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# Table of Contents

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>AOCD Editors</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Letter from the Co-Editor-in-Chief</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Letter from the Executive Director</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Letter from the President</td>
<td></td>
</tr>
</tbody>
</table>

## FEATURE ARTICLE:

Intraoperative Hemostasis in Dermatologic Surgery: A Review and Discussion of Varied Approaches

Leela Athalye, DO, Jacqueline Habasby, DO, Donna Tran, DO, David Horowitz, DO

## EDITOR’S PICKS:

Abdominal Pain: A Unique Presentation of Neurofibromatosis and Updated Review of the Condition

Brandon Nickle, DO, Blaze Emerson, MS, Kimberly Hull, DO, Brittany Smirnov, DO, Jaqueline Thomas, DO, FAOCD

Subungual Melanoma in a Haitian Male: A Case Presentation and Discussion

Stephanie Blackburn, DO, Jason Barr, DO, Richard Averitte Jr., MD, Michelle Goedken, DO, Sarah Estrada, MD

Cutaneous Sarcoidosis Identification in a Patient with Asymptomatic Third-Degree AV Block

Fatima Fahs, MD, Roxana L. Chapman, DO, FACP, FAAD, FAOCD

Successful Use of Liposomal Amphotericin B for Cutaneous Leishmaniasis in a Young Male Patient Treated with a TNF-alpha Inhibitor

John R. Moesch, BA, Caryn Bern, MD, MPH, Vincent A. Laufer, BA, Robin H. Dretler, MD, FIDSA

Childhood Dermatofibrosarcoma Protuberans, Giant Cell Fibroblastoma Variant: A Case Report and Discussion

Shannon McKee, MD, Mark A. Kuriata, DO

Diffuse Epidermolytic Epidermal Nevus and Genetic Counseling: A Case Report and Brief Review of the Topic

Christa M. Toms, DO, Peter Malouf, DO, Stephen Wei, DO

A Report of Kyrle’s Disease (Hyperkeratosis Penetrans) in a 43-Year-Old Male with End-Stage Renal Disease

Ryan Skinner, DO, Nina Sabzevari, BS, Daniel Hard, DO

Multinucleate Cell Angiohistiocytoma: A Case Presentation and Discussion

Angela Macri, DO, Jaclyn Hess, MD, Jonathan S. Crane, DO, FAOCD, FAAD

A Rare Case of Pili Annulati

Yuri Kim, DO, John Howard, DO, Gabriela Maloney, DO, Stanley Skopit, DO, MSE, FAOCD, FAAD

A Case of Progressive Macular Hypopigmentation

Mehreen Sheikh, BS, Jocelyn LaRocque, DO, FAOCD

Metastatic Melanoma Arising 10 Years after Treatment of Primary Lesion:

A Unique Case Representative of SOX-10’s Efficacy in Identifying Melanomas of Metastatic Origin

Natalie Steinboff, DO, Gabriela Maloney, DO, Richard Miller, DO, FAOCD

A Case of Twenty Nail Dystrophy and Review of Treatment Options

Emily Tongdee, BS, Shabtahan Shareef, BS, Tracy Favreau, DO, Khasha Touloei, DO

Wolf’s Isotopic Response: A Case Report

Gabriel Guerrero, DO, Nathan Jackson, DO, Schield Wikas, DO

A Rare Case of Well’s Syndrome

Donna Tran, DO, Nicole Rouse, BS, Paul Shitabata, MD, Leela Athalye, DO, Navid Nami, DO

A Rare Presentation of Atypical Fibroxanthoma: A Case Report and Discussion

Gabriel Guerrero, DO, Leela Athalye, DO, Luisa d’Almeida, MD, Paul Shitabata, MD, Navid Nami, DO
Dear Colleagues,

This is a very exciting time for the JAOCD. First, we are welcoming a second Editor-in-Chief to our Editorial Board. Derrick Adams, DO, will be upping his contribution to the journal, joining me at the helm of our growing publication, and we couldn’t be happier.

We are adopting a new format, as well. After this final print volume, the journal is transitioning to an online-only format, which will bring some new functionality and ease to each issue.

Academic sponsorship has been increasingly difficult to secure over the last few years, and many of our sponsors have reduced their scholarship divisions. Currently, it costs around $45K per year to manage and print the journal, exclusive of all the great volunteer work that the editorial board and AOCD donate. I was very fortunate to inherit a great foundation from Dr. Jay Gottlieb and the many others who helped build this journal, under whose financial stewardship established solvency during the first 10 years of the endeavor; that alone been the reason we have been able to continue producing the journal in its current form. Looking into the future, it made greatest sense to lower production costs in order to breathe another decade of existence into the journal during these tough financial times.

In tandem, the AOCD has embraced the digital age with a new website, whose capabilities will enhance the journal’s utility and accessibility. For example, with the online version, we will be able to catalogue the journal and make it easily searchable, a feature our authors have been requesting. In addition, we will appeal to the marketing and advertising divisions of our sponsors, which are typically more receptive to ad buys than to sponsorship. We will be able to showcase their support in the journal section of the AOCD website, much like what is being done by other major journals in our specialty.

In addition, Marsha Wise is working tirelessly to offer better CME opportunities through the journal. Currently, we are approved for 2A CME credit. However, with the implementation of quizzes (using our current website), we are applying to the AOA for approval of Category 1B credit! The AOBD requires 50 Cat 1 credits, 25 from live CME (1A), and the other 25 can be earned via 1B credits. This will be truly amazing for our members.

Finally, let us not forget the purpose of the journal. It serves as a platform for our osteopathic students, residents, and fellows to showcase their hard work and improve visibility for osteopathic dermatology. With the plans I outlined above, we are working to ensure the survivability of our journal as we navigate the foggy future of our specialty, and we are growing more opportunities for our readers and members.

Thank you,
Karthik Krishnamurthy, DO, FAOCD
Co-Editor-in-Chief, JAOCD
Hello, Everyone,

We’ve had a busy summer here in the AOCD office. We’ve been working diligently on our application for ACCME (Accreditation Council for Continuing Medical Education), which will allow us to award AMA CME in addition to AOA CME. To receive our two-year Provisional Accreditation, the AOCD must comply with ACCME criteria 1, 2, 3, and 7 through 12. To view these criteria, visit the ACCME site at http://www.accme.org/requirements/accreditation-requirements-cme-providers/accreditation-criteria.


To date, three of our residency programs have received Initial Accreditation from the ACGME: Beaumont Hospital in Farmington Hills, MI; Lehigh Valley Health Network in Allentown, PA; and St. Joseph Mercy Livingston in Howell, MI. Other programs have submitted applications and are awaiting ACGME site reviews.

Save the dates! (Look for more information in the upcoming edition of Dermline.)

- **2017 Spring Meeting: March 29 - April 2**
  Ritz Carlton Atlanta (at 181 Peachtree St. NE)
  Atlanta, GA

- **2017 Fall Meeting: October 24-28**
  Intercontinental New Orleans
  New Orleans, LA

- **2018 Spring Meeting: March 19-25**
  Hilton West Palm Beach
  West Palm Beach, FL

The new CME cycle began on January 1, 2016. The CME Guide for Physicians can be found at http://www.osteopathic.org/inside-aoa/development/continuing-medical-education/Pages/cme-guide.aspx. Please monitor your CME report. The AOA no longer provides this information to the AOCD office due to the group's privacy policy.

As always, should you have questions or concerns, please do not hesitate to call the AOCD office. If we cannot answer your question, we will direct you to the person(s) who can.

Sincerely,

Marsha Wise
Executive Director, American Osteopathic College of Dermatology
As President of the AOCD, I welcome you to the 36th edition of the Journal of the American Osteopathic College of Dermatology. A special thanks to Karthik Krishnamurthy, DO, our longstanding Editor-in-Chief, as well as his new partner in the job, Derrick Adams, DO. Without their dedication, this publication would not be possible.

Dr. Lin, our Immediate Past President, continues to support me in my role as President, ensuring I stay the course. I am grateful to each of you for your support throughout this year. Time flies at an unbelievable pace, and as I near the end of my term, I encourage you to continue your involvement in our college under the leadership of Karthik Krishnamurthy, DO, FAOCD, our President Elect.

Our meeting in beautiful Santa Monica, CA, was a powerful experience. The host of presenters and the myriad topics covered provided attendees with many new arrows for their quivers. Between Wednesday and Sunday, members received updates, new information, fellowship, and data. I hope those of you who missed our AOCD Fall Meeting will join us for the Spring 2017 meeting in Atlanta. I can assure you that you will find great value in attending it.

I am proud of who we are and where we are headed. My appreciation of our great organization is profound. The AOCD has nurtured me throughout my career and will continue to support members for generations to come. Please join me in working to preserve the AOCD. As osteopaths, our gift is our approach to understanding and healing the whole person. Let us not forget our purpose and those we serve!

The AOCD will remain a strong provider of service and support to dermatologists who chose osteopathy in preparation for their careers, providing high-quality professional development and support to our membership. Our publications will continue to share information and keep our members up to date on current topics. Our future will remain strong as long as we join together to keep the vision alive. Keep the main thing the main thing.

Please join us in Atlanta!

Alpesh Desai, DO, FAOCD
President, American Osteopathic College of Dermatology
Aurora Diagnostics’ dermatopathology laboratories are focused on providing unsurpassed dermatopathology services to our referring physicians. Our network of expertise consists of over forty board-certified dermatopathologists that are based locally throughout the country providing advanced technology and unparalleled customer support.

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Intraoperative Hemostasis in Dermatologic Surgery: A Review and Discussion of Varied Approaches

Leela Athalye, DO,* Jacqueline Habashy, DO,** Donna Tran, DO,*** David Horowitz, DO****

*3rd-year resident, Dermatology Residency Program, Western University and College Medical Center, Long Beach, CA
**Medical student, 3rd year, Western University of Health Sciences, Pomona, CA
***2nd-year resident, Dermatology Residency Program, Western University and College Medical Center, Long Beach, CA
****Program director, Dermatology Residency Program, Western University and College Medical Center, Long Beach, CA

Disclosures: None
Correspondence: Jacqueline Habashy, DO; jackiehabashy@gmail.com

Abstract
One of the most frustrating challenges in surgical dermatology is achieving effective hemostasis. Basic techniques such as taking a proper medical history and providing pre-operative patient education, as well as proper techniques during surgery have been the mainstays of achieving hemostasis. We intend to review these historical methods of hemostasis and discuss the various approaches intended to minimize surgical bleeding in order to achieve the best results.

Introduction
Dermatology is a diverse field that requires a physician to be competent clinically, histopathologically and surgically. Cutaneous surgery has allowed dermatologists to cure skin cancers such as basal cell carcinoma, squamous cell carcinoma and melanoma. One of the greatest challenges in surgery is the control of hemostasis, finding the balance between preventing extensive blood loss and maintaining sufficient blood flow to the surrounding tissue.1 The goal during most dermatological surgeries is to not only keep the surgical field clear but also prevent potential postoperative complications like infection, hematoma, tissue necrosis, delayed wound healing and delhiscence.2 Various techniques can be used to achieve hemostasis pre-operatively, intra-operatively and post-operatively in order to avoid complications and yield the best surgical results. We intend to provide a comprehensive review of hemostasis methods.

Medical History and Patient Education
One of the most important aspects in any surgical preparation is obtaining a complete patient history. An individual's medical history and social habits might render the task of achieving hemostasis difficult. A history of bleeding disorders, immune suppression, renal or liver failure, diabetes, hypertension, inflammatory skin disease, radiation therapy, and tobacco or alcohol use strongly influence hemostasis and the patient’s overall surgical outcome.

Tobacco use has proven to have damaging effects on dermatological surgeries by affecting cutaneous blood flow. The nicotine in cigarettes decreases blood flow perfusion, and the carbon monoxide decreases oxygenation of the skin. As noted by Delaney et al., a study by Goldminz showed that those who smoke one pack of cigarettes or more per day have a three-fold higher risk of developing necrotic complications compared to those who never smoke. It is recommended that patients stop smoking for a minimum of two days before surgery and at least a week after surgery.3 In addition, alcohol use significantly affects hemostasis. Acutely, alcohol directly impacts platelets, leading to prolonged bleeding time, and predisposes to hematoma formations, further compromising blood supply to the surgical site.4 Chronic alcoholism often results in hepatic insufficiency and associated coagulation dysfunction. A general surgery review noted that patients who consume three to four alcoholic beverages per day have a 50% higher complication risk compared to those who consume two or fewer drinks per day. Patients who have five or more drinks per day increase their risk by an average of 300%.2

Patients with a history of jaundice or hepatitis unrelated to alcohol may also have coagulopathies, which can be screened for by routine PT, PTT, and INR blood testing. In addition, patients with easy or unexplained bruising, bleeding gums, or unexplained hemorrhage stand a high chance for intraoperative bleeding and should be worked up accordingly. Beneficial questions to ask patients include whether they have unexplained nose bleeds, prolonged bleeding after injury or, if female, prolonged menstrual cycles or multiple heavy-bleeding days, as well as whether there is any history of blood transfusions after a surgical procedure.

A medication history is also imperative to the success of the procedure and must first emphasize the medications that directly increase intraoperative bleeding. These include warfarin, aspirin, NSAIDs, clopidogrel, heparin, and dabigatran. Current thought favors the continuation of warfarin during surgery because the risk of a thrombotic event from cessation far outweighs the potential intraoperative bleeding complications.5 All superfluous aspirin and NSAIDs should be stopped one to two weeks prior to surgery and resumed one day after surgery. A meta-analysis revealed that patients taking aspirin or NSAIDs were far more likely to develop blood loss and should be evaluated pre-operatively and not continued intraoperatively.

One of the main goals of surgery is to ensure proper wound healing and dehiscence. It is imperative that the surgical field clear but also prevent potential intraoperative and postoperative complications. A medication history is also imperative to the success of the procedure and must first emphasize the medications that directly increase intraoperative bleeding. These include warfarin, aspirin, NSAIDs, clopidogrel, heparin, and dabigatran. Current thought favors the continuation of warfarin during surgery because the risk of a thrombotic event from cessation far outweighs the potential intraoperative bleeding complications.5 All superfluous aspirin and NSAIDs should be stopped one to two weeks prior to surgery and resumed one day after surgery. A meta-analysis revealed that patients taking aspirin or NSAIDs were far more likely to develop blood loss and should be evaluated pre-operatively and not continued intraoperatively.

Table 1: Dietary supplement influencing anticoagulant activity5

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo</td>
<td>Platelet aggregation inhibitor</td>
<td>Clinical significance documented at ~120 mg to 240 mg.6</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Fibrin formation and platelet aggregation inhibitor</td>
<td>Interacts with warfarin at a dose of ~2 g.7</td>
</tr>
<tr>
<td>Ginger</td>
<td>Platelet aggregation inhibitor</td>
<td>Dose dependent between 250 mg and 1 g.8</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Platelet aggregation inhibitor</td>
<td>At high doses (~671 mg or higher), can add to warfarin effects.5</td>
</tr>
<tr>
<td>Willow Bark</td>
<td>Platelet aggregation inhibitor</td>
<td>Clinical significance not yet documented but may occur anywhere between 120 mg and 240 mg.10</td>
</tr>
<tr>
<td>Licorice</td>
<td>Platelet aggregation inhibitor</td>
<td>Presence of 3-arylcoumarin derivatives has significance at high doses (~30 mg/ml).11</td>
</tr>
<tr>
<td>Celery</td>
<td>Platelet aggregation inhibitor</td>
<td>Clinical significance at ~500 mg.12</td>
</tr>
</tbody>
</table>

Table 2: Dietary supplements influencing pro-coagulant activity

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Mechanism of Coagulation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfalfa</td>
<td>High vitamin K content</td>
<td>High vitamin K antagonizes coumarins in alfalfa at anywhere from 500 mg to 1,000 mg.13</td>
</tr>
<tr>
<td>Green tea</td>
<td>High vitamin K content</td>
<td>Presence of theanine inhibits platelet effects of warfarin at anywhere from 400 mg to 716 mg.14</td>
</tr>
</tbody>
</table>
more than twice as likely to have moderate-to-severe bleeding complications in comparison to controls. Screening patients regarding their use of vitamins, herbs, or over-the-counter supplements can also attenuate the risk of intraoperative bleeding. Dietary supplements known to have anticoagulant activity include gingko, ginseng, Vitamin E, willow bark, licorice, and celery (Table 1, p. 10). Alfalfa and green tea, on the other hand, have procoagulant activity (Table 2).

Preparing the Surgical Field
After a patient’s surgical risk for bleeding is addressed, a surgical field must be optimized to best procure hemostasis. The objectives are accessibility and visualization of the surgical field. In additions, a cool ambient temperature will ameliorate intraoperative bleeding by promoting cutaneous vasconstriction. To decreasing surgical risk factors, the operating room should be open and uncluttered, allowing for easy attainment of hemostatic supplies such as gauze, Q-tips, and chemical and electrical cautery. Additionally, positioning the patient at a 15-degree incline will allow gravity to reduce superior blood pooling.

Once the area is best visualized, the surgical site may be infiltrated with lidocaine and epinephrine to locally constrict blood vessels, which takes three to five minutes. This will be the first sign of how the patient responds to puncture and whether their history is accurate. In the case of any prolonged bleeding or bruising after the injection, extra caution should be taken to reach hemostasis. Ice compression is another valuable tool to utilize prior to anesthetizing. It serves the dual purpose of locally constricting blood vessels in a surgical site and blunting any patient discomfort during the injection.

Hemostasis Agents
Topical Hemostasis
Topical hemostasis agents are usually used in conjunction with additional hemostasis methods, which typically leads to more efficient and cosmetically sound results. Two of the more common topical agents include gel foam and a topical powder composed of hydrophilic polymer and potassium ferrate. Gel foam is a topical agent packaged as a sterile compressed sponge. It is derived from porcine-skin gelatin and works by creating a matrix that facilitates artificial clotting. A prospective study showed that deep-excision procedures had improved hemostasis and cosmesis with gel foam and secondary intention healing.

Another useful topical agent is a hydrophilic polymer mixed with potassium ferrate powder. The hydrophilic component absorbs blood, while the potassium salts form an artificial scab, both leading to successful and efficient hemostasis better tolerated than gel foam due to its non-biological properties. Additionally, an individual’s coagulation ability does not affect the ability to reach hemostasis with this product, making it ideal for patients who have prolonged bleeding disorders or take blood-thinning medications.

A study by Kircik et al. compared topical powders to sponges (gel foam) to see which topical agent is more effective in reaching hemostasis. Overall, both agents were effective, but they concluded that the topical powder caused significant hemostasis at a faster rate than the sponge, with the added benefits of less scarring and a reduction in wound size.

Chemical Hemostasis
There are three common chemical hemostatic agents to consider: aluminum chloride, Monsel’s solution, and silver nitrate sticks (Table 3). Chemical agents cause protein precipitation that helps achieve superficial bleeding cessation. These methods work best in a dry field, where the blood itself does not dilute their contents.

Physical Hemostasis
Physical interventions are paramount in controlling hemorrhage. The simplest physical modality involves placing firm pressure over a bleeding wound for 15 uninterrupted minutes. During this time, a physician and assistant should avoid the temptation to interrupt manual compression to check if bleeding has stopped and instead allow the appropriate time to pass. Manual compression is often sufficient in promoting the formation of a clot. Compression is typically applied downward and directly on the suspected source of the bleed; however, upward pressure may assist in tamponading vessels located near hollow openings where bleeding may be brisk, such as the nasal vestibule. In addition to manual compression, pressure hemostasis may also be obtained by using Q-tips, dental rolls or inflated Foley catheters.

One physical method for hemostasis includes using ring loops. Ring loops in surgical scissors and forceps can mechanically compress blood vessels to visualize a surgical site. This method is often used in areas such as the trunk, scalp, tongue or lips. Clalization ring forceps are placed around the lesion and screwed into position, immobilizing the lesion to stabilize and apply circumferential pressure to cause hemostasis. Additionally, using two skin hooks concomitantly can decrease blood pooling to promote a clear visual field. In this method, two skin hooks are placed on the edge of the skin and rotated toward the wound to both exert tension on the surrounding skin flaps and apply pressure to bleeding vessels. Once this is done, the surgical assistant can use electrodesiccation to control any additional hemorrhage. Aside from the surgical benefits, this method also improves coordination between surgeon and assistant.

Suturing Techniques
Overall, any suturing technique can obtain hemostasis, but certain approaches achieve the best results. A vertical mattress is a simple method of everting, closing any dead space of a defect, and also minimizing hemorrhage. Another valuable suturing technique involves the purse-string suture. The purse string not only enhances hemostasis but also reduces the size of the defect. This technique is done by placing multiple intradermal sutures in a sequence until a “purse-string” is created. This method is geared toward patients on anticoagulation or for patients who lead more sedentary lifestyles, where excessive physical activity will not potentially open the purse string.

In certain locations of the body, specific suture techniques can also reduce bleeding during a procedure. For punch biopsies of the scalp, which are notorious for bleeding, a horizontal suture

### Table 3. Chemical hemostasis

<table>
<thead>
<tr>
<th>Chemical Agent</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Benefits</th>
<th>Disadvantages</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum Chloride</td>
<td>Vasodilation, Activation of extrinsic coagulation pathway</td>
<td>May cause irritation</td>
<td>Clear color avoids staining, Avoids tissue necrosis, Safe for surrounding normal tissue</td>
<td>Delays healing, Adds scarring in deeper wounds</td>
<td>Preferred agent for hemostasis secondary to efficacy, speed of hemostasis, and cost.</td>
</tr>
<tr>
<td>Monsel’s Solution (ferric subsulfate)</td>
<td>Acidic and oxidizing qualities</td>
<td>Increase in inflammation, Dermal fibrosis</td>
<td>Bacteriotoxic</td>
<td>Temporarily stains the skin via iron deposition</td>
<td>Safe to use on mucosa, Ideal for small wounds</td>
</tr>
<tr>
<td>Silver Nitrate Sticks</td>
<td>Free silver ions form eschar by binding to tissue</td>
<td>Stinging sensation</td>
<td>Preformed sticks, Bacteriostatic properties</td>
<td>Temporarily stains the skin, Slower onset of action</td>
<td>Intended for small wounds (if used in large areas, can lead to argyria)</td>
</tr>
</tbody>
</table>
can be placed prior to punching the lesion. A 3-0 or 4-0 non-absorbable suture should be placed wide enough that it does not interfere with the punch biopsy. As the dermatologist removes the lesion using a punch, the surgical assistant can quickly pull in the sutures and tie them so as to preemptively stop any bleeding. This process creates immediate and complete hemostasis. For excisions of vascular lesions (for example, port wine stains), a double imbricating suture is indicated. A 3-0 polypropylene suture with a PS-2 needle is recommended for this method.16

Lasers/Radiofrequency
Lasers are a newer physical modality for achieving hemostasis. Rather than scalpels and other surgical blades, lasers can be used to incise a lesion. The CO2 laser with a wavelength of 10,600 nanometers (nm) can be used for tissue incision, because it not only cuts but also simultaneously seals blood vessels that are 0.5 mm in diameter. Recent literature supports the use of lasers instead of scalpels in order to reduce both intraoperative and postoperative bleeding.14 With many popular, pedunculated skin lesions, CO2 lasers have achieved better hemostasis results compared to the traditional method of removal with a cold scalpel. CO2 laser is a safe, efficient and precise incision option that simultaneously achieves hemostasis.14

In a similar manner, radiofrequency can be used for surgical, hemostatic and aesthetic purposes while removing benign cutaneous lesions. The most favorable radiosurgery wave is set at a frequency of 4.0 MHz for a consistency of 90% cutting and 10% coagulation. This setting causes the least lateral damage, ultimately producing an aesthetically pleasing result. The recommended technique is described as a light paint-brush motion moving laterally from one end of the lesion to the other, followed by a firm wipe with dry gauze; this process is done as many times as necessary to reach the base of the lesion.25

Wound Dressings
Wound dressing can also play an important role in hemostasis. Alginate dressings are ideal for wounds with minimal blood loss. A study by Steenfos et al. demonstrated significantly higher levels of blood absorption after 10 minutes with alginate dressings compared to mesh gauze dressings. Mineral zeolite can also help hemostasis. It works to enhance the initiation of the clotting cascade by transforming factor XII to its activated form. Finally, chitosan and chitin have also been found to be effective dressing material. When chitin is deacetylated, it forms chitosan. Both chitin and chitosan have significant hemostatic abilities in addition to demonstrating antimicrobial activity against gram negative bacteria.26

Conclusion
In all aspects of achieving hemostasis, efficacy, speed, and reliability have proved the most important factors when choosing an approach. We reviewed methods known to minimize operative bleeding risk and thus ensure the best possible surgical outcomes for our patients. There is no claim that one method is better than another, but rather that a combined approach can best address the issue of intraoperative hemostasis.

References
Abdominal Pain: A Unique Presentation of Neurofibromatosis and Updated Review of the Condition
Brandon Nickle, DO,* Blaze Emerson, MS,** Kimberly Hull, DO,* Brittany Smirnov, DO,* Jaqueline Thomas, DO, FAOCD***

*N*Dermatology resident, PGY-III, Broward General Medical Center, Fort Lauderdale, FL
**Medical student, OMSIII, Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, FL
***Board-certified dermatologist and fellowship-trained Mohs surgeon, Physician Regional Medical Group, Naples, FL

Disclosures: None
Correspondence: Brandon Nickle, DO; brandonnickle5@gmail.com

Abstract

Neurofibromatosis type 1 (NF1) is a common, autosomal-dominant neurocutaneous disorder affecting 1 in 3,000 people. It often presents with myriad cutaneous features, including neurofibromas, Lisch nodules, café-au-lait macules, axillary freckling, and plexiform neurofibromas. Many other non-cutaneous manifestations have been observed in NF1. Gastrointestinal stromal tumors (GIST), malignant peripheral nerve sheath tumors (MPNST), and adenocarcinoma are commonly found in the gastrointestinal tracts of NF1 patients and can manifest as complaints of abdominal pain. We present a unique case of NF1 with an initial presenting symptom of abdominal pain caused by plexiform neurofibromas located outside the gastrointestinal tract.

Introduction

Neurofibromatosis is a common condition, with a reported incidence of approximately 1 in 3,000.1-3 The diagnostic criteria originally established by the NIH in 1988 (Table 1, p. 14) has proved very specific and sensitive in correctly diagnosing NF1 patients in early childhood; however, many patients are not diagnosed until adolescence or early adulthood.4,5 As with our patient, many NF1 cases are identified through incidental imaging from a seemingly unrelated and somewhat unusual complaint.6 Exotic presentations of NF1 have been reported in the literature and range from signs of spinal cord compression, incontinence due to tumor growths in the bladder, breathing difficulties, epigastric pain, and gastric outlet obstruction.3,7-12 Abdominal complaints related to NF1 tumors are fairly common; however, the etiology is often due to gastrointestinal tumors, which are reported in 2% to 25% of NF1 patients.1,2

Case Report

A 17-year-old female was admitted for evaluation of non-radiating right upper quadrant abdominal pain that had been present for three days. The patient did not have a significant medical history or family history of NF1; however, during the initial patient interview, her mother was found to have multiple café-au-lait macules.

Physical examination revealed 24 café-au-lait macules on her limbs and torso, ranging in size from 0.5 cm to a 7 cm macule on her left lateral thigh (Figures 1 and 2). Additionally, she was found to have axillary freckling and three subcutaneous nodules on the face and neck. Preliminary ophthalmologic examination had shown multiple yellow-to-brown pigmented macules within the irises, clinically consistent with Lisch nodules (Figure 3). CT scan of the abdomen and pelvis with IV contrast was obtained and noted the presence of solid masses within the pelvis and surrounding the celiac and superior mesenteric arteries. Magnetic resonance imaging was subsequently performed to further classify the nature of these masses and confirmed multiple plexiform neurofibromas within the retroperitoneum and pelvis (Figures 4 and 5). Numerous plexiform neurofibromas surrounding and extending into thoracic and lumber neuroforamina were incidentally noted. Ultimately, MRI studies and subsequent esophagogastroduodenoscopy were negative for gastrointestinal tumor involvement.

Based on the imaging results obtained, the patient’s abdominal discomfort was secondary to external compression of abdominal structures by plexiform neurofibromas. Despite the extensive neurological findings on MRI, the patient lacked any clinical signs or symptoms of neurological involvement. Neurosurgical consultation was recommended and the patient underwent laparoscopic excision of the plexiform neurofibromas.
Table 1. Diagnostic criteria for NF1 (NIH consensus development conference, 1988)

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least two (2) required for NF1 diagnosis</td>
<td></td>
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<tr>
<td>Six (6) or more café au lait macules with diameters &gt; 5 mm in pre-pubertal and &gt; 15 mm in postpubertal individuals.</td>
<td>For each lesion, the longest diameter is measured.</td>
</tr>
<tr>
<td>Two (2) or more neurofibromas of any type or one (1) plexiform neurofibroma</td>
<td></td>
</tr>
<tr>
<td>Freckling in the axillary or inguinal regions</td>
<td></td>
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<tr>
<td>Optic glioma</td>
<td></td>
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<tr>
<td>Two (2) or more Lisch nodules</td>
<td></td>
</tr>
<tr>
<td>Bony dysplasia</td>
<td>With or without pseudoarthrosis.</td>
</tr>
<tr>
<td>First-degree relative with NF1</td>
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</table>

Table 2. Cutaneous Manifestations and Age of Onset for Patients with NF1

<table>
<thead>
<tr>
<th>Cutaneous Manifestation</th>
<th>Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café-au-lait spots</td>
<td>Birth through age 2</td>
</tr>
<tr>
<td>Axillary freckling and Lisch nodules</td>
<td>Ages 2 through 6</td>
</tr>
<tr>
<td>Subcutaneous and cutaneous neurofibromas</td>
<td>Adolescence</td>
</tr>
</tbody>
</table>

Discussion

Neurofibromatosis is a common genetic condition caused by inactivation of the NF1 gene on chromosome 17. It is inherited in an autosomal-dominant fashion, though approximately half of NF1 cases are due to spontaneous mutations with no family history. The diagnostic criteria is based upon the NIH consensus of 1988 (Table 1). Patients are prone to multisystem disease complications including but not limited to cutaneous and plexiform neurofibromas, MPNST, scoliosis, pseudoarthrosis of the tibia, learning disabilities, short stature, renal artery stenosis, phaeochromocytoma, epilepsy, optic and cerebral gliomas, sphenoid wing dysplasia, and aqueduct stenosis. These complications necessitate the involvement of a multi-disciplinary team including geneticists, pediatricians, neurologists, and dermatologists who specialize in the condition, as well as a neurofibromatosis specialty clinic, if available.

Dermatologists are often consulted to assist in the diagnosis of NF1 due to the early appearance of cutaneous findings (Table 2). Specific dermatological manifestations of NF1 include café au lait macules, skin freckling, hypo-pigmented macules, Lisch nodules, and cutaneous and plexiform neurofibromas, all of which were present in our patient. Café au lait macules are localized, light brown, benign areas of hyperpigmentation. The term is derived from its characteristic homogeneous color resembling “coffee with milk.” NF1 patients have shown an increased number of melanocytes in their café au lait spots as well as in their normal skin. Although café au lait macules are benign and have little propensity to differentiate into melanoma, it’s hypothesized that this proliferation may be related to a slightly increased risk of melanoma in NF1 patients, reported in 0.1% to 5.4% of patients. Lisch nodules are benign, pigmented iris hamartomas. They usually appear in early childhood but become more prominent through adolescence, and by age 20 approximately 80% to 90% of NF1 patients have Lisch nodules.

Although many patients present initially with both dermatologic and non-dermatologic manifestations sufficient to meet the NIH diagnostic criteria (see Table 1), NF1 is often overlooked. The presence of six or more café au lait patches, even in the absence of family history and other manifestations, is strongly predictive of the disease, as more than 95% of these patients will eventually be diagnosed with NF1. In a study by DeBella et al. involving 1,893 NF1 patients, it was determined that the NIH criteria is both very specific and very sensitive in older children and adolescents, but has a low sensitivity in patients under the age of 1.5 TheyTheir data revealed that 46% of infants under the age of 1 initially failed to meet diagnostic criteria; by age 8, 97% of patients met the criteria, and almost all met the criteria by age 20. Though most patients will have clinical features sufficient to meet diagnostic criteria at a young age, many are diagnosed late, when they present for an unrelated concern.

Abdominal complaints related to NF1 are fairly common and often lead to the incidental diagnosis of NF1. Visceral and gastrointestinal tumors are often asymptomatic but may present as pain, palpable masses, GI bleeding, vessel compression, or bowel occlusion. Patients with NF1 can present with a wide variety of abdominal tumors, including phaeochromocytomas, GIST, MPNST, and plexiform neurofibromas. The etiology of the abdominal pain is commonly due to gastrointestinal tumors, which are reported in 2% to 25% of NF1 patients. Our patient was unusual because her only complaint was abdominal distress, which was caused by plexiform neurofibromas located outside the GI tract.

Plexiform neurofibromas are present in approximately 25% of NF1 patients and are one of the most common culprits in morbidity and cosmetic impairment. Plexiform neurofibromas are benign tumors of peripheral nerves that arise from proliferation of neural cells in the nerve sheath and extend across multiple nerve fascicles. They often become very large, involve major nerves and compress surrounding structures, including the spinal cord. Plexiform neurofibromas tend to grow during early childhood, when exposed to increased hormones, as in puberty and pregnancy. Plexiform neurofibromas have a propensity for transformation to MPNST, occurring in approximately 2% of cases.

As was the case with our patient, it is not uncommon for plexiform neurofibromas to remain clinically undetected for many years. Using imaging studies, Schorry et al. identified thoracic plexiform neurofibromas in nine of 240 children with NF1. Three of these were symptomatic, but the others would have remained clinically undetected. In another study, Thakkar et al. performed MRI studies on 54 NF1 patients, and 35 were found to have spinal plexiform neurofibromas, with 12...
being asymptomatic.\textsuperscript{27} Chung et al. reviewed the cases of 95 children with NF1 and found 22% to have cervical plexiform neurofibromas, with 12 being asymptomatic at the time of the study.\textsuperscript{28} Although plexiform neurofibromas are common in NF1, there is limited data available to recommend routine screening imaging studies for early detection, and there is no well-defined protocol for their management.\textsuperscript{22}

Treatment for symptomatic or transformative plexiform neurofibromas is limited to surgical resection. Removal of plexiform neurofibromas is often difficult due to the deep-seated nature of the tumors, further complicated by the fact that these growths invade nearby structures such as bone and adjacent nerves. Damage to peripheral nerves during resection is common owing to the intimate nature of plexiform neurofibromas within the neural sheath and the easy spread of plexiform neurofibromas between nerve fascicles. As stated earlier, plexiform neurofibromas have a high rate of transformation to MPNST, which are often refractory to treatment because of high rates of metastasis and delays in diagnosis.\textsuperscript{22} Woodruff et al. estimates that the five-year survival for patients with MPNST ranges between 34% to 52%.\textsuperscript{26} The high rate of morbidity associated with these malignancies further highlights the need for prompt diagnosis and monitoring of patients with NF1.

**Conclusion**

This case should remind physicians to include NF1 in their differential when presented with a patient complaining of abdominal pain and dermatological signs of NF1. An accurate and timely diagnosis is important for prolonging and improving the patient’s life, since many with NF1 acquire debilitating plexiform neurofibromas. Management and monitoring of NF1 individuals with an interdisciplinary team of dermatologists, ophthalmologists, and neurosurgeons is suggested to limit the complications associated with this disease.

**References**

Subungual Melanoma in a Haitian Male:
A Case Presentation and Discussion

Stephanie Blackburn, DO,* Jason Barr, DO,** Richard Averitte Jr., MD,*** Michelle Goedken, DO,**** Sarah Estrada, MD*****

* Dermatology resident, 2nd year, Affiliated Dermatology/Midwestern University, Scottsdale, AZ
** Program director, Dermatology Residency Program, Affiliated Dermatology/Midwestern University, Scottsdale, AZ
*** Dermatologist/CEO, Affiliated Dermatology, Scottsdale, AZ
**** Dermatology resident, 3rd year, Affiliated Dermatology/Midwestern University, Scottsdale, AZ
***** Dermatopathologist and laboratory director, Affiliated Laboratories, Scottsdale, AZ

Disclosures: None
Correspondence: Stephanie Blackburn, DO; Stephanie3366@aol.com

Abstract
We report the case of a 61-year-old male of Haitian origin who presented with a lesion under his right first finger, which had been present for up to 15 years. Nail matrix biopsy showed subungual melanoma in situ. Acral lentiginous melanoma (ALM), the most common type diagnosed in black patients, is more likely to be detected at an advanced stage than other melanoma subtypes. The delayed diagnosis and treatment may lead to poorer prognoses for affected individuals.

Introduction
The lifetime risk for developing melanoma in Caucasians is estimated to be 1 in 50, while it is 1 in 1,000 in the black population. Black patients have a tendency to develop lesions on sun-protected mucosal and acral sites. Lesions are common on the foot, which is speculated to be related to traumatic injury and preexisting nevus. The major subtype of melanoma observed among blacks, Hispanic and Asian patients is acral lentiginous melanoma (ALM). It is estimated to account for more than 50 percent of all melanomas in black patients, compared to an estimated 5 percent in Caucasians. ALM is more likely to be detected at an advanced stage, with larger tumor size, than other subtypes of melanoma, attributed to a delay in appropriate management resulting from misdiagnosis.

Case Report
A 61-year-old male presented with the chief complaint of a pigmented lesion on the right first finger (Figure 1). The lesion had been present for 10 to 15 years. It started as a brown/black streak that traveled down the nail. The patient noticed widening of the lesion, to just over 8 mm, as well as color change. Upon examination, there appeared to be a Hutchinson or pseudo-Hutchinson sign evidenced by macular, deeper pigmentation at the eponychium. He reported black crust at the distal nail, which he would trim down with nail clippers weekly. He denied pain, trauma or bleeding. The lesion was evaluated by his PCP in Texas many years ago, and per the patient, the PCP was unsure of the diagnosis and offered the possible etiology of a fungal infection. At that time, no intervention or diagnostic workup was performed. Later, after moving to Arizona, he was seen by his current PCP and referred to our office.

The patient denied sunscreen use and denied any history of blistering sunburns in childhood. He grew up in Haiti and spent the first third of his life there. He moved to the United States and resided in New York and New Jersey for many years before transferring to Texas and then later Arizona. He reported very little time spent in the sun.

A complete review of systems was negative. The patient denied any significant past medical history and had no previous surgeries. His family history was noncontributory, and there was no family history of melanoma. Patient reported no prescription medications. His over-the-counter medications included a multivitamin, honey bee pollen, L-lysine and Echinacea. His allergies included hydrocodone, with reported nausea and vomiting. The patient worked as an engineer. He denied any chemical use or UV exposure related to hobbies or work. Social history was negative.
After the patient’s first office visit, it was highly recommended that he have a nail matrix biopsy to rule out melanoma. The patient stated that he wanted to discuss it with his wife and obtain a second opinion. He returned for a second opinion scheduled with another physician in the group, who again recommended nail matrix biopsy. The patient returned and had two punch biopsies taken of the nail matrix, which showed subungual melanoma in situ that extended to the lateral margin (Figure 2). He then underwent slow Mohs surgery with two layers to clear all margins (Figure 3). The surgery site was left to heal by secondary intention.

Discussion
Melanoma is a disease of malignant transformation of melanocytes. In Caucasians, the number of cases of the disease worldwide is increasing faster than for any other form of cancer.1,12 The lifetime risk for developing melanoma in Caucasians is estimated to be 1 in 50, while it is 1 in 1,000 in the black population.1 Black patients have a tendency to develop lesions on sun-protected mucosal and acral sites, particularly the foot, which is speculated to be related to traumatic injury and preexisting nevi.1,9 Low socioeconomic status is associated with poor survival independent of race or type of melanoma.15 The major subtype of melanoma in black, Hispanic and Asian populations is acral lentiginous melanoma.1 It is estimated to account for more than 50 percent of all melanomas in black patients, compared to an estimated 5 percent in Caucasians. Acral lentiginous melanoma is more likely to be detected at an advanced stage than other melanomas, attributable to treatment delays due to misdiagnosis. Common misdiagnoses include benign skin lesions such as wart, dermatophyte infection, foreign body, ulcer, callus, mole, traumatic wound, keratoacanthoma, ingrown toenail, infected toenail and subungual hematoma.1,2 Misdiagnosis is especially common with unpigmented lesions and lesions involving the nails.2

Relative to other anatomic sites, plantar and subungual melanomas exhibit a higher misdiagnosis rate.2 The delay in diagnosis leads to a higher incidence of thicker, more invasive tumors at presentation.3 Histologic prognostic predictors include size and shape of primary lesion, invasion, presence of ulceration and mitotic activity.4 Prognosis can be assessed by clinicopathologic variables including age, location, tumor thickness, presence of ulceration, stage of disease, and race. Overall survival time for black patients with cutaneous melanoma is significantly shorter than for Caucasians with the disease. Bellows et al. performed a chart review of 198 patients with melanoma presenting from 1975 to 1977 at Charity Hospital New Orleans, 44 of whom were black. The majority of the black patients developed melanoma on the acral surface of the foot. The authors reported that the mean survival time for black patients with cutaneous lesions was 45 months, compared to 135 months for Caucasian patients.3 There are conflicting data regarding whether the difference in survival is due to race or to advanced disease at presentation. It is debatable whether ALM is an inherently more aggressive form of melanoma or whether delayed diagnosis accounts for the lower survival rate. In a retrospective review by Ridgeway et al., it was found that only thickness was a prognostic variable for disease-free survival and overall survival in ALM cases. According to the authors, “this histologic subtype does not, in itself, affect the outcome” of patient survival when compared to patients with superficial spreading melanoma and nodular melanoma.6,7

There is also controversy related to whether race is an independent prognostic factor in survival. There is evidence that supports that melanoma in black patients follows a more aggressive course even after controlling for stage of disease, tumor thickness, ulceration, anatomic site, socioeconomic status and histologic type.1 There is also evidence refuting that race is an independent risk factor and that reliable prognostic variables include Clark and Wihm’s level, clinical stage, and ulceration.1,9 In a study by Cormier et al., patients who were Hispanic, black, American Indian or Asian were more likely to present with stage IV melanoma compared with patients who were Caucasian.10

Melanoma is one of the deadliest forms of skin cancer and is a public health concern for ethnic populations. Better understanding of the different presentations of melanoma in each ethnic background, and screening individuals of all backgrounds, will lead to earlier detection and help minimize the disparities in survival rates. As cutaneous melanoma is a visible disease of the skin, both the practitioner and the patient have a role in recognizing suspicious lesions and lesions that are evolving. The time taken to make a diagnosis depends on the patient seeking medical attention and also on the practitioner being prudent about biopsies and having a strong clinical suspicion when examining nontraditional areas for melanoma and nontraditional presentations. Richard et al. studied the reasons for delay in melanoma diagnosis in 590 patients and found that risk factors included male gender, increasing age and low education level.11 In a second examination regarding delays in physician diagnosis, risk factors included acral locations and lack of lesion pigmentation.12 It was also found in this study that when patients saw dermatologists rather than general practitioners, medical delays were shorter, doctor’s attitudes were frequently appropriate, and melanomas were thinner at diagnosis.14

Conclusion
The incidence of melanoma is rising. As the rate increases, especially in the younger population, there is a great need for screening and education. This includes patient education and also physician/healthcare provider education. Discussing the signs and potential symptoms of melanoma with patients will help them to seek out medical care at an earlier stage. The threshold for biopsy for the clinician should also be decreased. When a lesion is being treated and is not improving in the appropriate manner, a biopsy is warranted. Referring to a physician who is comfortable with nail matrix biopsy is also important in shortening the presentation-to-diagnosis time and improving morbidity and mortality.
References
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Cutaneous Sarcoidosis Identification in a Patient with Asymptomatic Third-Degree AV Block

Fatima Fahs, MD,* Roxana L. Chapman, DO, FACP, FAAD, FAOCD**

*Dermatology resident, 1st year, Beaumont Health System, Royal Oak, MI
**Associate clinical professor, Michigan State University College of Osteopathic Medicine, East Lansing, MI; associate professor, Oakland University William Beaumont School of Medicine, Rochester, MI; dermatologist, Beaumont Health System, Royal Oak, MI

Abstract

We present a case of cardio-pulmonary sarcoidosis in a 68-year-old African American male that was diagnosed when he presented to dermatology for treatment of an itchy scalp. Skin examination revealed male pattern hair loss without scarring or scale but with an annular pattern of mildly hyperpigmented indurated papules arranged in 2 cm to 3 cm plaques on his frontal and parietal scalp. A 3 mm punch biopsy was taken from the right parietal scalp lesion active edge, which revealed non-caseating granulomas, characteristic of sarcoidosis. This case stresses the need for a thorough history, biopsy and medical evaluation in order to diagnose and manage sarcoidosis effectively. Often, cutaneous lesions are the primary presenting sign of sarcoidosis, making the dermatologist the first physician called upon to make the diagnosis. This case also demonstrates the importance of correlating systemic findings, such as this patient’s two-year history of third-degree AV block, with cutaneous lesions.

Introduction

In dermatology, sarcoidosis is known as the “great imitator” because of its diverse morphological manifestations.1 Sarcoidosis is an antigen-mediated disease of unknown origin characterized by systemic, non-caseating granulomas present within organs and tissue. Granulomas can be found in the skin, lungs, lymph nodes, eyes, joints, brain, kidneys and heart.2 Cutaneous lesions are sometimes the primary presenting sign of sarcoidosis.3

The lifetime risk of disease is 0.88% in Caucasians and 2.4% in African Americans. Sarcoidosis carries a mortality rate of 5% to 6% due to cardiac involvement.4 There is also a larger incidence of sudden cardiac death (SCD) in patients with sarcoidosis than the average population due to structural and functional alterations in the heart.4 SCD as an initial indication of undetected disease makes early intervention and diagnosis of sarcoidosis essentially life saving.4 Clinical manifestations of cardiac disease are present in 5% to 10% of patients, but the actual incidence is reported to be much higher.5 This case demonstrates the importance of a dermatologist’s role in identifying internal disease that manifests cutaneously and impacting a patient’s mortality and life expectancy.

Case Report

A 68-year-old, well-developed, well-nourished African American male presented to Dermatology with complaints of an itchy scalp that had not responded to topical fluticasone and ketoconazole shampoo prescribed by another physician for presumptive seborrheic dermatitis. His past medical history was remarkable for diagnosis of complete AV block two years prior, though the patient had refused pacemaker implantation and had not seen his cardiologist for further management. He did not have any history of heart failure, liver disease, renal disease/nephrolithiasis or neurological impairment. On review of symptoms, the patient denied complaints of syncope, arthritis, eye inflammation, fever, tender leg lesions or edema. He noted shortness of breath with exertion.

On physical exam, the patient did not appear to be in acute distress. Skin examination revealed male pattern hair loss without scarring or scale but with an annular pattern of mildly hyperpigmented, indurated papules arranged in 2 cm to 3 cm plaques on his frontal and parietal scalp. According to the patient, these lesions had been present for one year. No facial lesions were noted, and the remainder of his skin exam was unremarkable.

The patient’s lesions were concerning for granuloma annulare or sarcoidosis, so a punch biopsy and chest X-ray were ordered. A 3 mm punch biopsy was taken from the right parietal scalp lesion active edge (Figure 1), which revealed non-caseating granulomas, characteristic of sarcoidosis (Figures 2 and 3). A histiocyte-rich infiltrate within the superficial dermis, composed of mononuclear cells with a variable amount of foamy cytoplasm and scattered, occasionally frequent multinucleated giant cells and granuloma formation was visualized. In addition, interspersed lymphocytes, plasma cells, and patchy neutrophils were noted. Grocott’s methenamine silver (GMS) stain for fungus and Kinyoun stain for acid-fast bacilli were both negative. A chest X-ray revealed hilar changes and infiltrates in the lungs (Figure 4, p. 20), likely contributing to his ongoing complaints of dyspnea.

Figure 1

Figure 1. Patient’s right parietal scalp, two years after skin biopsy and resolution of lesion. Residual scarring from biopsy remains.

Figure 2

Figures 2 and 3. Skin biopsy displaying nodular aggregates of superficial and deep epithelioid cell granulomas within the dermis, characteristic of sarcoidosis.

Figure 3
Results of the skin biopsy and chest X-ray were reviewed with the patient and his cardiologist. Although the patient had been reluctant to undergo the pacemaker insertion recommended by his cardiologist over a year ago, he decided to undergo the procedure after the cardiac and pulmonary work-up were completed and he was advised of potential risks and benefits of inserting the device because of his underlying sarcoidosis. The patient elected to receive a biventricular pacemaker with implantable cardioverter-defibrillator (ICD), which would ideally improve his cardiac output and correct for possible life-threatening arrhythmias. Absolute indications for pacemaker placement in this patient were: complete atrioventricular block (third-degree heart block) and cardiac resynchronization therapy with biventricular pacing.

Cardiac MRI revealed mild myocardial enhancement, biventricular enlargement with biventricular dysfunction and cardiomyopathy (Figures 5 and 6). Cardiac ECHO revealed a left ventricular ejection fraction of 28%, diastolic dysfunction, and dilated left ventricle. Cardiac positron emission tomography (PET) scan showed infiltration of the basal to mid inferior wall and possible involvement in the basal anterior wall, indicating active sarcoidosis. The patient had an elevated angiotensin-converting enzyme (ACE) of 68 U/L and some other minor laboratory changes including decreased platelets (125 K/uL), elevated blood urea nitrogen (27 mg/dL) and elevated creatinine (1.45 mg/dL). Pulmonary function testing SPIRO/DLCO revealed impairment with an FVC of 82%, FEV1 of 91%, and DLCO of 65% (not corrected for hemoglobin).

Currently, indications for primary prophylaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Findings</th>
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<tbody>
<tr>
<td>Papular</td>
<td>Numerous, non-scaly, 1–10mm papules ranging in color from yellow to brown. Frequently on the face (eyelids, nasolabial folds).</td>
</tr>
<tr>
<td>Nodular</td>
<td>Large collections of sarcoidal granulomas, each approximately 1–2cm in diameter. May resemble rhinophyma on the nose.</td>
</tr>
<tr>
<td>Subcutaneous (Darier-Roussy)</td>
<td>Nodular sarcoidosis predominantly involving subcutaneous tissue that presents with erythematous, hyperpigmented, indurated nodules found on upper extremities. Often form linear bands.</td>
</tr>
<tr>
<td>Maculopapular</td>
<td>Infiltrated, hyperpigmented, red-brown patches scattered with raised papules commonly found on the face, especially around eyelids and mouth.</td>
</tr>
<tr>
<td>Plaque</td>
<td>Oval or annular, well-demarcated, red-brown plaques with occasional scale that often involve the shoulders, posterior arms, back and buttocks.</td>
</tr>
<tr>
<td>Lupus pernio</td>
<td>Central facial distribution of violaceous, indurated papules, plaques and/or nodules. Usually found at the tip of the nose or cheeks. Greater risk of pulmonary involvement of sarcoidosis.</td>
</tr>
<tr>
<td>Hypopigmented</td>
<td>Well-demarcated, hypopigmented patches or slightly raised plaques. Affects dark-skinned individuals almost exclusively.</td>
</tr>
<tr>
<td>Atrophic/Ulcerated</td>
<td>Depressed, atrophic, hyperpigmented plaques that may become ulcerated. Three variants: morpheaform, necrobiosis-lipoidica-like, lipodermatosclerosis-like.</td>
</tr>
<tr>
<td>Angiolupoid (Brocq-Pautrier)</td>
<td>Slightly raised plaques with prominent telangiectasias, often developing on the central face or scalp. Variant of plaque sarcoidosis. (Rare)</td>
</tr>
<tr>
<td>Ichthyosiform</td>
<td>Asymmetrical, dry, polygonal gray-brown scales involving the pretibial lower extremities. (Rare)</td>
</tr>
<tr>
<td>Erythrodermic</td>
<td>Large, geometric, erythematous yellow-brown plaques covering large areas of the skin. Potential for desquamation. (Rare)</td>
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</table>
account for most ICD implants. Class I indication in this patient was a left ventricular ejection fraction (LVEF) less than 35% (NYA class II or III), Class IIA indication (benefit outweighs the risk and is reasonable to administer the treatment) was cardiac sarcoidosis.6 Prednisone was started at 40 mg per day for one month and subsequently tapered by 10 mg every month. The patient has been maintained thereafter with a 10 mg daily dose indefinitely and follows closely with both cardiology and pulmonology. Due to this patient’s low ejection fraction (28%) indicating a poorer prognosis, biologic therapy was not instituted. The patient recently returned for a visit with dermatology and showed resolution of his cutaneous lesions. He displayed gratitude for the multi-disciplinary specialty approach led by the dermatologist and extension of his life expectancy.

**Discussion**

Cutaneous manifestations of sarcoidosis are seen in greater than 25% of patients.2 Specific cutaneous eruptions, such as erythema nodosum, calcinosis cutis, Sweet syndrome and nail clubbing, can also present in patients with sarcoidosis.1 Erythema nodosum presents as inflammatory, tender nodules on the lower legs and was reported by one study to be found in 20% of patients with sarcoidosis and 62% of sarcoidosis patients with cutaneous lesions.4 Careful history and physical and skin examinations with biopsy are vital to early diagnosis and management of sarcoidosis. A biopsy was warranted in this patient to rule out a granulomatous process because of the annular morphology and the induration on palpation suggesting a dermal process. Absence of surface scale and erythema made the diagnosis of seborrheic dermatitis unlikely.

“Naked,” or non-caseating, granulomas characterize the histopathological findings of sarcoidosis and include aggregates of epithelioid histiocytes, giant cells and mature macrophages surrounded sporadically by CD4+ and CD8+ T-cell infiltrates.7 This arrangement differs from the dense, lymphocytic infiltrate classically seen in tuberculoid.5 Naked granulomas are estimated to be present in 71% to 89% of sarcoidosis lesions.10 What complicates this diagnostic picture is the fact that not all cutaneous lesions of sarcoidosis demonstrate classic histopathological findings.12,13 Other lesions may demonstrate elaborate lymphocytic infiltrates at the margin of granulomas, central caseating granulomas, vasculitis, or augmented dermal mucin.13,14

The differential diagnosis for sarcoidosis includes foreign body reactions, tuberculosis, leprosy, and fungal and atypical mycobacterial infections. Special staining is done to exclude these conditions. Treatment is individualized, and various systemic therapies have been used including prednisone, methotrexate, hydroxychloroquine, minocycline, tumor necrosis factor-alpha inhibitors (infliximab and adalimumab) and, less often, thalidomide, isotretinoin and allopurinol. Corticosteroids in topical, intralesional or systemic form are the mainstay therapy for systemic sarcoidosis.15

Sarcoidosis can involve multiple organ systems including the skin, lungs, lymph nodes, eyes, joints, brain, kidneys and heart.2 Endocrine (rarely diabetes insipidus) and exocrine dysfunction (< 10% parotid gland xerostomia) are also possible.15 Pulmonary involvement occurs in 90% of patients and ranges from alveolitis to granulomatous infiltration of the alveoli, blood vessels, bronchioles, pleura and fibrous septa.16 Routine chest films are frequently abnormal. Pulmonary function testing should be done initially and followed as symptoms warrant.16-17

Sudden cardiac death may be the initial presentation in 40% of patients with cardiac sarcoidosis.18 Only 40% to 50% of patients with cardiac sarcoidosis identified on autopsy received this diagnosis during their lifetime.5 One study reported five cases of facial cutaneous sarcoidosis with concurrent cardiac involvement, with four out of the five patients displaying annular facial lesions.19 Complete heart block and bundle branch blocks are among the most common manifestations of cardiac sarcoidosis, occurring in 23% to 30% and 12% to 32% of patients, respectively.5 These statistics should encourage cardiac evaluation in any patient identified with cutaneous sarcoidosis.

**Conclusion**

Sarcoidosis can present in myriad ways, making careful history, physical and skin examinations with biopsy vital to early diagnosis and management. Biopsy confirmation of cutaneous sarcoidosis should prompt review of chest X-rays because of the very high incidence of associated pulmonary disease. Further systemic evaluation should include cardiac assessment with electrocardiogram, prolonged Holter monitoring, echocardiogram, MRI and PET scan. Arrhythmias due to undetected cardiac structural damage can lead to sudden cardiac death either prior to or after initiation of therapy. Laboratory testing and imaging are necessary to determine the extent of organ involvement and choose the best form of therapy. Underlying liver disease and cardiac disease might preclude use of certain modalities such as methotrexate, hydroxychloroquine and biologics. Treatment must be tailored to the patient. Finally, this case serves as a reminder of how a dermatologist’s role can extend beneath the skin and impact a patient’s mortality and life expectancy.
References


Successful Use of Liposomal Amphotericin B for Cutaneous Leishmaniasis in a Young Male Patient Treated with a TNF-alpha Inhibitor

John R. Moesch, BA,* Caryn Bern, MD, MPH,** Vincent A. Laufer, BA,*** Robin H. Dretler, MD, FIDSA****

*Medical student, 4th year, Philadelphia College of Osteopathic Medicine, Suwanee, GA
**Medical epidemiologist, Department of Epidemiology and Biostatistics, University of California, San Francisco, CA; Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, GA
***Medical student, 4th year, University of Alabama School of Medicine, Birmingham, AL
****Infectious disease physician, Infectious Disease Specialists of Atlanta, P.C., Decatur, GA

Disclosures: None
Correspondence: John R. Moesch; johnmoe@pcom.edu

Abstract

We present a case of cutaneous leishmaniasis caused by the species L. panamensis in a young male patient with juvenile idiopathic arthritis (JIA), who was being treated with tumor necrosis factor-alpha inhibitor adalimumab. He had recently returned from traveling in Colombia. The patient was successfully treated with liposomal amphotericin B. We also discuss the most current diagnostic work-up and treatments for cutaneous, mucocutaneous, and visceral leishmaniasis.

Introduction

Leishmaniasis is a disease caused by an intracellular parasite of the genus Leishmania. The disease is endemic to every continent except Australia and Antarctica. Twenty disease-causing Leishmania species (Old World and New World) can be transmitted to mammalian hosts via the bite of a female sand fly (Table 1, p. 26). Once transmitted, the extracellular flagellated motile leishmanial promastigotes are taken up by macrophages, where they transform into intracellular, aflagellate amastigotes and multiply within the phagolysosome of the macrophage by binary fission (Figure 1). Depending on the species and host response, the resultant leishmanial infection can lead to cutaneous, mucocutaneous, or visceral syndromes.

Cutaneous leishmaniasis (CL), caused by several leishmanial species, is endemic to many areas of Latin America. The most common clinical picture is that of one or several gradually expanding nodules or plaques that become ulcerated or verrucous. The lesions are most commonly painless unless secondarily infected or overlying a joint due to the restricted mobility it causes during and after the healing process. The lesions commonly heal spontaneously over a period of several months and typically leave behind atrophic, cribriform scars with a hyperpigmented halo. The most common sites are the face, neck, arms, and legs. The most severe cutaneous form is diffuse (disseminated) leishmaniasis. It consists of many non-ulcerating, keloid-like lesions on the face and limbs and is seen in patients with defects in the cellular immune response. Nasal infiltration and ulceration can occur; however, nasal septum destruction does not occur in CL. The clinical severity of cutaneous leishmaniasis varies widely, depending on diverse factors, including the immune system-pathogen interaction, host genetic factors, acquired resistance to infection, age, and skin temperature. Leishmania parasites may persist in healed CL scars and lymph nodes despite adequate initial treatment. This subclinical colonization can result in reactivation during periods of immunosuppression.

Mucocutaneous leishmaniasis, usually due to parasites of the L. braziliensis complex, is much less frequent than localized CL. Mucocutaneous leishmaniasis presents as nasal congestion, bleeding, and mucosal erosions. Unlike diffuse leishmaniasis, it can cause destruction of the nasal septum, palate, and other mucosal structures. It commonly has an incubation period anywhere from a few months to more than 20 years. It may present years after cutaneous lesions have healed, making follow-up important for the patient. In some patients, tissue loss can become so extensive in the mouth and nose region that it causes a very characteristic “taper face” known as espadunda.

Visceral leishmaniasis (VL), or kala-azar, results from diffuse spread of the parasite in the bone marrow, liver, and spleen. The typical patient will present clinically with fever, wasting, cough, lymphadenopathy, and hepatosplenomegaly. Visceral disease may progress abruptly or follow a more insidious course. Complications that can lead to death in untreated patients include oronasal hemorrhage, pneumonia, nephritis and enteritis. Cutaneous findings are most commonly nonspecific in visceral disease. An interesting sequela of untreated VL is post-kala-azar dermal leishmaniasis. It appears clinically as diffuse hypopigmented macules, malar rash, papules, nodules, and plaques throughout all areas of the body. This complication is found almost exclusively in India and East Africa.

The efficacy of monoclonal tumor necrosis factor-α (TNF-α) inhibitors has spurred fast-growing clinical use for a variety of indications, a trend that promises to continue. However, the immune inhibition that makes TNF-α blockers so effective also results in increased susceptibility to a range of bacterial, fungal, viral,
and protozoan opportunistic infections as well as various cancers.8-11

We report a case of rapidly progressive cutaneous leishmaniasis in a young traveler who was taking adalimumab for juvenile idiopathic arthropathy (JIA). After diagnosis, the patient’s cutaneous disease rapidly improved on a short course of liposomal amphotericin B.

Case Presentation

An otherwise healthy, 14-year-old male with a history of mild idiopathic JIA presented to the infectious disease clinic with multiple skin ulcers. The patient had been treated with adalimumab for six months. The lesions first appeared four weeks after traveling to Colombia. Initially, cutaneous manifestations were limited to a painless, pruritic papule on the right ankle. Over the next week the patient developed adenopathy in his groin and axillae, the original ankle papule ulcerated, and additional ulcers appeared on his extremities, torso, and face. The patient was treated three times with TMP-SMX during the course of one month by other practitioners for presumed resistant Staphylococcus aureus abscesses, without improvement of symptoms.

On presentation, the patient denied any fatigue, night sweats, or weight loss. Vital signs were stable. Clinical examination revealed 12 painless ulcers with granulation tissue. The initial ulcer, located on his right ankle, was the most prominent (Figure 2). Based on clinical exam, he was presumed to have cutaneous leishmaniasis (CL). Tissue specimens were collected for examination by the Centers for Disease Control and Prevention (CDC). The patient was instructed to apply silver alginate dressings daily and was placed on an initial course of fluconazole 200 mg once daily to treat the potential cutaneous leishmaniasis infection.

Ten days later, the pathology was reported to be consistent with but not diagnostic of leishmaniasis, showing overlying epidermal hyperplasia with mixed areas of granulomatous inflammatory infiltrate and stromal fibrosis. Acid-fast bacilli stains were negative, ruling out infection with mycobacterial species. The nasal swab and two fresh skin biopsies sent to the CDC inimered short course of liposomal amphotericin B. The patient had been treated with adalimumab for juvenile idiopathic arthropathy (JIA). After diagnosis, the patient’s cutaneous disease rapidly improved on a short course of liposomal amphotericin B.

While awaiting diagnostic confirmatation, the patient’s lesions had enlarged, and an additional lesion occurred on his chin. He had also developed increasing rhinitis with sinus congestion symptoms. Because of the worsening cutaneous lesions and concern for mucocutaneous leishmaniasis, the patient was started on liposomal amphotericin B, and he showed rapid improvement. A total dose of 27 mg/kg was administered (3 mg/kg per day on days 1 through 7, 14 and 21). All lesions healed in four weeks without recurrence.

Discussion

Confirming the diagnosis of leishmaniasis can be difficult. The best results are obtained through a combination of clinical history, physical examination findings (including dermatoscopy), and specimen collection. A suggested algorithm for diagnosing a patient with suspected cutaneous leishmaniasis, according to CDC recommendations, is presented in Figure 3 and goes as follows:

A detailed history is obtained from the patient concerning possible sand fly bites or travel in endemic areas. A detailed medication reconciliation and past medical history will help target those patients at increased risk for leishmaniasis due to immunosuppression.

Next, a thorough clinical examination is performed. There is a broad spectrum of clinical findings in CL. Localized cutaneous disease caused by New World and Old World species usually presents as a small, well-circumscribed papule at the site of inoculation. The lesion may slowly enlarge over several weeks into a nodule or plaque that can further progress to an ulcerated or verrucous lesion. While solitary lesions are most common, multiple lesions do occur and can distribute along a sporotrichoid pattern. Visual examination of the lesions with a dermatoscope can increase the practitioner’s accuracy of diagnosing leishmaniasis. A 2015 review of 127 cutaneous leishmaniasis cases observed by dermatoscopy revealed characteristic findings including erythema, vascular structures, keratin plugging, and a white starburst pattern.12 The most commonly seen vascular structures were comma-shaped vessels (73%), linear irregular vessels (57%), dotted vessels (53%), polymorphous vessels (26%), hairpin vessels (19%), and arborizing telangiectasia (11%). A combination of two or more vascular structures was seen in 88% of cutaneous lesions.

After establishing that leishmaniasis is high on the differential, the next step is to contact the CDC to obtain specialized media used for culturing the highly fastidious organism. The specialized culture medium is a sterile buffered medium with a neutral pH (7-7.4). Commonly used culture media include Novy-MacNeal-Nicolle medium (NMN), brain heart infusion (BHI), Evan’s modified Tobie’s medium (EMTM), Schneider’s Drosophila medium, and Roswell Park Memorial Institute medium (RPMI). The CDC provides free isoenzyme analysis and polymerase chain reaction (PCR) testing of cultured organisms. In addition, it reviews the impression smear and pathology reports. While fresh tissue biopsy is most commonly used for impression smear and histopathology slides, needle aspirates can be used for culture and PCR testing, and dermal scrapings can be used for thin smear preparations.

Finally, if visceral leishmaniasis is suspected, one should obtain the rk39 serologic testing. The rk39 ELISA test detects circulating antibodies against the recombinant K39 protein. Recombinant K39 protein is an epitope present on amastigotes of Leishmania species that causes visceral infection. Research in India has shown an estimated sensitivity of 100% and specificity of 97% for detecting active visceral infection.13

Treatment of leishmaniasis is challenging. Due to the large number of Leishmania species, along with the variable efficacy and toxicity of many of the pharmacologic agents used to treat infections due to these species, systematic clinical-trial data is lacking. Preventing sand fly bites is crucial to avoid infection. In addition, due to the increasing use of immunosuppressant medications, it is prudent to warn patients that they must be cautious about traveling to leishmaniasis-endemic regions; and if travel to these countries cannot be avoided, to wear protective clothing made of fine-mesh netting, use N,N-Diethyl-meta-toluamide (DEET), and remain in well ventilated areas.1,3,13

While mild forms of cutaneous leishmaniasis commonly heal spontaneously and do not require treatment, visceral, mucocutaneous, and severe forms of cutaneous leishmaniasis have increased morbidity and should be treated. L. braziliensis complex members (L. braziliensis, L. guyanensis, L. panamensis, and L. peruviana) have the potential to progress into mucocutaneous leishmaniasis and should be treated.13

There are several treatment options for cutaneous disease. In addition to oral and parenteral medications, local therapies used on some forms of cutaneous leishmaniasis include cryotherapy, intralesional injection of .4 mL to .8 mL sodium stibogluconate, local heat therapy at 40 degrees Celsius to 42 degrees Celsius, and various topical paromomycin preparations (not readily available in United States).1,13
**Figure 3. Diagnostic algorithm for cutaneous leishmaniasis work-up**

<table>
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<tr>
<th>1. History</th>
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<td>Take detailed history (duration of lesions, nasal symptoms, prior treatment, medications). Ask about travel to regions in which leishmaniasis is endemic.</td>
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<th>2. Evaluation</th>
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<tr>
<td>Perform clinical and dermatoscopic evaluation of lesions. Look for erythema (100%), vascular structures (90%), yellow, tear-like structures corresponding with keratin-like plugs (40%-53%), and white starburst pattern (19%-39%). If any dermatoscopic criteria are positive or lesions are suspicious for leishmaniasis, go to step 3.</td>
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<th>4. Obtain fresh tissue</th>
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<tr>
<td>Obtain sterile punch biopsy specimen of youngest, most active, least contaminated ulcer border that contains affected and unaffected tissue. Remove hyperkeratotic eschar. Inject anesthetic into dermis through intact skin after cleaning with 70% alcohol (not iodine). After obtaining tissue, dissect specimen into three pieces. Specimen 1: Basic histopathology. Send to local dermatopathology staff fixed in 10% formalin, embedded in paraffin. Obtain H&amp;E, Giemsa, and special stains for other suspected microbes (mycobacterial, fungal, etc.) Send slides and pathology report to CDC for review. Specimen 2: Impression smear. Technique: Roll biopsy specimen on glass slide, fix with methanol, and stain with Giemsa stain. It helps to filet the biopsy specimen prior to rolling on glass slide to increase surface area. This can be done in office or at the CDC. Consult CDC about shipping/handling of smear. Specimen 3: Culture and polymerase chain reaction (PCR). Send to CDC on media provided free of charge; used for culture and PCR.</td>
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<th>5. Serologic Testing</th>
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<tr>
<td>Obtain serologic testing using the rK39 rapid test. This test detects antibodies against organisms in L. donovani species complex. This test can be done at CDC.</td>
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For the treatment of severe cutaneous disease, mucocutaneous and visceral leishmaniasis, other proven therapies are available. The mainstay treatment has been sodium stibogluconate (SSG), which is given intravenously or intramuscularly. Parenteral administration is preferred due to the large volumes needed. SSG is only available from the CDC under an Investigational New Drug protocol. It is available at 100 mg/mL. Each mL is diluted in 10 mL of 5% dextrose water, and administered over 15 minutes to prevent superficial thrombophlebitis. The recommended dose is 20 mg/kg/day (maximum 850 mg/day) for 20 to 28 days. Depending on the species and region, the cure rates have been reported at 80% to 100%. This agent has been used for the treatment of all forms of leishmaniasis in the United States. Resistance to treatment of visceral leishmaniasis with sodium stibogluconate has now been seen in Europe and regions of India.13 In the United States, when administering this medication, patients are either monitored as inpatients or, more appropriately, given the medication at infusion centers that complete full evaluations prior to administering the drug. Periodic evaluation of cardiac conduction with EKG monitoring is crucial. The patient should have an assessment done on complete blood counts, renal function, amylase, lipase, and serum transaminase levels. A study of parental SSG involving U.S. military personnel with cutaneous leishmaniasis due to L. panamensis confirmed the efficacy of a 10-day course of SSG, with a reduced side-effect profile compared to the standard 20 to 28 day course. Whether or not this result is applicable to other species of Leishmania is unknown.

Amphotericin B is an expensive yet effective agent against SSG-resistant mucocutaneous and visceral leishmaniasis. The newer lipid formulations, such as liposomal amphotericin B, are better tolerated than past preparations and are now being used as first-line therapy in the United States against visceral leishmaniasis. The standard dose for immunocompetent patients suffering from visceral disease is 3 mg/kg IV on days 1 through 5, 14, and 21. Response to liposomal amphotericin B may be suboptimal in patients with HIV because of increased immunosuppression, so the recommended dose for those patients is 4 mg/kg IV. An open-label study performed by Sundar et al. found that a single infusion of 5 mg/kg liposomal amphotericin B was as effective in the treatment of visceral leishmaniasis as a five-day course of once daily 1 mg/kg infusions. Past research on cutaneous disease has shown a mixed response to amphotericin B treatment. Our case offers further evidence of the success of liposomal amphotericin B in the treatment of cutaneous leishmaniasis.

One of the most significant breakthroughs in the management of leishmaniasis was the development of miltefosine, an affordable, orally administered and well-tolerated treatment for all forms of leishmaniasis. Phase II and III drug studies in India showed that miltefosine, at 2.5 mg/kg/day given for four to six weeks, was 95% to 97% effective in curing Indian visceral leishmaniasis. In March 2014, the FDA approved the use of oral miltefosine for visceral leishmaniasis due to L. donovani, cutaneous leishmaniasis due to L. braziliensis, L. guyanensis, and L. panamensis, and mucosal leishmaniasis due to L. braziliensis. The medication includes a black box warning against use during pregnancy because of risk of fetal harm.

Oral ketoconazole, itraconazole, fluconazole, allopurinol, and dapsone can be used to accelerate the healing of cutaneous lesions that do not progress to mucosal disease and will likely self-resolve. These agents have limited adverse effects and are a reasonable approach to patients with uncomplicated cutaneous disease. In addition to pharmacologic therapies, treatment of other negative factors including malnutrition, concurrent systemic illness, location secondary infection, and immunosuppressive medications must be addressed. TNF-alpha inhibitors are increasingly reported in the literature as a risk factor for leishmaniasis infection. Despite extensive research on this topic, the leishmaniasis immune response is not completely understood. While research aimed at examining the importance of TNF-alpha’s role in protecting individuals from leishmaniasis has produced mixed findings, most of the literature points to a protective role. Specifically, experiments done on mice revealed that TNF-alpha deficient mice were more likely to die from L. major compared to non-deficient TNF-alpha mice. Other research revealed higher mortality rates in those without TNF-alpha production and that TNF-alpha persisted in tissues after healing, indicating a role in preventing disease relapse. The TNF signaling pathways generate...
an inflammatory response and mediate resistance to infection by intracellular pathogens. One of the most important mechanisms by which TNF-alpha protects against this organism is by helping generate a pathway that produces nitric oxide, which kills the intracellular amastigotes.\textsuperscript{25}

**Conclusion**

Leishmaniasis is an increasingly common diagnosis in the United States due to an increase in international travel by U.S. citizens. Military personnel have been disproportionately affected in recent years. More than 2,000 laboratory-confirmed cases of cutaneous leishmaniasis and five laboratory-confirmed cases of visceral leishmaniasis were seen in American soldiers serving in Iraq and Afghanistan between 2003 and 2008.\textsuperscript{13} With cases on the rise, it is imperative that the U.S. dermatologist understand the diagnostic work-up and treatment of this disease in order to prevent morbidity and mortality.

This report adds to the literature suggesting that anti-TNF-alpha monoclonal antibodies may increase severity of leishmaniasis, and provides an additional case supporting the effectiveness of liposomal amphotericin B for CL. Although sodium stibogluconate is the traditional therapy for relatively severe CL, there is a recent trend to use liposomal amphotericin B based on known efficacy in VL, its good safety profile, and increasing information from cases series in the published literature.\textsuperscript{19,20} Our patient improved rapidly on liposomal amphotericin B after discontinuation of adalimumab. Furthermore, due to the 2014 FDA approval of the first successful oral medication (miltefosine) for leishmaniasis, we will likely see increasing use of this medication at the expense of previously used parenteral agents.

<table>
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<tr>
<th>Table 1. <em>Leishmania</em> species\textsuperscript{1-4}</th>
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<tr>
<td><strong>Species</strong></td>
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<tr>
<td>New World*</td>
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<tr>
<td><em>Leishmania mexicana</em> complex</td>
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<tr>
<td><em>L. mexicana</em></td>
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<tr>
<td><em>L. amazonensis</em></td>
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<tr>
<td><em>L. venezuelensis, pifanoi, garnhami</em></td>
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<tr>
<td><em>Leishmania (Viannia) braziliensis</em> complex</td>
</tr>
<tr>
<td><em>L. braziliensis</em></td>
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<tr>
<td><em>L. guyanensis</em></td>
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<tr>
<td><em>L. panamensis</em></td>
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<tr>
<td><em>L. peruviana</em></td>
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<tr>
<td>Old World**</td>
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<tr>
<td><em>Leishmania donovani</em> complex</td>
</tr>
<tr>
<td><em>L. donovani</em></td>
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<tr>
<td><em>L. infantum</em></td>
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<tr>
<td><em>L. chagasi</em></td>
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<tr>
<td><em>Leishmania tropical</em> complex</td>
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<tr>
<td><em>L. tropica</em></td>
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<tr>
<td><em>L. major</em></td>
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<tr>
<td><em>L. actinobipica</em></td>
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*Western Hemisphere, extending from central Texas to Central and South Americas (excluding Chile and Uruguay)
**Eastern Hemisphere, endemic in Asia, Africa and southern Europe


**Abstract**

Dermatofibrosarcoma protuberans (DFSP) is a fibroblastic tumor with low-grade malignant potential. DFSP is slow-growing, locally aggressive and has a high recurrence rate. It is most commonly seen in adults, but a small percentage is seen in the pediatric population. In children, there is typically a significant lapse between presentation and diagnosis. We present a case of a 14-year-old male with a longstanding lesion diagnosed as DFSP, giant cell fibroblastoma variant. This variant is commonly seen in the pediatric population and has specific histopathologic features. The cytogenetic profile and treatment options are similar for the giant cell fibroblastoma variant and other forms of DFSP, so they will be discussed as one entity. We present this case to raise awareness of the clinical presentation of DFSP in the pediatric population, with the goal of aiding in early diagnosis and prompt treatment to minimize functional and cosmetic disfigurement.

**Introduction**

Dermatofibrosarcoma protuberans (DFSP) is a slow-growing, locally aggressive, cutaneous fibroblastic mesenchymal neoplasm with low-grade malignant potential. DFSP is most commonly seen in individuals 20 to 50 years of age, but 6 percent of cases present in the pediatric population. Diagnosis is often delayed in the pediatric population, leading to increased lesion size and significant cosmetic disfigurement with treatment options. The delay in diagnosis may be due to the common clinical mimickers of early-stage DFSP in children, such as morphea or vascular lesions, which share the erythematous-to-blue hue of the atrophic plaque. We present a case of a 14-year-old male with a lesion that was present for 13 years before a diagnosis was made.

**Case Report**

A 14-year-old male presented with his mother for the evaluation of a skin lesion on the right aspect of the chest that had been present since 1 year of age. The mother stated that it started out as a dimple and continued to grow. The lesion was not painful, and there was no trauma to the area.

Clinical examination revealed a 4.9 cm x 4.5 cm atrophic, indurated, erythematous to violaceous plaque on the right superior aspect of the chest (Figure 1). Two punch biopsies were performed, showing a dermal proliferation of spindle cells that stained strongly positive for CD34 (Figure 2). Several multinucleate cells were seen at the periphery of the lesion, and mucinous stromal changes were noted. A diagnosis of dermatofibrosarcoma protuberans (DFSP), giant cell fibroblastoma variant was made.

The patient was referred to a tertiary center and underwent wide local excision with 2.0 cm margins. Pathology revealed residual DFSP extending to the deep margin of the specimen. Clear margins were obtained on re-excision, and the defect was repaired with a split-thickness skin graft. The patient will be followed every six months for skin examinations.

**Discussion**

Dermatofibrosarcoma protuberans (DFSP) is a slow-growing, fibroblastic neoplasm with low-grade malignant potential and high recurrence rates after excision. The incidence of DFSP is 0.8 to 4.2 cases per million per year. It is most commonly seen in patients 20 to 50 years of age. The most common locations for DFSP, in decreasing order of frequency, are the trunk, proximal extremities and head and neck. Ten percent to 15 percent of DFSPs contain a fibrosarcomatous component, indicating a more aggressive nature and thus an increased risk of recurrence and metastasis.

Clinically, a DFSP may present as a slow-growing, atrophic, indurated violaceous to red-blue plaque that develops nodules over time. This presentation broadens the differential diagnosis to include morphea, atrophoderma, vascular lesions and various scarring processes. There are currently several dermatoscopic features that are found in, but not specific to, DFSP. These include a delicate pigmented network, vessels, structureless light brown areas, white streaks, pink background and structureless hypopigmented areas. Cytogenetic studies have revealed a rearranged chromosomal sequence that is found in more than 90 percent of DFSP cases. This is a reciprocal translocation t(17;22)(q22;q13) that consists of a1 type 1 collagen (COL1A1; 17q21) and platelet-derived growth factor β-chain gene (PDGFB; 22q13). This translocation upregulates PDGFB, leading to activation and differentiation of mesenchymal cells, thus predisposing patients to DFSP. The genetic defects can be detected using FISH or reverse transcription polymerase chain reaction. Diagnosis is confirmed with punch biopsy and corresponding histopathology.

Histopathology for DFSP shows a poorly-circumscribed, dense collection of spindle cells in the dermis arranged in a storiform pattern. The spindle cells can invade the subcutaneous tissue in a honeycomb or lace-like pattern. The cells are bland in appearance with few mitoses. Spindle cells stain positive for CD34 and vimentin but negative for factor XIIIa, S-100 and desmin. The giant cell fibroblastoma variant of DFSP, as seen in our patient, is a juvenile form of DFSP characterized by the presence of multinucleated cells that stained strongly positive for CD34 and vimentin.
Treatment options for DFSP mainly rely on surgical excision with wide margins. There has been much debate on the appropriate margins to take when performing wide local excision. The goal is to maintain clear margins with excision, in order to decrease recurrence rate, while avoiding severe cosmetic disfigurement. Excision has been performed with anywhere from 1 cm to 5 cm margins.1,2,8,9 One study by Woo et al. assessed the long-term outcomes of surgical treatment in DFSP according to width of gross resection margin. Their assessment recommended wide local excision with a margin of 1.5 cm to 2 cm, with intraoperative frozen section analysis for initial treatment.9 Suggested margins for wide local excision vary; to our knowledge, there is no definitive recommendation regarding margins for initial excision for DFSP. Mohs micrographic surgery has been implicated in the treatment of DFSP on the head and neck, but should be performed by an institution with a surgeon and pathologist proficient in treating this type of tumor. DFSP is responsive to radiation, which can be considered as an adjuvant therapy in certain cases.1 There are no randomized studies assessing the efficacy of adjuvant radiation therapy in DFSP, but Chen et al. performed a systematic review and meta-analysis to evaluate outcomes. Although further studies are needed, there is evidence suggesting that adjuvant radiation may be effective in controlling recurrent tumors that were excised with narrow or positive margins, as well as obtaining control when clear margins could result in severe functional or cosmetic impairment.1 The chromosomal translocation discussed previously allows for targeted therapy for DFSP. Reports have shown that imatinib mesylate, a tyrosine kinase inhibitor that works by blocking PDGF signaling, has beneficial activity in metastatic, inoperable, or pre-operative downstaging cases.2,10 Dose ranges from 400 mg to 800 mg once daily of imatinib mesylate have been used. Although promising, further studies are needed to determine when and at what dosage imatinib mesylate should be utilized.

Conclusion
This case of a 14-year-old male diagnosed with a dermatofibrosarcoma protuberans (DFSP), giant cell fibroblastoma variant exemplifies the delayed DFSP diagnosis typical in the pediatric population. The giant cell fibroblastoma variant has specific histopathologic features but shares a cytogenetic profile and treatment options with other variants of DFSP. The mainstay of treatment is surgical excision with wide margin control. There are exciting treatment options underway that can be used in conjunction with surgical excision, including radiation therapy and imatinib mesylate, although further studies for their appropriate use are required. Physicians from multiple specialties that care for the pediatric population should be aware of the clinical presentation of DFSP to allow for early recognition and timely treatment to decrease morbidity and cosmetic disfigurement.

References
Abstract

A 16-month-old female presented with an extensive epidermal nevus demonstrating epidermolytic hyperkeratosis on histologic evaluation. Individuals with this disorder are at increased risk of bearing children with epidermolytic ichthyosis. This occurs because the same mutations causing cutaneous somatic mosaicism may also affect the gonads. Genetic counseling is advised for individuals with extensive epidermolytic epidermal nevus, as the generalized epidermolytic hyperkeratosis carries significant morbidity and mortality.

Introduction

Epidermal nevi are a class of hamartomas derived from ectoderm. They are relatively common, affecting 1 in 1,000 individuals. They may present as a single plaque or be more extensive, assuming a whorled appearance. This type of arrangement is also known as a Blaschkoid pattern, which is frequently seen in skin conditions displaying genetic mosaicism. Genetic mosaicism occurs when two genetically distinct cell populations proliferate in one organism. This can result in two or more phenotypically unique cutaneous lesions, as in the case of epidermal nevi.1,2

Keratinocytic epidermal nevi are those derived from ectoderm that goes on to differentiate into keratinocytes. There are more than 10 histologically distinct types of keratinocytic nevi. One such variant demonstrates epidermolytic hyperkeratosis and is thus known as an epidermolytic epidermal nevus. This entity is clinically indistinguishable from other subtypes within this category. Uniquely, this histologic finding is also seen in a generalized form, known as epidermolytic ichthyosis or bullous congenital ichthyosiform erythroderma. Generalized epidermolytic ichthyosis is an autosomal-dominantly inherited condition with significant associated morbidity and mortality, resulting from a mutation in the genes that code for keratins (K) 1 and 10. These same defects have been demonstrated in epidermolytic epidermal nevi in individuals who have born offspring with epidermolytic hyperkeratosis. This indicates that this postzygotic mutation may also result in gonadal mosaicism, especially in individuals with extensive lesions. We present a case of a patient with an extensive epidermolytic epidermal nevus to highlight the importance of genetic counseling, as these patients are at heightened risk for bearing children with epidermolytic ichthyosis.

Case Report

A 16-month-old Iraqi immigrant presented to the clinic with her parents for evaluation of a skin eruption. The lesions appeared when she was 3 weeks old and developed on her neck, arms, flanks, abdomen, and legs. The rash initially was red and scaly with no noted blisters. It was initially treated with triamcinolone acetonide 0.1% ointment, which improved the pruritus but did not alter the morphology of the lesions. Since the initial appearance of the lesions, some of the areas had become brown and scaly, others brown and warty. The mother reported an uneventful pregnancy and birth. The patient was the youngest of four sisters, none of whom had similar lesions. There was no family history of consanguinity, and the parents denied any members of the extended family with similar markings. On presentation to the clinic, the patient was being treated with isoniazid for latent tuberculosis. She was otherwise a healthy, well-developed toddler. Her parents denied a history of cognitive or developmental delays. They were concerned that the lesions were a result of a chicken pox vaccine she received in Iraq.

On physical exam, the patient was an alert 16-month-old in no acute distress. On cutaneous examination, there were whorled plaques of various morphologies in a Blaschkoid arrangement distributed on her neck, bilateral upper extremities, flanks, abdomen, and bilateral medial thighs (Figure 1). Verrucous brown papules coalesced into linear plaques on the left anterior neck, bilateral axillae, and crural folds. On the flanks were digitate erythematous plaques with white scale. A hyperpigmented plaque with large, plate-like, brown scale was located on the left lateral leg. No apparent unilateral hemihypertrrophy of the limbs or dysmorphic facies was appreciated.

Shave biopsies were obtained from a verrucous lesion of the left axilla and from an eczematous lesion on the left flank. These were submitted in formalin for standard pathologic evaluation.
Epidermal nevi represent a heterogenous group of hamartomas of ectodermal origin. Skin structures arising from ectoderm include the adnexa (hair follicles, sebaceous, and apocrine glands) as well as keratinocytes. Epidermal nevi are subdivided into organoid and nonorganoid nevi. An organoid nevus is a hamartoma consisting of more than one type of tissue, or in which identification of a single tissue of origin is not possible. Organoid nevi include nevus sebaceous, syringocystadenoma papilliferum, nevus comedonicus, porokeratotic eccrine and ostial dermal duct nevus (PEODDN, also known as porokeratotic eccrine nevus). Nonorganoid nevi are also referred to as keratinocytic nevi, denoting their ectodermal tissue of derivation. This group includes inflammatory linear verrucous nevus (ILVEN), linear porokeratosis, non-epidermolytic verrucous nevus, and, as in our patient, epidermolytic verrucous nevus.

Epidermal nevi appear at or shortly after birth as localized lines of epidermal thickening. Lesions may appear macerated at birth, but tend to become more verrucous with age. ILVEN, a variant of epidermal nevi, is a verrucous and erythematous lesion that can occur at any site but is most often seen on the limbs or perineum in females. Characteristic of epidermal nevi is the linear or whorled arrangement, which tends to follow the lines of Blaschko. This Blaschkoid pattern is thought to be due to the clonal proliferation of two genetically distinct cell lines that arise from a postzygotic mutation during embryogenesis, referred to as genetic mosaicism. A genetic mosaic is an organism composed of two or more genetically different populations of cells that originate from one genetically homogeneous zygote. There are two major categories of mosaic phenotypes: functional mosaicism, resulting from the Lyon effect of X inactivation, which can be transmitted from mother to daughter, and genomic mosaicism, which is caused by postzygotic autosomal mutations. This latter category is the type of mosaicism observed in epidermal nevi. The degree of clonal proliferation and the point at which the mutation occurred during embryogenesis determine the extent and distribution of an epidermal nevus, which may present as an isolated plaque or diffusely. They can involve an entire limb, half of the body in a unilateral distribution (nevus unius lateris) or both sides of the trunk, limbs, and face in a symmetric pattern with demarcation at the midline (ichthyosis hystrix).

At least 10 histologic variants of epidermal nevi have been delineated. Virtually all are characterized by hyperkeratosis, epidermal hyperplasia, acanthosis, papillomatosis, and variable parakeratosis. The inflammation of an inflammatory linear verrucous epidermal nevus refers to the clinical appearance of the lesion, as an inflammatory infiltrate is not typically characteristic on histologic observation. Other findings, such as epidermolytic hyperkeratosis, as in our patient, may also be seen. This is characterized by perinuclear vacuolization of keratinocytes and increased numbers of enlarged keratohyalin granules with overlying hyperkeratosis.

In patients with epidermolytic epidermal nevus, evaluation of affected tissue with epemodolysis has demonstrated mutations in KRT1 and KRT10, the genes that code for keratins 1 and 10 (K1 and K10). These abnormal keratins are found in the spinous and granular layer of the epidermis, where the epemodolysis occurs. Mutations in K1 and K10 are also seen in individuals with generalized epidermolytic hyperkeratosis. Generalized epidermolytic hyperkeratosis is usually transmitted as an autosomal-dominant trait. However, instances of individuals with extensive epidermolytic epidermal nevus bearing offspring with generalized epemodolysis have been observed. Studies of three unrelated persons with epidermolytic epidermal nevi demonstrated mutations in one of the two K10 alleles in keratinocytes cultured from lesional skin but not from nonlesional epidermis. Each of the patients had offspring with generalized epidermolytic hyperkeratosis, all with the same K10 mutations isolated from the parents’ epidermolytic EN.

It is crucial that persons with epidermolytic verrucous nevi who are planning pregnancy be aware of the possibility of bearing offspring with epidermolytic hyperkeratosis. Epidermolytic hyperkeratosis is also known as epidermolytic ichthyosis, bullous congenital ichthyosiform erythroderma of Brocq, or bullous ichthyosis. It presents at birth with erythroderma, erosions, and peeling, with widespread areas of denuded skin. Skin fragility and blistering decrease overtime, and marked hyperkeratosis supersedes. Epidermolytic ichthyosis can be severely disfiguring and have a tremendous impact on patient quality of life. Neonates are at high risk for sepsis as well as fluid and electrolyte imbalances. Later in life, issues with secondary skin infections, in addition to postural and gait abnormalities secondary to the severe hyperkeratosis, may develop. Awareness of these issues is essential for family planning.

The risk of recurrence of epidermolytic ichthyosis in future offspring is 50% if one parent is affected with generalized EHK. It is difficult to estimate the risk of a parent with an epidermolytic epidermal nevus producing a child with the generalized form. According to the mosaic hypothesis, the risk depends on the percentage of gonadal cells that are involved, ranging from 50% if all the cells were involved to 0% if no cells were involved. A correlation between the extent of cutaneous involvement and the likelihood of gonadal mosaicism may exist. Postzygotic mutations that occur very early in embryonic development may lead to more extensive epidermal nevus and may affect organ systems other than the skin, such as the gonads. At this...
time, it is not possible to accurately predict if a person with an epidermolytic epidermal nevus will have a child with generalized epidermolytic hyperkeratosis.

Prenatal diagnosis of epidermolytic ichthyosis was initially performed by ultrastructural analysis of fetal skin biopsies and amniotic fluid cells. The presence of keratin filament aggregates within these cells confirms the diagnosis. However, analysis of amniotic cells is not sufficient to exclude epidermolytic ichthyosis, as tonofilament clumping may not be uniformly present. The sensitivity of ultrastructural fetal skin analysis is improved by multiple fetal skin biopsies. Biopsies must be performed after 14 weeks gestational age, the earliest point at which K1 and K10 are expressed in the suprabasal layer.13 Rothnagel et al. demonstrated that direct gene sequencing of DNA from a parent with generalized epidermolytic hyperkeratosis could be performed to isolate the K1 and K10 mutations. Subsequent analysis of chorionic villus DNA sampled at 15 weeks could then be performed as a means of prenatal diagnosis.14 This method has also been used in prenatal testing for epidermolytic ichthyosis in parents with extensive epidermolytic epidermal nevi.1

Given the extent of our patient’s lesions, she and her family were advised to seek genetic counseling were she to become pregnant in the future. Genetic sequencing of lesional skin could be performed to isolate the specific gene mutation, which could then be compared to fetal DNA. This case is presented as a reminder that cutaneous postzygotic mosaicism can have an increased risk for gonadal involvement, resulting in offspring with generalized disease. Epidermolytic ichthyosis results in significant morbidity, further emphasizing the importance of early patient education in patients with epidermolytic epidermal nevi.

Acknowledgements

We would like to thank Dr. Ryan Hick of Propath Laboratory of Dallas, TX, for reviewing and discussing the pathology in this case.

References

A Report of Kyrle’s Disease (Hyperkeratosis Penetrans) in a 43-Year-Old Male with End-Stage Renal Disease

Ryan Skinner, DO,* Nina Sabzevari, BS,** Daniel Hurd, DO***

*Chief resident, Dermatology Department, LewisGale Hospital Montgomery, Blacksburg, VA
**4th-year medical student, Edward Via College of Osteopathic Medicine, Blacksburg, VA
***Program Director, Dermatology Residency Program, LewisGale Hospital Montgomery, Blacksburg, VA

Disclosures: None
Correspondence: Ryan Skinner, DO; ryan.skinner.do@gmail.com

Abstract
Kyrle’s disease, also known as hyperkeratosis penetrans or hyperkeratosis follicularis et parafollicularis in cutem penetrans, is a rare condition, classified as one of the perforating dermatoses. Clinical presentation is typically numerous red-brown nodules with a scaly crust and central hyperkeratotic plug. Although an identifiable cause has yet to be established, there appears to be a strong relationship with end-stage renal disease and diabetes mellitus. In this report, we present a case of Kyrle’s disease in a 43-year-old male with multiple comorbid medical conditions and provide a review of efficacious treatments.

Introduction
Perforating dermatoses, including Kyrle's disease (or hyperkeratosis follicularis et parafollicularis in cutem penetrans), perforating folliculitis, elastosis perforans serpiginosa, and reactive perforating collagenosis, are disorders of transepithelial destruction of dermal structures, commonly occurring secondary to chronic renal disease or diabetes mellitus. Kyrle’s disease was first described in 1916 and usually presents as an extensive, painless papular eruption with a hyperkeratotic central plug. It most commonly involves the lower extremities but can also involve the upper extremities and trunk. There is no involvement of the acral surfaces or mucous membranes. Histologically, there is epidermal atrophy with extension into the papillary dermis and the presence of a hyperkeratotic plug.

The etiology of Kyrle’s disease is unknown, and although in some cases it appears to be a primary perforating skin disorder, in others it occurs secondary to chronic kidney disease, liver disease, congestive heart failure or diabetes mellitus. Treatment is focused on managing underlying medical conditions, if present, as well as keratolytic agents, although no one treatment option has proven to be efficacious in improving the appearance of lesions.
Case Presentation
A 43-year-old African American male presented to our clinic with a chief complaint of bilateral pruritic papules on his upper and lower extremities of two to three months duration. He initially treated the lesions using a topical antifungal cream prescribed by his primary care physician, which was unsuccessful. His past medical history consisted of end-stage renal disease, diabetes mellitus, hypertension, thyroid disease, anxiety, and depression. Dialysis was initiated for five months prior to this cutaneous event due to worsening renal failure.

On clinical exam, the patient had numerous hyperpigmented, excoriated papules, with occasional hyperkeratotic central plaques, on the bilateral upper and lower extremities (Figures 1 and 2). A punch biopsy was obtained from a lesion on the right forearm, and pathology revealed epidermal hyperplasia surrounding areas of neutrophilic debris and fragmented elastic fibers in the epidermis and dermis (Figures 3 and 4). The appearance of the lesions, co-existing medical conditions, and pathologic findings confirmed a diagnosis of Kyrle’s Disease. The patient was given potent topical corticosteroids, and narrowband UVB therapy was recommended, but the patient failed to follow up.

Discussion
Kyrle’s disease is classified as one of the perforating dermatoses along with elastosis perforans serpiginosa, perforating folliculitis, and reactive perforating collagenses. It was first described by Austrian pathologist and dermatologist Josef Kyrle in 1916 as “hyperkeratosis follicularis et parafollicularis in cutem penetrans.” Despite efforts to identify a cause for the disease, it has yet to be determined whether there are any underlying hereditary links or if it is idiopathic in nature. The strongest associations thus far are with chronic renal failure and diabetes mellitus; it is estimated that about 10% of patients on hemodialysis will eventually develop Kyrle disease. In a study by Papali et al., of 21 patients with Kyrle’s disease, 12 were found to have diabetic nephropathy as well as elevated serum phosphorus levels. They proposed that because the skin lesions appeared to improve following dialysis, it is possible that hyperphosphatemia and uremic toxin buildup could be contributing factors to development of the lesions; however, further investigation of this relationship is needed.

Kyrle’s has also been linked to various other diseases, including, but not limited to, hepatic dysfunction, liver carcinoma, hypothyroidism, myelodysplastic syndrome, congestive heart failure, and tuberculosis lymphadenitis. In one case report of two Indian siblings affected with Kyrle’s Disease, ages 7 and 10, a possible autosomal-recessive genodermatosis was proposed, although evidence for a familial predisposition is still not well-studied.

Kyrle’s lesions typically manifest as a generalized eruption of multiple red-brown nodules with a scaly crust and central hyperkeratotic plug. In some instances, the lesions may coalesce to form larger plaques. Although the lower extremities are the primary sites of involvement in the majority of cases, the trunk may also be affected. Typically there is sparing of the mucous membranes, palms, and soles. The lesions are usually painless, but can be intensely pruritic and cosmetically bothersome.

Histologically, the lesions are characterized by a keratotic plug with basophilic cellular debris filling epithelial invaginations. Additionally, there may be parakeratosis in some parts of the plug as well as abnormal keratinization involving the entire epidermal thickness, leading to contact between keratinized cells and dermis. In some cases, there are neutrophils located where the keratinized cells contact the dermis. Lymphocytic and histiocytic infiltrates may also be seen.

Treatment targets the presumed underlying associated disease processes, such as adequate blood glucose control for diabetes mellitus and dialysis for end-stage renal disease, as well as direct treatment to the lesions and symptom relief with topical agents. One study showed that with better glycemic control, where fasting blood glucose was < 75 mg/dL, post-prandial plasma glucose was < 131 mg/dL, and HbA1c was < 7.5, the lesions completely healed in about eight weeks and left behind only a hyperpigmented scar. Other documented effective therapies include topical salicylic acid, oral isotretinoin, tretinoin cream, and hypallergenic emollients to soften the skin. To control pruritus, topical lotions including methanol or camphor may be soothing, and oral antihistamines like hydroxyzine, which can be sedating, may aid in symptom control at night. UV therapy can be helpful for those with diffuse skin involvement and individuals with renal or hepatic disease. The proposed mechanism of UV therapy is modification of keratinocytes in presentation skin. Carbon dioxide laser or cryosurgery can be used for smaller lesions; however, there are risks of skin hypopigmentation in individuals with darker skin, as well as the possibility of inducing diabetic foot infections in patients with diabetes mellitus or peripheral vascular disease. There is no randomized data to indicate a primary modality of treatment, and a variety of therapies can be implemented with special attention to the underlying comorbidity, if one is present.

Conclusion
In this report, we describe the case of a patient with end-stage renal disease and diabetes mellitus, currently undergoing dialysis treatments, who presents with Kyrle’s disease (hyperkeratosis penetrans). Although the disease has been presented in various case studies and associated with many systemic illnesses, there is no well-established cause or genetic link identified to date. However, because of the greater association with renal dysfunction and diabetes mellitus, it is important for physicians evaluating perforating dermatoses in patients with comorbid illnesses to be aware of this relationship to provide efficacious therapy and appropriate referrals for the management of underlying disease. Future studies are needed to further investigate the role of renal disease and diabetes in the development of Kyrle’s disease.

References
Multinucleate Cell Angiohistiocytoma: A Case Presentation and Discussion

Angela Macri, DO,* Jaclyn Hess, MD,** Jonathan S. Crane, DO, FAOCD, FAAD

*Dermatology resident, PGY-2, OMNEE / Sampson Regional Medical Center, Clinton, NC
**Rotating dermatology intern, PGY-1, New Hanover Regional Medical Center, Wilmington, NC
***Program director, Dermatology Residency Program, OMNEE / Sampson Regional Medical Center, Clinton, NC; Assistant professor, Dermatology, Campbell University School of Osteopathic Medicine, Buies Creek, NC; Senior attending, New Hanover Regional Medical Center, Wilmington, NC

Disclosures: None
Correspondence: Angela Macri, DO; angmacri17@gmail.com

Abstract
Multinucleate cell angiohistiocytoma is a rare, benign disease that occurs in middle-aged women and presents as reddish-brown to violaceous, dome-shaped papules on the extremities or face. These lesions can progress, and may become disseminated. Several therapies have been documented in the literature, with varying results. We present this case to increase awareness of multinucleate cell angiohistiocytoma and show that the KTP laser is an effective treatment for this rare condition.

Introduction
Multinucleate cell angiohistiocytoma is a rare, benign disease in which asymptomatic, reddish-brown to violaceous, dome-shaped papules develop over weeks to months, commonly on the extremities and face. Lesions can be distributed in a random, linear, or annular pattern and can rarely present generalized. To date there are fewer than 150 reported cases of this in international literature. This condition is found most frequently in middle-aged to elderly women, with a median age of 55 years old. There are no definitive treatments, but a number of different therapies have been attempted. Previously documented therapies include vascular lasers and topical steroids, although no one treatment has been shown to be superior.

Presentation
A 69-year-old white female with a history of hypertension presented with slow-growing lesions on her left medial knee that were tender, itchy, and progressing (Figures 1 and 2). They began appearing four years prior. Biopsies were obtained and demonstrated a proliferation of small, thin-walled vascular channels, surrounded by pericytes in the superficial and mid dermis (Figure 3). The surrounding dermis contained scattered multinucleated cells with angulated cytoplasm (Figure 4) and a background of somewhat hyalinized collagen bundles. A few inflammatory cells were noted. An immunostain for CD31 was used to highlight the vascular proliferation. HHV8 immunostain was negative. The findings were consistent with multinucleate cell angiohistiocytoma. A potassium titanyl phosphate (KTP) laser with a wavelength of 532 nm was used to treat the lesions, with a 2 mm spot size, fluence of 10 J/cm², a repetition rate of 5 Hz, and a 10 millisecond pulse duration. Two separate treatment sessions were completed one month apart (Figures 5 and 6).

Discussion
Multinucleate cell angiohistiocytoma was first described in 1985 by Smith and Wilson Jones. In 2015, a review of 142 cases by Frew found that 79% of patients were female, and the most commonly affected areas were the hands (30%), face (29%), legs (20%) and abdomen (10%). Clinically, these lesions may resemble Kaposi's sarcoma, acroangiodermatitis, granuloma
MCA is considered to be of fibrohistiocytic origin, and there is considerable histological overlap with entities such as fibrous papule of the nose, the vascular atrophic variant of dermatofibroma, and others. The main histologic findings include bizarre basophilic multinucleated cells, small-vessel inflammation, mild dermal fibrosis, epidermal hyperplasia, and sparse lymphohistiocytic infiltrate. Immunohistochemical studies are variable in their results but have shown that vascular endothelial cells stain positive for CD68, normally a macrophage or histiocytic marker, as well as for factor VIII, CD31, and CD34. The multinucleated cells are negative for endothelial markers factor VIII and CD34 and positive for macrophage/histiocytic markers factor XIIIa and CD68.

The pathogenesis of MCA may be an underlying inflammatory stimulus that leads to vascular changes and eventually a fibrotic response that precipitates further lesion development. CD68 positivity in endothelial cells may be related to an inflammatory response involving migrating macrophages that are responsible for the increased dermal vascularity. Findings of macrophages and fibrosis are consistent with lesions that are longstanding, which may be why some multinucleated cells in MCA are negative for CD68. An overexpression of estrogen receptor alpha has been found in spindle cells and multinucleated cells of MCA, also suspected to be responsible for the vascular hyperplasia.

The overexpression of estrogen receptors in these lesions may be why MCAs are found predominantly in females. MCA slowly progresses, but some cases have spontaneously resolved. There has been no statistically significant association between MCA and neoplasia. Several treatments have been used for MCA, including argon laser, intense pulsed light, carbon dioxide laser, cryosurgery, surgical excision, and intralesional steroids in combination with pulsed dye laser. Because of the progressive nature and disturbing cosmetic appearance of the lesions, our patient requested treatment. We used the 532 nm potassium titanyl phosphate laser; to our knowledge, this is the first documented case of this laser being used to treat MCA. It was chosen based on its ability to treat superficial vascular lesions, as vascular proliferation is a prominent finding in MCA. The patient underwent two treatments with the KTP laser and reported a decrease in size and erythema and a smoother texture to the lesions. She experienced only slight pain at the time of the procedure but did not experience any bruising, a benefit of the KTP compared to the PDL laser. She underwent two treatments and experienced approximately a 50% overall improvement in the appearance of the lesions. We suspect that with further treatment she will improve even more.

Conclusion
Multinucleate cell angiohistiocytoma is a rare, benign condition that may be under-recognized by dermatologists. Because of its progressive nature and disturbing cosmetic appearance, treatment of these lesions is often desired. Our case shows that the KTP laser is a practical treatment option for MCA based on its ability to treat superficial vascular lesions.

References
Abstract
Pili annulati is a rare hair disorder characterized by the presence of bright and dark bands on the hair shaft when viewed by reflected light. The appearance of light bands is due to clusters of air-filled cavities within the hair shaft and reduplicated lamina densa in the region of the root bulb. The condition is inherited in an autosomal-dominant fashion and requires no treatment. We report a case of an 18-year-old female diagnosed with pili annulati with no other associated dermatologic conditions.

Introduction
Pili annulati, also known as ringed hair or spangled hair, is a rare, autosomal-dominant hair disorder characterized by shiny and speckled hair with a pattern of alternating light and dark bands. Pili annulati was first described in 1866 by Landois et al., and there have been fewer than 50 reports describing it in the literature. This condition most commonly occurs in scalp hair, but can also occur in other regions of the body. It has a variable age of onset. The disease expression can vary along each individual hair shaft and between hairs in the same individual. Hairs can also present with other surface abnormalities such as trichorrhaxis nodosa; however, the tensile strength and growth are not affected.

Case Report
An 18-year-old female presented to our outpatient dermatology clinic for evaluation of moles on her trunk with no complaints of her hair. Her skin examination was normal with the exception of her hair findings. On physical exam, her hair demonstrated a blonde speckled appearance affecting the length of an entire hair strand, involving every hair strand of her scalp (Figures 1, 2). On closer inspection, each hair strand had alternating blonde and light brown bands. Her scalp exam was unremarkable with no evidence of scaling, flaking, erythema, or scarring. The patient denied having any hair products in her hair. She denied any itch or discomfort of her scalp and denied fragility of her hair. She stated that her hair developed these features in childhood. She admitted to her maternal grandmother possessing the same hair quality and texture. Microscopic evaluation of a single hair strand showed alternating light and dark bands.

Discussion
Clinical presentation and pathogenesis
The clinical presentation of pili annulati is fairly typical between patients. There are alternating light and dark bands on the hair shaft when viewed by reflected light. Clinically, bands that appear light to the unaided eye correspond to dark bands by light microscopy. They are seen as air-filled cavities within the cortex of the hair shaft by electron microscopy. It is this periodic occurrence of air-filled cavities along the hair cortex that scatter and reflect the light while preventing it from being transmitted. Those cavities have a keratin-lined inner surface and are believed to occur as a result of failure in the assembly of cytokeratins or other structural proteins, resulting in an insufficient formation of microfibrils. Other proposed mechanisms include a matrix formation defect and a defective regulatory protein involved in the extracellular matrix formation.

Histology
There are no histological abnormalities noted on scalp biopsies, and the cytokeratin distribution noted with immunohistochemical studies of the scalp of affected individuals demonstrates the same pattern as the unaffected scalp. However, a wavy basement membrane zone has been reported in affected cases. Electron microscopy studies of the scalp of patients with pili annulati have demonstrated the root bulb exhibiting a reduplicated lamina densa, in contrast to the single thin electron-dense band seen in control specimens.

Genetics
Pili annulati has been reported to have an autosomal-dominant mode of inheritance. The gene locus 12q24.32-24.33, with a critical interval of 3.9Mb, has been mapped to pili annulati. However, no specific mutations responsible for this region have been identified in the coding or promoter sequences. It is currently believed that regulatory gene elements may be implied in the pathogenesis of pili annulati. A possible phenotypical expression of nonsense Wnt mutations (highly conserved signaling molecules) affecting the ligand or receptor regions has also been suggested.

Associations with other diseases
Alopecia areata has been reported in association with pili annulati in some cases. However, there have been extensive studies, including family pedigree analyses, that have failed to identify a strong correlation between the two conditions.
as they seemed to have occurred independently. Linkage studies and nucleotide polymorphism tests on regions responsible for alopecia areata have not identified the pretense of the loci known to be responsible for pili annulati. In addition, the locus for pili annulati contains the gene Frizzled 10, which is involved in organogenesis and development. The regions associated with alopecia areata are associated with genes expressed in the hair follicle and involved in T cell-mediated immunity.2

Pili annulati has also been described in association with alopecia areata, blue nevi, leukonychia, melanoderma, syndactyly, and polydactylism.5 Osorio et al. described a case of an African American female with central centrifugal cicatricial alopecia whose trichoscopy evaluation revealed the spangled light and dark pattern of the hair shafts characteristic of pili annulati.6 It has been proposed that individuals with autoimmune disease could be predisposed to have antigenic alterations in the hair root that could lower the threshold for developing conditions such as pili annulati. Thus, genes from different locations could result in a synergistic combination of autoimmunity and molecular changes to the hair bulb that result in frequent occurrence of both alopecia areata and pili annulati.2

**Differential Diagnoses**

When a pili annulati diagnosis is suspected, the clinician should also consider pseudopili annulati and monilethrix. Pseudopili annulati is a twisted-hair phenotype that has a normal hair shaft under light microscopy but clinically appears as a banding pattern. Monilethrix, an autosomal-dominant condition, appears as alternating nodes and constrictions under light microscopy; it also presents with fragile hair.3 Other differentials include trichorrhexis nodosa, trichorrhexis invaginata, and pili torti, which can be differentiated by close inspection and fragility of the hair.

**Treatment**

There is no current treatment for pili annulati. Patients rarely have any complications with the condition. Nevertheless, patients may benefit from minoxidil; it stimulates normal hair matrix production, which may help with hair structure abnormalities.7

**Conclusion**

Pili annulati is a hair disorder not commonly encountered in practice. Our case represents a typical clinical presentation of the rare condition. The patient did admit to her maternal grandmother having the same pattern that can be traced to the autosomal-dominant mode of inheritance. Our patient had no associated hair conditions or history of autoimmune conditions. She had no complaints about her hair and did not seek treatment. Often, patients present with rare but benign findings in dermatology practice. It is important to recognize and reassure our patients of the benign nature of their condition and be mindful of possible associated findings and differential diagnoses. In the case of our patient, after close inspection and microscopic evaluation, she left our clinic educated about pili annulati.

**References**


A Case of Progressive Macular Hypopigmentation

Mehreen Sheikh, BS,* Jocelyn LaRocque, DO, FAOCD**

Abstract
Progressive macular hypomelanosis (PMH) is defined as a localized loss of pigmentation seen mostly on the trunk, sometimes with extension into the upper extremities and head/neck region. The pathogenesis of PMH is not known, but it has been speculated that certain strains of *P. acnes* residing in hair follicles may produce a depigmenting factor, which causes PMH. This case presents a female with PMH lesions located on her back, neck, and lower extremities bilaterally. Herein, we discuss PMH pathogenesis, clinical presentation, differential diagnosis, and patient management.

Introduction
Progressive macular hypomelanosis (PMH) is a localized loss of pigmentation presenting mostly commonly on the trunk, though it may extend to the upper extremities and head/neck region.1,2 Hypopigmented, confluent macules arise without prior onset of injury, inflammation, or known infection.2 They are ill-defined and non-scaly in nature, with a predilection for young females aged 18 to 25 years old.3,4 Affected individuals most commonly have skin type IV, which may be due to the ease of lesion recognition in contrast to the surrounding pigmented skin.4 The pathogenesis of PMH is not known; however, it has been speculated that certain strains of *P. acnes* residing in hair follicles may produce a depigmenting factor, which causes PMH.1 Treatments have been geared toward *P. acnes* reduction and repigmentation with the use of antimicrobial, ultraviolet light and anti-inflammatory therapies. Success has been shown in the use of isotretinoin in PMH lesions, further supporting an underlying *P. acnes* origin of this disease.5

PMH is not a commonly diagnosed entity. Dermatologists may want to consider the condition when hypopigmented lesions do not respond to typical therapies like topical steroids and anti-fungal treatments. A case of PMH is described here to highlight the importance of recognizing this cutaneous disorder.

Case Study
A 58-year-old female with skin type IV presented with pigment loss of unknown cause, most prominently located on the midline of her lower back, neck, and lower extremities bilaterally (Figures 1, 2). The lesions had been present for months, and previous treatments included clobetasol propionate and betamethasone dipropionate, which did not lead to improvement of the condition. Clinically, she had asymptomatic, ill-defined, hypopigmented, and non-scaly macules that were coalescing into patches. They had rapidly progressed over several weeks. The lesions were not inflammatory. Distribution did not follow Blaschko’s lines. The non-affected skin appeared uniformly tan in comparison to the hypopigmented regions.

The patient’s only past medical history included hypothyroidism and hypercholesterolemia.

A 4 mm punch biopsy was obtained from the right lower back. Pathology showed subtle changes that included mild, scattered superficial perivascular inflammation and dermal pigment deposition (Figures 3, 4). These results clinically and histologically support PMH, where other findings have included a ring of pigment around the dermal papillae, but decreased melanin content.6

Upon follow-up, the patient received benzoyl peroxide wash daily and minocycline HCl 100 mg capsules BID for eight weeks. The patient discontinued minocycline after one week due to GI upset and was switched to doxycycline 100 mg capsules BID for the remaining seven weeks. Appearance of lesions was improved at the eight-week appointment. The hypopigmented patches were still present, but repigmentation had occurred compared to initial presentation, and the lesions were not spreading.

Discussion
In the 1980s, Guillet et al. first defined PMH as a skin pigment disorder designated for people of mixed ethnicity. It is currently postulated that PMH presents in skin types IV-VI.1 Many terms around the world have been used to describe PMH, such as “Creole dyschromia” and “cutis trunci variaita.”7

Because of the variation in names of PMH, it is important to elucidate an etiology behind the hypopigmentation. A study conducted by Westerhof et al. showed that biopsies from sites of hypopigmentation contained a mild perifollicular lymphocytic infiltrate as well as positive *P. acnes* from cultures.2,4 Wood’s lamp illumination over the hypopigmented areas produced a red-colored follicular fluorescence.1 Healthy, pigmented skin, when observed histologically and cultured, did not show signs of infiltrate or bacteria.
PMH is often unrecognized in the clinical setting and mistaken for other skin disorders that present similarly. Once a diagnosis of PMH is considered, several other differentials must be ruled out, including, but not limited to, pityriasis alba, vitiligo, tinea versicolor, lichen sclerosis, and mycosis fungoides. Pityriasis alba also presents with patches of hypopigmentation. However, it is most commonly seen in children and adolescents, whereas PMH is mostly seen in females aged approximately 20 to 30 years old. Furthermore, pityriasis alba lesions present with fine scale, which is not present in PMH. Vitiligo may also be part of the differential; however, this is a process attacking melanocytes that results in loss of pigmentation, rather than a decrease in the amount of pigmentation. Histologically, this patient had melanocytes present that were confirmed by immunohistochemical staining, further arguing against a diagnosis of vitiligo. Tinea versicolor can also cause pale patches distributed on the trunk; however, these lesions are scaly, whereas the lesions of PMH are not. Tinea versicolor is also fungal in origin, and the patient presenting with PMH will fail traditional topical anti-fungal treatments for suspected tinea versicolor. Other considerations for hypomelanosis include mycosis fungoides and lichen sclerosis, but pathology did not support either of these.

PMH proves to be a diagnosis of exclusion. Recent studies have argued in favor of a pathogenesis of Propionibacterium acnes as the underlying cause of PMH, and the variation in subtypes that can cause the hypopigmentation. P. acnes is found in pilosebaceous glands, which are in high concentration on the trunk. However, acne is not a nidus for PMH nor does it worsen in those who have PMH. Different strains of P. acnes could explain why those who have facial acne do not experience the hypopigmentation found from the strains of PMH. One study conducted by Relyveld et al. employed amplified fragment length polymorphism for the 16S rRNA gene of P. acnes to elucidate the differences between strains in acne and PMH. Of the 14 patients studied, eight P. acnes strains were substantially different from those with acne.

With the possible pathogenesis of P. acnes, treatment has been geared toward resolving the underlying acne strains. A study conducted by Relyveld et al. used a sample size of 45 patients to test the effectiveness of repigmentation between the treatments of 5% benzoyl peroxide/hydrogel/1% clindamycin lotion in combination with UVA irradiation compared to 0.05% fluticasone propionate cream in combination with UVA irradiation. The results showed that antimicrobial treatment for repigmentation was superior (photometric measurements $P=0.007$, patient assessment $P=0.0001$, and dermatologist assessment $P=0.0001$). This sheds further light on the source behind PMH.

Another study employed narrowband UVB (NB-UVB) treatment for patients with PMH. More than 90% repigmentation was documented for nine of the 16 patients who received biweekly NB-UVB. Though the sample size was small, this may suggest another means of therapy for those with PMH.

More recently, a case study showed improvement of PMH pigmentation with oral isotretinoin treatment. The patient had been treated for PMH and rosacea with NB-UVB without success of repigmentation. Once 10 mg daily oral isotretinoin was added to the regimen for treatment of rosacea, the patient experienced resolution of PMH lesions within one month. These lesions did not return once isotretinoin was discontinued. This could be due to the reduction of sebum found in the pilosebaceous unit alongside P. acnes, further supporting P. acnes as the pathogenesis of PMH.

One PMH study has shown positive effects with the use of isotretinoin. This patient was prescribed benzoyl peroxide as well as 100 mg doxycycline to treat her hypopigmented lesions. At eight-week follow-up, repigmentation was evident on the trunk and back, again lending credence to the P. acnes theory.

Conclusion

PMH is a diagnosis of exclusion, and it is often misdiagnosed. Patients are often prescribed corticosteroids or antifungals. The pathogenesis behind PMH is not completely understood, but the identification of P. acnes strains within the pilosebaceous units of affected skin indicates a possible source. Further studies are needed to understand the relationship between P. acnes and the pigmentary changes of PMH; however, dermatologists should consider this diagnosis in a patient presenting with dyschromia.

References

Metastatic Melanoma Arising 10 Years after Treatment of Primary Lesion: A Unique Case Representative of SOX-10’s Efficacy in Identifying Melanomas of Metastatic Origin

Natalie Steinhoff, DO,* Gabriela Maloney, DO,** Richard Miller, DO, FAOCD***

*Dermatology resident, PGY-II, Nova Southeastern University College of Osteopathic Medicine, Largo Medical Center, Largo, FL
**Traditional rotating intern, PGY-I, Nova Southeastern University College of Osteopathic Medicine, Largo Medical Center, Largo, FL
***Program director, Dermatology Residency Program, Nova Southeastern University College of Osteopathic Medicine, Largo Medical Center, Largo, FL

Disclosures: None
Correspondence: Natalie Steinhoff, DO; nataliejsteinhoff@gmail.com

Abstract
Metastatic melanoma has a five-year survival rate of 10% to 20%, with a median survival of about nine months. Clinical presentation and histopathology may vary, making diagnosis difficult. In this case, immunohistochemical markers can lend significant help in identifying metastatic melanoma. A variety of immunohistochemical markers that help characterize malignant melanoma of metastatic origin now exist. SOX10, a transcription factor involved in differentiation of neural crest cells to melanocytes, is suggested to be superior in sensitivity, specificity, staining intensity and ease of interpretation compared to other, previously commonly used markers. We describe a unique case of a 45-year old female who presented with metastatic melanoma appearing 10 years after the primary lesion was treated with Mohs and interferon therapy. Although the lesion appeared vascular in nature, both clinically and surgically, the positivity for the SOX10 marker and the clinical history helped hone the diagnosis of malignant melanoma of metastatic origin.

Introduction
Melanoma is the most common cancer in adults ages 25 to 29, and rates are increasing faster in women ages 15 to 29 compared to men of the same age. Risk factors include sun exposure, family and/or personal history, multiple nevi, skin type and immunosuppression.1 Due to its metastatic potential, melanoma causes more than 75% of skin cancer deaths. Ninety percent of all melanoma recurrences happen during the first five years following the primary diagnosis, with the greatest risk of recurrence in the first two years. Individuals with distant metastatic melanoma have a five-year survival rate of 10% to 20%, with a median survival of approximately nine months.2,3

Up to 45% of patients with metastatic melanoma develop cutaneous metastases, making melanoma among the most common malignancies that metastasize to the skin. Melanoma makes up 12% of cutaneous metastases in women and 32% of cutaneous metastases in men. For men and women combined, the percent of all primary melanoma patients with cutaneous metastases is 18%.4

Signs of cutaneous metastatic melanoma may consist of papules or nodules that vary in color from skin-toned, pink-red, blue, brown or black, and secondary ulceration or bleeding may be present.4 The location of melanoma metastasis is commonly the lower extremity, but may occur elsewhere. There are often multiple lesions located between the original cancer site and regional lymph nodes (likely from cancer cells in lymphatics). Some other, less common presentations include a hematoma-like lesion, pedunculated tumor, zosteriform distribution, miliary pattern, diffuse melanosis and inflammatory metastases.1

Diagnosis requires histopathologic examination. A classic histological feature is epithelioid cells with prominent nucleoli; however, metastatic melanoma mimics a wide variety of other tumors.4 Clinical presentation and histopathology may vary, making diagnosis difficult. Immunohistochemical markers can help identify metastatic melanoma. Common immunohistochemical markers used to diagnose metastatic melanoma include vimentin, S100, tyrosinase, Melan-A (MART-1), HMB45 and MITF.5,6

Case Report
A 45-year old female presented with an enlarging, right upper quadrant cutaneous nodule. Her past medical history included melanoma on the right triceps, treated in 2005 with Mohs and skin graft along with one year of interferon therapy. The lesion appeared approximately one month before presentation, with no inciting events prior to the appearance of the nodule. The patient had no
systemic symptoms, pain, pruritus, perilesional ecchymosis or bleeding.

The lesion was bullous, violaceous, and measured 5 cm × 5 cm × 3 cm (Figure 1, p. 41). A CT scan of the abdomen was performed and demonstrated a 5.8 cm × 6.2 cm lesion with well-defined and enhancing rims in the skin and subcutaneous fat of the upper right abdominal wall, appearing to minimally infiltrate the underlying rectus abdominis musculature without intraperitoneal communication (Figure 2, p. 41). After surgical excision, the lesion was found to have an abnormal-appearing capsule and was sent to pathology for further evaluation. The patient was discharged with outpatient follow-up instructions, but returned about three months after surgical excision due to a recurring, fast-growing mass at the previous surgical site (Figure 3, p. 41).

Preliminary pathological findings of the original mass were consistent with invasive high-grade undifferentiated malignant neoplasm. Further immunohistochemical testing revealed that the tumor cells were positive for SOX10, vimentin, EMA, and Ki-67, and negative for Mart1, HMB45, pan-cytokeratin, desmin, smooth muscle actin, CD31, CD34, ERG and tyrosinase (Figures 4, 5, p. 41). Given the clinical history, the morphologic and immunophenotypic findings were found consistent with malignant melanoma of metastatic origin. Further testing revealed positivity for BRAF VE1 and BRAF V600E, further confirming the diagnosis.

Discussion

Clinical presentation and histopathology of metastatic melanoma vary, making diagnosis difficult. In this instance, IHC markers provided significant assistance in identifying metastatic melanoma. In the past, the IHC marker of choice in detecting melanoma metastases in sentinel lymph nodes has been S100, as it has high sensitivity for melanocytes. Yet recognition of micrometastases and solitary melanoma tumor cells may be difficult at times due to presence of S100-positive dendritic cells. Other IHC markers suggested as useful (in combination) consist of SOX10, HMB-45, Melan-A/Mart-1, tyrosinase, Ki-67/Mib-1, MITF, and vimentin, among others.

Metastatic melanoma immunophenotype is typically different from that of primary tumors, with higher expression of Ki-67 and mutant p53 protein as well as loss of CD117 typically seen in metastatic cancers. This is in contrast with cutaneous primary lesions, which usually show lower expression of Ki-67 and p53 and positive CD117.5 Ki-67 (Mib-1) is a nuclear proliferation marker expressed in all phases of the cell cycle, but it is not cell-type specific.8 In a series of 202 nodular melanoma cases, Ki-67 was found to be a superior prognostic indicator compared to mitotic count.9

HMB-45, a premelanosome marker and marker of normal melanocyte maturation, has been found to stain positive in 58% to 95% of metastatic melanomas.3,10 Melan-A/Mart-1, two antibodies that stain the same epitope, stain melanocytic lesions.8 In contrast to S100, Melan-A is not expressed in dendritic cells in lymph nodes. Melan-A has a sensitivity of about 57% to 92% for metastatic melanoma.10 MITF (microphthalmia-associated transcription factor) is a nuclear melanocytic marker, and is positive in roughly 80% to 100% of melanomas; however, specificity is low, as it can be expressed in a variety of epithelial and mesenchymal neoplasms.8,10 Vimentin, a general marker for sarcomas, stains melanocytes as well as mesenchymal cells, endothelial cells, fibroblasts and others, but not keratinocytes or other epithelia.8

SOX10, a transcription factor involved in differentiation of neural crest cells to melanocytes, is suggested to be more sensitive and specific compared to S100 and others.10 Ordonez performed a review of material on IHC markers used in diagnosing melanoma and found that, in the limited number of studies published at that time, SOX10 was very sensitive (97% to 100%) for primary and metastatic melanomas. SOX10 has been found to be expressed in all subtypes of melanoma, including roughly 80% to 100% of desmoplastic melanomas.10 In addition to primary, desmoplastic and metastatic melanomas, SOX10 has proved a sensitive marker in spindled melanoma.8

Wills et al. compared the IHC profile of SOX10 to S100 protein, HMB-45 and Melan-A in 58 metastatic-melanoma-positive lymph nodes. A statistically significant increase in staining intensity was found with SOX10 compared to S100, HMB-45 and Melan-A, with P=0.000, 0.000 and 0.003, respectively.7 Vrotsos et al. performed immunohistochemical stains for S100 protein, SOX10 and KBA.22 on 50 metastatic-melanoma-proven lymph nodes. SOX10 stained 100% (50/50) of the cases. Also, there was no “background” staining of normal cellular components. This is in contrast to S100. Although 48/50 cases, or 96%, of metastatic melanoma cases were detected with S100, the authors reported instances of significant difficulty distinguishing cells of benign reticulum from single-cell metastatic melanoma due to S100-positive dendritic cells.11

Conclusion

There are a variety of immunohistochemical markers that help characterize malignant melanoma of metastatic origin. This case is a unique presentation of metastatic melanoma, in that it appeared 10 years after the primary lesion was treated with Mohs and interferon therapy. Even though the lesion appeared vascular in nature, both clinically and surgically, the positivity for the SOX10 marker and the clinical history helped hone the diagnosis of malignant melanoma of metastatic origin.

References

A Case of Twenty Nail Dystrophy and Review of Treatment Options

Emily Tongdee, BS,* Shahjahan Shareef, BS,** Tracy Favreau, DO,*** Khasha Touloei, DO****

*Medical student, Florida International University Herbert Wertheim College of Medicine, Miami, FL
**Medical student, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL
***Dermatologist, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL
****Dermatology resident, 3rd year, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL

Disclosures: None
Correspondence: Shahjahan Shareef; shahjahanshareef@gmail.com

Abstract

Twenty nail dystrophy (TND), also known as trachyonychia, is an abnormality of the proximal nail matrix. It presents as a homogenous roughness, giving the nail a sandpaper-like appearance.1-3 Idiopathic trachyonychia most commonly presents with spongiotic inflammation with exocytosis of inflammatory cells.1,3-5 This disease has been shown to spontaneously resolve within about five to six years, but that may be too long for some patients, as this nail disorder can be cosmetically disfiguring, further impacting quality of life.6,7 We present a case of idiopathic TND and provide an updated review of the literature and the various treatments that have been utilized to treat the condition. Griseofulvin injections, PUVA, systemic steroids, oral retinoids, cyclosporine A, and nail plate dressings have shown to be highly successful treatment options. TND is a self-limiting disease. If treatment is sought, various options are available that can shorten the disease course, although no one particular treatment is considered the gold standard.

Introduction

Twenty nail dystrophy (TND), also known as trachyonychia, was first mentioned by Hazelrigg et al. in 1977 to describe nail dystrophy occurring in all 20 nails of six children.8 However, since not all 20 nails are always affected in this condition, it has since been termed “trachyonychia.”9 Trachyonychia is a specific type of proximal matrix abnormality that is marked by diffuse homogenous roughness.2 In several case studies, it has been reported as an autosomal-dominant condition of idiopathic origin.9,12 TND has also been described in monozygotic twins. Girls and boys are affected equally, and the condition can occur in adults as well.13-16 Often, the disease presents at birth and evolves slowly, or it may present in infancy or childhood and progress from there.15,17 The peak age range is from 3 to 12 years old.18 It is more commonly seen in males than females when associated with alopecia areata.1

Most commonly, TND presents as nail dystrophy with excessive longitudinal ridging and striations that give the nails a rough or broken appearance. It can involve any number of nails in the upper or lower limbs.1 Additionally, numerous superficial pits on nail surfaces leave the nails with a shiny appearance. In mild cases, alternating elevations along the nail surface, longitudinal ridging and/or pitting are almost always observed.15 In severe cases, TND may present with a sandpaper-like, opaque appearance. Severity of disease may vary between nails, but generally, the nails evolve over time into a muddy, white-grayish discoloration.15,18

Case Report

A 34-year-old Filipino female presented to the clinic with nail disease in all 20 of her nails, starting with the thumb and progressing one by one beginning about two years earlier. She had seen previous dermatologists who said fungal cultures were negative and was empirically treated with oral antifungal medications for months with no improvement. She denied any significant past medical history, surgical history, and hospitalizations. Her family history was significant for type 1 diabetes mellitus and hypertension in her father and mother, respectively. She denied any use of alcohol, tobacco or illicit drugs and said she was not taking any prescription medications, herbal supplements, or vitamins. She also denied any allergies or recent travel. Physical exam revealed thickened dystrophic nails with pitting, longitudinal ridging, and onycholysis (Figure 1). The patient was diagnosed with idiopathic twenty nail dystrophy, as all twenty nails were involved and no associations were seen. We presented the patient with many different treatment options, including intralesional steroid injections. Our patient elected to take 20 mg of biotin daily. She was also given reassurance.

Discussion

The etiology of TND is controversial. It can either present as its own entity or as a manifestation of another condition, including lichen planus (4% to 18.5% of cases), alopecia areata (45% to 83% of cases), or psoriasis (13% to 26% of cases).1,19-22 TND has also been associated with incontinentia pigmenti, vitiligio, ichthyosis vulgaris, ichthyosis, immunoglobulin IgA deficiency, hemolytic abnormalities, koilonychias, eczema, primary biliary cirrhosis, alopecia universalis and sarcoidosis.4,9,13,14,18,20,21-24 Alopecia areata is the most common disease associated with trachyonychia.25-26 Trachyonychia has a pathognomonic presentation of thin, brittle nails with longitudinal ridging secondary to fine, superficial striations seen in a regular, parallel pattern, giving it a sandpaper-like appearance.1,18 The cuticle is commonly hyperkeratotic and ragged.1 Shiny trachyonychia, a less common, milder variant, presents with

Figure 1
multiple small punctate depressions that are spread in a geometric pattern within parallel lines.\textsuperscript{2}

Since the disease affects the nail matrix, a nail matrix punch biopsy or longitudinal nail biopsy may be performed, but this is not recommended; the risk/benefit ratio is not advantageous, as the procedure is invasive and the condition can be diagnosed clinically.\textsuperscript{18} In idiopathic TND and TND associated with alopecia areata, histology of the nail will most commonly demonstrate spongiosis inflammation of the nail matrix and exocytosis of inflammatory cells (lymphocytes) into the nail epithelia.\textsuperscript{1,3-5}

When the disease is caused by psoriasis or lichen planus, histology will display findings typically associated with both of these conditions. Histology consistent with nail lichen planus will reveal hyperkeratosis, hypergranulosis, and saw-tooth acanthosis containing a band of lymphohistiocytic infiltrate with vacuolar degeneration of basal keratinocytes.\textsuperscript{15} Histology consistent with psoriasis will reveal acanthosis and focal parakeratosis affecting the proximal nail fold and nail matrix.\textsuperscript{15} Also, polymorphonuclear leukocytes along the whole length of the dorsal nail plate are commonly observed in TND histologically consistent with psoriasis.\textsuperscript{14} Focal areas of nail hypergranulosis can be seen in idiopathic trachonychia, nail lichen planus and nail psoriasis. Inflammation in the matrix can affect keratinization, causing an increase of keratohyalin granules.\textsuperscript{16} Here, histology may reveal a mild to moderate lymphohistiocytic infiltrate in the superficial dermis of the proximal nail fold and matrix.\textsuperscript{15} The ventral portion of the nail fold sometimes demonstrates hyperkeratosis of the cuticle. Other possible findings include longitudinal clefts containing zones of eosinophilic onychocytes and parakeratotic cells that may reside in the nail plates. The proximal nail matrix and the ventral proximal nail fold are typically affected more than the distal matrix. This displays clinically in the dorsal nail plate. Furthermore, nail plate abnormalities are more present in the dorsal layer.\textsuperscript{18}

Clinically, trachonychia secondary to lichen planus or psoriasis appears identical to trachonychia due to spongiosis features.\textsuperscript{1} However, due to the distinctive presentation of this nail plate abnormality and the risk of permanent nail damage from biopsy, diagnosis will usually be made clinically. Trachonychia can often be misdiagnosed as onychomycosis, so laboratory studies are recommended before initiating antifungal therapy for the treatment of onychomycosis.\textsuperscript{4} Due to the many dermatological associations, a thorough skin examination looking

### Table 1. Treatments used for TND

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Route</th>
<th>Dose</th>
<th>Time</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids (general)\textsuperscript{31}</td>
<td>Topical</td>
<td>1% ointment</td>
<td>4 months</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone\textsuperscript{40}</td>
<td>Intranasal</td>
<td>0.5 mg/kg - 1 mg/kg</td>
<td>Bimonthly for 4 months</td>
<td>Relapse, painful, proximal nailfold, need long-term compliance (effective in 4 children)\textsuperscript{40}</td>
</tr>
<tr>
<td>Prednisone\textsuperscript{27}</td>
<td>PO</td>
<td>0.5 mg/kg</td>
<td>Alternate days for 4 weeks</td>
<td>No relapse</td>
</tr>
<tr>
<td>Triamcinolone acetonide\textsuperscript{32}</td>
<td>IM</td>
<td>(10 mg/ml)\textsuperscript{3}</td>
<td>2 times per week for 8 months</td>
<td>Proximal and lateral nailfolds</td>
</tr>
<tr>
<td>Betamethasone\textsuperscript{38}</td>
<td>PO</td>
<td>4 mg</td>
<td>Mini pulse therapy (2 consecutive days every week for 2 months)</td>
<td>Shown to be effective. Usually fewer side effects vs. the daily dose of corticosteroids over weeks and months.</td>
</tr>
<tr>
<td>Tazarotene\textsuperscript{18}</td>
<td>Topical</td>
<td>0.10%</td>
<td>Nightly for 3 months</td>
<td>Required 2 courses, with side effects of peeling, erythema on proximal nailfold (showed improvement in 1 patient with alopecia areata)\textsuperscript{38}</td>
</tr>
<tr>
<td>Acitretin\textsuperscript{39}</td>
<td>PO</td>
<td>0.3 mg/kg</td>
<td>Daily dose for 3 months</td>
<td>Psoriatic trachonychia (improvement in roughness, ridging, pitting, subungual hyperkeratosis)</td>
</tr>
<tr>
<td>Cyclosporine A\textsuperscript{42,65}</td>
<td>PO</td>
<td>3 mg/kg/day\textsuperscript{42}</td>
<td>Daily for 2.5 months</td>
<td>Psoriatic trachonychia (successful in 5 patients)</td>
</tr>
<tr>
<td>Acetone</td>
<td>PO</td>
<td>2 mg/kg/day - 3.5 mg/kg/day\textsuperscript{65}</td>
<td>6 months</td>
<td>Idiopathic trachonychia, in case series of 15 patients 87% showed significant improvement after 6 months of therapy.</td>
</tr>
<tr>
<td>PUVA\textsuperscript{44}</td>
<td>n/a</td>
<td>0.7 J/cm\textsuperscript{2} - 1.4 J/cm\textsuperscript{2}</td>
<td>3 times a week for 7 months</td>
<td>All treated nails showed significant improvement, untreated remained dystrophic.</td>
</tr>
<tr>
<td>5-fluorouracil\textsuperscript{59}</td>
<td>Topical</td>
<td>5%</td>
<td>Every 2-4 days for 16 weeks</td>
<td>Psoriatic trachonychia; periungual irritation limits the drug’s use.\textsuperscript{39,57}</td>
</tr>
<tr>
<td>Griseofulvin/steroid\textsuperscript{22,24}</td>
<td>PO/ intramatrix</td>
<td>10 mg/kg</td>
<td>6 months</td>
<td>LP trachonychia, general anesthesia used.</td>
</tr>
<tr>
<td>Biotin\textsuperscript{64,67}</td>
<td>PO</td>
<td>20 mg</td>
<td>Daily</td>
<td>Primary biliary cirrhosis patient.</td>
</tr>
<tr>
<td>Petrolatum\textsuperscript{61}</td>
<td>Topical</td>
<td>Not known</td>
<td>Not known</td>
<td>Partial resolution seen.</td>
</tr>
<tr>
<td>Nail plate dressings (ultra-thin adhesive layer with lactic acid, silicon dioxide, aluminum acetylacetonate, vinyl copolymer, azelaic acid)\textsuperscript{90}</td>
<td>Topical</td>
<td>Once a week</td>
<td>6 months</td>
<td>Significant improvement at 3 months; near complete resolution at 6 months</td>
</tr>
<tr>
<td>Vitamin supplement\textsuperscript{83}</td>
<td>PO</td>
<td>Not known</td>
<td>Not known</td>
<td>Partial resolution seen</td>
</tr>
</tbody>
</table>
for psoriatic features, dermatosis, and/or hair loss should be performed.

Treatment of trachyonychia is aimed primarily at the underlying cause, if found. TND usually remits spontaneously over several years, as it is a self-limited condition. Therefore, counseling and reassurance for parents and patients is important, as is explaining to them that the disease is self-resolving. In about 50% of patients, nail changes will reveal significant improvement or resolve within five to six years. Waiting this long can be hard for some patients, as this condition can negatively affect quality of life. Currently, no specific treatment exists for the condition, and treatment is done only for cosmetic reasons. The disease does not leave any scars.

The basis of treatment involves regulating the differentiation of keratinocytes and/or decreasing the inflammation in the nail fold or nail matrix.3

Treating TND associated with psoriasis or lichen planus with systemic therapies may involve corticosteroids, oral retinoids, or cyclosporine (Table 1, p. 44).1 There have been several reports of treatment success. One article reported success with griseofulvin in an intra-matrix steroid injection in a 6-year-old boy diagnosed with lichen planus-related TND under general anesthesia over a period of six months.34,35 This method has been quite successful for TND with associated lichen planus.35-38 Relapse has been seen with intramuscular injection of corticosteroid, and compliance is reduced due to pain.39 Tosti et al. treated a lichen planus trachyonychia patient with oral prednisone 0.5 mg/kg on alternate days for four weeks. Four months after stopping the treatment, the nails demonstrated only mild longitudinal ridging, with no relapse over three years.1 They also attempted intramuscular triamcinolone acetonide 0.5 mg/kg to 1 mg/kg per month in 15 children with typical nail lichen planus with successful results.2 Silverman et al. treated a 9-year-old girl with lichen planus-related TND using potent steroids for six months, which did not result in any improvement.22

In psoriatic TND, recurrence of nail changes is usually seen when treatment is stopped.3 Still, a study using an oral retinoid (acitretin) 0.3 mg/kg daily for three months showed improvement in roughness, ridging, pitting and subungual hyperkeratosis.40 Topical 0.10% retinoid (tazarotene) did not achieve the same effect, but resulted in peeling and erythema on the proximal nail folds; however, mild improvement was seen in one patient with alopecia areata.41 Two studies also showed success with oral cyclosporine A at 3 mg/kg/day: Pierard et al. administered it daily for two and half months with success in five patients with psoriatic trachyonychia,42 and a case series of 15 patients with idiopathic trachyonychia saw an 87% improvement after six months of therapy.43

When treating idiopathic trachyonychia, good results were seen with PUVA three times a week for seven months at strengths of 0.7 J/cm² to 1.4 J/cm².44 Topical 5-fluourouracil, on the other hand, was not successful and resulted in periungual irritation that limited its use.45 Arias-Santiago et al. used nail plate dressings that consisted of an ultra-thin adhesive layer containing lactic acid, silicon dioxide, aluminium acrylacetate, vinyl copolymer, and azelaic acid that were applied once a week for six months. This particular method showed significant improvement at three months and close to complete resolution at six months.46 Mittal et al. took the unique approach of administering PO 4 mg betamethasone two consecutive days every week for two months. This mini pulse therapy was shown to be effective, with fewer side effects when compared to daily oral steroids for weeks or months.47 Petrolatum and vitamin supplementation showed only partial resolution.46,48 Biotin was used successfully to treat TND in two patients with primary biliary cirrhosis.46,49

Conclusion

TND, also known as trachyonychia, is a disease that can present independently, idiospathically, or in association with other conditions. Nail matrix biopsies are usually not recommended, as they risk leaving the patient with permanent nail damage and the diagnosis can usually be made on a clinical basis. To date, no particular treatment has been universally accepted. Positive results have been achieved with griseofulvin injections, PUVA, systemic steroids, oral retinoids, cyclosporine A, and nail plate dressings.4 But in a large majority of cases, trachyonychia is a self-limiting disease and, as a result, treatment should only be given if absolutely essential, such as when the patient’s quality of life is detrimentally affected. In this population, there are treatment options that can significantly shorten the duration of the disease.5,18 Patients should be aware of the treatment choices and the associated risks. Patients should also be reassured that abstaining from therapy is also an acceptable and safe option due to the benign nature of the disease.
References
Wolf’s Isotopic Response: A Case Report

Gabriel Guerrero, DO,* Nathan Jackson, DO,** Schield Wikas, DO***

*Dermatology resident, PGY2, Northeast Regional Medical Center, Kirksville, MO
**Dermatology resident, PGY4, LECOM/Tri-County Dermatology, Cuyahoga Falls, OH
***Program director, Dermatology Residency Program, LECOM/Tri-County Dermatology, Cuyahoga Falls, OH

Disclosures: None
Correspondence: Gabriel Guerrero, DO; Drgabeguerrero@gmail.com

Abstract
We report the case of a 53-year-old white female who presented with a mildly pruritic rash on the left chest wall, left shoulder, and left posterior neck of two weeks’ duration. Patient history included herpes zoster several months prior, and clinicopathologic findings supported perifollicular granulomatous dermatitis as an isotopic response following a healed herpes zoster episode — a rare phenomenon known as Wolf’s isotopic response (WIR). In WIR, a new skin disorder occurs at the site of another, unrelated, and already healed skin disease. In many cases of WIR, the initial dermatosis is herpes zoster, and the isotopic response is a granulomatous process. The suggested pathophysiology involves local immune dysregulation due to peripheral nerve damage. Our patient’s WIR resolved spontaneously after symptomatic treatment for pruritus.

Introduction
When injured skin looks healed and normal, the logical assumption is that the skin has returned to its non-injured state. But in 1995, Wolf et al. coined the term “isotopic response” to describe the occurrence of a new skin disorder at the site of another, unrelated, and already healed skin disease. (The term was later expanded to “Wolf’s isotopic response” to avoid any apparent correlation with radioactive isotopes, which are unrelated.)

Wolf’s isotopic response (WIR) is a rare phenomenon, with fewer than 200 cases reported in literature. WIR should be distinguished from Koebner’s isomorphic response, isomorphic meaning “same morphology” and indicating the recurrence of the original disease at the original site of injury. Since the isotopic response often follows a herpes reaction, the term “post-herpetic isotopic response” (PHIR) is often used. We describe a perifollicular granulomatous dermatitis arising as an isotopic response following a healed herpes zoster episode.

Case Report
A 53-year-old white female presented for a mildly pruritic rash on the left chest wall, left shoulder, and left posterior neck of two weeks’ duration. The rash consisted of 1 mm to 3 mm, discrete and confluent, firm whitish papules on an erythematous base (Figures 1, 2). This eruption was non-tender and without lymphadenopathy. The patient reported an episode of herpes zoster about three to four months prior, which had lasted six weeks. Based on clinical examination, a differential diagnosis of post-herpetic dermatitis such as granuloma annulare, unilateral eruptive xanthomas, or colloid milia was supported.

Two punch biopsies were performed, both of which indicated perifollicular granulomatous dermatitis (Figure 3, H&E, 40x). Pathology reported, “Sections demonstrate essentially unremarkable epidermis. Within the dermis is a superficial and deep predominantly perifollicular spilling into the interstitial collagen lymphohistiocytic infiltrate with ill-formed collections of the epithelioid histiocytes with associated multinucleated giant cells. Neutrophils and eosinophils are not identified.” Additionally, there was no mucin, elastophagocytosis, or necrobiosis. Pathology concluded, “The cutaneous pattern of injury is quite supportive of the clinical impression of post herpetic granulomatous dermatitis. Residual (active) herpes viral cytopathic changes are not identified. Special stains performed on both biopsies (GMS and AFB) are negative for fungal organisms and acid-fast bacilli, respectively.”

Based on the clinical and histopathologic findings, the diagnosis of post-herpetic granulomatous dermatitis as a secondary isotopic response to a primary herpetic infection was made. With the original herpes zoster dermatosis already resolved, the patient’s secondary granulomatous reaction was treated symptomatically for pruritus, and the eruption soon spontaneously resolved.

Discussion
WIR is used to describe the occurrence of a new skin disorder at the site of another, unrelated, and already healed skin disease. In most cases, the initial dermatosis is herpes zoster, although the condition is also seen with herpes simplex virus, varicella, thrombophlebitis, and scrofuloderma. Although many consider isotopic responses a herpes-specific phenomenon, Wolf’s definition included a wider range of initial dermatoses, which would have implications for the underlying pathophysiology.

The dermatoses that appear on healed sites are mainly granulomatous and lichenoid reactions but may also be infiltrations by hematologic malignancies, skin tumors, and infections. In a large review of 188 cases of PHIR, 64 were granulomatous reactions, 37 were malignant tumors, 27 were dysimmune reactions, 17 were infections, 15 were leukemic or lymphomatous infiltrations, 12 were comedonic-microcystic reactions, and 17 were “other.” The interval from the first dermatosis to the second has been reported as anywhere from days to years.

In general, WIR occurs due to the continuation of microscopic and physiologic changes in apparently...
healed skin. The most widely accepted theory of its pathogenesis points to cutaneous nerve damage that, in addition to altering sensation, may alter immunity. This could lead either to hyperactivity, which could cause an inflammatory process such as granulomatous or lichenoid dermatitis, or to immune suppression, which could lead to tumor infiltrations such as leukemia cutis or infectious diseases. The pathophysiology of herpes virus supports this theory, as herpes viruses infect and damage peripheral cutaneous nerves, and local immune dysregulation will occur due to a change in the release of neuromediators like substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide. This pathogenesis may or may not apply to isotopic responses to dermatoses other than herpes. In cases involving herpes, the actual virus does not seem to play a direct role, as studies and case reports rarely demonstrate viral DNA in the isotopic lesions except when the interval between the dermatoses is short. It has also been suggested that incompletely degraded varicella zoster envelope glycoproteins may cause a delayed-type hypersensitivity reaction. Others theorize the initial inflammation may disrupt the local vascular network, leading to an isotopic response.

Supporting the hypothesized pathophysiology of immune dysregulation is the phenomenon known as “inverse isotopic response” or “isotopic nonresponse,” in which a second dermatosis spares the site of previous skin injury. In one case, a widespread cutaneous T-cell lymphoma spared a resolving herpes zoster lesion. In a case series of WIR manifesting as postherpetic granuloma annulare, a unique histopathology was found. Findings included a perineural vascular or perifollicular pattern of lymphohistiocytic infiltration, including multinucleated giant cells that occurred following a herpes zoster or herpes simplex infection. These findings are unusual for idiopathic granuloma annulare. Although our case involved a nonspecific granulomatous dermatitis, the finding of perineural and/or perifollicular inflammation may help narrow the histopathological diagnosis down to post-herpetic granulomatous dermatitis. This correlates with a herpes pathophysiology in that the virus travels along nerves to nerve endings at the hair follicle isthmus, leading to folliculosebaceous spread.

Treatment in our case involved easing the patient’s pruritus. Since herpes DNA is rarely found in the isotopic lesion, especially when the interval between the two dermatoses is many months apart, antiviral therapy is not indicated. Treatment of herpes zoster does not correlate with a decrease or an increase in the rate of PHIR. Underlying malignancy such as lymphoma or leukemia has been observed in cases of WIR and PHIR, so biopsy is recommended for clinically atypical cases.

Conclusion

The WIR phenomenon sheds light on the physiology of the skin. Some authors have used the term "post-herpetic isotopic response" (PHIR) when dealing with reactions following a herpes dermatitis, which may be beneficial since pathophysiology may differ based on the initial dermatitis. It is important to be aware of the WIR phenomenon, as it may be under-recognized. Routinely inquiring specifically about a patient’s herpes-related medical history may help with diagnostic accuracy.

References

A Rare Case of Well’s Syndrome

Donna Tran, DO,* Nicole Rouse, BS,** Paul Shitabata, MD,*** Leela Athalye, DO,**** Navid Nami, DO*****

*Dermatology resident, PGY4, Western University of Health Sciences, Pomona, CA
**Medical student, Western University of Health Sciences, Pomona, CA
***Director of dermatopathology, Western University of Health Sciences, Torrance, CA
****Dermatologist, Island Dermatology, Newport Beach, CA
*****Program director, Dermatology Residency Program, Western University of Health Sciences, Pomona, CA

Disclosures: None
Correspondence: Donna Tran, DO; DonnaDTran@gmail.com

Abstract

Wells’ syndrome is a rare, idiopathic dermatosis characterized clinically by an acute, erythematous plaque resembling cellulitis and histopathologically by an eosinophilic dermal infiltration and flame figures. Also known as eosinophilic cellulitis, it was first described by Wells in 1971, and since then only 80 to 100 cases have been reported. The etiology of Wells’ syndrome is largely unknown.3-6 Although often self-limited, the disease has a tendency to recur. We describe a rare case of Wells’ syndrome presenting on the left lower leg of a 68-year-old woman and review the literature on the topic.

Case Report

A 68-year-old woman with no significant medical history presented with a pruritic eruption on her left lower extremity of several months’ duration. She denied history of insect bite or trauma prior to the onset of the lesion. Physical examination revealed a large erythematous plaque with surrounding erythematous papules over the lateral aspect of the left lower extremity (Figure 1). Laboratory investigations, including a complete blood count and total leukocyte counts, were within normal limits.

Histopathologic examination from a biopsy of the plaque revealed a superficial and deep infiltrate of lymphocytes and eosinophils with flame figures (Figures 2, 3). Based on clinicopathologic correlation, a diagnosis of Wells’ syndrome was established. Her skin lesions improved significantly with topical high-potency steroids.

Discussion

Wells’ syndrome, also known as eosinophilic cellulitis, is a rare but usually benign dermatosis that has been reported in all age groups.6 It often presents as a mildly pruritic, tender, erythematous plaque that most frequently affects the extremities. The edges are annular or arcuate with violaceous borders.8 The plaque’s color generally evolves from bright red to gray over the course of a few days, and it often resolves without scarring.6 Although Wells’ syndrome most commonly presents as a plaque or nodule, it may also present as papules, vesicles, or hemorrhagic bullae.

The diagnosis of Wells’ syndrome is based on clinical features and histopathologic findings of eosinophilic infiltration limited to the epidermis and dermis, though it may extend into the subcutaneous tissue and underlying muscle. An infiltrate of eosinophils, eosinophilic debris, and histiocytes between collagen bundles form the classic “flame figures.” Eosinophilic degranulation may also be visualized with immunofluorescent stains showing eosinophilic major basic protein (MBP).9 Infiltration into the epidermis causes epidermal spongiosis and vesiculation. Subdermal infiltration results in bullae formation. Blisters of Wells’ syndrome contain eosinophils and are predominantly subepidermal, multiloculated, and spongiotic.6

Peripheral blood eosinophilia may or may not be found. Other laboratory findings associated with Wells’ Syndrome include increased eosinophilic cation protein (ECP), and increased interleukin-5 (IL-5). ECP and IL-5 levels correlate with severity of disease.

Although its etiology is largely unknown, the proposed mechanism of Wells’ syndrome is an activated line of CD3+ and CD4+ T-cells that result in hyper-secretion of IL-5. This cytokine promotes eosinophil recruitment and degranulation.10 Eosinophils play a role in parasitic and allergic reactions. They contain toxic cationic proteins that play a role in inflammation and local tissue damage. MBP damages parasites, but also damages mammalian cells and tissue. Eosinophil-derived neurotoxin plays a role against viral infection, but as the name implies, it is neurotoxic. Other proteins secreted by eosinophils promote histamine release, neutrophil activation, tumor lysis, peroxidation, serotonin release, and clot formation.4 The various functions of eosinophils are useful in many circumstances,
but may generate edema, erythema, pruritus, and tissue damage in the presence of eosinophilia.

Although flame figures are a hallmark of Wells’ syndrome, they are not a specific finding. They can be found in other conditions with eosinophil-rich infiltrate, such as atopic dermatitis, contact dermatitis, tinea, scabies, arthropod bites, and bullous pemphigoid. Infectious cellulitis and erysipelas are very similar in clinical presentation to Wells’ syndrome, but differ in that their infiltrates are predominantly neutrophilic.6 Febrile eosinophilic cellulitis with toxocariasis infection presents with eosinophilia, migrating cellulitis, and Toxocara larvae on serology.6 Other differentials to consider include drug eruption, granuloma annulare, hypereosinophilic syndrome, chronic urticaria, and Churg-Strauss syndrome.

Wells’ syndrome has an excellent prognosis; however, it has the tendency to recur, which may prolong resolution.6 Systemic associations occur in fewer than 25% of patients with Wells’ syndrome and can include malaise, fever, arthralgia, and asthma, among other conditions. An association between the bullous form of Wells’ disease and non-Hodgkin lymphoma has been reported.9 The most common complication of Wells’ syndrome is blistering; however, long-term complications, such as reticular pigmentation and scarring alopecia, do rarely occur.5

Treatment of Wells’ syndrome depends on its severity. Mild cases may resolve with potent topical corticosteroids. Severe cases usually improve dramatically with systemic corticosteroids. Calcineurin inhibitors, griseofulvin, antihistamines, cyclosporine, dapsone, colchicine, minocycline, and antimalarials have also been proven effective.20

**Conclusion**

Wells’ syndrome is a rare condition with few documented cases and should be included in the differential of resistant cellulitis, granuloma annulare, chronic urticaria, and drug eruption. A detailed history regarding triggers and medications should be done to exclude other diseases that can mimic Wells’ syndrome clinically and histologically. The lesions generally respond well to treatment but have a tendency to recur.

**References**

Introduction

Atypical fibroxanthoma (AFX) is a rare skin condition, and both its cause and its classification are still debated. AFX is currently known as a rare cutaneous fibrohistiocytic tumor, but the term AFX was first used by Helwig in 1961 to describe a dermal tumor of atypical spindle cells. Clinically, two variants of AFX have been described. The more common clinical variant presents on sun-exposed areas, such as the head and neck, in older patients (median age 69). The less common clinical variant presents in non-sun-exposed areas in younger patients (median age 39), as it did in our patient. Histologically, this tumor had to be differentiated from other malignant skin cancers. In addition, it has been argued that this tumor may be a superficial undifferentiated pleomorphic sarcoma (UPS). This case report brings awareness to this rare skin cancer, delineates its two clinical subsets, and discusses its controversial histological origins.

Case Report

A 38-year-old man presented to the clinic with a 7 mm, erythematous papule with rolled borders and a central ulcer on the right posterior thigh (Figures 1 and 2). The lesion was originally observed by the patient approximately two months prior to his office visit. The patient reported a change in both the size and color of the lesion, as well as episodes of bleeding. There were no associated symptoms of pain or pruritus. Medical history was unremarkable. A shave biopsy was performed to rule out a keratoacanthoma versus squamous cell carcinoma versus pyogenic granuloma. Pathology revealed an ulcerated, atypical spindle cell proliferation (Figures 3a, 3b). The atypical dermal spindle cells were CD68 (Figure 4) and CD163 positive but negative for melan-A, S100, factor 13A, and CD34. Smooth muscle actin (SMA) stained positively around blood vessels. The immunohistochemical findings were consistent with fibro-histiocytic differentiation and most consistent with AFX. Treatment as a low-grade sarcoma was recommended. A complete excision was performed, and the patient has experienced no recurrence of the lesion.

Discussion

AFX is a rare cutaneous fibrohistiocytic tumor of low to intermediate metastatic potential. Due to its rarity, the incidence of AFX is unknown. AFX mainly occurs on sun-exposed skin in elderly white males during the eighth decade.
of life. However, there is a subset of younger patients with AFX on non-sun-exposed areas, such as the trunk and extremities, during the fourth decade of life. AFX usually presents as a rapidly growing lesion on sun-damaged skin such as the nose, cheeks, ears, neck or scalp. The median time between onset and biopsy or excision is four months. The lesion is usually a red or pink, solitary, asymptomatic papule or dome-shaped nodule that is less than 2 cm in diameter and may be eroded or ulcerated. The non-sun-exposed clinical variant tends to be slightly larger and has a longer duration from onset to biopsy or excision. Clinically, an AFX lesion may resemble SCC, basal cell carcinoma (BCC), or necrotic pyogenic granuloma. Since AFX has nonspecific clinical features, diagnosis requires a biopsy. A personal history of skin cancers like BCC or SCC is common in patients with AFX.

The histopathology of AFX generally demonstrates a dermal circumscribed hypercellular tumor that may extend deep into the reticular dermis and consists of a mixture of highly pleomorphic spindle cells, epithelioid cells, and multinucleated giant cells. The proportion of cell types in a lesion varies, and the neoplastic cells display a pronounced atypia despite the condition’s relatively benign nature. Histologically, AFX resembles spindle cell SCC, spindle cell or desmoplastic melanoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma (UPS, formerly known as pleomorphic malignant fibrous histiocytoma [MFH]). UPS is a soft tissue sarcoma that occurs primarily in deep soft tissue. Since the histology of AFX and UPS is identical, some consider AFX to be a less aggressive, superficial variant of UPS. Histologic differences exist between the two clinical variants (head and neck/sun-exposed areas versus trunk and extremities/non-sun-exposed areas) (Table 1). Lesions of the head and neck (the more common variant’s location of presentation) tend to be relatively smaller and better demarcated than lesions on the trunk and extremities. Lesions on the head and neck only occasionally extend into the subcutis, whereas lesions on the trunk and extremities frequently extend into the subcutis. The overlying epidermis of the lesions on the head and neck are usually atrophic or ulcerated, and hyperkeratosis and parakeratosis is common. In contrast, the epidermis of lesions of the trunk and extremities is often normal or acanthotic. Finally, the adjacent skin on the head and neck shows actinic damage, whereas adjacent skin on the trunk and extremities is usually normal. These histological differences are subtle and usually do not affect the histological diagnosis, although some may use these findings to support a diagnosis of UPS. Currently, no single immunohistochemical marker is specific for AFX. Therefore, multiple markers must be used, including those for other similar histologic diseases. Specifically, immunohistochemistry helps differentiate AFX from spindle cell SCC, desmoplastic melanoma, and leiomyosarcoma. Due to the cellular origin, cytokeratins are negative for AFX and positive for spindle cell SCC. In a similar fashion, S100 and melan-A are usually negative for AFX, yet positive for desmoplastic melanoma.

CD10, although non-specific, is strongly positive in AFX and usually negative in spindle cell SCC and desmoplastic melanoma. CD10 can also stain positive in UPS, which contributes to the debate around whether or not AFX is a variant of UPS. Desmin is positive in leiomyosarcoma and negative in AFX, helping distinguish between the two. Other markers that can be useful in differentiating AFX from spindle cell SCC and desmoplastic melanoma include CD68, CD163, procollagen-1 (PC1), p63, and vimentin.

Table 1. Histologic comparison of anatomic variants of AFX (adapted from Fretzin and Helwig)

<table>
<thead>
<tr>
<th>Location</th>
<th>Head and Neck</th>
<th>Trunk and Extremities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Relatively smaller</td>
<td>Relatively larger</td>
</tr>
<tr>
<td>Demarcation</td>
<td>Moderate to well</td>
<td>Moderate</td>
</tr>
<tr>
<td>Invasion</td>
<td>Occasionally extends into the subcutis but does not invade the deeper soft tissue</td>
<td>Frequently extends into the subcutis</td>
</tr>
<tr>
<td>Overlying epidermis</td>
<td>Usually atrophic or ulcerated; hyperkeratosis and patchy parakeratosis common</td>
<td>Normal; sometimes acanthotic; grenz zone sometimes present</td>
</tr>
<tr>
<td>Adjacent skin</td>
<td>Usually closely abutted upon the epidermis; adjacent skin showed actinic damage</td>
<td>Usually normal</td>
</tr>
</tbody>
</table>

Table 2. Immunohistochemical studies of AFX compared to other cutaneous neoplasms.

<table>
<thead>
<tr>
<th>Marker</th>
<th>AFX</th>
<th>Spindle Cell SCC</th>
<th>Desmoplastic Melanoma</th>
<th>Leiomyosarcoma</th>
<th>UPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratins</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Melan-A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Desmin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD68</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>CD163</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>PC1</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>LN-2</td>
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<td>+</td>
</tr>
</tbody>
</table>
patients, who have a defect in repair mechanisms of UV-induced DNA lesions. These patients may also have AFX in addition to sun-induced conditions like actinic keratosis, squamous cell carcinomas, and basal cell carcinomas.\textsuperscript{11-13} The presentation of AFX in a non-sun-exposed region, combined with histology demonstrating no actinic damage, is a reason to look for alternate causes and to consider UPS.

Immunosuppression is known to increase the incidence for SCC and BCC. For example, transplant recipients have an increased incidence of cancer presenting in the head and neck, and the vast majority of them are cutaneous in origin.\textsuperscript{14} This may lead some to assume that immunosuppression may also be a factor that would increase the incidence of AFX. With the true incidence of AFX unknown due to its rarity, establishing an increase in incidence may be difficult. One study mentioned only two AFX cases out of 8,724 (.023\%) de novo malignancies in 8,191 solid-organ transplant recipients.\textsuperscript{15} A second study found one case of AFX out of 642 renal transplant recipients.\textsuperscript{16} The same study also found two case of MFH (UPS). If AFX and UPS are considered the same, then the incidence may in fact be elevated in immunosuppressed patients. Finally, a third study did not mention AFX out of 484 cutaneous neoplasms in cardiothoracic transplant recipients.\textsuperscript{14} Although other substantially larger studies of AFX have been conducted, they did not specifically address immunosuppression as a factor.\textsuperscript{17}

AFX is thought to have a very low metastatic potential, with some favoring a diagnosis of superficial UPS for the rare instances of metastasis seen in patients diagnosed with AFX. Since there is a small chance of recurrence and metastasis, treatment of AFX requires surgical techniques such as Mohs micrographic surgery (MMS) or wide local incision (WLE).\textsuperscript{18,19} MMS seems to have a higher cure rate with fewer recurrences than WLE and allows for tissue sparing, making it the treatment of choice when possible.\textsuperscript{1,4} Follow-up for two years is recommended, with examination of the surgical site and palpation of the regional lymph nodes.\textsuperscript{4}

**Conclusion**

AFX typically presents in the sun-exposed areas of older white males, although a less common clinical variant presents in non-sun-exposed areas in a younger population. Epidemiology and histology differ between the clinical variants. The immunohistochemistry is important to help rule out other malignant cutaneous neoplasms. Although the prognosis is usually good, MMS is recommended for the small chance of recurrence or metastasis. Finally, the less common clinical variant may provide some insight into the causes of AFX and help with classification of AFX versus UPS.
References

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