to be 1:2,000 to 1:5,000.\textsuperscript{2} The incidence of the triple association of JXG, JMML and NF1 is unknown.\textsuperscript{2} JXG in the setting of JMML has two features that differ from sporadic JXG: The first is that they are more often multiple, and the second is that the eruption is more frequently papular and confluent on the scalp and face.\textsuperscript{6} Although it is important to be aware of these associations, most cases of JXG are confined to the skin and are self-limiting and benign. Lesions usually regress within three to six years; however, some post-inflammatory hyperpigmentation, atrophy or anetoderma may remain.

**Histology**

Histologically, there is a well-demarcated, dense histiocytic infiltrate in the dermis, the depth of which depends on the size of the lesion. Earlier lesions can be more difficult to identify with their numerous monomorphic histiocytes and abundant eosinophilic cytoplasm.\textsuperscript{5,3} In more mature lesions, the histiocytes begin to accumulate lipid in their cytoplasm, imparting a foamy or “xanthomatous” appearance, and this allows for easier diagnosis.\textsuperscript{8} Touton giant cells, which have a wreath-like arrangement of nuclei within them, are a characteristic finding in JXG but are not diagnostic. Touton giant cells are either absent or present in reduced numbers in extracutaneous JXG.\textsuperscript{7} The inflammatory cells consist of lymphocytes, eosinophils and plasma cells scattered throughout. Anti-stabilin-1 antibody expression is highly specific for cutaneous non-LCH, but the immunohistochemistry specific to the dermal dendrocyte in JXG will reveal positivity for vimentin, HAM56, CD68 and factor XIIIa, with CD1a being consistently negative.\textsuperscript{16}

**Differential Diagnosis**

Dermoscopy may be a useful, non-invasive tool to help aid in the diagnosis of JXG when it is not possible to obtain histology, such as in a small, uncooperative child. Dermatoscopic characteristics of JXG include an orange-yellow background coloration with clouds of paler yellow deposits.\textsuperscript{19} Further studies of dermoscopic features of JXG with histologic correlation are needed. JXG is often mistaken for other diagnoses. The most common diagnoses that JXG is mistaken for are LCH and the non-LCHs.\textsuperscript{19} BACH and generalized eruptive histiocytoma can be distinguished from JXG by the absence of Touton giant cells on histopathology. LCH can be easily distinguished with immunostains, as Langerhans cells will be positive for CD1a and S-100, both of which are negative in JXG, and the classic racquet-shaped Birbeck granules are found on electron microscopy in the cytoplasm of LCH cells only.\textsuperscript{13} JXG must also be distinguished from molluscum contagiosum, which can be excluded usually on clinical appearance alone. JXG may also resemble a Spitz nevus, keloid, pyogenic granuloma, or fibrous histiocytoma, all of which can be distinguished by histopathologic examination.

**Treatment**

Generally, no treatment is required for cutaneous JXG due to the self-limiting and benign nature of the eruption.\textsuperscript{1,3} There is a case report of CO2 laser therapy being used for multiple cutaneous JXG in an adolescent female but not routinely reproducible. This treatment was well tolerated, and five-year follow-up revealed no recurrent lesions; there was, however, some residual scarring.\textsuperscript{10} Referral to an ophthalmologist may be important to rule out ocular involvement, which, if present, may require intervention, such as topical corticosteroids for iris lesions or excision for limbal lesions.\textsuperscript{11} It is unclear whether or not routine ophthalmologic screening of children with cutaneous JXG will result in earlier diagnosis and treatment and decreased morbidity, but the consensus in the literature is that it is prudent to refer these children for a screening exam.\textsuperscript{2} Evaluating patients for extracutaneous JXG (other than ocular) is not recommended unless the patient is exhibiting symptoms to suggest JXG.\textsuperscript{11} In the case of patients with JXG and NF1, it is important to monitor for the development of JMML.\textsuperscript{1} Due to the infrequent nature of systemic involvement, there are only isolated case reports of chemotherapeutic trials, radiation therapy, high-dose corticosteroids and cyclosporine, and no optimal treatment guidelines have been established.\textsuperscript{1} Visceral involvement may also be safely observed with no treatment until spontaneous involu.

Figure 1

Figure 2

Figure 3: JXG medium magnification

Figure 4: JXG high magnification
USE OF ETANERCEPT FOR PATIENTS WITH SEVERE PLAQUE PSORIASIS IN THE SETTING OF ADVANCED SOLID MALIGNANCIES

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ABSTRACT

Etanercept is a recombinant human chimeric protein obtained from the fusion of two soluble human TNF receptors (p75) and the constant fraction of human IgG11. It inhibits the activity of TNF by competitively binding to both TNFα and TNFβ showing efficacy in the treatment of several inflammatory diseases. It is currently FDA approved for treatment of moderate to severe plaque psoriasis in adults, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis. Plaque psoriasis and psoriatic arthritis can be treated with Etanercept with caution. Although it is not generally recommended, patients with advanced malignancies and severe psoriasis can be treated with Etanercept with caution. The potential risk of lymphoma induction by TNF inhibitors is a much-debated issue. Existing data from clinical trials suggest that patients treated with etanercept are at an increased risk of developing lymphomas when compared to the general population. However, it is also known that patients with rheumatoid arthritis, inflammatory bowel disease and psoriasis are at increased risk of developing lymphomas when compared to the general population. Consequently, the role of etanercept in the possible development of lymphomas is still not clear. However, there have been numerous anecdotal cases of lymphomas reported in patients being treated with TNF inhibitors, and some of these have resolved after discontinuation of the drug. Therefore, one should carefully consider the decision to use TNF antagonists in patients with a history of malignancy, particularly lymphoma.

Introduction

Tumor necrosis factor (TNF) is a cytokine involved in normal inflammatory and immune responses. Elevated levels of TNF are found in involved tissues and fluids of patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis. Etanercept binds specifically to TNF and blocks its interaction with cell-surface TNF receptors, showing efficacy in the treatment of several inflammatory diseases. Since tumor necrosis factor (TNF) plays an important role in host defense and tumor-growth control, etanercept, like other TNF inhibitors, has been associated with the development of lymphomas and solid malignancies as well as an increased risk of serious infections. In several clinical trials, compared to control patients, more cases of lymphoma were observed among patients receiving TNF blockers; however, patients with rheumatoid arthritis and other inflammatory disorders, particularly those with highly active disease, may be at a higher risk for the development of lymphoma. Therefore, the potential role or impact of TNF-blocking therapy on the development and course of malignancies is not fully understood. We report our experience using etanercept safely in two patients with severe psoriasis and advanced solid malignancies. While this approach is not generally recommended, patients with advanced malignancies and severe psoriasis can be treated with Etanercept with caution.

Case Report

Case 1

A 61-year-old female patient with a 34-year history of psoriasis and psoriatic arthritis had undergone several treatments, including methotrexate, PUVA, NB-UVB, cyclosporine and infliximab. She also had previous history of hypothyroidism and chronic hepatitis C. She started treatment with etanercept (Enbrel) 50 mg twice a week in April of 2006, and in September of 2007, while on treatment with Enbrel, she developed a hepatocarcinoma, which required treatment with right hepatic lobectomy. The treatment with etanercept was stopped, but after six months of only topical corticosteroids, she developed a severe flare-up of her psoriatic arthritis, which required the restarting of etanercept. Now, after two years of treatment with etanercept, the psoriasis remains stable and the hepatocarcinoma is in remission.

Case 2

A 71-year-old female with personal medical history of psoriasis for 50 years and psoriatic arthritis for 15 years had been treated with several drugs including methotrexate, cyclosporine, acitretin, PUVA, narrow-band UVB and topical corticosteroids. A diagnosis of colon cancer was made in 1996. At the time, her psoriasis was being treated with methotrexate 15 mg weekly. She was treated by surgery (left hemicolectomy) and chemotherapy. Six years later, etanercept 50 mg twice a week was prescribed for a severe psoriasis flare-up. She was treated for 18 months, but then she developed liver metastases. At that point, etanercept was stopped and a right hepatic lobectomy was performed, followed by six cycles of chemotherapy (oxaliplatin). However, two months after surgery she developed a severe flare-up of pustular psoriasis that required systemic therapy with cyclosporine and etanercept to gain control. She had remained on etanercept for three years when she developed new primary colon cancer, which was treated by complete colectomy. Three months after surgery she was re-started on etanercept, and after 18 months of therapy she has good control of her cutaneous and articular signs and symptoms without any evidence of malignancy recurrence.

Discussion

TNF inhibitors have been available for more than 12 years, mostly for inflammatory bowel disease and rheumatoid arthritis, with more than 1.5 million patients treated. In recent years, the indications for use of TNF inhibitors have expanded to include psoriasis and psoriatic arthritis, among other diseases. Nevertheless, the current knowledge about the long-term safety of TNF inhibitors is mainly derived from observations made in their use in rheumatoid arthritis and inflammatory bowel disease. Patients with both rheumatoid arthritis and inflammatory bowel disease are often treated with a combination of TNF inhibitors and an immunosuppressive agent (methotrexate, 6 MP, or azathioprine), whereas patients with psoriasis are most often treated with TNF inhibitors as monotherapy. However, the potential risk of lymphoma induction by TNF inhibitors is a much-debated issue. Existing data from clinical trials suggest that patients treated with etanercept are at an increased risk of developing lymphomas when compared to the general population. However, it is also known that patients with rheumatoid arthritis, inflammatory bowel disease and psoriasis are at increased risk of developing lymphomas when compared to the general population. Therefore, one should carefully consider the decision to use TNF antagonists in patients with a history of malignancy, particularly lymphoma.

There have also been descriptions of melanoma and non-melanoma skin cancer, although it is not clear whether these lesions can be attributed to psoriasis itself or to treatments received previously, such as phototherapy, cyclosporine, or methotrexate. It is not known whether etanercept can influence the development of solid malignancies.
tumors. Prostate, lung, and breast tumors have been described in clinical trials and post-marketing reports of the use of etanercept.11,12 However, an important, large observational study of patients with rheumatoid arthritis demonstrated no increased risk of solid cancers in patients treated with biologic agents.5 These findings contrast with the results of a meta-analysis of rheumatoid arthritis studies examining patients treated with adalimumab and infliximab, which revealed an increased risk of solid cancers.13

On the other hand, in recent clinical trials involving 16 patients with advanced breast cancer refractory to conventional therapy and nine patients with advanced carcinomas, in which patients with hematological malignancies were excluded, etanercept showed safety and biological activity in the treatment of solid malignancies when used as monotherapy or in combination with other chemotherapeutic agents on the theoretical basis that treatment with etanercept reduces multiple proinflammatory cytokines and adhesion molecules and decreases cell trafficking and angiogenesis.14,15

In our cases, we used etanercept at a standard dosage for the treatment of severe plaque psoriasis (50 mg twice weekly),2 and it demonstrated efficacy in controlling the signs and symptoms of severe plaque psoriasis and psoriatic arthritis in both patients. No remarkable side effects were shown in our patients apart from mildly pruritic injection site reactions. At this time, cutaneous and articular signs and symptoms are very well controlled in both patients (PASI 2.4 and 3.3, respectively), and their malignancies appear to be in remission. One could argue that patient 2 developed metastases after etanercept. However, the short evolution and successful intervention without recurrence argues against this. The other patient also developed her malignancy while on etanercept therapy. She was, however, hepatitis C positive, which implies an increased risk of liver cancer.

In our opinion, taking into account the risk-benefit of the treatment, biologic therapies represent an interesting therapeutic option for patients with severe psoriasis associated with advanced solid malignancies, allowing an improvement in the patients' quality of life without negative influence in the neoplastic process.

In summary, we report our experience using etanercept in two patients with severe psoriasis in the setting of advanced solid malignancies. Etanercept showed efficacy in our cases and, given that both patients are in remission, also safety. More and larger case series are necessary in order to confirm our findings.

References
PAPULAR-PURPURIC GLOVES AND SOCKS SYNDROME: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT
Papular Purpuric Gloves and Socks Syndrome (PPGSS) is a self-limited exanthem that appears typically in young adults. The rash is characterized by a painful and pruritic symmetric erythema and edema with papular-purpuric lesions of the hands and feet. A hallmark of the syndrome is a sharp demarcation at the wrists and ankles, known as a gloves-and-socks distribution. The condition progresses to petechiae and purpura and may develop into vesicles and bullae with skin sloughing. Although there are many infectious causes, two-thirds of the cases are due to Parvovirus B19. It is important to recognize this syndrome in order to reassure patients that it is benign and treatment is based on symptomatic relief.

Case Report
We report the case of a 42-year-old African-American female who initially presented with “bumps” for two weeks on her hands and one week on her feet. The patient described the bumps as tender to the touch but not pruritic. The patient also stated that she had been experiencing bilateral hip pain that started at the same time, as well as feeling very fatigued. Upon further questioning, the patient stated that her symptoms had started shortly after visiting her niece who was hospitalized with mononucleosis. During review of systems, the patient stated that she had recently had an upper respiratory infection with sore throat and enlarged lymph nodes for which she had been prescribed Augmentin, and the infection had resolved.

Physical exam showed a healthy-appearing female in no acute distress. There was an ovoid papulosquamous eruption and psoriasiform dermatitis on the patient’s bilateral wrists and ankles (Figure 1). Furthermore, there were purpuric subcutaneous nodules and papules present on the palmar and plantar surfaces (Figure 2).

Our differential diagnosis included diseases with acral and/or petechial skin lesions, including Rocky Mountain spotted fever, meningococcemia, erythema multiforme, syphilis, palmoplantar pсорiasis, drug-induced exanthems, and contact dermatitis. Furthermore, we contemplated whether this was a unique presentation of an eruption typically associated with adolescents such as Gianotti–Crosti syndrome, Kawasaki syndrome, and hand-foot-mouth disease.

Our initial plan was to obtain a CBC with differential, ANA titer, sedimentation rate, and RPR. On follow-up, the blood test results were all within normal limits. At this time it was decided to do a 4 mm punch biopsy of the left dorsal hand and the right medial foot, areas where the lesions were active. The patient was asked to return in 10 days to remove the sutures and review the pathology reports. The pathology report described the left dorsal hand specimen as benign, a mild subacute spongiotic dermatitis most consistent with a mild eczematous dermatitis. The microscopic description stated that the epidermis was acanthotic and papillomatous. There were hypergranulosis and overlying orthokeratotic hyperkeratosis with focal hyperkeratosis. Within the dermis, there were mild edema, and foci with exocytosis of lymphocytes. In the superficial dermis, at low power there was a mild superficial perivascular infiltrate consisting of lymphocytes (Figure 3). The right medial foot biopsy was read as mild superficial perivascular lymphocytic dermatitis. The epidermis was acanthotic with orthokeratotic hyperkeratosis. Within the dermis, there were prominent vessels. A mild lymphocytic infiltrate was present in the superficial dermis, around vessels, with focal extension into the epidermis. A 200x magnification showed some extravasated red blood cells, corresponding to petechiae, and subtle interface (Figure 4). A PAS stain for fungus was negative for both specimens.

New papules continued to erupt on the patient’s palms and feet for two weeks after her initial visit (Figure 5). At that time, additional laboratory evaluation included HIV-antibody screen, HSV-1 and -2, CMV, parvovirus B19, Rickettsia, and VDRL. Laboratory results showed positive IgG antibodies for CMV IgG, parvovirus B19, and HSV-1. The rickettsial antibody and typhus-fever antibody tests were IgG positive, which is suggestive of infection at some undetermined time or of past infection or early recurrent response to infection. Most significant, the Epstein Barr virus IgG and IgM antibodies were positive, suggesting a recent infection.

When the patient presented for follow-up to the office, her papulosquamous eruption was desquamating further, but no new papules were present. Due to the test results and the patient’s disease history of purpuric papular palmoplantar lesions, her diagnosis was consistent with papular-purpuric gloves and socks syndrome (PPGSS). Her infection with the Epstein Barr virus was responsible for not only the PPGSS but also the mononucleosis. Another component contributing to her papulosquamous eruption was the use of Augmentin to treat her mononucleosis. The rash is a common reaction that occurs when a beta-lactam antibiotic is prescribed to treat pharyngitis, which was a symptom masking the mononucleosis diagnosis.

Discussion
Papular-purpuric gloves and socks syndrome (PPGSS) is a characteristic exanthem, originally described in 1990 by Harms, Feldmann, and Saurat. It is a self-limited febrile illness of mostly infectious origin that preferentially appears in young adults, although pediatric and adult cases have also been described. Cases of PPGSS occur mostly in the late spring and summer months. Two-thirds of the PPGSS cases have been associated with acute parvovirus B19 infection, and the others have been associated with hepatitis B, cytomegalovirus, Epstein-Barr virus, measles, coxsackievirus B, rubella, human herpes virus types 6 and 7, and drug-induced by sulfamethoxazole and trimethoprim. Patients with PPGSS are considered infectious when presenting with the rash. The syndrome is self-limited and resolves within seven to 14 days under symptomatic therapy, accompanied by desquamation and usually without relapse.

In cases of immunosuppression, however, the illness may lead to persistent anemia and pruritus and a prolonged duration of skin lesions. The rash is clinically characterized by a painful and pruritic, symmetric erythema and edema with papular-purpuric lesions of the hands and feet extending proximally with less severity. A hallmark of the syndrome is a sharp demarcation at the wrists and ankles in a gloves-and-socks distribution. The condition gradually progresses to petechiae and purpura and may develop into vesicles and bullae with skin sloughing. Involvement of additional sites, including the cheeks, elbows, knees, inner thighs, buttocks, or genitalia and oral mucosa, has been reported.

Normally, the purpuric lesions of PPGSS spare the face. There have been reports of a PPGSS-like presentation in patients who also had involvement of the perioral region and the chin, known as “acropetechial syndrome.” The various oral manifestations, which have been described for more than half of PPGSS patients, include petechiae, erythema and swelling, vesicles, aphthous ulcers and Koplik spots on the hard and soft palates and the labial and buccal mucosa.

The genital mucosa may be affected with painful edema, erythema, and small ulcers, sometimes accompanied...
by dysuria. Extracutaneous signs and symptoms may precede or occur simultaneously with the skin lesions and are usually mild and transient. Systemic symptoms, such as asthenia, anorexia, low-grade fever, lymphadenopathy, myalgias, and arthralgias may accompany the skin eruption but are generally only mild to moderate. During the course of infection, laboratory findings include leukopenia, anemia, thrombocytopenia and elevated liver enzyme levels. The erythrocyte sedimentation rate and C-reactive protein level are infrequently increased.

The pathogenetic pattern and subsequent clinical presentation may be the result of a complex interplay of the host’s humoral and/or cellular response, viral load, and even co-infection with another virus. Direct immunofluorescence analysis of skin biopsy specimens reveals granular deposition of IgM antibody and C3 in the walls of the papillary dermal vessels, suggesting a vascular reaction to an antigenic stimulus. The histopathologic findings include slight acanthosis, predominantly CD3/CD30 lymphocytic perivascular and interstitial inflammatory infiltrate of lymphocytes with some neutrophils and eosinophils in the papillary dermis, edema in the papillary and reticular dermis, extravasation of erythrocytes, lymphocytic exocytosis with necrosis of basal keratinocytes, and vacuolar degeneration of the basal layer of the epidermis with a lichenoid inflammatory infiltrate. Focal vasculitic changes with fibrin deposition in the vessel walls, thrombi, nuclear dust, and hemorrhages can also be observed. Although not pathognomonic for PPGSS, these findings are consistent with a virus-induced rash.

The causative agent can be confirmed by serologic analysis. It may also be confirmed by ELISA or PCR analysis for DNA in the serum and in cutaneous biopsy specimens. Many patients have immunoglobulin M and immunoglobulin G antibodies to the causative agent, which can be detected from lesional skin with the use of PCR. The observation of seroconversion from negative for antibodies on admission analysis to positive for both immunoglobulin M and immunoglobulin G antibodies later in the disease process has been reported in several cases.

PPGSS is a benign eruption that can mimic other acral skin lesions. PPGSS is distinguishable by a sharp demarcation at the wrists and ankles of a painful and pruritic, symmetric erythema and edema with papular-purpuric lesions. The information gleaned from clinical laboratory data in coordination with molecular techniques can help identify the causative agent. It is important to reassure patients that the rash is self-limiting, and treatment is solely based on symptomatic relief.

References

Kaposi’s sarcoma is a vascular neoplasm likely related to a viral infection with human herpes virus 8. Four subtypes exist: classic, African-endemic, AIDS-associated, and iatrogenically induced in immunocompromised individuals. Cutaneous lesions can present as pink to blue-purple patches, plaques or nodules. We present a case of classic Kaposi’s sarcoma in a 70-year-old Caucasian Jewish male.

Case Report

A 70-year-old white male presented for a routine skin exam without any chief complaints. A patch of blue-red discoloration was noted on the plantar aspect of the right foot extending to the dorsum of the toes. A small focus of similar discoloration was also noted on the left foot (Figures 1-2). When questioned further, the patient denied any history of trauma or the use of blood thinners. He stated he was previously evaluated by podiatry for the discoloration, but he required no further treatment at that time. The discoloration was present for several months and was asymptomatic. His medical history was significant for Parkinson’s disease, hypertension, and non-insulin-dependent diabetes. A punch biopsy of a representative area was sent to pathology. The differential diagnosis included Kaposi’s sarcoma, pseudo-Kaposi’s, trauma-induced bruising, and senile purpura.

Histopathology

H and E staining revealed slit-like vascular spaces lined with spindled endothelial cells in the dermis and extravasated red blood cells (Figures 3-5). A diagnosis of Kaposi’s sarcoma was made.

The patient was tested and found to be HIV negative. He was referred to oncology for further treatment and elected to be followed closely by observation. The possible use of sirolimus was discussed if he developed progressive disease.

Discussion

Kaposi’s sarcoma (KS) is a chronic disease primarily affecting elderly men of Jewish, Eastern European or Mediterranean descent. Four subtypes have been described: classic, African-endemic, AIDS-associated, and iatrogenically induced in immunocompromised individuals. All types are thought to be virally induced by human herpes virus 8 (HHV8). Kennedy et. al evaluated 16 cases of early Kaposi’s sarcoma for the presence of HHV8 using PCR. They found 87% of the cases were positive, suggesting HHV8 is the etiological factor in the pathogenesis of the disease.

Classic KS is more prevalent in men of Jewish or Mediterranean descent, with many developing this form after the age of 50. The lower extremity is the most common location, and it can present as red to purple to brown patches, plaques or nodules.

Endemic Kaposi’s in Africa is more common in males. Seroepidemiological studies have shown horizontal transmission, suggestive of transmission routes other than sexual. Passage from mom to baby may occur via infected saliva in masticated food. Subtypes of the endemic form include nodular, florid, infiltrative and lymphadenopathic. The lymphadenopathic type is more common in children and carries a worse prognosis.

The incidence of HIV-associated Kaposi’s has decreased with the advent of HAART therapy; however, it remains one of the most common tumors in HIV-infected patients.

In immunosuppressed patients, such as organ-transplant patients, it has been shown that HHV-8 can reactivate after transplantation, and replication of the virus increases significantly. The lesions have also been shown to regress after discontinuation of the immunosuppressive agent.

Histopathology

On histology, lesions of Kaposi’s sarcoma display slit-like vascular spaces with spindled epithelial cells in early patch lesions. In older lesions, dilated blood vessels may predominate with extravasated red blood cells. Promontory sign, the stroma of blood vessels projecting into the vascular space, may be present. Stains for CD31, CD34 and HHV-8 can be used for confirmation.

Treatment

Several treatment options exist and should be based on the etiology and stage of the disease. Kaposi’s can be treated with local destruction by cryotherapy or topical alitretinoin gel. Other anti-HHV8 agents include pegylated liposomal doxorubicin, paclitaxel or interferon alpha. In some AIDS-related cases, HAART therapy may cause regression. Treatment in transplant patients is less well established. Immunosuppressive drugs need to be tapered; however, this increases the risk of graft rejection. The use of sirolimus has been shown to be effective in some of these patients. In limited disease without other underlying pathology, a watchful waiting approach may be undertaken, as in the case of our patient.

References

Figure 1: Sharply demarcated blue-red patch

Figure 2: Blue patches on dorsum of foot

Figure 3. Low-power H&E

Figure 4. Medium-power H&E: Slit-like vascular spaces and extravasated red blood cells

Figure 5. High-power H&E: Spindle cells, slit-like vascular spaces and extravasated red blood cells
ASHY DERMATOSIS WITH NOVEL HOMEOPATHIC TREATMENT USING ENOXAPARIN: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

The debate between lichen planus pigmentosus (LPP) and ashy dermatosis (AD) has gone on for decades. Previous authors have made valid points for and against these entities being the same disease. Clinically, LPP and AD present with different morphologies. However, histologically they can be interchangeable on both hematoxylin and eosin (H&E) and direct immunofluorescence (DIF). Both are found in traditional lichen planus and supports the theory that LPP is a related condition.

Case Report

We present a case of a 48-year-old, Columbian-born male with a one-year history of advancing, slate grey-blue colored patches with a slightly erythematous border on his back and extremities (Fig. 1&2). Previous treatments included topical tacrolimus 0.1% ointment BID and clofazimine, without improvement. Upon our initial visit, we obtained two biopsies of the leading edge of a patch and sent them for H&E and DIF. The patient was also treated for acne on his back using benzoyl peroxide 5% lotion and clindamycin 1% lotion. Further noted were macules of post-inflammatory hyperpigmentation at previous sites of acniform lesions, as well as a Becker’s nevus on the right upper back.

H&E: Revealed abundant pigment incontinence in the papillary dermis with subtle interface changes, focal basal vacuolopathy and few dyskeratotic keratinocytes.

DIF: Showed dense linear and shaggy fibrin deposits, IgM+ cytoid bodies, and negative for IgG, IgA, C3 and C5-9.

Both biopsy findings are consistent with ashy dermatosis/lichen planus pigmentosus. Clinically, the lesions were most consistent with ashy dermatosis. We commenced treatment with weekly 30 mg subcutaneous injections and monitored the patient every six weeks.

At his first follow-up, the AD patches had not progressed, and the erythema of the leading edge had faded (Fig 3&4). In addition, the slate grey-blue pigmented patches appeared to have faded into his normal skin tone. The patient actually missed his 12-week follow-up and was rescheduled for one week later. Consequently, he missed one injection, and he remarked that he could feel the lesions becoming moderately pruritic. Upon examination, there was mild erythema at the border, but the patches remained faded. The patient did not report any bleeding complications or have visible purpuric lesions. He is ultimately satisfied with the treatment and continues on enoxaparin therapy.

Discussion of Ashy Dermatosis vs. Lichen Planus Pigmentosus

Ashy dermatosis is characterized clinically by blue-grey to ashy colored patches, sometimes with an active red border. AD is usually disseminated and is characteristically located on the upper extremities, trunk and face.1 In contrast, lichen planus pigmentosus lesions are typically well-circumscribed, brown-black pruritic patches on the sun-exposed and flexural areas and can be seen with an erythematous border. On histology, AD and LPP are thought to have a vacuolar change, colloid bodies, melanin incontinence, and perivascular or interface lymphocytes.2 In a clinicopathologic study of 31 patients by Vega et al., it was noted that in a portion of LPP patients there were hyperkeratosis/hypergranulosis and/or a lichenoid infiltrate observed on histology, both of which are found in traditional lichen planus and supports the theory that LPP is a related condition.

The AD direct immunofluorescence is not always positive and does not yield information that allows for definitive diagnosis. The following phenomena have been observed: fibrin deposition at the dermoepidermal junction, a mixture of IgM, IgG, IgA and, rarely, complement-positive colloid bodies, thought to be due to basal cell apoptosis.3,4,5 The DIF findings of LPP do not allow for definitive diagnosis, either. Convit et al. report that the lichenoid variant has similar structural and immunofluorescence patterns to AD.6 However, there is a paucity of exact DIF results reported for confirmed cases of LPP. Similar to both AD and LPP, traditional lichen planus has a mixed DIF pattern with possible IgM, IgG, IgA, and C3-positive colloid bodies and fibrin deposition.7

The geographic and ethnic distributions of these diseases also support the notion that they are separate entities. AD has a high incidence in women, favoring development in the first to third decades,8 LPP, and other Asians. A retrospective study of 124 patients with LPP also found concomitant traditional lichen planus in 19 patients, further supporting LPP’s inclusion into the disease spectrum.9 In multiple studies, low-dose enoxaparin has been shown to be effective in treating traditional lichen planus. In T-cell-mediated diseases such as lichen planus, these lymphocytes must traverse the extracellular matrix. The ability of these cells to express heparinase, which degrades the heparin-sulfate moiety of the proteoglycan matrix, is essential to this process.10 Both in vivo and in vitro studies have shown that low-dose heparin suppressed the expression of T-lymphocyte heparinase activity, leading to inhibition of T-cell migration and delayed-type hypersensitivity reactions.11 Low-dose, low-molecular-weight heparin administered to mice has shown to inhibit experimental T-lymphocyte-mediated disease and allograft rejection.12 Low-molecular-weight heparin was found to inhibit allergic contact dermatitis in humans, as well.13

Our effective treatment of ashy dermatosis with homeopathic enoxaparin likely recapitulates its effectiveness in other T-cell-mediated processes. The lack of pruritus while receiving therapy could correlate to the lack of infiltration by lymphocytes and disease activity. The return of pruritus when our patient missed his dose also supports this theory. Certainly, it appears that lichen planus pigmentosus, ashy dermatosis, and lichen planus are related based upon their histology and the latter two’s response to low-dose enoxaparin. However, these diseases may only share a T-cell-mediated process that manifests differently in certain genotypes. Clearly, a double-blind, placebo-controlled study would help to realize the full potential of this treatment. In our opinion, low-dose enoxaparin represents a safe alternative when conventional therapies prove to be ineffective.

References

A 23-year-old woman presented to our office with a 3mm diameter lesion of 8 months duration on her right chin. There was no history of trauma to the site. She had very fair skin, and further inspection of her face and scalp showed no other locations of nevi. The patient had a family history of melanoma (mother). A biopsy of the chin lesion was taken for microscopic diagnosis. She was diagnosed with a Spitzoid Blue Nevus with Dysplasia. Conservative excision of the blue nevus was performed.

Discussion

The common blue nevus was first described by Tièche in 1906; before that, similar lesions had been described as chromatophora and melanofibroma. The two variants of the blue nevus that are currently diagnosed are the common blue nevus and cellular blue nevus.

The common blue nevus can be seen as a macule, plaque, or papule with a flat surface that is slightly elevated. It usually has a gray to bluish-black pigmentation. These lesions commonly occur on the head, pelvis, and upper surfaces of hands and feet. The patient described here has an uncommon blue nevus on the surface of her right chin with an irregular shape.

Nevi are atypical moles. The term “dysplastic” characterizes nevi that tend to be larger than regular atypical moles. They also have the features of irregular borders and mixed colors and may be present in larger numbers. Regular nevi tend to be benign, while dysplastic nevi can give rise to malignant melanoma.

The cellular blue nevus has similar characteristics to the common blue nevus but tends to be larger. It can measure anywhere from 1cm to 3cm in diameter. Blue nevi are most common in Asian populations, where the prevalence is estimated to be 3-5% in adults. They are found in 1-2% of Caucasians and are rarely found in dark-skinned individuals. Blue nevi are uncommon at birth or in the first few years of life, with an estimated prevalence of less than 1 case per 1,000 population.1

The homogeneous blue pigmentation is caused by the Tyndall effect, resulting from a dense dermal infiltrate of heavily pigmented dendritic melanocytes.2 Although the homogeneous blue color is the most classic pattern, peculiar dermoscopic-histopathologic variants of blue nevi have been described recently, namely blue-blue nevi, black-blue nevi, brown-blue nevi, white-blue nevi and polychromatic blue nevi.3 Blue color per se is a highly unspecified dermoscopic feature that can be found in a series of skin tumors, including nodular melanoma, melanoma metastases or pigmented basal cell carcinoma.4 Blue nevi should be diagnosed upon seeing that there is no history of changes. Nodular melanoma and melanoma metastases show a history of changes and history of previous melanoma, respectively. The pigmented basal cell carcinoma shows a history of progressive growth.

There have been several rare cases of cellular blue nevi being associated with malignant melanoma.5 Dr. Rudolf Roth notes that malignant change in cellular blue nevi may be heralded by a sudden increase in size and occasionally ulceration.6 This key feature of malignant growth can be used to distinguish common blue nevi from different types of melanoma. However, many melanocytic lesions have been shown to display various types of coloration and features that may be difficult to diagnose. A recent study identified differences in the dermoscopic pattern of nevi between individuals with a personal history of melanoma and a healthy control group.7 The majority of patients in this study exhibiting mixed patterns of nevi had melanoma, compared to the healthy patients who had simple, uniform nevi patterns. Therefore, individuals harboring nevi with a complex pattern seem to be at higher risk of melanoma development and may require closer surveillance than individuals with nevi in a uniform pattern.8 Although there is no medical therapy for common or cellular nevi, a biopsy should be performed on any changing, pigmented lesion, and in many cases simple excision is curative in solitary lesions. In the rare cases of persistent blue nevi, satellite lesions may manifest around the original excision site. These must be distinguished from malignant blue nevus, and re-excision is recommended.

References

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CENTRAL CENTRIFUGAL CICATRICAL ALOPECIA: A CASE PRESENTATION AND LITERATURE REVIEW

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ABSTRACT

Etiology of central centrifugal cicatricial alopecia is thought to be multifactorial, ultimately resulting in injury to hair follicles and fibrous restructuring of tissue. Mechanical, chemical, and thermal insults applied chronically to scalp hair may lead to irreversible destruction of pilosebaceous units. Inflammatory damage to both the hair matrix and the follicular stem cells results in progressive scar formation. The environmental impact, personal grooming and hairstyling practices, as well as yet to be elucidated genetic predispositions may play a role in the pathogenesis of this formidable condition.

Case Report

History and Clinical Presentation

A 35-year-old African-American female presented for a follow-up visit regarding an ongoing case of parietal scalp alopecia. Her hair loss had started one year prior as a “sore” and ulcerating lesion on the vertex of the scalp. Her condition had initially seemed to improve, but subsequently deteriorated and expanded in the involved area. The patient was now complaining of scalp “flaking,” tenderness, and pruritus, which upon further questioning were linked to her recent hairstyling practices. She was initially treated with mupirocin 2% cream.

Upon her return to the office after two weeks, the patient had sustained some degree of improvement. She felt her scalp was “healing well” and that the medications were effective. At that time, her scalp showed an almost completely healed site of ulceration, with no signs of infection noted and some return of hair growth. The patient was instructed to continue ketoconazole 2% shampoo but continue with the Luxiq 0.12% foam applications as prescribed.

The patient returned to the office one year later with continued complaints of the parietal scalp alopecia. She reported that during a hairdressing session several days prior she had “tight braids taken out” and hair-relaxing chemicals administered to her hair. At that time, she noticed a large amount of hair coming out in patches from the crown area of the head, as well as profuse scalp bleeding, which was somehow curtailed by the hairdresser. The patient admitted to itching and drainage following the procedure, resulting in crusty exudates over the lesion. She also indicated “rubbing” the area often, but denied any scratching. Inspection of the parietal scalp revealed a circular area of hair loss and limited muco-purulent drainage with good granulation tissue. The patient was given prescriptions consisting of hydroxyzine, cephalexin, trimacinolone 0.1% cream, and mupirocin 2% cream.

Physical Examination

The patient came back for a follow-up visit two weeks later, at which time she reported some improvement with treatment. Scalp inspection revealed a 4.5 cm x 3.2 cm shiny patch of cicatricial alopecia to the vertex (crown) region of the head (Figure 1).

Some stranded hairs in an otherwise denuded vertex of the scalp were appreciated. No other scalp, cutaneous or oral lesions were discovered.

Histopathology

A parietal-scalp tangential shave biopsy sample was obtained, and it demonstrated hyperkeratosis, hypergranulosis, and irregular epidermal hyperplasia with vertically oriented fibrosis in some areas of the papillary dermis. Presence of a perivascular inflammatory infiltrate of lymphocytes and occasional eosinophils was noted. The lesion was eroded, and subpapidermal fibrosis was prominent. GMS stain was negative for fungal organisms.

Diagnosis

Central centrifugal cicatrical alopecia (CCCA)

Differential Diagnoses

- Alopecia mucinosa
- Classic pseudopelade of Brocq
- Dissecting folliculitis (cellulitis)
- Erosive pustular dermatosis
- Folliculitis decalvans
- Folliculitis necrotica
- Lichen planopilaris
- Neurodermatitis
- Prurigo nodularis
- Traction alopecia
- Trichotillomania
- Tufted folliculitis

Course and Treatment

Following a discussion of possible treatment options, Kenalog 10 mg/cc was injected intralesionally. The patient was also started on clobetasol 0.05% solution to be applied to the affected scalp area as directed. The treatment plan was reviewed with the patient, and she was instructed to return to the office for follow-up visits.

Discussion

Clinical Features of CCCA

Central centrifugal cicatrical alopecia (CCCA) occurs predominantly in women of African descent and begins at the vertex of the head, spreading centrifugally and progressively. Patches or tufts of normal hair may be evident within the zone of atrichia, but once the follicles are destroyed, scar tissue develops and hair does not grow back. CCCA may be the most common type of alopecia seen in the United States, and although it impacts black women primarily, African-American men as well as Caucasians can be affected.3

Early in the course of the disease, patients may experience pruritus, tingling, tenderness, tightness, and scalp paresthesia. The alopecia occasionally extends to the frontal hairline, but the lateral and occipital scalp are generally spared.3

Alopecia can be emotionally devastating, as it bears strongly on self-esteem, social interactions and personal relationships. Correct diagnosis, prevention, and choosing the appropriate line of treatment affects the wellbeing of the patient, regardless of what caused the disorder.1

Dermatohistopathology

Even though CCCA overtly looks non-inflammatory, dermatohistopathology characteristically exposes mononuclear cell infiltration and replacement of hair follicles by fibrosing concentric lamellar columns.3 Additionally, lichenoid perifolliculitis with progressive fibrosis and presence of lymphocytic reactions may be evident.2 Another striking feature of CCCA is a premature disintegration of the inner portion of follicular infundibulum and corresponding sebaceous glands, followed by scar tissue formation. Since the inflammatory attack commences on the upper part of hair follicle, containing stem cells and sebaceous units, the possibility of hair regeneration is forfeited and permanent hair loss results.5 In end-stages of the disease, foreign-body granulomatous reactions occur in the dermis as giant cells encircle hair infundibula.3

Some studies suggest both histopathologic and direct immunofluorescence (DIF) examination for incontrovertible diagnosis. Nonetheless, traditional histopathology evaluation seems to be sufficient in the majority of cases, with increasing utility of DIF in inconclusive or ambiguous instances.3 Furthermore, the combination of vertical and transverse tissue segments has optimal diagnostic value. With a single biopsy specimen available, it may be cut either vertically or transversely at the discretion of the dermatopathologist. Regardless of the directionality chosen
by the pathologist, serial step sections are needed in order to diminish the danger of missing critical histological findings.⁷,⁸

**Differential Diagnosis**

Distinguishing CCCA from other forms of hair loss presents a unique challenge, as all primary cicatricial alopecias share overlapping characteristics.⁹ An irrefutable diagnosis may be elusive both clinically and histologically. CCCA is classified under focal (patchy or localized) and cicatricial—or scarring—hair loss.² Diagnostic hallmarks of CCCA at its onset include perifollicular lymphocytic infiltration, inflammatory pustules, and focal atrichia in the shape of a circle at the crown. Follicular ostia may be diminished or missing in the bald spot. As the disorder gradually advances, epidermis atrophies, and follicles are reconstituted by fibrous scarring.¹⁰ In general, other scarring alopecias also tend to deform hair follicles, remodeling them with fibrous scar tissue and producing permanent deficits in hair density. Selected causes of hair loss may be excluded more easily. Androgenetic alopecia, for example, features a non-scarring and diffuse hair loss principally affecting the frontal scalp. Moreover, family history of androgenetic alopecia and/ or male-pattern balding can mostly be elicited, and the condition can be treated with topical minoxidil solution.⁹ Similarly, patchy hair loss can be attributed to infections by fungal organisms (tinea capitis) or bacteria, which should be ruled out by culturing any present exudates, examining scalp scrapings, or performing histopathological stains.¹¹

Drug-induced alopecia is quite common and mostly associated with abnormal hair cycling or excessive shedding. Telogen effluvium—or temporary increase in hair loss—has been attributed to ACE inhibitors (enalapril), antimitotics (colchicine), oral contraceptives, interferon, anticoagulants, antiparkinsonian agents (levodopa), beta blockers (metoprolol, propranolol), and drugs (lithium, valproic acid), H2 blockers (cimetidine), and retinoids. Other disturbances may be contributory, including endocrine (hyper- or hypothyroidism), nutritional (calorie, mineral, or vitamin deprivation), and physical or psychological stress (anemia, surgery, illness). Anagen effluvium—or diffuse scalp balding—has been reported with antineoplastic agents, radiation therapy, systemic chemotherapy, heavy-metals poisoning (mercury, thallium, boric acid), and severe protein deficiency or malnutrition. Certain autoimmune diseases have cutaneous manifestations, notably lupus erythematosus and alopecia areata.¹²

In solving the diagnostic dilemma of scarring alopecias, a thorough evaluation and follow-up of the patient must be undertaken. A scalp biopsy is vital, but even more significant is the exact area chosen for sampling, since it has to be undergoing active disease process rather than in the final “burnout” stages.¹³ Histopathological results need clinical corroboration; detailed patient demographics as well as descriptions of the hair loss pattern and surrounding circumstances should be supplied by prudent practitioners.¹¹ Even with excellent tissue sampling and expert interpretation, primary cicatricial alopecia variants are exceedingly difficult to classify, further magnifying the importance of collecting meticulous patient history.¹⁴ High index of suspicion should initiate a biopsy at the site of erythema to establish causative factors, often followed by a second biopsy of the balding area, which may demonstrate scarring.¹⁵ Diagnostic scarring may be curtailed with early recognition and treatment of this insidious ailment.

**Pathogenetic Hypotheses**

CCCA is a variant of primary cicatricial alopecia, synonymous with follicular degeneration syndrome (FDS), sometimes described in the literature under such terms as “hot comb alopecia” and “ethnic variant of cicatricial alopecia.”¹⁰ The pathogenesis of CCCA is not fully understood, but physically and chemically traumatic hair styling techniques are cited as common denominators in the instigation of the condition in most patients. Still, it is uncertain whether the incipient follicular disruption is intrinsically or extrinsically mediated, and whether the progressive fibrosis of the primary or secondary to the underlying inflammation.

Since the malady is chiefly seen in blacks, we will briefly describe some pertinent characteristics specific to ethnic hair. African-American hair is elliptical in shape, tightly coiled, and features spiral—but less dense—hair follicles, which impede sebaceous secretions from nourishing hair shafts. Additionally, its low water content and poor tensile strength translate into dryness, fragility, difficulty in combing, and relative vulnerability to thermal injury."¹⁵

Review of animal models sheds new light on the etiology of hair loss, particularly from the genetic and molecular points of view. Mice with sebaceous gland abnormalities display histopathology reminiscent of human cicatricial alopecias. Mutated genes code for the stearoyl- CoA desaturase-1 (Scd1), a rate-limiting enzyme in conversion from saturated to mono-unsaturated fatty acids. The absence of a gene crucial to lipid reactions leads to sebaceous gland ablation, prolonged anagen phase, and gradual follicular replacement by scarring. If sebaceous glands are not working properly, the hair follicles are obliterated and fibrosed.¹⁴ Hypoplastic sebaceous glands under-produce the sebum that is required for optimal pilosebaceous unit functioning.¹⁵ Sebaceous glands may prove to be the initial as well as the propagating injury site in the pathogenesis of CCCA.¹⁶

Cutaneous autoimmunity can also be implicated in scarring alopecia pathobiology. It is postulated that potent pro-inflammatory triggers destroy epiderhal hair-follicle stem cells via immune dysregulation. Whether these events happen secondary to interferon-mediated cytotoxicity or loss of follicular immune privilege remains to be elucidated. Although the veracity of this theory still hangs in the balance, it offers appealing future frontiers for immuno-protective therapies aimed at follicular stem cells as well as re-establishment of desired immunosuppression.¹⁶

Hair-specific keratins may play a role in CCCA via disturbing effects on follicular architecture. Structural integrity of hair varies with keratin genetic polymorphisms or various gene expressions, suggesting that keratin breakdown may result in follicular demise, spillage of epithelial debris into the dermal layer, and consequent inflammatory response.¹⁷ A defective inner root sheath structure that leads to premature desquamation may be responsible for the pathobiology of CCCA. On the molecular level, premature loss of cytokeratin 75 appears to be habitual within the follicles.¹⁸ It is evident that even in the absence of traumatic hair-care practices, some people will be more prone to hair damage and loss simply due to the inherently weaker follicular structures supported by their genetically pre-programmed keratins. CCCA appears to be a complex polygenic affliction shaped by an as-of-yet undetermined combination of nature and elusive exogenous factors.

**Personal Grooming Practices**

It is clinically relevant to underscore that with alopecias, hair grooming history is exceedingly more important with African-American than with Caucasian or Asian patients.¹³ The American Academy of Dermatology reported in 2004 that alopecia was an epidemic among women of color owing to tight hairstyles and unrefined chemicals injuring hair shafts and follicles.¹⁹ Approximately 80% of African-American women in the U.S.A. use chemical hair relaxing, risking contact or chemical burns, damaging tensile strength of hair, and ultimately leading to CCCA.²⁰ Other aggressive hair-care practices include methods such as hot comb styling (using heated metal implements and chemicals), temporary hair tension (tight braids or cornrows, weighty hair styles), chemical straighteners with alkali-containing compounds, and chemical color processing.²¹ One study reported a solid association between the use of hair weaving (sewn-in and glued-in hair), cornrows, artificial hair extensions, or braided hairstyles and CCCA. Women with this disorder tended to relay a history of scalp tenderness following hair dressing appointments.²²

Trauma to hair follicles leading to chronic dermal inflammation seems to be paramount in the etiology of CCCA. Sufferers frequently remember pain or burning of the scalp during or immediately after hair styling procedures.¹ Nevertheless, the degree of physical or chemical damage, scalp hair loss is slowly progressive in the majority of patients.²ⁱ Some authors contend that this clinical entity is really a permutation of traction alopecia, or end-stage traction alopecia, caused by irreversible processes related to hair-styling techniques.²² CCCA could be feasibly explained as a final common pathway reciprocating myriad pathologies.
Course, Treatment, and Prognosis

The course of CCCA is typically prolonged, and baldness is classically irreversible. The affected individuals may go through periods of relative clinical remission followed by reactivation and exacerbation of the alopecia. Since the exact causative agent has yet to be elucidated, management of CCCA is controversial. Treatment options, anecdotal and experimental at best, mainly target inflammatory changes with intralesional as well as topical corticosteroids. When treating with intralesional steroids, central vertex as well as peripheral injections are advised for several months with hopes of stimulating new hair growth once the inflammation has subsided.

Anti-inflammatory properties of oral antibiotics have been exploited with positive results, using a regimen of oral tetracycline with topical corticosteroids. Innovative approaches include topical immunomodulators such as tacrolimus (Protopic) and pimecrolimus (Elidel) and immunomodulators such as tacrolimus (Protopic) and pimecrolimus (Elidel) and may be especially effective in combating early signs of irritation. Antimalarial (chloroquine, hydroxychloroquine) have been tried on account of its anti-inflammatory effects, along with oral mycophenolate mofetil and cyclosporine, a calcineurin inhibitor exerting its action by suppressing gene transcription. Topical minoxidil can foster hair re-growth as well as nourish any remaining non-scarred follicles. Additionally, the Cicatricial Alopecia Research Foundation describes topical applications of Derma-Smoothe scalp oil to the affected areas in the repertoire of therapeutic measures.

Although termination of chronic hair trauma may not reverse or even curtail the progression of the underlying disease process, the use of strong heat, chemicals, and excessive traction should be discouraged. Patients may be advised to wear hairstyles designed to camouflage parietal hair loss. Wigs, hair pieces, hats, and scarves offer useful disguises. Hair transplantation or grafting may be contemplated for purely cosmetic and psychological benefits. Surgical excision of the scarred dermis is considered as a last resort, and only if the disease has been inactive for a number of years. Another surgical procedure that is sometimes feasible is scalp reduction for hair restoration, which involves removal of the hairless area through direct closure of the defect with hair-bearing scalp. Healthy hair-containing scalp can be surgically folded over a bald spot using a technique called an advancement flap. Atrichia correction can also be accomplished with scalp expanders, reduction through serial excisions, and reconstruction by composite hair-covered scalp grafts.

Recommended hair care products and shampoos need to be gentle and non-irritating to the scalp, with some options available by prescription only. Infrequent shampooing, styling hair with emollient pomades, air drying rather than blow drying, and regular removal of split ends are also advocated to minimize hair damage and optimize recovery. Some experts confer that abrasive hair grooming practices are detrimental to hair cells and should be stopped by patients exhibiting CCCA. Theoretically, if the rapidly progressive situation is thwarted in its infancy, the inflammatory changes could subside, and the scalp may be allowed sufficient time and milieu to self-heal.

Conclusion

No standardized treatment methods exist for CCCA, but the use of anti-inflammatory and immunomodulating agents is the first line of defense. Practitioners must advocate non-aggressive hair-care routines among their patients, including minimal use of heat, chemical processing, and decreased hair traction.

Hereditary contributors to the condition remain to be ascertained, but congenital follicular defects, sebaceous gland polymorphisms, and various hair keratins are all theoretical contenders. Further clinical and basic science research should aim to extrapolate causes of the disease as well as define novel directions for improved therapeutic modalities.

References


Figure 1. The scalp is shiny, smooth, and flesh-colored, with decreased hair density at the vertex (crown) region.
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