Muir-Torre Syndrome: A Case Report and Review of Screening Recommendations

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- Keloidal Variant of Atypical Fibroxanthoma
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Dear Members,

It is with great pleasure that I announce that our Journal now qualifies for AOA CME credit! Over the last year, I submitted proposals to the AOA Committee for Continuing Medical Education (CCME). This April, the CCME approved reading of the Journal for 6 credits during a three-year cycle, under Category 2-B. At the back of this volume, you will find a tear-away form that only needs to be submitted once (at the end of each cycle) for these CME credits. The form is also available on the AOCD web site (www.AOCD.org).

I am also proud of the enthusiasm of our Editorial Board. We have recruited more reviewers. Derrick Adams, DO, has been promoted to Associate Editor. The Associate Editors have tremendous responsibility and workload. Please thank all of our Editors and Reviewers for their service whenever you see them.

The next step, should we choose to pursue it, would be qualification for AOA Category 1-B credit. However, this entails the development of a short quiz in each volume, grading, and reporting to the AOA. I urge all our young members to consider joining the effort in actualizing the full potential of this publication. In the electronic age, developing a workflow for this should be simple; we just need interested point-people.

In these unsure merger times, many are wondering about the future and viability of osteopathic dermatology, our college, and the Journal. As of today, all current AOBD board-certified dermatologists, under the terms of the AOA-ACGME merger, will remain segregated from ACGME in terms of board certification, recertification, maintenance of certification (OCC), and required osteopathic CME. The merger only applies to future graduates. Current DO board-certified physicians will still be required to fulfill osteopathic CME just as we do now; the AOCD will continue to exist, providing required osteopathic CME for all of us. And now, so will the Journal.

All the best,
Karthik Krishnamurthy, DO, FAOCD
Editor-in-Chief, JAOCD
Greetings, Everyone!

Our next Annual Meeting, taking place October 25th through 28th in Seattle, is being chaired by Dr. Rick Lin. Look for meeting information on our web site, www.AOCD.org. We will also update everyone through the regular Thursday Bulletin. Members should register for this meeting via the AOA website at http://www.osteopathic.org/inside-aoa/events/omed/Pages/default.aspx.

Please note that the first day of lectures will be Sunday, October 26th. This is a new meeting cycle the AOA is implementing. Monitor the AOCD and AOBD web sites (www.aobd-derm.org) for updates concerning the conference schedule and testing dates and locations. During our 2014 business meeting in Seattle, members will have a chance to vote on several by-laws changes. Be sure to attend and cast your vote! The AOCD is your organization!

Save the Dates!
Our 2015 Spring Meeting will take place from April 23rd through 26th at the Ritz Carlton in Charlotte, NC. The Program Chair is Dr. Daniel Ladd.

The 2016 Spring Meeting will take place from March 30th through April 3rd at the Ritz Carlton Battery Park in New York, NY.

The 2017 Spring Meeting will take place from March 29th through April 2nd at the Ritz Carlton Atlanta in Atlanta, GA.

Single GME Accreditation System
The Board of Trustees of the AOCD continues to monitor the unfolding of a new, unified accreditation system. In May, the AOCD BOT held an informational conference call with Dr. Boyd Buser and Dr. Robert Juhasz from the AOA. BOT members had a chance to ask questions and voice their concerns. Many affiliate organizations submitted resolutions to the AOA House of Delegates either in support of or against the single GME accreditation system. The American College of Osteopathic Family Physicians submitted a resolution calling for the AOA to withdraw from the Memorandum of Understanding if specific issues were not addressed by the end of 2015. The AOCD signed on in agreement to that resolution. Visit the AOA’s web site to view all of the resolutions presented at the July House of Delegates and the final actions taken by the AOA.

As always, if you have questions or concerns, please feel free to contact me (see “Contact Us” at AOCD.org), and I will be happy to assist you.

Sincerely,

Marsha Wise
Executive Director, American Osteopathic College of Dermatology
Dear AOCD Members,

Welcome to our newest addition of the JAOCD. We once again are showcasing our local talent. Our residents sure do make us proud. Needless to say, so does all our staff at the AOCD and the journal editors and reviewers. Thank you to all the program directors and faculty for working with the residents to produce these outstanding papers.

I am so proud to be your president in these trying times. The AOCD remains diligent in doing what is best for our members. The Board of Trustees has met many times to keep our college running smoothly. The AOA/ACGME single accreditation process is being looked at and evaluated to the best of our abilities. We will continue to press for equality of board certification and guaranteed spots for DO residents.

I would like to congratulate all graduating residents. As you go forward in your lives, I hope the AOCD will remain part of your family. We look to forward your involvement in our college, be it as a committee member, a teacher of other residents, a member of the Board of Trustees, or a lecturer at one of our conferences. You are the means of survival for our college. Please don't be a stranger.

Lastly, welcome to all of our new first-years. We hope your future is as bright as ours has been and continues to be.

Sincerely,
Suzanne Sirota-Rozenberg, DO, FAOCD
President, AOCD
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¹ According to IMS Health (a) National Prescription Audit, July 2010/March 2012.

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Muir-Torre Syndrome: A Case Report and Review of Screening Recommendations

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Abstract

Muir-Torre syndrome is an uncommon genodermatosis that affects a small subset of patients with Lynch syndrome. It involves sebaceous tumors and/or multiple keratoacanthomas in association with internal malignancy. Suspicion and early diagnosis is critical to institute appropriate cancer-screening recommendations. We describe a 64-year-old male with a history of colon cancer who presented with changing skin lesions which were pathologically confirmed sebaceous adenomas. The patient underwent genetic testing, which revealed a mutation in mismatch repair proteins; subsequently, he was diagnosed with Muir-Torre syndrome (MTS). Screening was performed, and a previously undiagnosed gastric tumor was discovered. This case report exhibits the importance of instituting appropriate screening recommendations in patients with MTS.

Introduction

Muir-Torre syndrome (MTS) is a rare, autosomal-dominant cancer syndrome considered a subtype of hereditary non-polypsis colorectal cancer (HNPCC, or Lynch syndrome). It is characterized by sebaceous tumors in association with internal malignancies.1,5 The sebaceous tumors found in MTS include sebaceous adenomas and carcinomas.6,7 Additionally, keratoacanthomas can also occur in MTS patients.3,4 Muir and Torre first described this condition in 1967 and 1968, respectively.1,6 The true incidence of MTS is difficult to determine, but as of 1999, only 205 cases had been reported in the literature.9 Current evidence suggests that there are two types of MTS. The first variant involves defects in mismatch repair genes mutS Homolog 2 (MSH2) and mutL Homolog 1 (MLH1).1 Also, the lack of mutS Homolog 6 (MSH6) and postmeiotic segregation increase 2 (PMS2) expression has been demonstrated in MTS patients.1 Defects in these mismatch repair proteins result in microsatellite instability (MSI) and a predilection to developing certain tumors. The second variant does not show defects in mismatch repair genes, and its current pathogenesis is unknown.1,4 The age at presentation of malignant disease ranges from 23 to 89 years, with a median age of 53.4 It occurs in men almost twice as often as in women.7 The most common internal malignancy is colorectal cancer, which accounts for approximately 50% of underlying tumors; genitourinary, breast, lung, gastric, intestinal and hematologic malignancies have also been reported.1,3,5,7 Internal malignancy can manifest several years before or after skin findings. Recognition of the cutaneous manifestation of MTS can assist in early detection of visceral malignancy and lead to proper dermatologic surveillance in patients and families with history of Lynch syndrome. We describe a male of middle-to-late age diagnosed with MTS and review current screening recommendations for this condition.

Case Report

A 64-year-old Caucasian male presented to our outpatient dermatology clinic for routine skin examination and evaluation of a changing “bump.” The patient described a lesion on his right side that was present for three months and had been slowly increasing in size. Review of systems was negative for any other pertinent findings. The patient’s past medical history consisted of multiple non-melanoma skin cancers; two superficial malignant melanomas; colon cancer (adenocarcinoma) twice, at ages 38 and 39, with adjuvant chemotherapy; Barrett’s esophagus; multiple colon polyps; and hypertension. Past surgical history was significant for a yearly colonoscopy, two partial colectomies and multiple excisions of skin cancers. Current medications included aspirin, hydrochlorothiazide, meloxicam, omeprazole, and irbesartan. No known drug allergies existed. The patient was married and had only adopted children. He admitted to rare alcohol consumption and no tobacco use. Family history included his father, deceased at age 66 from unknown cancer; a living sister with a history of uterine cancer in her 30s; and a paternal cousin with a history of colon cancer in his 60s. Upon physical examination, the patient exhibited a solitary, 1 cm x 1 cm, pink-red nodulocystic lesion with overlying telangiectasias on the right torso. We explained our findings to the patient and discussed different treatment options. Upon

Figure 1. Suspicious lesion on left forehead.
follow-up for the planned primary excision of the initial lesion on the right torso, the patient expressed concerns regarding a new lesion on the left forehead demonstrating a small, pink-yellow umbilicated papule 0.4 cm x 0.4 cm in size. The remainder of the physical examination was unremarkable. Consequently, the initial lesion was completely excised, and the new lesion on the left forehead (Figure 1) was shave biopsied and sent to pathology for evaluation. The histological shave specimen from the left forehead was described as a well-circumscribed nodular lesion with basaloid round cells and sebaceous differentiation. The excised specimen from the right torso (Figure 2) revealed a well-circumscribed nodular proliferation of basaloid round cells and multiple foci of sebaceous differentiation. The tumor had uniform round nuclei with fine chromatin, conspicuous nucleoli and numerous mitotic figures. Sebaceous carcinoma was considered, but due to the lack of infiltrative growth, necrosis, atypical mitotic figures, nuclear pleomorphism and pagetoid spread, the lesion was felt to be low-grade and best classified as a sebaceous adenoma. Specifically, the tumor was thought to be a sebaceoma because the basaloid/germination proliferation occupied greater than 50% of the tumor. The findings of these benign sebaceous tumors triggered additional testing by the dermatopathologist for evaluation of mismatch repair protein defects. Clinical correlation of the sebaceous tumors coupled with the patient’s medical history of early colon cancer initiated an evaluation for an underlying genetic mutation.

Ancillary immunohistochemical testing revealed an abnormal DNA mismatch repair panel (MLH1, MSH2, MSH6 and PMS2) including complete loss of expression for MSH2 and weak MLH1 and PMS2 expression within the sebaceous adenoma tumor (Figures 3-6). These findings suggested, at minimum, a somatic mutation within the sebaceous tumor.

The results were discussed with the patient, and further genetic testing was recommended to investigate for an underlying germline mutation. The patient was evaluated by medical genetics, and analysis confirmed a germline mutation for the MSH2 gene (1351C>T). Genetic counseling suggested that the patient’s father was the likely carrier of the MSH2 mutation due to the family history of uterine and colon cancer on the father’s side. Additionally, it is likely the patient’s sister carries the mutation since she had a history of uterine cancer at an early age. The patient’s niece and nephew would also have a 50% chance of carrying the MSH2 mutation due to the autosomal-dominant expression of this condition. Recommendations were made regarding screening for the patient and any family members with Muir-Torre or Lynch syndrome.

We had an extensive discussion with our patient regarding the diagnosis of Muir-Torre syndrome and the need for appropriate screening. A follow-up appointment with his gastroenterologist was arranged for a possible upper endoscopy, and we coordinated with all of his physicians to assure he was up-to-date on recommended screening (Table 1).

The patient had an esophagogastroduodenoscopy that demonstrated a gastric mass with central ulceration on the greater curvature in the distal stomach. A biopsy of this lesion revealed a gastrointestinal stromal tumor (GIST). A combined endoscopic and laparoscopic procedure
was performed to completely excise this low-grade tumor. At present time, the patient is doing well and has a good prognosis.

Discussion
Muir-Torre syndrome (MTS) is a rare variant of Lynch syndrome cancer syndrome with malignant potential. It can initially present with sebaceous tumors and/or keratoacanthomas. A dermatologist’s ability to assimilate various clinical findings, as seen in MTS, can be life-saving. Being aware of these skin lesions is critical in the care of patients, made evident by the case presented herein.

Upon suspicion for an underlying genodermatosis, our patient was sent for genetic testing, which confirmed the diagnosis of MTS. However, the reality of this condition is that it can be difficult to diagnose, and a delayed diagnosis of MTS is fairly common. Approximately 60% of patients with MTS can develop metastatic disease.7 Thus, a delay in diagnosis or screening can be detrimental to the patient’s overall outcome. In our case, the diagnosis of MTS was confirmed with genetic testing, and appropriate screening recommendations were initiated. The most common mutation in MTS is the MSH2 gene, which is the case in our patient.6 He underwent testing, which revealed a gastric mass consistent with a GIST tumor. This gastric tumor is a somewhat rare entity, occurring in less than 1% of all internal malignancies associated with MTS.5

Even after the diagnosis of MTS, there may be several obstacles to the management of the patient. Following a long discussion with our patient regarding genetic testing and counseling, our patient questioned if there is “any benefit in knowing.” Certainly, his question is not unreasonable. In many medical situations, if there are no treatment options or modalities to alter the course of a disease, it may not be prudent to perform extensive testing for little benefit other than academic purposes. However, we did explain to our patient that the genetic testing could give more insight into his condition, determine what screening may be needed, and expose family members who may be at risk.

Genetic screening for family members can present a challenge to the clinician. In our case, while the patient did not have biological children, his sister, niece and nephew could be potential carriers. A good family relationship is helpful when it comes to discussing these topics. However, this is not the case in all situations, and a poor family relationship could jeopardize appropriate genetic counseling, leading to missed screening opportunities in susceptible family members. In one reported case, a family with confirmed MSH2 mutation and MTS did not comply with screening recommendations for various social and cultural reasons.10 In today’s medical-legal climate, privacy, informed consent, and protection of patient information must be considered and could potentially impair appropriate screening.

MTS is a well-described condition in medical literature. There are many published articles that describe different screening recommendations, but significant variation exists in these recommendations. Many of them lack clear evidence to support their use and are based solely on expert opinion or anecdotal experience. Of note, even with recommended screening guidelines, our patient did not entirely fulfill criteria to have an upper endoscopy. Thus, it is possible that the diagnosis of his gastric tumor would have been delayed. Clearly, this is an area where guidelines are potentially limited, and good clinician judgment takes priority in managing patients.

Conclusion
MTS is a rare but important condition with potentially life-threatening sequelae. We demonstrated a 64-year-old patient who was diagnosed with MTS and found to have an occult gastric tumor. This case demonstrates the importance of screening recommendations and clinical management, not just for the patient but also for other family members who may be affected.

References

Table 1. Screening recommendations for Muir-Torre syndrome1,5,6,11,12

<table>
<thead>
<tr>
<th>Annual Physical Exam:</th>
</tr>
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<tbody>
<tr>
<td>- Age-appropriate cancer screening, including prostate and testicular examination in men, and breast and gynecologic examination in women.</td>
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<tr>
<th>Colon Cancer Screening:</th>
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<tr>
<td>- Starting at age 20 to 25, or else 2-10 years before the earliest age of colorectal cancer in the family if it was diagnosed before the age of 25; annually after age 40.</td>
</tr>
<tr>
<td>- Colonoscopy every 1-2 years (recommended).*</td>
</tr>
<tr>
<td>- Consider carcinoembryonic antigen, complete blood count, fecal occult blood testing.</td>
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<tr>
<th>Gastric and Small Bowel Cancer Screening:</th>
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<tr>
<td>- Consider upper endoscopy with extended duodenoscopy in select families with history of gastric cancer.</td>
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<tr>
<td>- Consider capsule endoscopy for small bowel cancer.</td>
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<th>Urothelial Cancer Screening:</th>
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<td>- Consider annual urinalysis beginning at age 25-35, with urine cytology every 1-2 years.</td>
</tr>
<tr>
<td>- Consider renal ultrasound every 1-2 years in families with history of renal-tract cancer.</td>
</tr>
<tr>
<td>- Consider prophylactic colectomy in patients with germline mutation.</td>
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Additional Considerations for Women

Endometrial and Ovarian Cancer Screening:
- Mammography (every 1-2 years to age 50, and then yearly).
- Consider transvaginal ultrasound and/or endometrial biopsy in patients with gene mutation, starting at 25-35 years of age.
- Consider carbohydrate antigen-125 (CA-125).
- Consider prophylactic bilateral salpingo-oophorectomy (BSO) as a risk-reducing option for women who have completed child-bearing.**
- Consider cervical smear.

*Good evidence to support screening.
**Fair evidence to support screening; no clear recommendation for or against.

Unless noted, recommendations above have no clear evidence or insufficient evidence to support screening.

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Palisaded Neutrophilic and Granulomatous Dermatitis: A Case Presentation and Discussion

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Abstract

Palisaded neutrophilic granulomatous dermatitis (PNGD) is a rare clinical entity that describes patients with immune complex diseases, most commonly rheumatoid arthritis (RA), that show a variety of cutaneous expressions. The histology is also variable; however, the histologic variability is likely due to lesion maturation in relation to the timing of biopsy. The lack of clear definition of PNGD and its overlap with other diseases such as interstitial granulomatous dermatitis highlight the theory that PNGD exists on a spectrum of disease. Herein we report a case of PNGD, associated with RA, presenting with symmetric papules on extremities.

Case Report

A 55-year-old female with a history of rheumatoid arthritis (RA) presented to our outpatient clinic with a two-year history of papulonodules on the elbows and buttocks. Complete review of systems was negative aside from mild discomfort from the lesions with pressure-bearing activities such as sitting and leaning. The lesions developed during treatment for her RA with adalimumab and methotrexate. The lesions persisted when adalimumab and methotrexate were discontinued for pulmonary fibrosis, after which she was treated with prednisone 10 mg daily by mouth, etanercept 50 mg weekly subcutaneous injections, leflunomide 10 mg daily, and hydroxychloroquine 200 mg daily. This was her regimen at the time of presentation.

Physical examination revealed scattered dermal nodules on the bilateral elbows, some appearing to perforate the epidermis, and red-violaceous erythematous papules and nodules in an annular configuration on the buttocks and thighs (Figures 1-2). A 10-mm punch biopsy was obtained from a nodule on the left elbow, and another was obtained from a nodule on the left buttock.

Figure 1. Nodules on left elbow.

Figure 2. Papulonodules on left buttock/thigh.
Histologic examination of the biopsy from the elbow showed discrete areas of palisading histiocytes surrounding collections of degenerating collagen fibers, and mucin with a perivascular and periadnexal, mixed inflammatory infiltrate including numerous neutrophils, lymphocytes and scattered eosinophils (Figure 3). Histologic examination of the biopsy from the buttock revealed discrete areas of palisading histiocytes surrounding collections of mucin with perivascular lymphocytes and neutrophils (Figure 4). Based on the clinical presentation and pathology, a diagnosis of palisaded neutrophilic and granulomatous dermatitis was made (PNGD).

Given the patient's multiple medications for rheumatoid arthritis, the risk-to-benefit profile for an additional systemic medication, such as dapsone, was not deemed favorable. Several lesions on the buttocks were injected with triamcinolone 10 mg/mL. At four-week follow-up, they appeared moderately improved (Figure 5).

**Discussion**

PNGD is a rare clinical entity that describes patients with immune complex diseases, most commonly rheumatoid arthritis (RA), who develop symmetric papular lesions on the extremities. Based on the fewer than 100 reported cases, there is a female predominance of 72%, with disease onset occurring at a mean age of 49 years. A majority of patients have an underlying connective-tissue disease, vasculitis, or malignancy. The most common association is RA, found in 26/92 cases; then lupus, found in 11/92 cases; and then allergic granulomatosis, seen in 10/92 cases. Other reported disease associations include systemic vasculitis, systemic sclerosis, lymphoproliferative disorders, inflammatory bowel disease, sarcoidosis, thyroid disorders, and diabetes. To date, there are only three reported cases of PNGD with no underlying illness. Given that a majority of patients with PNGD have an underlying connective-tissue disease, a majority of PNGD patients have also had long-standing treatment with prednisone, hydroxychloroquine, cyclosporine, cyclophosphamide and/or non-steroidal anti-inflammatory drugs. Thus, the development of PNGD may be associated with immunologic alteration, either from long-term immune-modulator use, as for connective-tissue disease, or from immune alterations inherent to lymphoproliferative disorders. Finally, cases of PNGD induced by tumor necrosis factor inhibitors and methotrexate have been reported. We cannot rule out adalimumab- and/or methotrexate-induced nodules in our case; however, the lesions persisted after both medications were discontinued.

The historic nosology of PNGD found in the literature confounds interpretation but will be briefly summarized. In 1965, Dykmman et al. described linear subcutaneous bands on the lateral trunk in patients with RA, and pathology of the lesions showed rheumatoid nodules. In 1978, Ackerman described rheumatoid neutrophilic dermatitis. In 1983, Finan and Winkelmann described Churg-Strauss granuloma, or cutaneous extravascular necrotizing granuloma. Smith et al. described rheumatoid papules as an entity they termed "superficial ulcerating rheumatoid necrobiosis." Finan, in 1990, opined that rheumatoid papules, Churg-Strauss granuloma, and extracutaneous necrotizing granuloma are the same entity. Five years later, Gottlieb et al. described linear subcutaneous bands in patients with RA. It was not until 1994 that the name "palisaded neutrophilic granulomatosis dermatitis," or PNGD, was coined by Chu et al. to establish one term that encompass the spectrum of clinical and histologic observations. The term PNGD has now persisted in the literature.

The classic clinical presentation of PNGD consists of the symmetric distribution of pink-violaceous, smooth, umbilicated and/or ulcerated 2 mm to 10 mm papules, nodules, or plaques. They are located on the upper extremities in approximately half of cases; on the lower extremities in just under one-third of cases; and on the trunk, head and neck in roughly one-fifth of cases. However, a broader spectrum of lesions have been reported, from urticarial-like eruptions to indurated, cord-like bands. The lesions may be asymptomatic, pruritic or tender, and roughly 20% of cases exhibit spontaneous resolution. The lack of clear clinical criteria for PNGD is reflective of the variable historic nosology. The clinical differential diagnosis is expansive and includes granuloma annulare, rheumatoid neutrophilic dermatitis, annular elastolytic giant-cell granuloma,
molluscum contagiosum, cutaneous sarcoidosis, verruca vulgaris, calcinosis cutis, Churg-Strauss disease, Wegener's granulomatosis, urticaria, and, of particular note, interstitial granulomatous disease (IGD).

The histology of PNGD also lacks clear definition. In general, early lesions are distinguished from later lesions. Early lesions of PNGD exhibit a dense dermal neutrophilic infiltrate with leukocytoclastic vasculitis and degenerated collagen. However, late lesions of PNGD exhibit palisaded granulomas, dermal fibrosis and sparse neutrophils. Thus, the histologic differential diagnosis depends on the stage of the lesion. Early lesions may resemble urticaria, leukocytoclastic vasculitis, or Sweet’s syndrome. Late lesions resemble granuloma annulare or necrobiotic lipoidica. Clinical-pathologic correlation is essential in the diagnosis of PNGD.

IGD, also known as Ackerman’s syndrome, presents clinically with the rope sign or annular plaques on the trunk, axillae or medial thighs. Histology of IGD shows a sparse, palisaded histiocytic infiltrate with necrobiosis, a variable neutrophilic infiltrate, and a lack of vasculitis. Gulati et al. describe a 42-year-old female with systemic lupus erythematosus who presented with the burning rope sign clinically and PNGD histologically, with lesion resolution with mycophenolate mofetil. Inversely, there are reports of cases with clinical presentation of PNGD and histology representative of IGD. Given these reports, either the rope sign should not be considered pathognomonic for IGD or IGD and PNGD should be considered to exist on a spectrum of disease. The term “autoimmunity-related granulomatous dermatitis” (ARGD) has been proposed to lump together the overlapping clinical and pathological manifestations of IGD and PNGD.12

**Treatment**

The evidence for treatment efficacy in patients with PNGD is purely anecdotal. Resolution has been observed with treatment of the underlying disease. Lesions of PNGD may also spontaneously resolve after months or years. For lesions unresponsive to management of the underlying disease, the following therapies have been tried with some success: intra-lesional glucocorticosteroid injections, oral prednisone up to 20 mg daily, colchicine, cyclosporine, cyclophosphamide, hydroxychloroquine, non-steroidal anti-inflammatory drugs, and oral dapsone with or without intra-lesional glucocorticosteroid injections.13,14 Recurrence has been noted after surgical excision combined with oral prednisone.

**Conclusion**

This case represents a classical presentation of a rare disease: PNGD associated with RA. In our case, moderate improvement was observed with intra-lesional corticosteroid injections, which the patient found satisfactory. The concept of PNGD has been in evolution since the mid-20th century, and its complicated historic nosology makes sense due to its protean clinical presentations, variable pathology based on lesion maturity, and overlap with several dermatoses, most notably IGD. PNGD may exist on a spectrum with IGD. Due to the rarity of the disease, treatment is anecdotal, although resolution has often been observed with management of the underlying disorder.

**References**


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Abstract

AFX is an uncommon, superficial dermal tumor of intermediate malignancy, best described as a low-grade form of sarcoma. Originaly described by Helwig in 1961, AFX typically presents on the sun-exposed areas of the head and neck of elderly white men or on the trunk and limbs of younger patients. It can appear as a flesh-colored or erythematous, firm, asymptomatic papule or nodule with ulceration and bleeding. Keloidal atypical fibroxanthoma (AFX) is a rare variant of AFX that should be considered in any patient presenting with a non-traumatic keloidal lesion on the head or neck, with emphasis on the ear.

Introduction

We present a case of a keloidal atypical fibroxanthoma (AFX), a rare form of AFX. Clinically and histologically, the keloidal variant of AFX can mimic a variety of malignant and nonmalignant lesions. Therefore, immunohistochemical staining plays a major role in proper diagnosis. This case demonstrates the importance of maintaining a high index of suspicion for keloidal AFX in any patient presenting with a non-traumatic keloidal lesion on the head or neck, with emphasis on the ear. Following the case is a discussion that includes a brief history of AFX, diagnostic methods, differential, and management considerations.

Case Presentation

A 65-year-old white male presented to the resident clinic for full skin exam. He had a history of actinic keratosis but was otherwise in good health. He had noticed a lesion on his left helix for the past eight months; it had been slowly increasing in size but did not bleed or bother him in any way. Physical exam noted a 2.0 cm x 1.8 cm, flesh-colored keloidal nodule without ulceration (Figure 1). There was no cervical or supraclavicular lymphadenopathy. He denied any history of surgery or trauma at the area that would have precipitated a keloid. Shave biopsy of the lesion noted an atypical spindle-cell sarcomatoid neoplasia with keloidal collagen (Figure 2). Immunohistochemistry was positive for vimentin, CD68, and smooth-muscle actin. Pertinent negative markers included desmin, S100, HMB45, pancytokeratin, and CK5/6. The final diagnosis was AFX/superficial malignant fibrous histiocytoma with myofibroblastic differentiation arising in a pre-existing keloid.

Discussion

In 1961, the term atypical fibroxanthoma (AFX) was first used by Helwig to describe a dermal tumor with atypical spindle cells and a relatively
benign clinical course. After a review of 140 cases of AFX, Helwig and Fretzin observed that AFX typically presents on the sun-exposed areas of the head and neck region of older adults as a solitary, rapidly enlarging exophytic polypl or dome-shaped nodule. It occurs more commonly in elderly white men, with an average age greater than 65, while having a male to female ratio described variously as 2:1, 8:1 and 7:2. In younger adults, with an average age less than 65, AFX has been described as more commonly occurring on the trunk and limbs. Most AFX lesions are 1 cm to 2 cm, but they have been reported to range in size from 1 cm to >6 cm in diameter. AFX tumors on the head and neck are frequently nonspecific, typically presenting as a pink or red, asymptomatic, solitary, firm, papule or nodule. On the extremities and trunk, however, the lesion presents most often as nodular, slower growing, usually larger, and with less-defined borders. In our patient, the lesion occurred on the left helix; in a study performed at the Mayo Clinic, of the 78 AFX tumors found on the face, 41% were located on the ear. Risk factors associated with AFX include: elderly male, UV and X-ray radiation exposure, xeroderma pigmentosum, and organ transplant recipients. AFX tumors have also been noted to occur in sites such as the ethmoid sinus, eyelid, cornea, and the ocular surface.

The biologic behavior of AFX and subsequent risk of metastasis has been a matter of debate for many years. Terminology in the literature is also a confusing matter: Some pathologists use the term malignant fibrous histiocytoma (MFH) to mean a superficial variant of AFX, while others consider AFX to be a superficial variant of undifferentiated pleomorphic sarcoma (UPS). Moreover, others have proposed that AFX and MFH/UPS should be considered a continuum of the same malignancy. Regardless of the nomenclature, it is suggested that UPS is much more aggressive than AFX, and that most cases of the “metastasizing” AFX tumors reported in the past were in reality misdiagnosed cases of UPS, undifferentiated squamous cell carcinoma (SCC), or spindle-cell melanoma. Generally, perineural or lymphovascular invasion and necrosis are not features of AFX; if present, a more aggressive type of lesion should be considered. If the tumor is larger than 2 cm, penetrates subcutaneous tissue, fascia or muscle, or shows vascular invasion, the histology should be diagnosed as UPS rather than AFX. When “metastases” of AFX do occur, they have been noted in the parotid glands, lymph nodes, lungs, diaphragm and peritoneum, with five reported deaths thought to be due to “AFX metastasis.” Whether these historically reported cases of metastasis were truly an aggressive variant of AFX, UPS, undifferentiated SCC, or melanoma remains a topic of debate.

**Histology**

Histologically, AFX lesions are characterized by a mixed population of spindled and bizarrely shaped cells with numerous mitoses and irregular nuclei embedded in fibrous stroma. The current theory is that AFX is derived from a myofibroblast, or fibroblast-like cell. Most commonly, the histologic pattern of AFX is noted to be pleomorphic with spindle and epithelioid cells. Other common histologic features of AFX include multinucleated giant cells, foamy cells, hyperchromatism, atrophic epidermis, ulcerations, and severe pleomorphism. Histologic grading for AFX is not performed because the extremely bizarre appearance would classify them as high-grade tumors. Histologic variants of AFX have been described as keloidal, clear cell, granular cell, chondroid, pigmented, and AFX with osteoclast-like giant cells, with keloidal AFX being an extremely uncommon variant. Of the keloidal AFX lesions appearing on the head and neck, the majority presented on the ear. As in our patient, the stroma of keloidal AFX has an exaggerated keloidal collagen within AFX may result in an inaccurate diagnosis of a dermatofibroma or scar. Although nonspecific, AFX consistently stains positive for vimentin and CD68. However, vimentin is also expressed in spindle-cell SCC and desmoplastic melanomas, making a definitive diagnosis difficult at times. Since spindle-cell SCC and desmoplastic melanoma can resemble AFX both clinically and immunohistochemically, it is imperative that both pancytokeratin and melanocytic markers be used to distinguish them from AFX. Procollagen 1 and actin are commonly expressed by AFX. CD10 is another marker which should be used only in the support of diagnosis for AFX due to its relatively common expression in spindle-cell SCC. Leiomyosarcoma is distinguished from AFX by its tendency to be highly positive for desmin. On occasion, AFX may present with nearly diffuse, xanthoma-like cytoplasmic alteration with exaggerated histiocyte-like cytomorphology, with this immunophenotype prominently expressing procollagen and CD10.

**Differential**

Clinical differential diagnoses for AFX should include basal-cell carcinoma (BCC), Merkel-cell carcinoma, adnexal tumors, pyogenic granulomas, spindle-cell melanoma, leiomyosarcoma (LMS), and malignant fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma (UPS). Histologically, AFX must be differentiated from spindle-cell squamous-cell carcinoma (SSCC), desmoplastic or spindle-cell melanoma, and undifferentiated pleomorphic sarcoma (UPS). Unlike AFX, UPS carries a poor prognosis as a high-grade tumor, recurring and metastasizing frequently. It is generally recognized that lesions resembling AFX should be classified as UPS when the tumors are >2 cm in diameter and present with deep subcutaneous involvement or penetration into the fascia or muscle; necrosis; and vascular invasion.

**Treatment**

With local excision, AFX rarely recurs; in most cases, this treatment is curative. In a recent retrospective review at the Mayo Clinic, the recurrence rates of 82 AFX tumors were examined, comparing treatment results with Mohs micrographic surgery (MMS) vs. wide local excision (WLE). Fifty-nine were treated with MMS and 23 with WLE, and it was found that patients treated with MMS showed no recurrences, whereas two of the patients treated with WLE had single recurrences. In this study, the median margin needed with MMS to ensure clear margins was 0.4 cm, compared with 1.0 cm to 2.0 cm with WLE. The incidence of recurrence was 0% for MMS and 8.7% for WLE, and the recurrences occurred within 24 months of the first excision. Considering the possibility of recurrence, the recommended standard of care for AFX is removal of the tumor with MMS and follow-up for at least two years with examination of the surgical site and palpation of regional lymph nodes.

**Conclusion**

Our case represents a rare variant of AFX, which is under-recognized and easily confused with both benign and malignant lesions. Keloidal AFX should be considered in any patient presenting with a non-traumatic keloidal lesion, especially on the head or neck.

**References**


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Benign Migratory Glossitis in a Patient with X-linked Ichthyosis: A Case Report and Review of the Literature

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Abstract

X-linked ichthyosis results from a mutation in the ARSC1 gene, which most commonly encodes for the enzyme steroid sulfatase, also known as arylsulfatase C. It presents within the first few months of life with mild, polygonal brown scales that begin on the neck and progress to involve most of the body with relative sparing of the flexural folds, palms, soles, and central face. Several associated conditions have been presented in the literature, most notably cryptorchidism with an increased risk of testicular cancer. Benign migratory glossitis is not a known associated condition. We present the unique case of a patient with both of these conditions. To our knowledge, this is the first report of an association between X-linked ichthyosis and benign migratory glossitis. One should be aware of associated diagnoses in patients with X-linked ichthyosis.

Introduction

X-linked ichthyosis is the second most common type of ichthyosis, with an incidence of 1:2,500-5,000, and is inherited in the X-linked recessive fashion.1,2 X-linked ichthyosis presents with mild scaling in the first few days to months of life and then evolves into brownish, polygonal, adherent scales. In infancy, scaling presents on the posterior neck, upper trunk and extensor surfaces of the extremities. In childhood, the scaling evolves and is found on the scalp, preauricular skin and posterior neck. In adulthood, the scaling fades on the head and is found more notably on the trunk and extremities, sparing the palms and soles.3 Ocular abnormalities and cryptorchidism are most commonly associated with X-linked ichthyosis.4,5 A review of the literature failed to reveal a reported association between X-linked ichthyosis and benign migratory glossitis. We present a case demonstrating this unique association and briefly review both conditions.

Case Presentation

A 5-year-old Caucasian boy presented for evaluation of asymptomatic, dry, scaly skin that began shortly after birth. He also complained of an intermittent burning sensation of his tongue that grew worse with hot, spicy, and salty foods. He was accompanied by his mother, who served as his historian and appeared reliable. She reported a normal labor and delivery without complications. Past medical history was significant for seasonal allergies and asthma. He had been hospitalized for acute exacerbations of asthma. Current medications included loratadine and albuterol. His childhood immunizations were up-to-date. Family history was positive for an uncle and two male cousins with similar “dry skin” symptoms on the maternal side.

Physical examination revealed brown, firmly adherent scale with increased prominence on...
the extensor surfaces, posterior neck, and trunk with relative sparing of flexures, palms, soles, and central face. Examination of the oral mucosa revealed sharply demarcated erythematous and atrophic areas with a serpiginous, white, slightly raised border that appeared scalloped. A biopsy was discussed but deferred, and a conservative treatment approach was undertaken. We recommended an over-the-counter urea lotion to be applied liberally every day along with other lubricating moisturizers and mild cleansing soaps. Upon re-evaluation six months later, the patient was without any evidence of dry, scaly skin. Based on clinical examination, past medical and family history, and subsequent response to topical treatment, the likely diagnosis of X-linked ichthyosis was rendered. Genetic testing would be necessary for confirmation and will be considered if the patient worsens or fails to respond to conservative treatment. We recommended thorough physical examination by his pediatrician yearly and continued monitoring for testicular abnormalities as well as evaluation by an ophthalmologist should the patient experience any changes in his vision. For the benign migratory glossitis we recommended avoidance of exacerbating foods and daily use of Biotene® oral solution.

**Discussion**

X-linked ichthyosis is the second most common type of ichthyosis and is inherited in the X-linked recessive fashion.2 It shows no significant racial or geographical differences.4 X-linked ichthyosis results secondary to mutations of the STS gene coding for steroid sulfatase on Xp 22.31.6,7 Typically, complete deletions result in X-linked ichthyosis; however, point mutations resulting in nonsense mutations have recently been discovered.8,9 Further, a deficiency in steroid sulfatase causes an accumulation of cholesterol sulfate in the stratum corneum. Excess cholesterol sulfate results in partial retention hyperkeratosis and excess scaling by delaying cornodesmosome degradation, leading to cornocyte detachment. Excess cholesterol sulfate also results in separation in the spaces between cornocytes and an abnormal skin barrier.10 Comma-shaped corneal opacities may be found in a majority of affected individuals and are easily detectable by slit-lamp examination as discrete and diffusely located near Descemet’s membrane; they do not affect vision.11 Deuteronopia has also been described.12 Cryptorchidism is also commonly associated with X-linked ichthyosis and is seen in 20% of individuals with the condition, possibly imparting an increased risk for testicular cancer.12-14 Orthopedic diseases, including chondrodysplasia punctata, and neurological findings such as mental retardation, epilepsy, and reactive psychological disorders have also been described in case reports in association with X-linked ichthyosis.12,15 Rarely, X-linked ichthyosis has been associated with pyloric hypertrophy, congenital defect of the abdominal wall, acute lymphoblastic leukemia, periventricular nodular heterotopia, ESRD and epidermolysis bullosa.12,16 Adjacent gene involvement in patients with X-linked ichthyosis can also result in an array of syndromes such as Kallmann’s syndrome.5

A thorough review of PubMed-indexed English-language literature failed to reveal any association with benign migratory glossitis. Benign migratory glossitis, also known as geographic tongue, results from unknown etiology and is commonly described as multiple, variably sized, well-demarcated, erythematous areas typically surrounded by a slightly elevated, yellowish-white, circinate linear border. It usually is found on the anterior two-thirds of the dorsal aspect of the tongue, and it resembles land masses and oceans on a map.17,18

Benign migratory glossitis is often asymptomatic; however, some patients experience sensitivity to spicy foods, acidic beverages and fruits.19 Geographic tongue is characterized by bouts of remission and aggravation. New lesions occur in new locations, demonstrating a migratory pattern. Additionally, periods of remission are not associated with scar formation. Prevalence of benign migratory glossitis among adults ranges from 1.0% to 2.5% according to most studies.17 Geographic tongue is more prevalent among white and African American individuals than among Mexican Americans.18

Associations between geographic tongue and risk factors such as hormonal disturbances and oral contraceptives, psychological findings, diabetes mellitus, hay fever and rhinitis have been suggested. Links have also been made with dermatological diseases such as psoriasis, seborrheic dermatitis, pityriasis pilaris and Reiter’s syndrome. However, these associations were all made by studies employing bivariate analysis, which has a lack of statistical power. A more recent statistical multivariate analysis revealed no significant association with the previously described risk factors.18 The same study did find a significant association with fissured tongue and systemic steroid use, and an inverse association with cigarette smoking.18

Treatment generally consists of topical corticosteroids and systemic cyclosporine. A recent paper reported successful treatment using the immunosuppressive macrolide tacrolimus.20

**Conclusion**

A diagnosis of X-linked ichthyosis is generally made shortly after birth with the presence of a family history. Diagnosis can then be confirmed through biochemical or genetic analysis. Skin biopsies are generally not helpful diagnostically because microscopic changes are often subtle and nonspecific. X-linked ichthyosis is incurable, but a majority of cases improve with age and do not require treatment. Symptoms improve during the summer months, and a humidifier can be helpful in the winter months. Once X-linked ichthyosis is diagnosed, topical therapy is generally initiated with cutaneous hydration, lubrication, and keratolytics such as lactic acid, glycolic acid, and salicylic acid.20 Retinoic acid, such as isoretinoin, has also been successful in the treatment of patients.21

**References**

**Polymorphous Light Eruption in a 50-year-old Female on Bilateral Extensor Surfaces of the Upper Extremities**

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**Abstract**

Polymorphic light eruption (PMLE) is the most common photosensitivity disorder, estimated to affect 10% to 20% of the U.S. population. It usually begins during the second and third decades of life. PMLE belongs in the category of idiopathic photodermatoses, which are dermatoses that occur in healthy individuals from exposure to sunlight. It is a polymorphic syndrome with multiple morphologic variants, characteristically appearing as a recurrent pruritic eruption of papules, vesicles and/or plaques following sun exposure. These lesions typically heal with no residual scarring. The etiology of PMLE is uncertain; however, an immunologic basis has been theorized.

**Introduction**

There are four types of photodermatoses: acquired idiopathic photodermatoses, DNA repair-defective photodermatoses, photo-exacerbated dermatoses, and photosensitization by exogenous or endogenous drugs or chemicals. The acquired idiopathic photodermatoses include polymorphous light eruption (PMLE), actinic prurigo, hydroa vacciniforme, chronic actinic dermatitis, and solar urticaria. Among these, PMLE comprises more than 90% of all photo-induced eruptions, affecting 10% to 20% of the population. It is characterized by an intermittent skin reaction to ultraviolet (UV) radiation exposure, consisting of non-scarring pruritic erythematous papules, vesicles or plaques that develop on light-exposed skin. Polymorphous light eruption was first described in 1817 by Robert Willan and further studied by Haxthausen in 1918.

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**Case Report**

We present the case of a 50-year-old female who presented to our clinic with multiple, coalescing bullae on an erythematous base on the bilateral extensor surfaces of the upper extremities (Figures 1-3). The patient stated that the lesions were asymptomatic, denying any pruritus or pain in the area. She stated that she had noted similar lesions annually, in the month of May, for the previous eight years, with her clinical findings becoming increasingly pronounced over the years.

The patient’s history and clinical presentation was consistent with a diagnosis of bullous polymorphous light eruption. A biopsy was obtained from the left dorsal forearm, and the patient was started on systemic corticosteroids for one week and topical triamcinolone ointment twice daily for two weeks. The patient was also instructed to limit any sun exposure.

Ten days following initial presentation, the patient demonstrated tremendous improvement, with slightly hyperpigmented patches bilaterally on the dorsal extensor forearms. The vesicles and bullae had resolved.

**Discussion**

PMLE presents on sun-exposed areas, most commonly the upper chest, shoulders, V of the neck, lower legs, and dorsal aspects of the arms. It typically occurs in the spring or early summer and tends to improve as the summer progresses. In a given patient, the eruption tends always to affect the same skin sites. The face can be involved, though it appears to be a more common site of involvement in children. The skin lesions usually present as a delayed-type hypersensitivity reaction, appearing 30 minutes to several hours post sun exposure, and resolve after approximately seven to 10 days with no residual scarring or signs of disease. Pruritus and burning may occur prior to the onset of visible skin lesions. Lesions are polymorphous but are generally characterized...
by pruritic, erythematous or tan-colored papules of varying size coalescing into large plaques with either a smooth or rough surface. Vesicles, bullae, and confluent, edematous swelling may also occur in rare variants.9

Some patients show progressive worsening of their symptoms over the course of their disease, while others exhibit continuing improvement due to a phenomenon called skin hardening.10 Skin hardening is the buildup of tolerance in the skin to the most intense UVR due to repetitive exposure during the summer months. Hardening works by suppressing the immune reactions of PMLE.11

Several morphological variants of PMLE have been described. These include papular PMLE, pinpoint papular PMLE, which shows distinct histologic features in the acute versus subacute lesions, papulovesicular, plaque-type, eczematous, insect bite-like, hemorrhagic, and erythema multiforme-like.12 Other, rare variants of PLE have been reported, as well. Dover and Hawk reported a pruritic form of PLE with no visible skin eruption called PLE sine eruption.13 A mild, delayed-onset clinical variant of PMLE named benign summer light eruption, occurring on vacation after intense sun exposure, has also been described.14 Another rare variant has been reported in children and is characterized by a self-limiting eruption of grouped pruritic papules and vesicles on the light-exposed ear auricles in early spring, termed juvenile spring eruption.15 Our patient presented with the rare vesiculobullous variant of PMLE, classified by edema with multiple vesicles and bullae on an erythematous base following sun exposure. The clinical and histological features of each variant are summarized in Table 1.

Histology

The histopathologic picture of PMLE is characteristic and shows a moderate perivascular lymphocytic infiltrate in the upper and middle corium with subepidermal edema, vacuolization of basal cells, and spongiosis in the lower epidermis. This inflammatory infiltrate is often seen in conjunction with dermal edema and endothelial-cell swelling. Epidermal changes usually consist of vacuolar degeneration of basal cells, and occasionally spongiosis and exocytosis.16

In addition to the general histologic picture of PMLE, each variant has its own distinct histologic characteristics. Norris et al. studied skin biopsies from PMLE lesions experimentally induced by low doses of UVR that demonstrated a prominent dermal perivascular infiltrate of T cells present at five hours post radiation and peaking at 72 hours.17 It was found that CD4+ T cells were more abundant early on, at 5 hours, and CD8+ T cells were more abundant at 72 hours. In addition, macrophages comprised less than 12% of the infiltrate, and the CD1-positive Langerhans cells were increased. E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) were also increased in lesional keratinocytes above areas of dermal leukocyte infiltration, which further supports the role of a delayed-type immune hypersensitivity in PMLE.18

The most important differential diagnoses are solar urticaria, photosensitive erythema multiforme, and lupus erythematosus (LE). Cutaneous lesions of PMLE can be very difficult to distinguish from those of cutaneous lupus erythematosus and...
can share the same pathogenesis. In a study by Millard et al., there was a high incidence of PMLE not only in patients with LE but also in the first-degree relatives of patients with subacute cutaneous lupus erythematosus and discoid lupus erythematosus. In addition, a study of 337 patients with LE by Nyberg et al. reported an increased prevalence of PMLE versus the general population. The development of PMLE is influenced by not only biochemical factors but also genetic ones.

### Etiology

Several etiologies have been implicated in the pathogenesis of PMLE. First of all, genetic factors have been shown to play a role in the disorder but are not well understood. A family history of PMLE was reported in up to 50% of subjects in a study by Jansen et al. Millard et al. studied 420 pairs of adult female twins to assess the role of heritability in PMLE and reported the prevalence of PLE to be 21% in monozygotic twins and 18% in dizygotic twins. The development of PMLE is influenced by not only biochemical factors but also genetic ones.

### Table 1. PMLE Variants: Clinical and Histological Features

<table>
<thead>
<tr>
<th>Variants of PMLE</th>
<th>Clinical Appearance</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papular</td>
<td>- Most common</td>
<td>- Perivascular lymphocytic infiltrate</td>
</tr>
<tr>
<td></td>
<td>- Coalescent erythematous papules and plaques</td>
<td>- Subepidermal edema</td>
</tr>
<tr>
<td></td>
<td>- First three decades of life</td>
<td>- Vacuolization of basal cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Spongiosis in the lower epidermis</td>
</tr>
<tr>
<td>Pinpoint papular</td>
<td>- Seen mainly in skin types IV-V</td>
<td>Acute lesions (0-3 days):</td>
</tr>
<tr>
<td></td>
<td>- Young and middle-aged</td>
<td>- Spongiosis, edema</td>
</tr>
<tr>
<td></td>
<td>- 1-2 mm or 2-3 mm, skin-colored or red papules with minimal erythema or vesicular component</td>
<td>- red-blood-cell extravasation</td>
</tr>
<tr>
<td></td>
<td>- Usually on the extensor forearm</td>
<td>- perivascular and interstitial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- lymphocytic infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- eosinophils</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Subacute lesions (1-4 weeks):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- parakeratosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- atrophic epidermis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- lichenoid lymphocytic infiltrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- histiocytes</td>
</tr>
<tr>
<td>Papulovesicular</td>
<td></td>
<td>Numerous neutrophils</td>
</tr>
<tr>
<td>Plaque-like</td>
<td>- Band-like infiltrate in the upper dermal layers</td>
<td>- Subepidermal edema</td>
</tr>
<tr>
<td>Visculobullous</td>
<td>Edematous with multiple vesicles and bullae on an erythematous base</td>
<td>- Spongiotic vesicles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Severe subepidermal edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Blist formation</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td>- Erythrocyte extravasation in the papillary dermis</td>
</tr>
<tr>
<td>Eczematous</td>
<td>Speculated to be a form representing chronic actinic dermatitis</td>
<td>- Epidermal spongiosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Upper dermal perivascular lymphohistiocytic infiltrate</td>
</tr>
<tr>
<td>Erythema multiforme-like</td>
<td>More prominent dermal edema</td>
<td></td>
</tr>
<tr>
<td>Insect bite-like (strophulus)</td>
<td>Profound epidermal changes with focal necrosis of keratinocytes</td>
<td></td>
</tr>
<tr>
<td>PLE sine eruption</td>
<td>- Pruritic</td>
<td>- Subepidermal edema</td>
</tr>
<tr>
<td></td>
<td>- No visible skin eruptions</td>
<td>- Blist formation</td>
</tr>
<tr>
<td>Benign summer light eruption</td>
<td>-Mild, delayed onset occurring on vacation after several days of sun exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Small papular form generally sparing the face</td>
<td></td>
</tr>
<tr>
<td>Juvenile spring eruption</td>
<td>-Children</td>
<td>- Self-limiting eruption of grouped pruritic papules and vesicles on the light-exposed helices of the ear</td>
</tr>
<tr>
<td></td>
<td>- Early spring</td>
<td>- Spongiosis, edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Subepidermal edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vacuolization of basal cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Spongiosis in the lower epidermis</td>
</tr>
</tbody>
</table>

In a study by Millard et al., there was a high incidence of PMLE not only in patients with LE but also in the first-degree relatives of patients with subacute cutaneous lupus erythematosus and discoid lupus erythematosus. In addition, a study of 337 patients with LE by Nyberg et al. reported an increased prevalence of PMLE versus the general population. The development of PMLE is influenced by not only biochemical factors but also genetic ones.
Kolgen et al. also found a significant radiation, leading to the clinical manifestations of despite the immunosuppressive effects of UVB to be present in the epidermis in considerable the formation of a hypersensitivity reaction. In healthy skin. These cells play an important role in disappearance of epidermal Langerhans cells, whereas in individuals with PMLE, this migration of Langerhans cells to the lymph nodes does not take place. The disappearance of Langerhans cells in the epidermis of normal individuals prevents the formation of a hypersensitivity reaction. In patients with PMLE, Langerhans cells continue to be present in the epidermis in considerable numbers at 24 and 48 hours after exposure despite the immunosuppressive effects of UVB radiation, leading to the clinical manifestations of PMLE. Kolgen et al. also found a significant reduction in UVB-induced infiltration by CD11b+ macrophage-like cells in PMLE skin versus healthy skin. These cells play an important role in the secretion of the immunosuppressive cytokine IL-10. Also, Schormagel et al. demonstrated a reduction in UVB-induced infiltration of neutrophils, indicating a role for neutrophils in the pathogenesis of PMLE. Janssens et al. showed that UVB hardening significantly normalizes UV-induced cell migratory responses of Langerhans cells and neutrophils in patients with PMLE.

Abnormalities of arachidonic acid metabolism and prostaglandins have been also reported in PMLE. Topical application of indomethacin for 2 hours after irradiation inhibited UVB-induced erythema in 13 of 23 subjects with PMLE.

### Treatment

Mild forms of PMLE are effectively controlled by decreased sun exposure at times of high UV intensity, use of protective clothing, and the regular application of broad-spectrum sunscreens with high-protection factors, including UVA filters.

Phototherapy and especially photopheresis including psoralen and UVA/PVUA are effective ways to decrease sensitivity to light. UV therapy involves the buildup of immune tolerance to an endogenous UV-modified antigen in addition to increased skin melanization and thickening of the stratum corneum. The use of phototherapy produces the phenomenon of hardening and works to stimulate photoadaptation with small bouts of regulated UVR without inducing the typical skin eruption of PMLE.

Systemic treatment with chloroquine or beta-carotene has been controversial. In subjects who experience occasional bouts of the disease, oral steroids can effectively suppress the PMLE reaction; the common treatment in such cases is a short course of prednisone or prednisolone administered at the very beginning of the eruption, or prophylactically prior to a short risk period. A treatment protocol is summarized in Table 2.

### Conclusion

Of the four classifications of immunologically mediated photodermatoses, polymorphic light eruption (PMLE) is the most common, classically appearing in the third decade of life. Since the clinical pattern of PMLE varies from patient to patient, treatment is based on removal of the photosensitizer along with restriction of UVR exposure. A sunscreen with effective defense against UVA and UVB can successfully prevent the development of PMLE. Further studies are needed to examine whether regular application of sunscreen under everyday conditions could be an equivalent alternative to UV-hardening therapy.

Overall, photodermatoses form a significant group of skin conditions that can be extremely disabling to the patient and are difficult to diagnose; therefore, knowledge of these disorders is imperative in the management of these patients.

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Elephantiasis Nostras Verrucosa

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*****Affiliated Dermatology, Scottsdale, AZ

Abstract

Elephantiasis nostras verrucosa (ENV) is a rare, chronic deforming disorder characterized by dermal fibrosis, hyperkeratosis, and verrucous, papillomatous lesions resulting from end-stage, chronic non-filarial lymphedema. Morbid obesity, soft-tissue infections and heart failure are the predominant risk factors for ENV, with obstructive tumors, trauma/surgery to lymphatic ducts, pulmonary hypertension and radiation posing risks to a lesser degree. Long-standing edema allows repeated bacterial infections, fibrotic skin changes and, if neglected, verrucous growths. We present a case of ENV in a 42-year-old male with undiagnosed heart failure.

Introduction

Elephantiasis nostras verrucosa (ENV) is a rare cutaneous manifestation of end-stage (stage 3), non-filarial chronic lymphedema. Lymphedema is a type of edema caused by disruption of the lymphatic channels and subsequent interstitial accumulation of protein-rich lymphatic fluid. It has been divided into primary and secondary causes, either of which can progress through lymphedema stages 0 through 3 (Table 1).1-4 Compared to regular edema, lymphedema is more likely to be unilateral, localized to an area of lymph disruption, non-pitting (stages 2 and 3), and positive for Stemmer’s sign. Stage 3 lymphedema is considered elephantiasis and is most commonly reached via secondary causes, as primary causes are rare. The most common cause of elephantiasis worldwide is filarial parasites blocking the lymphatic channels. Reports in the literature have mainly been isolated case reports with the exception of a 21-patient series, representing the largest attempt to classify ENV to date.5 Judging by the photographs in the literature, our case appears to be among the most advanced and extensive. We report a case of ENV in a 42-year-old male with undiagnosed heart failure, in which a lack of past medical history and the extreme nature of the lesions added difficulty to the diagnosis.

Case Report

A 42-year-old male arrived at the ER via emergency medical services, who were called by neighbors due to the extremely foul odor

Table 1. Causes of Lymphedema

<table>
<thead>
<tr>
<th>Primary Lymphedema</th>
<th>Secondary Lymphedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Congenital malformation of the lymphatic vessels</td>
<td>• Wucheria spp (most common cause worldwide)</td>
</tr>
<tr>
<td>• Congenital lymphedema, defined by onset of swelling at birth to 2 years</td>
<td>• Cancer and its treatment, such as lymph-node dissection (most common cause in U.S.)</td>
</tr>
<tr>
<td>Ex: Turner syndrome, Noonan syndrome, aplasia of thoracic duct, Noone-Milroy disease</td>
<td>• Lymphatics damaged secondary to cancer, surgery, radiation, infection, chronic inflammatory conditions, obesity</td>
</tr>
<tr>
<td>• Lymphedema praecox (most common primary cause), typically arising during puberty or pregnancy, with onset prior to age 35</td>
<td>• Lymphedema tarda, defined by onset after age 35</td>
</tr>
<tr>
<td>Ex: Meige disease, yellow nail syndrome, hypotrichosis-lymphedema-telangiectasia syndrome</td>
<td></td>
</tr>
</tbody>
</table>

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emanating from the patient’s home. Upon arrival, the patient was found to be in atrial fibrillation with rapid ventricular response and impressive lower-extremity lesions. Infectious Disease medicine and Dermatology were consulted to diagnose the unusual lower-extremity lesions.

Obtaining a complete medical picture was difficult, as the patient did not remember specifics. He said he first noticed “pimples” six months prior on his lower leg after taking a bath. He stated that he scratched the lesions, which caused them to spread up his legs. The patient denied pain or pruritus at this time and was unsure when the swelling in his legs developed. He denied any travel outside the country in the past 10 years. When asked how he cared for the lesions, the patient reported he did not often shower and did not use any products on the lesions. He recalled a similar problem 10 years ago, in which he was hospitalized and treated. He could not recall what treatments were used. Review of past medical history, surgical history and current medications was unfruitful. The patient appeared to be completely indifferent to his leg lesions. Further history obtained from his father revealed that these lesions had been present for years, and that there was a family history of heart disease.

On physical exam, bilateral legs revealed extensive non-pitting edema with overlying hyperkeratotic, verrucous plaques (Figure 1). Lateral aspects of the calves bilaterally revealed ulceration. The largest ulceration measured 7 cm. Bilateral thighs revealed several scattered, papillomatous, cobblestone-like papules and plaques (Figure 2). The lesions were malodorous.

Cultures of the lesions revealed heavy growth of gram-negative bacilli and few gram-positive cocci in pairs, chains and clusters, for which the patient was started on meropenem and linezolid. Blood cultures were negative. Further workup revealed ejection fraction of 20%, moderate-severe pulmonary hypertension, and no evidence of DVT. Laboratory findings indicated the patient was also in renal failure.

A punch biopsy was taken from the advancing edge of the verrucous plaque from the right lower leg, which revealed mild acanthosis with diffuse dermal fibroplasia, vascularity and chronic inflammation. A shave biopsy was taken from the cobblestone lesion on the upper thigh, which revealed mild papillary epidermal hyperplasia with dermal edema, delicate fibroplasias and sparse chronic inflammation (Figure 3), compatible with the clinical diagnosis of ENV.

Treatment for our patient consisted of compression stockings, leg elevation, and bleach baths (1/3 cup bleach in a 40 gallon tub). To prevent bacterial infection, antibiotic therapy was continued. A combination of urea 40% cream BID and clobetasol cream 0.05% BID was applied to the verrucous areas to smooth the verrucous plaques. Aggressive long-term compliance is needed to treat this disease.

Discussion

Elephantiasis nostras verrucosa (ENV) is rare and represents end-stage development of two more common conditions: edema and stasis. Prolonged edema and stasis are a common theme in many of the known risk factors, including congestive heart failure, chronic venous insufficiency, obstructive tumors, previous surgery or trauma to lymphatic ducts, obesity, pulmonary hypertension, cellullitis and radiation. In patients with multiple risk factors like ours (heart failure, cellulitis, and pulmonary hypertension), there is a correlation with more widespread disease. Further classification reveals that almost all patients are morbidly obese (91%), have bilateral lower extremity involvement (86%), and have concurrent cellullitis or other skin infections (86%). Seventy-one percent of the time, ENV occurs alongside the skin changes of chronic venous insufficiency (stasis dermatitis, lipodermatosclerosis, ulceration), which has recently been recognized as an emerging risk factor for ENV. The classic ENV patient is most likely to be seen in a cardiology or vascular-surgery office. Those with mental illness are particularly vulnerable due to their inadvertent neglect of their health. However, ENV has been reported in non-dependent areas such as the back, ears and abdomen, making diagnosis challenging.

Pathogenesis is due to accumulation of interstitial protein-rich fluid. This static fluid leads to an inflammatory state and a localized weakened immune response. Cytokines from chronic inflammation stimulates fibroblasts and keratinocytes, transforming the initially soft-pitting edema seen in stage 1 lymphedema, into hard, fibrotic skin. Histologic examination confirms this, showing fibrous tissue hyperplasia, pseudopelthelomatous hyperplasia, dilated lymphatic spaces, and chronic inflammation.

The weakened immune response provides a fertile ground and nidus for repeated bacterial infections, further fibrosing the tissue. It appears that lymphedema and stasis alone will cause indurated fibrotic skin but stop short of the cobblestoned and verrucous lesions characteristic of ENV. Bacterial superinfection is needed to develop these characteristic ENV lesions. We cannot comment on whether a bacterial infection set off our patient’s ENV as we were not able to obtain a detailed history, but he was heavily colonized at the time of presentation. The chronic inflammation and infection impart increased risk for malignancy development, which needs to be ruled out by biopsy.

Early disease is marked by fibrotic skin with clusters of indurated papillomatous nodules, which has prompted use of the descriptive term “cobblestone.” We feel our patient’s cobblestone-like nodules above the knee represented early disease and were key in making the diagnosis (Figure 1). These cobblestoned areas progress with verrucous projections and ulcerations in late-stage disease, as seen in our patient (Figure 2).

The differential diagnosis for ENV is venous stasis dermatitis, lipodermatosclerosis, pretibial myxedema, filariasis, lipedema, chromoblastomycosis, and papular mucinosis. Pretibial myxedema can be ruled out by a TSH or lack of mucin in the biopsy specimen. Filariasis can be evaluated with a history of travel to endemic areas and peripheral blood smear or tissue stain identifying microorganisms. Lipedema, or the abnormal accumulation of fat, would show normal histology on biopsy and likely...
have a family history.15 Chromoblastomycosis would have culture positive for fungus and is more likely in tropical and subtropical climates. Venous stasis dermatitis can be ruled out clinically as it has pitting edema. Papular mucinosis would show acid glycosaminoglycan deposition on biopsy. Lipodermatosclerosis would have similar fibrotic skin but have fibrin deposits around capillaries.

**Treatment**

Treatment is not standardized but should be focused on relieving the lymphedema; this can be improved with extremity elevation and compression stockings or bandages. Many different approaches, all with some degree of success, have been reported, including topical keratolytics, oral retinoids, complex lymphatic physical therapy, prophylactic antibiotics to prevent infections and, in extreme cases, surgical debridement.10,19-23

**Conclusion**

Here we present one of the most extensive cases of ENV found in the literature. Common causes of lymphedema include heart failure, obstructive tumors, previous surgery or trauma to lymphatic ducts, obesity, pulmonary hypertension, cellulitis and radiation, all of which can provide the background for ENV to develop. The diagnosis continues to be clinical, with testing focused at discovering the cause of lymphedema. Treatment is focused on improving underlying lymphedema. Adjunctive treatments include topical keratolytics, oral retinoids and surgical debridement in severe cases.

**References**


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Abstract

We present a very rare case of unilesional folliculotropic mycosis fungoides with follicular mucinosis. The prognosis of these combined subtypes in one entity is under special evaluation. We intend to stress the importance of clinical suspicion as well as direct attention to the diagnostic options available for this rare disease entity.

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. In MF, a clonal accumulation of T lymphocytes infiltrates the skin. Establishing a diagnosis may be tricky, as the disease presents itself in many diverse forms including patches, plaques, tumors, and/or erythroderma. Diagnosis is based on clinical presentation and histopathology. Once a definitive diagnosis is established, staging determines prognosis and treatment considerations.

Unilesional folliculotropic mycosis fungoides is a rare, mixed variant whose prognosis necessitates close evaluation, as it varies for unilesional- versus follicular-type MF. Early-stage disease can be managed with skin-directed therapies; however, if the skin disease progresses or presents in advanced-stage disease, systemic treatment is warranted.

Report of a Case

A previously healthy, 67-year-old Caucasian male presented with a well-demarcated, hairless plaque with follicular prominence on the left lateral leg of two months’ duration. The patient denied pruritus, pain, bleeding, or swelling in the area, but did admit to diffusely xerotic skin. No other lesions were noted on the body. His medications included 81 mg of aspirin and PreserVision. The patient did not have any known drug allergies.

On physical exam, an 8 cm, erythematous, indurated plaque was observed on the left lateral calf with surrounding alopecia and follicular accentuation (Figure 1). A skin biopsy specimen was obtained. Histopathology showed a mixed, dense and diffuse infiltrate containing many histiocytes and multinuclear lymphoid cells. Away from the granuloma, a partly band-like infiltrate involving the epidermis was present (Figure 2a). There were several areas of epidermotropism (Figure 2c) and follicular proliferation (Figure 2d), and some follicles revealed mucin (Figure 2e).

The patient was diagnosed with unilesional folliculotropic mycosis fungoides likely with follicular mucinosis.

The patient was started on 15 mg of methotrexate IM. His CBC with differential was closely monitored. The patient was continued on 25 mg of methotrexate IM injections every 10 days for approximately six months. After multiple injections, the follicular accentuation and alopecia surrounding the lesion showed clinical...
improvement, and the plaque itself was beginning to flatten. However, the patient developed a new tumor, which ended up being a biopsy-proven Merkel cell carcinoma, and methotrexate injections were discontinued.

PCR analysis of the T-cell receptor gamma gene followed by capillary electrophoresis revealed a positive study supporting the presence of clonal T-cell population.

Discussion

MF is the most common type of cutaneous T-cell lymphoma. The follicular extension and destruction of hair follicles involved in the pathogenesis of this lesion can be clinically recognized by the presence of follicular accentuation with surrounding alopecia. These clinical signs present commonly in evolution of a follicular lymphoma, T-cell type. Follicular mucinosis is a histopathologic feature associated with the clinical appearance of alopecia mucinosa with follicular prominence. Although these lesions typically appear on the head and neck, they can occur on the lower extremities, as we present here. Alopecia mucinosa/follicular mucinosis is equivocal to MF in adults.

It is important to consider the many variants of mycosis fungoides (MF), including erythrodermic, follicular, syringotropic, papular, granulomatous, hypo- and hyperpigmented, and unilesional, because the prognosis of each varies dramatically. Unilesional mycosis fungoides (uMF), although rare, has an excellent prognosis, with a 90% five-year survival rate; folliculotropic mycosis fungoides (FMF), which has a more aggressive course, has a five-year survival rate of 60%.

The histopathological differential diagnosis for FMF includes scarring alopecia, folliculitis, follicular lichen planus, and lichen planus. Analysis is often obscured by a host of other patterns often identified in FMF, including cosinophilic folliculitis, basaloid folliculolymphoid hyperplasia, a granulomatous reaction, and follicular cystic changes with subtle atypical lymphocytes in the cyst wall. Typical immunohistochemistry results reveal an abundance of mucin accumulation in the follicular epithelium, positive CD2, CD3, and CD5, and negative CD7. PCR analysis of the T-cell receptor gamma gene followed by capillary electrophoresis and a positive study supports the presence of a clonal T-cell population. False-positive PCR gamma rearrangements can occasionally be seen in an immature lymphoid malignancy, autoimmune diseases, and congenital and acquired immune deficiency syndromes.

The International Society of Cutaneous Lymphoma published an algorithm for diagnosing early patch-phase MF, shown in Table 1. A positive diagnosis requires 4 points. This particular algorithm could not be used in our patient due to lack of immunopathologic workup.

Staging of MF is extremely important as it determines each patient’s prognosis and treatment considerations. Many systems have been published for staging MF, including ones by the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC). Although treatment regimens for MF vary depending on stage of disease, all therapies meet the common goal of reducing tumor burden and protecting immune function of patients. Current literature supports skin-directed treatment regimens for early-stage disease, including topical emollients, topical steroids, nitrogen mustards, and UV-radiation exposure. The refractory or advanced-stage disease can be targeted with chemotherapy and/or radiation and biologic/immunologic therapies. Given that our patient was diagnosed with a more aggressive subtype, follicular, we elected to treat with a biologic option. Local radiation to the single MF lesion would have also been an acceptable treatment option. Chemotherapy is reserved for advanced-stage disease. Recently, antileprosy multidrug therapy, such as rifampin, ofloxacin and minocycline, has been used in patients with FMF with follicular mucinosis, leading to rapid and complete resolution with no recurrence on extended follow-up.

Table 1. Algorithm for Diagnosing Early MF

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Scoring System (4 points=Diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>1 point for one or more criteria</td>
</tr>
<tr>
<td>Persistent and/or progressive patches/ thin plaques</td>
<td>1 point for basic criteria and one additional criterion</td>
</tr>
<tr>
<td>Additional</td>
<td>2 points for basic criteria and two additional criteria</td>
</tr>
<tr>
<td>1) Non-sun-exposed location</td>
<td></td>
</tr>
<tr>
<td>2) Size/shape variation</td>
<td></td>
</tr>
<tr>
<td>3) Poikilodermal</td>
<td></td>
</tr>
<tr>
<td>Histopathologic</td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>1 point for one or more criteria</td>
</tr>
<tr>
<td>Superficial lymphoid infiltrate</td>
<td>1 point for basic criteria and one additional criterion</td>
</tr>
<tr>
<td>Additional</td>
<td>2 points for basic criteria and two additional criteria</td>
</tr>
<tr>
<td>1) Epidermotropism without spongiosis</td>
<td></td>
</tr>
<tr>
<td>2) Lymphoid atypia</td>
<td></td>
</tr>
<tr>
<td>Molecular biological</td>
<td></td>
</tr>
<tr>
<td>Clonal TCR gene rearrangement</td>
<td>1 point for clonality</td>
</tr>
<tr>
<td>Immunopathologic</td>
<td></td>
</tr>
<tr>
<td>1) &lt;50% CD2+, CD3+, and/or CD5+ T-cells</td>
<td>1 point for one or more criteria</td>
</tr>
<tr>
<td>2) &lt;10% CD7 + T-cells</td>
<td></td>
</tr>
<tr>
<td>3) Epidermal/dermal discordance of CD2, CD3, CD5, or CD7</td>
<td></td>
</tr>
</tbody>
</table>

Source: International Society of Cutaneous Lymphoma

References


Conclusion

Here we present a rare case of unilesional FMF. The combination of folliculotropic and unilesional subtypes is very unusual, with only four cases reported to date. Special attention should be paid to the prognosis of this unique diagnosis in future patients.
Rhinophyma primarily affects Caucasian men in the fifth to seventh decades of life. Phymatous rosacea is the least common rosacea subtype. In one cross-sectional study of 348 individuals, 78 were found to have rhinophyma, but only one patient had rhinophyma. The histology of rhinophyma features sebaceous-gland hypertrophy and hyperplasia of connective tissue and blood vessels. Rhinophyma has a strong social stigmatization and can be cosmetically disfiguring. It is reported that J.P. Morgan, one of the richest men in the world, suffered from severe rhinophyma, his disfigurement so disabling he avoided pictures and reportedly used his umbrella to chase away a photographer due to embarrassment. Rhinophyma can also cause functional impairments due to obstruction of the nares and progressive difficulty in nasal breathing.

Treatment options for rhinophyma include both medical and surgical therapies, depending ultimately on disease severity. Patients with early rhinophyma exhibiting minimal skin thickening without nasal deformity may benefit from medical therapy. Oral antibiotics and oral retinoids are the mainstay of medical treatment; however, they cannot reverse established disease, and conclusive evidence of efficacy is lacking. Surgical management is necessary in advanced rhinophyma to restore a normal nose contour. Surgical modalities include electrosurgery, laser ablation, dermabrasion, and surgical excision. The literature reflects controversy regarding which surgical modality is best. Electrosurgery destroys tissue with heat produced by high-frequency electrical current. It is able to make precise cuts while providing adequate hemostasis. Various tips and modes (cutting, blended cutting and coagulation, hemostasis) can be used with this device depending on the clinical indication. Electrosurgical devices are relatively inexpensive compared to laser modalities and, in our experience, work extremely well for correction of disfiguring rhinophyma.

Basal cell carcinoma has been reported in 5% of patients with rhinophyma, and some authors have advocated sending the shaved specimens for pathologic examination. With CO2 laser or other ablative techniques, this cannot be accomplished. With electrosurgery, loop shavings can be saved and sent to pathology, although when multiple shavings are sent in, identifying the site at which the cancer is located can be problematic. Still, shaving off the phymatous tissue may effectively treat the skin cancer, if present. Therefore, it is our opinion that the shavings do not warrant pathological review, and instead the newly formed nose can be monitored over time for skin-cancer development. Alternatively, topical imiquimod cream may be applied after shaving the nose to not only help with scarring but also minimize cancerous-growth formation.
Case Report
A 52-year-old man presented with a 10-year history of a progressively enlarging nose. He had been treated with oral antibiotics (doxycycline) combined with topical metronidazole over the past several years. During this time period, he noticed that his nose still continued to enlarge. Physical exam revealed significant sebaceous and subcutaneous tissue hypertrophy of the nose (Figure 1). Due to the severe nasal deformity, we decided to treat his nose using a surgical modality. After discussing risks and various surgical treatment modalities, informed consent was obtained. The area was sterilized with chlorhexidine-gluconate solution and draped appropriately. Local anesthesia was achieved using 8 cc of 1% lidocaine with epinephrine injections in a ring around the nose. We introduced the needle at each side of the nasal ala and injected upward toward the bridge of the nose, then came across the upper cutaneous lip. The Ellman Surgitron was used along with a vacuum evacuator to suction the plume. Initially, a wire loop tip was used to shave off the redundant tissue and debulk the nose. The wire tip was then used to establish a normal nose contour, and hemostasis was controlled using the coagulation mode. The power-control dial was set between 3 and 5 depending on the intensity needed during the procedure. The area was covered with a thick layer of polymyxin B/bacitracin topical ointment and bandaged. The entire procedure lasted 30 minutes. The phymatous tissue was not sent for pathology.

Postoperative wound care included the application of polymyxin B/bacitracin topical ointment at least qid for two weeks. After two weeks, the patient’s nose had reepithelialized with minimal residual erythema and no scarring (Figure 2). Initially the patient was told that several treatments may be required, but fortunately he was thrilled after the first treatment. He felt that this was a life-changing event and felt dramatically better about himself after this procedure. It changed his outlook on life in a positive way.

Discussion
Rhinophyma is a condition that causes significant disfiguration. It is easily treatable with either laser or electrosurgery modalities. We have found that the Ellman electrosurgical unit, using a circular loop and a straight line, is the most efficient and simple way to remove large sections of skin. Considering the cosmetic improvement and life-changing nature of this treatment, we recommend this modality as a viable surgical option for advanced rhinophymatous disease. Initially, it is often a good idea to let patients know that full correction may take several treatments. Often, with minimal experience, skilled dermatologists may be able to treat rhinophyma in a single treatment. Online-teaching videos found on YouTube demonstrate these practical treatment techniques. The ease and availability of electrocautery to treat rhinophyma should increase the access patients have to this life-changing treatment option; as dermatologists, we owe it to our patients to use this valuable technique.

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Atypical Presentation of a Granular Cell Tumor: A Case Report and Review of the Literature

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Abstract

Granular cell tumors (GCTs) are rare, mesenchymal tumors that occur on any skin or mucosal surface and comprise a small percentage of all soft-tissue tumors. They are typically slow-growing, asymptomatic, solitary, benign tumors of neural origin, though rarely they can be malignant. GCTs can occur anywhere in the body and most commonly are found in the head and neck region, more specifically on the tongue. The primary modality of treatment for GCT is surgical excision, with low rates of recurrence even without clear surgical margins. We present a case of a 41-year-old Hispanic female who presented with a firm, rubbery textured, non-mobile mass on the upper back. We also review the clinical and histopathological findings and recommendations for both benign and malignant granular cell tumors.

Introduction

Granular cell tumors are rare mesenchymal tumors accounting for about 0.5% of all soft-tissue tumors.1 These slow-growing, benign tumors of neural origin can occur anywhere in the body. They are generally asymptomatic and usually solitary, though rarely they can be multifocal.1 The tongue is the most common site involved. Other affected areas include the chest wall, upper extremities, vulva, breast, larynx, bronchus, gastrointestinal tract, anus, bile ducts, pancreas, urinary bladder, uterus, brain, pituitary gland and soft tissues.1 GCT may occur at any age but are commonly diagnosed in the third to fifth decades of life.2 The cell of origin is now accepted to be the Schwann cell due to strong S100 protein expression on immunohistochemistry.2 Granular cells contain lysosomal vacuoles with myelin figures, a prominent basal lamina, and intracytoplasmic filaments ultrastructurally.2 Treatment of these tumors ultimately depends on the size and location, but it typically consists of surgical removal of the GCT.

Case Report

A 41-year-old Hispanic female presented to our clinic with the chief complaint of a large, firm, non-mobile mass on her right upper back. The patient reported that the lesion had appeared a few years prior and stated it was increasing in size. She denied any pruritus, pain, or discomfort from the lesion. The patient was an otherwise healthy female with no other medical comorbidities. She denied any recent history of travel or trauma to the site of the lesion.

On physical exam, there was a solitary, 2 cm, round, firm, non-mobile skin-colored tumor on her right upper back. The lesion did not demonstrate a central punctum or have any other epidermal changes besides a light brown hue covering the tumor. An initial impression of a lipoma was made based on the morphology of the lesion; however, the lesion was much more firm than a lipoma. After the lesion was anesthetized (Figure 1), an incisional biopsy was performed around the tumor.

Figure 1

DANE, JENSEN, PUI, LACASSE
Pathology of the lesion demonstrated pseudoepitheliomatous hyperplasia and large polygonal cells with eosinophilic granular cytoplasm and central nuclei (Figures 2 and 3). Caution was taken not to misdiagnose the overlying pseudoepitheliomatous hyperplasia as squamous-cell carcinoma. Giant lysosomal granules were noted as well. A periodic acid-Schiff stain was positive. No spindled or pleomorphic nuclei were noted, negating the diagnosis of a dermatofibroma or atypical fibroxanthoma. Clinically, the lesion was not exophytic, and histologically, no nuclear pleomorphism or frequent mitoses were noted, ruling out a primitive polypoid granular cell tumor. In addition, an S100 stain was performed and stained positive (Figure 4). Based on the clinical and histopathologic presentation, a diagnosis of a granular cell tumor was made.

Due to their rare potential for malignant transformation, it was recommended for the patient to have the GCT completely excised. Although no current guidelines exist for surgical margins for GCT removal, a gently curved, S-shaped elliptical excision was performed around the lesion (Figure 5) including clinically clear margins to ensure appropriate removal of the lesion and decrease the appearance of the surgical scar (Figure 6). Final pathology showed complete excision of the GCT with clear margins.

Discussion

Granular cell tumors are rare mesenchymal tumors that can occur on any skin or mucosal surface. They are most commonly located in the head and neck area, with the majority being located on the tongue. Granular cell tumors are rare; some authors have suggested that they make up around 0.5% of all soft-tissue tumors. Frequent locations are the tongue, breast, respiratory tract, and esophagus.

GCTs primarily affect adults between the second and the sixth decades, affecting females more often than males. GCTs can also occur in children. A malignant GCT is rare and is often difficult to distinguish from a benign GCT clinically. Of note, GCTs can also appear on mucous membranes and may involve the respiratory or gastrointestinal tract and/or the central nervous system.

A GCT commonly presents as an asymptomatic,
slow growing, solitary, painless nodule that may have either smooth or hyperkeratotic overlying skin. The lesions are usually less than 3.0 cm in diameter and may undergo partial regression. Preoperatively, other differential diagnoses of GCT include dermatofibroma, keloid, fibromatosis, or lipoma. Multiple GCTs have been reported in less than 10% of cases, most notably in children and teenagers.2 Multiple GCTs are reported in association with neurofibromatosis, Watson’s syndrome, Lentiginosis profusa, Noonan syndrome, facial and ocular alterations, cardiovascular abnormalities, muscle and bone malformations, and neurologic deficits.2 In rare instances, multiple GCTs are reported in association with an internal malignancy. Squamous-cell carcinoma of the esophagus, adenocarcinoma of the prostate, and small-cell lung cancer are among the reported associations.2

On histology, benign GCTs are characterized by the presence of polygonal cells often crowded together with abundant granular cytoplasm.1-3 Granular cells may be round, oval, polygonal or spindle-shaped, and their nuclei may be dark or vesicular, located in different positions within the cell.3 Typically there are discrete, round, eosinophilic lysosomal granules present as well. The granules contain large amounts of hydrolytic enzymes and are strongly PAS-positive, diastase-resistant, and positive for Luxol fast blue and myelin basic protein. In addition, the tumor cells stain positive for S100 proteins, calretinin, neuron specific enolase (NSE), laminin and CD68 (Kp1); however, they do not react with antibodies to neurofilaments or glial fibrillary acidic protein (GFAP).2,3 Granular cell tumors can be divided into neural type, with S100 reactivity, and non-neural type, without S100 reactivity.4

Malignant granular cell tumors are typically more cellular, with greater variability in size and shape of cells. Because of the histological similarity and the lack of reliable clinical criteria, the distinction between malignant and benign GCT can be difficult to achieve. This distinction requires great attention during not only the clinical examination but also the histopathological examination of GCT and immunohistochemical staining.5 Recent morphologic criteria for malignancy set forth by Fanburg-Smith and colleagues include spindling of tumor cells, increased nuclear-to-cytoplasmic ratio, pleomorphism, necrosis, vesicular nuclei with large nucleoli, and increased mitotic activity (>2 mitoses per 10 high-powered fields at 200x magnification).4 The presence of three or more of these features strongly suggests histologic malignancy.

Surgical excision is the primary treatment modality for GCTs.2,5,6 The recurrence rate for granular cell tumors has been reported as low as 2% when local wide excision has been undertaken.4 They are most often benign tumors and recurrences are fairly rare, even in lesions whose excision is incomplete. Most granular cell tumors can be easily managed by wide local excision with clear clinical margins. In cases of benign granular cell tumors in which wide local excision takes place, there is 2% to 8% recurrence with negative margins and >20% recurrence with positive margins, emphasizing the importance of margin control.6 Although there are no current guidelines on specific surgical margins regarding removal of GCT, wide excision with clear surgical margins and close histologic examination will aid in providing negative margins. In cosmetically sensitive areas, where tissue preservation is vital, Mohs micrographic surgery has been used.7 Malignant behavior is seen in up to 2% of cases.6 Prognosis is poor in patients with malignant granular cell tumor, with frequent metastasis (>50% overall) and 30% to 50% mortality over three years in two case series.3 Metastatic disease is often present upon diagnosis of malignant GCT. Metastasis can also become apparent long after surgical excision. Treatment has been largely unsatisfactory, especially for metastatic disease. Radiation therapy and multi-agent chemotherapy generally do not improve prognosis.6

Patients with malignant granular cell tumors should undergo a full physical examination geared toward localization of potential metastatic disease. In order to exclude metastases, some providers advocate screening of patients with malignant granular cell tumor with lymphatic and hepatic sonography, chest, abdominal, and pelvic computed tomography, thoracic X-ray, and bone scintigraphy.7 Evaluation for metastasis should be individualized based on consultation and evaluation by an oncologist. In addition, patients should have lifelong follow-up with their dermatologist and oncologist since metastases have been reported years after initial diagnosis.6 Consequently, dermatologists and other healthcare providers must be keen, clinically suspicious, and maintain a variety of differential diagnoses if a patient presents with firm, non-mobile, asymptomatic tumors. Granular cell tumor should be considered as a differential diagnosis in these instances, and further clinical workup should be initiated. After biopsy, wide local excision with clear clinical margins should be implemented, and close histological examination can help determine whether the GCT is benign or malignant.

References

DANE, JENSEN, PUI, LACASSE
Abstract

Idiopathic atrophoderma of Pasini and Pierini (IAPP) presents as sharply demarcated, depressed, hyperpigmented lesions on the skin. The condition is characterized by a distinct edge described as a “cliff-drop border” that represents dermal atrophy. We present a case of IAPP in a young male patient who responded to treatment with doxycycline despite negative Borrelia burgdorferi serology.

Introduction

Idiopathic atrophoderma of Pasini and Pierini (IAPP) presents as sharply demarcated, depressed, hyperpigmented lesions on the skin. The lesions are round to ovoid and have a characteristic abrupt edge described as a “cliff-drop border” or “footprints in the snow.” This edge is the result of dermal atrophy, which describes this skin condition. IAPP is commonly hyperpigmented, but lesions can appear hypopigmented or skin-colored as well. The involved areas can be single or multiple and range from a few millimeters to several centimeters in size. If multiple, they are most commonly symmetric and bilateral. It is also not uncommon for multiple lesions to coalesce over time, creating a “moth-eaten” appearance to the skin. IAPP most frequently presents in the second or third decades of life, with a female to male ratio of 2:1. The lesions are found on the back in most cases, but they can also be located on the chest, abdomen, thighs, and arms. IAPP usually spares the face, hands, and feet. IAPP is an uncommon dermatologic manifestation, and its etiology is currently unknown.

In 1923, Pasini was the first to describe this type of dermal atrophy. He named it “progressive idiopathic atrophoderma.” Later, in 1936, Pierini and Vivoli further defined this condition and proposed a link to morphea. In 1958, Canizares et al. reviewed the dermatologic literature on the subject and renamed the disease “idiopathic atrophoderma of Pasini and Pierini.” They also classified IAPP as a distinct entity from morphea.

Case Report

A 34-year-old Caucasian male presented to our dermatology practice for an evaluation of two large lesions on his right upper back that he noted as slowly enlarging over the past year (Figure 1). He was otherwise asymptomatic. He had no family history of similar lesions or of scleroderma. Physical exam revealed that the involved lesions were depressed below the level of surrounding skin, such that superficial veins could be visualized beneath the epidermis. The area within the lesion was freely movable and without evidence of induration. In addition, both areas were hyperpigmented. The rest of his physical exam was unremarkable.

A 6 mm punch biopsy of the lesion was performed, and histopathologic examination revealed reduced dermal thickness when compared to adjacent tissue. There was no involvement of the epidermis, sweat glands, or pilosebaceous units. Homogenization and swelling of the dermal collagen bundles was noted (Figure 2).

Based on the clinical and histologic findings, a diagnosis of atrophoderma of Pasini and Pierini was made. As Borrelia burgdorferi has been reported as a possible etiology of IAPP, serum IgG and IgM Borrelia burgdorferi titers were drawn, and the patient was empirically placed on doxycycline 150 mg daily with a follow-up appointment arranged in four weeks.

Upon follow-up, the patient’s plaques had improved. The depth of the depressions appeared less noticeable. Both IgG and IgM titers for Borrelia burgdorferi were negative. Despite the negative titers, clinical improvement was noted, and it was therefore recommended that the patient continue the doxycycline 150 mg daily for an additional month. The patient did not return for follow-up.

Discussion

Some authors believe that IAPP is a variant of morphea. This is due to similarities both clinically and histopathologically. In addition, there is an IAPP/morphea overlap syndrome in which patients can develop lesions of both diseases. The lesions are differentiated by subtle clinical differences. Others debate that IAPP is a separate entity from morphea. Clinically, there are differences to be noted. IAPP is characterized by an early onset and longstanding course. Its lesions lack sclerosis, inflammation, and lilac coloring around the border. The lesions of IAPP often coalesce over time, creating a moth-eaten appearance that is not characteristic of morphea. The lesions of morphea are often sclerotic with
a white center and a characteristic peripheral lilac rim.\textsuperscript{2,3} Yokoyama et al. found that skin glycosaminoglycans extracted from both types of lesions showed different weights once broken down, suggesting a unique form of metabolism in IAPP.\textsuperscript{6}

Our patient had plaques that were hyperpigmented but lacked any sign of sclerosis or lilac border, steering us away from a diagnosis of morphea.

The cause of IAPP remains unknown; however, recent studies demonstrate a possible link between the disease and infection with Borrelia burgdorferi. A study conducted by Buechner and Rufli demonstrated that 38\% (10/26) of patients with diagnosed IAPP had elevated serum IgG antibodies to Borrelia burgdorferi.\textsuperscript{7} Still, there have been many reported cases of IAPP in which patients had negative titers, such as the patient presented here. The link is unclear, but Borrelia burgdorferi may play some role and can sometimes aid in the diagnosis of this disease.

There is no consistently reliable treatment for IAPP. Many treatments have been suggested and used with variable efficacy, including topical and systemic corticosteroids, antimalarials, D-penicillamine, antibiotics, and phototherapy. The results of treatment with antibiotics have been deemed inconclusive, but patients with new, early-onset IAPP are recommended to begin the standard treatment course for Lyme disease. This is especially true if the patient has positive serologic titers to Borrelia burgdorferi, but the recommendation is not limited to this sub-group.\textsuperscript{1,3} In the Buechner and Rufli study, 80\% (20/25) of patients treated with either oral penicillin or oral tetracycline for two to three weeks showed clinical improvement with no evidence of new lesions.\textsuperscript{7} These patients were treated regardless of their titer results.

IAPP most commonly follows a benign course. The lesions of this disease usually progress very slowly, beginning in the second or third decade of life. They are often asymptomatic and can remain stable for many years. IAPP is not associated with any significant complications or mortality.\textsuperscript{1,3} A poor cosmetic outcome may be the only disturbing factor for patients suffering with this disease.

References

Cutaneous Metastasis of Gastrointestinal Stromal Tumor (GIST): A Case Presentation and Discussion

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Abstract

We report a case of cutaneous leiomyosarcoma in a 77-year-old African American male. The patient initially presented with lesions on his scalp that were misdiagnosed on pathology. Further investigation led to a diagnosis of gastrointestinal stromal tumor (GIST). We review the present understanding of the disease process and accepted treatments.

Case Report

A 77-year-old African American male presented with a lesion on his cutaneous right upper lip and nodules on his occipital scalp. The patient’s referring dermatologist had biopsied the lesion on his right upper lip and a scalp lesion, which pathology initially interpreted as atypical fibroxanthoma. Mohs surgery was recommended, and a consult was placed.

When the patient was seen for Mohs surgery, it was noted that he had several additional lesions. On physical exam, he had multiple dermal nodules on the occipital scalp (Fig. 1-2). Additional biopsies were performed, which were composed of spindled cells with blunt-ended nuclei arranged in closely crowded fascicles within the reticular dermis extending into the adipose tissue (Fig. 3-4). Immunohistochemical staining showed the following: S-100 negative, tyrosinase negative, melanosome negative, keratin negative, CD34 negative, desmin negative, smooth muscle actin positive. It was interpreted as high-grade leiomyosarcoma. It was suspected that these dermal lesions represented a metastatic process, and he was referred to oncology for further workup.

A complete review of systems was done, which was negative except for the cutaneous finding. A complete blood count (CBC) and chemistries were accomplished, which were unremarkable, and a computed topography (CT) scan of the chest, abdomen, and pelvis were ordered. The patient was also referred for upper and lower endoscopy. His endoscopies did not show a primary tumor but did show Helicobacter pylori, and he was treated appropriately. The CT scan of the chest, abdomen, and pelvis showed pulmonary nodules consistent with metastatic disease as well as liver disease. His leiomyosarcoma was classified as a gastrointestinal stromal tumor (GIST) based on his presentation and workup, even though a primary location was not established. It was recommended that he start imatinib due to its efficacy in treating gastrointestinal mesenchymal tumors and its low toxicity. A positron emission tomography (PET) scan was also ordered to evaluate his baseline so his response to treatment could be measured at a later date.

The patient’s screening PET scan revealed multiple subcutaneous nodules involving the left scalp, left posterior base of the neck, and right periscapular area, consistent with malignant implants. There were multiple muscular implants, liver and pulmonary involvement, as well as a rib lesion. He tolerated imatinib well, experiencing few side effects, and his follow-up labs were unremarkable during his course of initial treatment.

At his follow-up PET scan three months later, he had progressive disease. His pulmonary and hepatic diseases had progressed, and there was enlargement of the rib lesion. Since he had no response to imatinib, the patient was started on sunitinib. He underwent three cycles of sunitinib therapy and tolerated the medication well. He did develop thrombocytopenia, neutropenia, and erythema of the feet, which were all secondary to

Table 1. Percent of Patients Progression-free During Long-term Follow-up

<table>
<thead>
<tr>
<th>Tumor Size (cm)</th>
<th>Mitotic Rate (HPFs*)</th>
<th>Primary Site</th>
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<td>&gt;10</td>
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*High-power fields | **Data are combined for tumors >5 cm. | ***Small number of cases.
sunitinib. At his follow-up two months later, he noted an 8-kilogram weight loss and increased fatigue. A repeat PET scan showed widely metastatic disease. The subcutaneous nodules had improved, but there was a new mass in the pancreatic body and multiple intra-abdominal masses. A clinical trial was considered in this patient, but due to his deterioration, further treatment was not recommended. He died from his disease a few months later.

Discussion

There are different types of mesenchymal tumors that arise in the gastrointestinal (GI) tract. The most common one is a gastrointestinal stromal tumor (GIST), which is a type of smooth-muscle tumor that can arise from any part of the GI tract but most commonly affects the stomach, usually presenting in adults of both genders.1 Less-common types of mesenchymal GI neoplasms include lipomas, leiomyomas, liposarcomas, desmoid tumors, schwannomas, peripheral nerve sheath tumors, and leiomyosarcomas. These tumors can start in the GI tract but are also found in smooth muscle throughout other areas of the body.3 Mesenchymal tumors that start in the GI tract, such as leiomyosarcomas, are grouped together as GIST.

Many GISTs present without any obvious clinical symptoms and are often detected when a patient is being worked up for an unrelated reason. If there are any symptoms, patients typically present with upper abdominal pain, gastrointestinal bleeding, and/or signs of obstruction.3 The tumors are often too small to produce any significant symptoms. About 10% to 30% of GISTs are estimated to be malignant.3 The evidence is mixed on risk factors for GIST. It appears to have a male predilection, more commonly affects people older than 50 years of age, and rarely has a genetic component.1 GIST and leiomyosarcoma have many histological similarities and can be difficult to differentiate on pathology. In fact, before advances in immunohistochemistry staining, GISTs were classified as leiomyosarcomas. The cellular morphology of GIST is made up of spindle cell, epithelioid, and mixed, with the spindle-cell pattern being by far the most common type (Fig. 3–4). GISTs as a whole are usually positive for CD117 (KIT), which is one of the unique features for this group of tumors (in the case presented here, the CD117 results were not available). Leiomyosarcomas are made up of multinucleated giant cells, and the immunohistochemistry can be positive for smooth-muscle actin, desmin, or both. Leiomyosarcomas typically have a high-grade mitotic rate.4

The tissue, node, and metastasis (TNM) classification is used to stage GISTs. Computed tomography, esophagogastroduodenoscopy, colonoscopy, and PET are all used for initial evaluation. PET scans are commonly used to follow progression. Predicting the likelihood of GISTs metastasizing has been difficult, and many different parameters have been used. The morphological features that have been most widely accepted for outcomes are mitotic rate and tumor size, although smaller tumors and those with low mitotic rates still metastasize. Immunohistochemistry along with factors such as tumor necrosis and high cellularity have not shown consistent results in predicting outcomes. Due to this difficulty, it has been suggested that treatment providers assume certain cases will have an unpredictable behavior.5

Depending on location and size, many GISTs can be surgically resected, but more than 50% of patients will have recurrence of disease.6 Imatinib has been found effective in metastatic GISTs. Imatinib inhibits tyrosine kinase by blocking the ATP binding site of KIT and platelet-derived growth factor, which are important receptors involved in the growth of these tumor cells.7 This means it is critical to identify the tumor specifically as GIST in order for treatment to be successful.7 The side-effect profile of imatinib is relatively low, and it has a good response rate, though mutations in KIT can cause resistance. Sunitinib is also a tyrosine kinase inhibitor that acts against many receptor sites vital to GIST proliferation.7 If a primary tumor is found, resection should always be considered. The Armed Forces Institute of Pathology (AFIP) conducted one of the largest studies on GISTs from different primary sites and reported on the percent of patients who did not have disease progression, which is depicted in Table 1.9 The National Comprehensive Cancer Network (NCCN) uses the same table to estimate prognosis.

Leiomyosarcomas can also be present as primary skin tumors. They represent less than 10% of all soft-tissue sarcomas and can be divided into two groups by their primary site of origin: Cutaneous leiomyosarcomas arise from the arrector muscles of the hair and sweat glands, while subcutaneous leiomyosarcomas come from the muscular coats of vessels. In the literature, cutaneous leiomyosarcomas present more in females and typically between the ages of 40 and 60. Etiology is largely unknown, but trauma and radiation exposure are thought to be possible triggers.10 Clinically, cutaneous leiomyosarcomas usually appear as single, round, pinkish-to-brownish nodules that can be found on any part of the body. They are commonly seen on the extensor surfaces of the extremities as well as the head and neck.11 Occasionally, they can occur in groups and have characteristics such as scaling or crusting. Many nodules presenting together can be more indicative of metastases from primary visceral locations.12 Painful lesions are rare but are more common in subcutaneous tumors. The differential diagnosis can include dermatofibromas, basal-
squamous-cell carcinomas, dermatofibrosarcoma protuberans, appendageal tumors, and epidermoid cysts. It is critical to biopsy these lesions and perform immunohistochemical staining, which can confirm the diagnosis.

Microscopically, the tumors are composed of spindle-shaped cells with elongated nuclei. Subcutaneous leiomyosarcomas are well-circumscribed and surrounded by a rim of collagen, displaying a less-fascicular pattern than cutaneous tumors. S-100 staining can be present with a dermal and/or focal tumor.

A strong consensus on treatment has been difficult due to the rarity of these tumors. A 2013 review of the literature on the treatment of superficial leiomyosarcomas showed excision with wide margins to be the treatment of choice, though Mohs micrographic surgery showed curative potential in one case series of 11 patients. Mohs would ensure clear margins at time of resection. The use of adjuvant radiation following excision is controversial due to the evidence of recurrence after such treatment in some case studies, which makes long-term follow-up essential. The recurrence rate can range from 32% to 62% and is more common with subcutaneous tumors.

Conclusion

Leiomyosarcomas can represent a type of gastrointestinal stromal tumor that arises from smooth muscle of the GI tract. The case presented here was unusual in that the first clinical manifestation was cutaneous metastasis. Leiomyosarcomas may also arise as primary cutaneous tumors. Repeat biopsies should always be considered when the clinical picture doesn’t fit the diagnosis or when treating more-complicated cases. The patient in our case was not started on a clinical trial after treatment with sunitinib. His condition quickly deteriorated, and he died approximately 15 months after diagnosis. A primary location of his cancer was never identified.

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A Case of Tattoo-Related Keratoacanthomas

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Abstract
Keratoacanthoma (KA) is a rapidly growing cutaneous neoplasm of unknown origin that is commonly found on sun-exposed skin surfaces. KA tends to be solitary and will spontaneously involute with time, prompting uncertainty for proper management. Until recently, literature reports of tattoo-induced KA were scarce. There is still disagreement among dermatologists and pathologists as to whether KA represents a true malignancy or a benign epithelial neoplasm. Despite this lack of consensus, the risk of developing invasive squamous-cell carcinoma is a real possibility, and proper care should be taken when managing patients with rapidly growing KA. We report the case of a 40-year-old woman who presented with two persistently raised, tender nodules on the bilateral anterior lower legs directly overlying two recently acquired tattoos. The diagnosis of KA was confirmed histopathologically with biopsy. Surgical excision was curative.

Introduction
A keratoacanthoma (KA) is a rapidly growing cutaneous neoplasm that is most commonly found on sun-exposed skin surfaces in older individuals. It is characterized by rapid growth and spontaneous regression. Cipollaro described the first reported case of a KA in 1973. KA is a commonly encountered problem in dermatology practices worldwide. These squamous proliferations have a distinct, characteristic crateriform architecture. Histologically, they are composed of nodules and strands of squamous cells with cellular atypia and mitotic activity. As the KA matures, these findings disappear, requiring a biopsy during the initial progression of the KA to determine the exact diagnosis based on cellular findings. Whether a KA is benign or malignant remains unclear and is the subject of controversy. Many dermatologists classify KA as a type of low-risk squamous-cell carcinoma (SCC) that usually rapidly regresses and rarely evolves into an invasive SCC. However, some regard KA as a benign squamous proliferation that rarely has the potential for malignant transformation to SCC, indicating a more conservative treatment approach.

Tattoo-related KA may be more common than once thought. Until recently, the literature revealed very little documentation on this specific diagnosis. It is thought that KAs originate from the pilosebaceous unit, though the exact pathogenesis of KA is not entirely understood. There are various reports of KAs arising within sites of trauma resulting from burns, scars, and cryotherapy, which could be a contributing factor in tattoo-induced KA development. Prospective studies with long-term follow-up of tattooed patients could provide a more accurate estimate of the frequency of tattoo-induced complications with regard to KA. Most patients diagnosed with tattoo-induced KA are lost to follow-up after successful treatment.

Case Presentation
A 40-year-old Caucasian female presented to our dermatology clinic for consultation after evaluation by her primary care physician for a four-week history of two persistent, raised and tender nodules arising from two separate tattoos that she received four months earlier. The tattoos were located on the left anterior lower leg and the right lower lateral leg. Two similar tattoos were observed on the lower extremities, but they were uninvolved. Review of systems failed to reveal any history of fever, chills, weight loss, shortness of breath, or cough. Her past medical and dermatologic histories were unremarkable. Family history was non-contributory. Medications included an oral contraceptive and fluoxetine.

Physical exam revealed a well-developed and well-nourished female with two crateriform nodules arising from two tattoos on the left anterior lower leg and right lower lateral leg. The tattoo was primarily composed of red and bluish-purple ink (Figure 1). It was not clear if the nodule arose from the red or bluish-purple inked portion. Popliteal, inguinal, and axillary lymphadenopathy was absent on exam.

Sarcoidosis, atypical mycobacterial infection, pseudolymphoma, allergic contact dermatitis and keratoacanthoma arising from a tattoo were among our top differential diagnoses.

A cutaneous biopsy of the two cutaneous nodules demonstrated a well-differentiated squamous proliferation with associated atypia and pallor in the presence of tattoo ink, consistent with keratoacanthoma (Figure 2,3). In-situ hybridization failed to reveal the presence of either low- or high-risk HPV types. Given the clinicopathological correlation, the diagnosis of KA arising from a tattoo was made. Treatment options were discussed in-depth with the patient. Ultimately, the KA was excised without recurrence. The patient was subsequently referred for laser tattoo removal.

Figure 1: Tattoo located on the right lower extremity. Biopsy site of the tattoo-related keratoacanthoma is seen at the superior aspect.

Figure 2: Invasive squamous-cell carcinoma, KA type, arising within a tattoo (2x).

Figure 3: Tattoo pigment within the dermis (4x).
The first reported complication related to tattoos occurred at the end of the 19th Century. In 2002, Jacob divided the most common tattoo-induced reactions into three categories: inoculation/infection, granulomatous/eczematous, and coincidental lesions. Table 1 demonstrates the general risks and complications associated with tattooing. Of note, any carcinoma development associated with a tattoo is categorized under the coincidental category due to the large number of people tattooed on a daily basis and the rarity of this finding. 

Tattoos are created by the injection of specific ink particles through the epidermis and into the underlying dermis. This foreign material accumulates in the upper one-third of the dermis and activates the immune system to undergo phagocytosis of the pigment particles. After healing occurs, the pigment remains trapped within fibroblasts located directly below the epidermal/dermal boundary. In some cases, a granulomatous, lichenoid, pseudoeopitheliomatous, or eczematous reaction may occur shortly following injection of tattoo ink particles; these reactions are the most commonly reported adverse effects following the acquisition of a tattoo. It has been hypothesized that the body responds to the red ink as a foreign body substance and acts to eliminate this substance via a cellular or humoral immune response. 

According to recent literature, KA-type SCC and SCC are the only reported cancers arising from tattooed skin and are well-differentiated, non-invasive lesions. When a KA occurs, it usually develops within one to 10 months following a tattoo procedure. KAs generally mature over a period of six to eight weeks, demonstrating a characteristic central keratin plug. Involution is thought to occur spontaneously through terminal differentiation over a course of three to six months. Most dermatologists treat these nodules more aggressively due to the possible risk of development into an invasive SCC. Although reactions do occur with other ink pigments, red tattoo ink reactions are reported to be the most common cause of tattoo-induced dermatoses. One study concluded that 82% of tattoo-induced KAs were associated with red tattoo ink. There are many forms of red ink, with the most common being mercuric sulfide, sienna, sandalwood, brazilwood, and aromatic azoic compounds. As reported in one article, the Food, Drug, and Cosmetic Act of 1976 decreased the concentration of mercury in tattoo pigment. This act prompted the removal of cinnabar (mercuric sulfide) from tattoo ink in the United States, the goal being to eliminate the immune response associated with adverse tattoo reactions. The FDA has yet to implement specific regulations on tattoo ink components, thus contributing to the variable compositions of each pigment. Unlike other chemicals, manufacturers are not required to report the composition of their tattoo inks to the general public. Despite the ever-changing composition of tattoo ink over the last 20 years, red pigment remains the leading cause of tattoo-related skin reactions. There are reports of other ink pigments that contribute to the development of cutaneous reactions. These reactions are commonly caused by aseptic inflammation and sensitivity to the ink pigments. 

Although far less common, chromium in green pigments, cadmium in yellow pigments, and cobalt in blue pigments all have been reported to cause adverse cutaneous reactions. It has been documented in recent literature that tattoo ink may be composed of compounds that have the potential to initiate a procarcinogenic process. Baumler et al. demonstrated in an in-vitro study that while 3,3-dichlorobenzene is not found in tattoo ink, it is produced as a by-product after UV- or laser-induced ink degradation within the skin. Although it is difficult to determine the relevance of this study to the development of KA, more research is clearly needed in the area of procarcinogenic properties of tattoo ink by-products. 

Tattoo ink is deliberately injected through the epidermis into the underlying dermis. The human body responds naturally to this foreign substance by using mechanisms directed at isolating or eliminating this pigment from surrounding cellular structures. Two mechanisms have been reported for this immune response: 1) the body isolates this substance by stimulating granuloma formation; or 2) the initiation of a cytotoxic or humoral immune response induces lysis of the foreign substance. The process of transepidermal elimination of the tattoo ink was reported after discovering the presence of red ink aligned along the borders of multiple tattoo-associated KAs and the development of adnexal hyperplasia. These findings, along with the tendency of KAs to spontaneously regress, point more toward a reactive condition associated with red tattoo ink pigment than toward a neoplastic etiology. Various treatment plans exist for managing KA. Due to the clinical variation in presentation, conservative medical therapy is not always the initial treatment plan. Intrallesional steroid
injections have shown good response and are a common treatment modality. Other intralesional injections that have demonstrated improvement include methotrexate, bleomycin, and 5-fluorouracil. Topical treatments are also effective for isolated lesions, including imiquimod as a single treatment or in combination with an oral retinoid like acitretin, which acts by inhibiting keratinization and growth of atypical keratinocytes. The recommended dose is 25 mg once daily for resistant KA or for patients who may not be surgical candidates. Surgical excision remains the primary treatment for a KA that fails to involute following a six- to eight-week period of medical treatment. Margins anywhere from 4 mm to 6 mm are recommended, along with close follow-up due to the potential for development into a frank squamous-cell carcinoma, as reported in various studies.

Conclusion

Although rare, tattoo-related KAs have been described in the literature. The exact etiology of these KAs is unknown. The majority of tattoo-related KAs demonstrate a relationship to red ink pigment, especially cinnabar (mercuric sulfide). Treatment modalities of tattoo-related KAs may include topical, intralesional, and oral medications. Surgical excision remains the primary treatment modality for a KA that fails to involute within six to eight weeks. In the case presented here, the patient presented with a four-week history of two clinical KAs arising from a tattoo. The diagnosis was confirmed histopathologically. After discussing the treatment options thoroughly with the patient, the KAs were excised with clear margins, and the patient was referred for tattoo removal. The patient remained without recurrence for six months but was lost to additional follow-up.

References


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A Rare Case of Acquired Epidermodyplasia Verruciformis

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Abstract

Epidermodyplasia verruciformis (EV) is a rare genodermatosis that presents in early childhood and predisposes patients to widespread human papillomavirus (HPV) infection. The condition is characterized by flat, wart-like lesions affecting the dorsal hands, extremities, face, and neck. Most cases of EV can be linked with a mutation in either EVER1 or EVER2. A minority of EV cases occurs in association with immunosuppression. If left untreated, malignant transformation to squamous-cell carcinoma frequently develops by the fourth to fifth decade of life. We describe a case of acquired EV, discuss important clinical aspects of the condition, and review a wide range of therapies available in the current literature.

Case Presentation

An 8-year-old African-American male presented with his mother to our pediatric dermatology office with a complaint of "dark spots on his head" present for about two to three years (Figures 1-3). They gradually got worse, spreading to the neck and chest. Some spots seemed to become lighter with time. The patient tried clobetasol propionate and mometasone topical solutions in the past, which did not help. History was significant for X-linked hyper-IgM deficiency (XHIGM) diagnosed in early infancy. His immunodeficiency condition was being managed by a pediatric immunologist with monthly intravenous immunoglobulin (IVIG) therapy. Physical exam revealed diffusely scattered, dark brown, slightly raised, flat-topped verrucous papules involving the entire scalp, with patchy focal involvement around the neck and upper chest. A shave biopsy was taken from the left scalp, and the findings were consistent with EV, showing mild hyperkeratosis and acanthosis along with vacuolated keratinocyte cells in the upper epidermis with a bubbly, bluish cytoplasm and thickened granular layer (Figure 4). Our patient is currently undergoing treatment with topical 5-fluorouracil. He is not compliant with follow-up.
activated T-lymphocytes. As a consequence, disease is caused by a defect or deficiency of infections. Most patients develop signs and symptoms during the first decade of life and persisting through adulthood. 

Most cases of EV are considered congenital and autosomal-recessive. They are frequently linked to a mutation in either EVER1/TMC6 or EVER2/TMC8 on chromosome 17q25. It has been hypothesized that these mutations down-regulate cell-mediated immunity within the epidermis, decreasing the ability of T-lymphocytes to clear EV-HPV-infected keratinocytes. Patients with EV have an increased susceptibility to specific HPV genotypes, including 3, 5, 8, 9, 10, 12, 14, 15, 17, 19-25, 28, 29, 36, 46, 47, 49, and 50. 

A minority of EV occurs in association with immunosuppressive states such as renal transplantation, Hodgkin’s lymphoma, systemic lupus erythematosus, and HIV infection. According to recent literature, patients who develop EV-like lesions in the background of impaired cell-mediated immunity, as with our patient, are said to have “EV-like syndrome” or “acquired EV.” These patients do not possess the EVER1 or EVER2 mutation. It is postulated that their impaired cell-mediated immunity makes them more susceptible to contracting EV-HPV types that are considered innocuous to the general population. 

Our patient had an underlying primary immunoglobulin deficiency disorder known as XHIGM, an extremely rare immunodeficiency seen in males that predisposes patients to recurrent sinopulmonary and gastrointestinal infections. Most patients develop signs and symptoms during the first decade of life. The disease is caused by a defect or deficiency of CD40 ligand, a protein found on the surface of activated T-lymphocytes. As a consequence, the T-lymphocytes in patients with XHIGM are unable to instruct B-lymphocytes to class-switch their production of immunoglobulins from IgM to IgG, IgA and IgE. Thus, these patients develop defective cellular immunity and are susceptible to opportunistic infections like Pneumocystis carinii pneumonia (PCP); autoimmune disorders like lupus, thyroiditis, and hemolytic anemia; as well as skin infections like poydermas and extensive warts. Diagnosis is based on clinical presentation, a high index of suspicion, low or absent serum IgG levels, and normal or elevated serum IgM levels.

Treatment is primarily based on severity of disease state. Most patients receive some form of chronic prophylactic antibiotic treatment (e.g., trimethoprim/sulfamethoxazole for PCP prophylaxis). More rigorous cases are treated with IVIG or hematopoietic stem-cell transplantation. The onset of lesions in congenital EV varies between the ages of 1 and 20 years (average age is 9.29 years). In acquired EV, the onset is less predictable, and the clinical presentation can mimic a disease with or and verruca plana. A skin biopsy is usually warranted under the right clinical setting, especially if the lesions do not respond to conventional topical therapy (e.g., corticosteroids or antifungals). Histologically, EV presents with mild hyperkeratosis and acanthosis, as well as vacuolated keratinocyte cells in the upper epidermis with a bubbly, bluish cytoplasm and thickened granular layer.

Malignant transformation of lesions to squamous-cell carcinoma occurs in 30% to 50% of reported cases, usually presenting by the third to fourth decade of life; it is less common in darker skin types. EV-HPV, specifically genotypes 5 and 8, play an important role in the induction of malignant transformation. There seems to be a synergistic relationship between EV-HPV induction and ultraviolet radiation (UVR), since the majority of skin cancers in EV patients develop on sun-exposed sites. The oncogenic nature of EV-HPV and how it works with UVR to induce carcinogenesis still remains unclear. HPV 5 does not function like the well-known, high-risk HPVs 16 and 18, where the viral DNA integrates into host DNA, and its E6 oncoprotein degrades the p53 tumor suppressor gene.

Treatment is governed by severity of presentation, ranging from topical immunomodulators to surgery. Early diagnosis and regular skin surveillance is essential for the prevention of skin cancer, as is strict sun avoidance and protection. Since the condition is rare, evidence-based treatment protocols are very limited, and most therapeutic considerations in the current literature come from anecdotal case reports of congenital or acquired EV. Many first-line therapeutic modalities have been attempted with varying success, including electrodessication, surgical excision, cryotherapy, topical retinoids, contact sensitization, 5-fluorouracil, and podophyllotoxin, among others. 

Second-line strategies found in the literature are numerous as well. Topical imiquimod has been used with varying success. One report mentions the successful use of imiquimod at five times weekly for 17 weeks, achieving complete clearance of EV lesions even at 17 weeks’ follow-up. Oral retinoids as monotherapy are helpful in decreasing overall lesion number, but recurrence is common after discontinuation of medication; however, low-dose maintenance retinoids may prevent recurrence. One patient with EV did well after six months of isotretinoin dosed at 0.8 mg/kg/day and was maintained with low-dose isotretinoin dosed at 0.3 mg/kg/day. Four patients achieved near-clearance of EV with etretinat dosed at 1 mg/kg/day for four months, but the lesions returned after cessation of treatment. Another EV patient was successfully treated with acitretin dosed at 0.5-1 mg/kg/day for six months; however, the lesions returned after discontinuation. Two additional cases of EV achieved near clearance of lesions with etretinate dosed at 1 to 1.5 mg/kg/day; those lesions also returned after withdrawal of therapy.

Combination therapy with interferon alfa and imiquimod or systemic retinoids has been used with some success. In one case, a patient was treated with intralesional interferon alfa-2a, 3 million units, three times weekly, in combination with acitretin dosed at 50 mg/day for six months. The patient had near complete resolution of lesions. The lesions recurred three months after cessation of treatment but were resolved again after another three-month course of acitretin. In another case of EV, a patient was given subcutaneous peg-interferon alfa, 1 μg/kg/week, in combination with acitretin dosed at 0.2 mg/kg/day; this patient relapsed clinically shortly after peg-interferon was discontinued. Most of the lesions achieved resolution after increasing the acitretin dose to 0.5 mg/kg/day for another six months. In HIV-positive patients, the use of HAART therapy for treatment of EV lesions has been successful in some cases, perhaps owing to enhanced cellular immunity.

Oral cimetidine, a histamine-2 antagonist with known ability to suppress mitogen-induced lymphocyte proliferation and T-suppressor-cell activity, has been attempted in the treatment of EV lesions but was found to be unsuccessful in eight patients.

**Conclusion**

EV is a skin disorder with elusive malignant transformation potential. More research is needed to elucidate the exact mechanism involved in the malignant transformation of keratinocytes in the skin lesions of EV. Exposing the underlying mechanism can lead to new targets for therapeutic strategies. Most of the treatment modalities attempted in the current literature lack evidence-based review given the rarity of the disease, especially regarding acquired EV. In fact, many case reports do not take into account potential differences in the efficacy of therapeutic modalities when treating congenital vs. acquired EV. A systematic review may provide additional information into the treatment of each type of EV. In addition, novel treatment modalities such as topical cidofovir or intralesional candida antigen treatment have shown promise.
have yet to be studied, though they continue to show promising results in the treatment of common warts.

References

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An Atypical Presentation of Lichen Sclerosus et Atrophicus: Guttate Lesions Presenting in Bilateral Axillae and Inguinal Regions

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Abstract

Lichen sclerosus is a chronic lymphocyte-mediated skin disorder that belongs to a group of autoimmune connective-tissue diseases, localized to the cutaneous and mucosal surfaces. It shows a predilection for the anogenital area. There is significant focal atrophy of the mucosa seen with lesions, and the associated symptoms usually include itching, pain, and burning. The etiology is not fully understood, but genetic, infectious, hormonal and autoimmune factors are all commonly suggested. It was first identified in 1887 by Hallopeau and named “lichen plan atrophique,” describing an atrophic form of lichen planus.1 In 1892, Darier described the histologic features of the disease, calling it “lichen planus scléreux.” Early diagnosis and appropriate treatment is important to avoid further complications.

Introduction

Lichen sclerosus (LS) is a chronic inflammatory disorder of the skin and mucosal surfaces that most commonly involves the anogenital region, though it also rarely affects sites like the feet, hands, and axillae. The etiology of LS remains unknown; however, multiple causative agents have been reported in the literature, including autoimmune mechanisms, viruses such as the human papilloma virus and spirochetes, the Koebner phenomenon, and genetic factors. We present the case of a 55-year-old female with an atypical appearance of LS in the axillary region.

Case Report

A 55-year-old Caucasian female presented with multiple guttate, hypopigmented, atrophic lesions on the bilateral axillary and inguinal regions (Figures 1, 2). The patient first presented with lesions in 2006, described as initiating with one lesion that increased in number over a period of several months (Figure 3). A biopsy done in 2006 was consistent with lichen sclerosus. The patient was lost to follow-up for eight years and then returned to the clinic for an irritated seborrheic keratosis. During this visit, the axillary lesions were reexamined. Per history, the number of lesions had remained consistent over the past several years. The patient had not used any topical treatment during this time period.

Pertinent medical history included type 2 diabetes mellitus, hypertension, hyperlipidemia, hypothyroidism, gastroesophageal reflux disease, degenerative joint disease, and obesity, with a body mass index of 44.1.

Discussion

Lichen sclerosus was originally described by Hallopeau in 1887.1 LS is a chronic atrophic disease of the skin presenting with macules or white patches with erythematous halos early on. The lesions then progress to become atrophic,
sclerotic plaques, appearing shiny and porcelain. In some cases, bullae develop, which are often hemorrhagic. Severe hyperpigmentation can also develop at the outskirts of the lesions, and the individual papules shrink, leaving the skin wrinkled and white. An estimated prevalence of at least 1 in 900 has been reported in the literature.

LS particularly occurs in the genitalia and around the anus (85% to 98% of cases); however, extramucosal locations have been reported, including the front of the wrists, neck, upper back, shoulders, breasts and around the umbilicus symmetrically (15% to 20% of patients), which present as ivory white atrophic papules coalescing into plaques. There has been a case reported of linear LS of the face following Blaschko’s lines; however, this is very rare. To date there have only been a handful of reported cases with this presentation of LS in this distribution, involving bilateral axillae. Smith et al. report a 66-year-old Hispanic male with LS of reported cases with this presentation of LS in association with human papilloma virus (HPV), with a mid-dermal band-like infiltrate. In addition, the underlying normal-appearing collagen by collagen in the upper one-third, separated from the underlying normal-appearing collagen by a thin epidermis and effaced rete ridges, and the palms, pinna or nipples, thus escaping bactericidal antibiotic activity.

Hormonal factors also have been shown to play a role in the pathogenesis of LS. In a 1945 study by Cinberg et al., the use of topical testosterone to treat vulvar lichen sclerosis in 14 post-menopausal women showed positive results, leading to many other researchers investigating the efficacy of oral hormonal therapy. The use of testosterone propionate in petrolatum by researchers to treat a total of 142 biopsy-proved cases of vulvar lichen sclerosis reported improvement in 135 patients. This prompted Friedrich et al. in 1984 to conduct a study that determined whether or not serum androgen and estrogen levels are altered in patients with untreated lichen sclerosus. They found significant differences in serum dihydrotestosterone (DHT) and androstenedione levels, and not estrogen levels, where the DHT and androstenedione levels were significantly lower and levels of free testosterone were significantly higher in patient suffering from LS. Most of these patients showed clinical improvement of their disease after testosterone therapy, and serum levels were restored. This study suggests that due to an increase in serum testosterone and a decrease in serum DHT, a possible onset of this disease may be based on a decreased activity of the enzyme 5-alpha reductase. There is, however, no mention of whether this may be due to an increased metabolism of DHT instead.

Autoimmune phenomena with antibodies to a protein called extracellular matrix protein-1 (ECM-1) have also been implicated in the etiology of LS. ECM-1 controls keratinocyte differentiation in the epidermis and structural organization in the dermis, binding to several proteins such as perlecan, matrix metalloproteinase-9, and fibrin. In a study by Oyama et al., circulating IgG antibodies were detected against the ECM-1 protein in 74% of women with anogenital LS as compared to 7% in controls. ECM-1 autoreactivity, however, was seen more often in individuals diagnosed with LS for more than a year or with more severe disease, which suggests the role of autoreactivity to ECM-1 to be more involved in the progression of the disease than in the initial development. In addition, lipoid proteinosis, a rare autosomal-recessive genodermatosis presenting with deposition of hyaline material in the skin, mucosa, and viscera, has recently been linked to mutations in the gene encoding the ECM-1 protein.

It has been shown that LS is more prevalent in female patients with previous autoimmune diseases than in males. A large study by Mayrick et al. revealed that 21.5% of 350 women had one or more autoimmune-related diseases, with the most common diseases being autoimmune thyroiditis (12%), alopecia areata (9%), vitiligo (6%), and pernicious anemia (2%). Hoffer et al. suggest an association of LS in men with increased body mass index, coronary artery disease, diabetes mellitus and smoking.

The most pertinent differential diagnosis of LS includes lichen planus, atrophic type; vitiligo, a depigmenting cutaneous disease; morphea; Bowen’s disease; squamous-cell carcinoma (SCC) in situ; extra-mammary Paget’s disease; and malignant atrophic papulosis, which initially appears as pink papules that later become umbilicated and porcelain-white, covered with scale and an erythematous border. Acrodermatitis chronica atrophicans (ACA) should also be included in the differential. ACA is the last stage of European Lyme borreliosis and presents with cutaneous atrophy that resembles tissue paper. Finally, idiopathic atrophoderma of Pasini and Pierini (IAPP) can also present like LS, and a biopsy should be performed to rule out LS, as both lesions present clinically with dermal atrophy; however, IAPP presents with sharply demarcated hyperpigmented patches.

**Treatment**

Treatment is often ineffective, though potent topical steroids have proved helpful and are considered first-line treatments. There is a risk, however, for young patients with LS to develop vulvodynia in adulthood, as the steroid may not completely reverse the lichen sclerosus. Also, 2% to 3% testosterone propionate in a water-miscible base twice a day has been reported as useful. Treatments like photodynamic therapy with 5-aminolaevulin acid, PUVA, long-wave UVA, topical testosterone and estrogen, topical tacrolimus or pimecrolimus, and topical retinoids have also been tried. Although the 1984 Friedrich study showed improvement with topical application of testosterone in patients with LS, a 2006 study by Strittmatter et al. showed that...
topical estrogen and progesterone treatments as well as cyclosporine were not very effective treatment options.\textsuperscript{11,22}

In childhood, topical calcineurin inhibitors have been shown to provide a safe and effective therapeutic approach to LS.\textsuperscript{22,23} The calcineurin inhibitor tacrolimus 0.1% cream twice a day over a period of 16 weeks has helped many patients, especially those with genital lichen sclerosus. Although their effectiveness is not as immediate as potent topical corticosteroids, they have the benefit of not causing dermal atrophy, tachyphylaxis, striae, rebound flares, or hypothalamic-pituitary axis suppression.\textsuperscript{22,23} Tacrolimus cream improves not only the itching and pain in these patients, but 70% of patients suffering from genital LS in a 2002 prospective study experienced complete clinical remission.\textsuperscript{21}

In addition, as mentioned above, the use of antibiotics in those patients with biopsy-proven presence of spirochetes in the LS lesions may help to suppress the disease; however, relapses do occur, as the spirochetes tend to lie dormant in the tissues.\textsuperscript{24}

Surgical excision or laser ablation of vulvar lichen sclerosus have both been suggested but are not recommended, as both would involve mutilating the female genital region for a relatively benign disorder. Circumcision, however, may be helpful in treating genital lichen sclerosus in males.\textsuperscript{25}

**Conclusion**

We present an atypical presentation of inverse guttate LS in an obese Caucasian female. Lichen sclerosus can be a psychologically devastating disease that can cause depression and isolation with its often relapsing nature even after appropriate treatment. There are several ongoing research studies being conducted with the NIH, in addition to a stem-cell lift procedure that may bring a new perspective to the treatment of lichen sclerosus and atrophicus in the near future. There are also various support groups for patients suffering from lichen sclerosus, such as “Worldwide Lichen Sclerosus Support” and “Living with Lichen Sclerosus,” that help patients deal with this distressing disease. Physicians should encourage all patients to seek support if they develop feelings of depression.

**References**


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Pseudochromhidrosis: A Case of Blue-Green Facial and Hand Discoloration

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Abstract
Pseudochromhidrosis is a disorder of unknown incidence characterized by colored sweat due to an exogenous agent such as colored dyes or chromogenic bacteria. Patients often present with focal skin discoloration that may be correlated temporally with exposure to the exogenous agent. We present a case of pseudochromhidrosis of the face and hands caused by unwashed bed linens and poor hygiene.

Introduction
Pseudochromhidrosis is a rare disorder that occurs after colorless sweat mixes with an exogenous pigment to cause colored sweat. It is distinguished from chromhidrosis in that sweat discoloration of pseudochromhidrosis is due to an exogenous source such as dyes, chemicals or bacteria, and occurs after secretion rather than primarily within the apocrine or eccrine gland. Patients often complain of skin discoloration at the site of exposure to the coloring agent.

Case Report
A 49-year-old Caucasian male presented with a one-week history of asymptomatic, gray-green discoloration of his hands and face (Figures 1, 2). The pigment could be washed off, but it would return the next day. He denied ever having the discoloration before, and nobody else in the household was affected. He denied exposure to any new green-colored materials, although his wife stated they recently purchased blue bed linens that had not been washed yet. Past dermatologic history was unremarkable. Past medical history was notable for hypertension, gastroesophageal reflux disease, anxiety and depression, for which he took metoprolol, omeprazole, bupropion and sertraline, respectively. A 12-point review of systems was unremarkable.
Discussion

Pseudochromhidrosis is a condition characterized by colored sweat and subsequent skin discoloration. It is distinct from chromhidrosis in that the patient’s sweat is secreted as normal, or colorless, until it comes into contact with pigment from dye, chemicals or chromogenic bacteria. Chromhidrosis is also a colored sweat disorder, but it is caused by endogenous lipofuscin pigment accumulation in the apocrine or eccrine glands themselves, which leads to colored sweat upon secretion. Any material that contains dye, such as clothing, linens, and upholstery — particularly those that are new and have not been washed — are capable of causing pseudochromhidrosis. Exogenous chemicals are also possible sources, as reported by industrial workers who had blue sweat from copper-salt exposure. The bacteria implicated are those that produce pigment such as corynebacterium, pseudomonas, bacillus, and Serratia species. Localized skin warmth and a prickling sensation have been reported as possible symptoms of chromhidrosis, but there are currently no reported symptoms associated with pseudochromhidrosis. The most well-known report of non-microbial pseudochromhidrosis is the 1980 “epidemic” of flight attendants who reported red spots on their skin. The bacteria implicated are those that produce pigment such as corynebacterium, pseudomonas, bacillus, and Serratia species. Localized skin warmth and a prickling sensation have been reported as possible symptoms of chromhidrosis, but there are currently no reported symptoms associated with pseudochromhidrosis. The most well-known report of non-microbial pseudochromhidrosis is the 1980 “epidemic” of flight attendants who reported red spots on their skin. The bacteria implicated are those that produce pigment such as corynebacterium, pseudomonas, bacillus, and Serratia species.

Conclusion

We were convinced that the main source for our patient’s discoloration was the new bed linens that had not been washed, but we also suspected that bacterial overgrowth may have contributed due to the patient’s poor personal hygiene. The presence of chromogenic bacteria would explain why he manifested clinical signs of pseudochromhidrosis while his wife did not. The most commonly reported bacteria in microbial pseudochromhidrosis are the corynebacterium species, so we chose to empirically treat with azithromycin. Topical clindamycin lotion was also added at a later follow-up. Currently, there are no studies examining the relationship between pseudochromhidrosis, hygiene and microbial overgrowth. This is an area in need of further research, as we suspect there may be a causative relationship.

References


Correspondence: Sarah Belden, BA; sebelden@gmail.com
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CONTRAINDICATIONS
Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS
- Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifested as Cushing’s syndrome, hyperglycemia, and glucosuria in some patients.
- Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.
- Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. 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.
- 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.
- This medication is to be used as directed by the physician. It is for dermatologic use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
- Patients should report any signs of local adverse reactions especially under occlusive dressing.
- Pregnancy Category C: 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.
- Systemically administered corticosteroids are excreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

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

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