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FEATURED ARTICLE
Purpura: A Clinical Review
Helia Eragi, DO, Khasha Touloei, BS, David C. Horowitz, DO, FAOCD.................................................................9

JAOC Editors..............................................................................................................................................................................4
Letter from the Editor-in-Chief.........................................................................................................................................................5
Letter from the Executive Director.....................................................................................................................................................6
Letter from the President....................................................................................................................................................................7
Dermatofibroma-Like Glomus Tumor On The Knee
Zhi Zhong Wang, MD, MSc, Andrew A. Simone, MD..........................................................15
Day Spa Disasters: Patients’ Injuries on the Rise
Jonathan Crane, DO, FAOCD, Richard Flexner, JD, David Jackson, BS..................................................16
Transient Reactive Aquagenic Acrokeratoderma on the Palms of a 62-Year-Old Female
Brent Loftis, DO, Donna D. Tran, MSIV, Yoon Cohen, DO, Bill V. Way, DO, FAOCD............................19
A 49-Year-Old Male With Tender Firm Nodules On His Posterior Lower Legs
Paul Aanderud, DO, R. Scott Thomas, MSIV, George Murakawa, MD..................................................21
Plaque of the Glans Penis: Differential Diagnosis
Melinda F. Greenfield, DO, Joseph M. Dyer, BS...........................................................................25
Advancement Flap for Distal Nasal Defects
Albert E. Rivera, DO, FAOCD, Roger I. Ceilley, MD, Andrew K. Bean, MD, Joshua B. Wilson, MD,...27
Amelanotic Spindle Cell Melanoma in a Hispanic Male
Charlotte Noorollah, DO, Suzanne Friedler, MD, Marvin Watsky, DO, FAOCD.................................29
Cutis Marmorata Telangiectatica Congenita: A Case Report and Discussion
Mari M. Batta, DO, Brandon G. Shutty, BS, Stephen Kessler, DO, Ronald C. Hansen, MD................31
A Suspicious Lesion Arising in a 28-Year-Old Female After Administration of Melanotan II
Daniel Child, BS, Paul Aanderud, DO, Steven Grekin, DO, FAOCD....................................................33
Herpes Simplex Vegetans: An Uncommon Presentation in Human Immunodeficiency Virus Infection
Theresa Cao, DO, Angela Combs, DO, Tracy Favreau, DO, David Droller, MD, Eli Piatigorsky, MD....34
Microcystic Adnexal Carcinoma in a 7-Year-Old Female
Cathy Koger, DO, Chris Weyer, DO, Lloyd J. Cleaver, DO, Michael B. Morgan, MD.........................36
Periocular Verruca Plana Following Use of a Carbon Dioxide Laser
Roxanna Menendez, DO, Jacqui Thomas, DO, Matthew Uhde, PA-C, Layne Nisenbaum, DO, FAOCD....41
Hypopigmented Patches in a Young Columbian Boy
Kurt Greleck, DO, Sheena Nguyen, BS, Andleeb Usmani, DO, Robin Shecter, DO, FAOCD..................44
Reed Syndrome: Hereditary Leiomyomatosis and Renal Cell Cancer
Peter J. Morrell, DO, FAOCD...................................................................................................................46
Primary Cutaneous Anaplastic Large-cell Lymphoma
Ali Daneshvar, Indira Misra-Higgins, DO, FAOCD..............................................................................48
A Case of Segmental Neurofibromatosis
Alison Hines, DO, Kristi Hawley, DO, Dawn Sammons, DO..........................................................50
Combined Nevus: Blue Nevus and Balloon Cell Nevus
Justin Rubin, DO, Panagiotis Mitropoulos, DO, Carlos Gomez-Meade, DO, FAOCD, Evangelos Poulos, MD, Tracy Favreau, DO, FAOCD, Angela Combs, DO, FAOCD............................55
A Case of Telangiectasia Macularis Eruptiva Perstans (TMEP)
Samuel M. Wilson, DO, R. Scott Thomas, Allison K. Divers, MD, Daniel S. Hurd, DO, FAOCD........57
Clinically Benign-appearing Papule: A Treatment Conundrum
Brooke Walls, DO, David Dorton, DO, FAOCD...........................................................................63
Dear AOCD Members and Residents,

It is with great honor that I assume editorship of this fine journal. After 10 years of dedicated service, Dr. Jay Gottlieb has left our college with a proud legacy, and one that will continue to prosper.

The JAOCD and the AOCD, sharing the same not-for-profit status, are more intimately connected starting this year. Owing to this, and to foster transparency, I have created an Associate Editors Committee to serve as a resource for decision-making and future development.

Aaron Bruce, DO, Michelle Foley, DO, Michael Scott, DO, and Scott Wickless, DO, have graciously stepped up to this task. Each is fit to bring a fresh prospective and lend to the integrity of the articles we publish: Dr. Bruce in surgery, Dr. Foley in general dermatology and cosmetics, Dr. Wickless in dermatopathology, and Dr. Scott in dermatological wisdom that cannot be taught but only developed through experience. In addition, we continue to boast a robust Editorial Board, currently consisting of 55 reviewers! I am constantly amazed by the loyalty and dedication of the members of our College.

Please remember what a unique resource this journal is for our subspecialty college and the potential it possesses. Please continue to submit your articles and encourage your colleagues to do so, too. The better we make it, the broader its impact. “Continued quality” will be the first focus going forward, relying on the following litmus tests:

1) The article is written in brief language and in a professional, medical tone.
2) The submission includes clinical photographs and/or pathology, when applicable.

In the next year, with the implementation of stricter submission criteria, I hope to have the JAOCD approved for CME reading credits!

I would like to thank my family for their support of my involvement in the College, as well as Dr. Cindy Hoffman, my program director, without whom I would not be practicing dermatology and experiencing all the happiness that brings. I would also like to thank Marsha Wise, who is a fantastic resource in our home office. Dr. Gottlieb, thank you for all your dedication and for entrusting me with your “baby.” Thank you to Ranbaxy, Global, Bayer/Intendis, Medicis, and Galderma, whose generous donations keep the journal in print and coming to you. Finally, I would like to thank Julia Layton, our copy editor, who is a pleasure to work with and without whom the JAOCD could not exist.

Best,
Karthik Krishnamurthy, DO, FAOCD
Editor-in-Chief, JAOC
Third Vice President, AOCD
Greetings, everyone!

The 2012 Annual Meeting is now behind us, and new officers were elected at our annual business meeting on Monday, October 8, 2012. The AOCD has many committees working for the entire AOCD membership. If you would like to be a member of a committee, please contact the AOCD office for more information.

AOCD OFFICE UPDATE
The AOCD is excited to announce that the office will be moving to a larger space. The move should be completed by December 21, 2012. Our post office box, 7525, is our preferred mailing address, and all correspondence should be sent there. We will continue to accept shipments at our 1501 E. Illinois St. address until the move is completed, and notice of our new physical address will be sent to the membership.

2013 AOCD Dues Renewal
Notices were handed out in San Diego to those who attended OMED. If you did not attend, or did not pick up a renewal notice, we will mail your notice to you.

In addition to renewing your AOCD dues, you may also designate additional funds to go to accounts earmarked for the AOCD Educational Research Fund, the Koprince Award, AAD Camp Discovery, the Dermatopathology Fund (to help support fellowship candidates enrolled at the Ackerman Academy), and the Foundation for Osteopathic Dermatology.

Meetings Update
AOCD Midyear Meeting 2013 will be held January 23-26, 2013, in Winter Park, CO. Please call the Winter Park Hotel directly for your room reservations.

Meeting Evaluations and Surveys
AOA requirements for CME continue to evolve. Thank you to everyone for participating in the various surveys throughout the year and for returning meeting evaluations. The results are tabulated and reviewed by the Board of Trustees and the CME committee. Locations for future AOCD Midyear Meetings will be chosen based on survey results.

ACGME UPDATE
The American Osteopathic Association (AOA), the Accreditation Council for Graduate Medical Education (ACGME), and the American Association of Colleges of Osteopathic Medicine (AACOM) have entered into an agreement to pursue a single, unified accreditation system for graduate medical education programs in the United States beginning in July 2015.

As developments and details unfold, information for the osteopathic family can be found at www.osteopathic.org/acgme. There, you can find answers to frequently asked questions, the AOA’s joint press release, a timeline of the issue, and other resources.

The AOCD Board of Trustees and the staff at the National Office wish everyone a happy and healthy holiday season.

Marsha Wise
Executive Director, AOCD
Our annual meeting in San Diego was filled with beautiful weather, great lectures and the opportunity to renew friendships. I would like to acknowledge my fellow Program Chairs, Brad Glick and Suzanne Rozenberg, for their assistance with putting together and running an outstanding meeting. I also want to thank the faculty and resident presenters who made this meeting both educational and interesting.

The AOCD Board of Trustees made several significant decisions while in San Diego. First, we approved the move of our national office in Kirksville to a larger building, a much-needed move for our cramped executive director, Marsha Wise, and staff. Second, we are looking to improve our website, with the goal of having a more user-friendly site for our members, residents, and the public. You should see some of these changes in 2013. In other technologic news, our college already has an iPhone App and is close to releasing an Android version. Three new members of the American Osteopathic Board of Dermatology were approved by the BOT: Rene Bermudez, Tanya Ermolovich, and Scott Wickless. At our annual business meeting, Reagan Anderson was re-elected as an AOCD trustee, and three new trustees were elected: Danica Alexander, Bryan Sands, and Dan Ladd.

On the political front, the AOCD is partnering with the AAD to stand firm against the new nurse practitioners’ doctorate degree, which would give nurses the title "doctor" and would therefore, we believe, deceive the public. Also, recently, the Women’s Dermatologic Society had a bylaws change that reclassified osteopathic-trained dermatologists from active members to associate members. With the help of several leaders in the AOCD, the WDS President, Janet Hickman, M.D., and Immediate Past President Diane Benson, M.D., issued a letter stating that the Society leadership unanimously agrees to return osteopathic members to active status, pending membership approval.

First VP and Program Chair Rick Lin is busy preparing an outstanding lineup of speakers for our upcoming Midyear meeting at the Winter Park Lodge in Winter Park, Colorado, January 23-26, 2013. Please join us for the meeting, and later on the slopes for some great skiing!

Best regards to you and your families,
David L. Grice, DO, FAOCD
President, AOCD
Important Safety Information

Oracea® (doxycycline, USP) is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. In clinical trials, the most common adverse events reported were gastrointestinal upsets, nasopharyngitis/pain, and nasal congestion/sinusitis. Oracea® should not be used to treat microbial infections, and should be used only as indicated. This drug is contraindicated in people who have shown hypersensitivity to any of the tetracyclines, and, like other tetracycline drugs, may cause fetal harm when administered to a pregnant woman. Oracea® should not be used during pregnancy, by nursing mothers, or during tooth development (up to the age of 8 years). Although photosensitivity was not observed in clinical trials, Oracea® patients should minimize or avoid exposure to natural or artificial sunlight. All contraindications, warnings, and precautions associated with tetracyclines must be considered before prescribing Oracea®. The safety of Oracea® treatment beyond 9 months has not been established.
ABSTRACT: Purpura is a common and nonspecific term used in medicine to describe the appearance of red or purple discoloration of the skin that does not blanch when pressure is applied. Purpura, petechiae and ecchymosis are caused by extravasation of red blood cells into the dermis. Petechiae are less than 5mm, purpura 5mm to 1 cm, and ecchymosis greater than 1 cm. Purpura is a common presenting problem at both inpatient and outpatient medical settings, with an extensive variety of underlying causes. This paper will review different case scenarios for patients presenting with purpura, differential diagnoses, and workups and algorithms necessary to rule in or rule out the underlying cause for the presenting symptom.

Case 1: Purpura secondary to thrombocytopenia

A 23-year-old female presents complaining of a two-day history of a rash involving both lower extremities. She also reports some gingival bleeding that she first noticed a couple of days ago. She states she just got over a severe flu, but is feeling better. Her past medical history is unremarkable, she denies a family history of bleeding disorders, and she is taking no medications. Vital signs are normal. Physical examination demonstrates small, non-palpable, punctate purple lesions involving bilateral lower extremities. CBC shows hemoglobin 14.0 g/dL (normal 12-16g/dL), hematocrit 42% (normal 36-46%), leukocyte count 7,000/mm³ (normal 4,000-12,000/mm³), and platelet count 10,000/mm³ (normal 150,000-400,000/mm³). Coagulation studies shows prothrombin time (PT) of 10 seconds (normal 10-13 seconds), partial thromboplastin time (PTT) of 35 seconds (normal 25-39 seconds), and international normalized ratio (INR) 1.5 (normal 0.8-1.2). Fibrinogen and fibrinogen degradation products are both within normal limits. What is the diagnosis?

Thrombocytopenia is either due to decreased platelet production, increased platelet destruction, or platelet sequestration (1). Clinically, thrombocytopenia can manifest as purpura, petechiae, ecchymosis, mucosal bleeding, meno-metrorrhagia in females, easy bruising, epistaxis, gastrointestinal bleeding, hematuria or intracranial bleeding (2). Bleeding doesn’t usually occur until platelet count drops below 20,000 (3). Table 1 may be used to determine which tests should be ordered to rule in or out a specific disease.

Based on the history, physical exam findings and the algorithm above, the patient has immune thrombocytopenic purpura (ITP). ITP presents as an isolated thrombocytopenia one to six weeks after a viral infection, secondary to an autoimmune process, and undergoes spontaneous resolution within two months (4). Among adults under the age of 50, such as in the above case, the condition is more chronic and persists longer than six months. The disease mainly affects women between 20

Differential Diagnosis:

- Immune thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Glanzmann disease (GD)
- Hermansky-Pudlak syndrome (HPS)
- Langerhans histiocytosis
- Bernard Soulier disease (BS)
- von Willebrand disease (vWD)

<table>
<thead>
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<th>Table 1</th>
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<tr>
<td><strong>Purpura, normal platelet count</strong></td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>In utero exposure to drugs</td>
</tr>
<tr>
<td>Hemophilia A/B</td>
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<tr>
<td>Child abuse</td>
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Algorithm 1:
and 40 years of age (5). Chronic ITP commonly occurs in patients with a history of alcohol or heroin abuse and patients with AIDS and/or prior rubella exposure (6). Chronic ITP most often presents with scattered petechiae of the distal arms and legs and possibly with deep-lying ecchymoses. One distinguishing factor of ITP is that it is rarely accompanied by splenomegaly (7).

Hemolytic uremic syndrome (HUS) presents with purpura in the lower extremities, hemolytic anemia, thrombocytopenia, and renal failure and is associated with E. coli 0157:H7. Thrombotic thrombocytopenic purpura (TTP) has many similarities to HUS, but this disease mainly affects adults (8). TTP also exhibits neurological defects and fever, which this patient did not exhibit. The patient in the above case did not have an increased partial thromboplastin time (PTT) or family history of bleeding disorders, which rules out von Willebrand disease (6). Glanzmann disease (GD) is another differential that should be considered. The disease is characterized by improper platelet aggregation and manifests with multiple bruises and purpura (9). Bernard Soulier manifests with severe bleeding during injury or surgery (10). However, this patient had no history of trauma or surgery. Patients with Langerhans histiocytosis also present with thrombocytopenia, but will have other physical manifestations such as lymphadenopathy, hepatosplenomegaly, anemia and a papular, vesicular, and purpuric rash. This syndrome is diagnosed by skin biopsy (11).

Another disease that may present with purpura secondary to platelet dysfunction is Hermansky-Pudlak syndrome (HPS), which is a very rare genetic disorder characterized by oculocutaneous albinism and accumulation of ceroid lipofuscin, a lipid-protein complex, in lysosomes. The disease is commonly found in albino Puerto Ricans. Diagnosis is made by clinical presentation, a platelet function test, and electron microscopy to analyze the dense-body granules in platelets (12).

Case 2: Purpura secondary to a coagulation disorder

A 25-year-old male presents with a purpuric, swollen, tender right thigh with some joint swelling after bumping into a table in his living room. Pulsation is decreased over the left popliteal artery. He has a family member who suffered from a clotting disease with bleeding into joints. Given his family history of bleeding disorder, what is the diagnosis?

**Differential Diagnosis:**

- Hemophilia A
- Hemophilia B
- Disseminated intravascular coagulation (DIC)
- Hematoma secondary to contusion/trauma
- Liver failure
- Vitamin K deficiency

**Algorithm 2:**

Based on the history, physical exam, and the algorithm, the patient has either hemophilia A or B, X-linked recessive bleeding disorders secondary to deficiency of either factor VIII or IX, respectively. Spontaneous bruising occurs in patients with hemophilia and presents as palpable ecchymosis but is not as common as hemarthrosis, observed most commonly in knee joints (13). Large-area bruising occurs with vitamin K-dependent factor deficiency more so than with hemophilia. The vitamin K-dependent factors are II, VII, IX and X, protein C, and protein S. Causes of vitamin K deficiency include cholestasis, fat malabsorption, prolonged antibiotic use, and cystic fibrosis (14). A patient with DIC will have a history of septicemia, trauma, or shock (15). In liver failure, the liver is unable to synthesize coagulation factors (16). The findings are similar to DIC but will also include decreased levels of the vitamin K clotting factors. This can also present with purpura, but more so with ecchymosis and other bleeding disorders (17). Liver function tests are helpful for diagnosis, and risk factors for liver disease should be investigated.

**Case 3: Purpura in age group birth to 2 years

A 12-month-old boy is referred for evaluation of white eye reflex. His mother suspects a hearing problem because he does not respond when she calls out his name. The physical examination reveals a continuous, machine-like murmur over the second right intercostal space and purple lesions on his arms and chest that were apparent since birth. The initial investigation reveals thrombocytopenia. What is the most likely diagnosis?

**Differential Diagnosis:**

- Purpura, normal platelet count
- Purpura, decreased platelet count
- Purpura with sepsis
- Vitamin K deficiency
- Alloimmune thrombocytopenia
- Trauma
- Maternal autoimmune thrombocytopenia (MAT)
- In utero exposure to drugs
- Congenital amegakaryocytic thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Hemophilia A/B
- Wiskott-Aldrich syndrome (WAS)
- TORCH infections
- Child abuse
- Immune thrombocytopenic purpura (ITP)
- Leukemia

**Algorithm 3:**

The classic triad of congenital rubella syndrome is sensorineural deafness, cardiac malformations, and cataracts (18). The purpuric rash described in the above case, also known as blueberry muffin baby, along with history and physical exam is consistent with congenital rubella, which is one of the TORCH infections (toxoplasmosis, other [syphilis], rubella,
cytomegalovirus, herpes simplex virus). A baby with congenital rubella infection can appear purpuric, but this condition must be differentiated from purpura fulminans secondary to protein C or S deficiency. Clinically, purpura fulminans manifests as large ecchymoses, diffuse purpura, and gangrene of the extremities. The ecchymoses become bullous and necrotic (19). Platelet typing should be ordered to rule out neonatal alloimmune thrombocytopenia (NAT), which can also present as diffuse purpura with a normal platelet count and without coagulation abnormalities (20). Maternal autoimmune thrombocytopenia (MAT) is different from NAT, as it has a lower platelet count and typically presents after three months of age (21). If thrombocytopenia is present in the first year of life, and the family history shows absent thumbs or absent radii, the diagnosis points toward absent radius syndrome (22).

A child with recurrent infections, atopic dermatitis, and thrombocytopenia should point toward Wiskott-Aldrich syndrome (WAS), a congenital, immune-mediated X-linked disorder. Patients with WAS commonly present with atopic dermatitis and secondary skin infections due to Streptococcus pneumonia, Neisseria meningitides, and Haemophilus influenza. The platelet count in WAS is less than 50,000, and the mean platelet volume is also reduced. In WAS, the young child or infant may initially present with a reddish brown or blue, tender skin lesion which rapidly evolves into a W ASS, the young child or infant may initially present with a reddish skin infections due to Streptococcus pneumonia, Neisseria thrombocytopenia should point toward Wiskott-Aldrich syndrome (22). Maternal autoimmune thrombocytopenia (MAT) is different from NAT, as it has a lower platelet count and typically presents after three months of age (21). If thrombocytopenia is present in the first year of life, and the family history shows absent thumbs or absent radii, the diagnosis points toward absent radius syndrome (22).

In a patient with unexplained purpura and an inconsistent history, the clinician should perform an eye exam and a complete body scan for fractures, as child abuse should be suspected. Young children exposed to abuse or falls can exhibit purpura on various regions of the body (26). After birth trauma, caput succedaneum may form and cause purpura on the head (27).

**Case 4: Purpura secondary to infection**

An 18-year-old woman comes to the ER because of acute onset of headache, muscle pain, and nausea. These symptoms had been present for one day, arising soon after she returned from a camping trip. The illness started with fever and muscle pain that progressed to include headache and nausea over the next several hours. She states that she went hiking twice during the trip and participated in many outdoor activities with her friends. She has no other medical problems. Her temperature is 102 F, blood pressure 90/60, pulse 120/min, and respirations 18/min. Physical examination shows a stiff neck with pain to passive flection. Her skin reveals few purpuric lesions on both legs. Examination of the cerebrospinal fluid (CSF) reveals: glucose 25mg/dl, WBC 2000/cm. What is the likely diagnosis? Examination of the cerebrospinal fluid (CSF) reveals: glucose 25mg/dl, WBC 2000/cm. What is the likely diagnosis?

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>More Common</th>
<th>Less Common</th>
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<tbody>
<tr>
<td>Meningococcemia</td>
<td>Leptospiriosis</td>
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<tr>
<td>Scarlett fever</td>
<td>Rickettsia prowazekii</td>
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<tr>
<td>Endocarditis caused by</td>
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<tr>
<td>Streptococcus viridans/Staphylococcus aureus</td>
<td>Ehrlichiosis</td>
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<tr>
<td>Rocky Mountain spotted fever</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Staphylococcus-induced toxic shock syndrome</td>
<td>Dengue hemorrhagic fever</td>
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<tr>
<td>TORCH (covered in Case 3)</td>
<td>Atypical measles</td>
</tr>
</tbody>
</table>

**Case 5: Purpura not due to infection, thrombocytopenia or coagulation disorder**

A patient presents with purpura scattered on lower extremities. The patient is negative for infection, thrombocytopenia and coagulation disorders. What is the next step?

Once infection, thrombocytopenia, and coagulation disorders have been ruled out as the cause of purpura, there are several methods that can be used to narrow the differential diagnosis. The first step should be to obtain a thorough history of present illness, including diet, medications, family history, complete review of systems, and physical exam. The following algorithm can be followed (see next page).

A patient with a recent history of surgery, radiation or chemotherapy may exhibit purpura due to disruption in coagulation or platelet activity. Cholesterol emboli can manifest with purpura in the lower extremities. Other findings include livedo reticularis, gangrene, and occasionally ulceration of the skin (30).

Based on the CSF results and clinical symptoms, the patient in case 4 is suffering from meningitis. However, with the sudden onset of rash along with the other clinical symptoms, one must consider Waterhouse-Friderichsen syndrome secondary to a Neisseria meningitides infection. This disease most commonly affects children between birth and 18 months but can also affect adults. Any patient with meningitis and sudden onset of rash and purpura should have a culture and gram stain of blood and CSF. Initially, the patient will have oropharyngeal petechiae and purpura that eventually become confluent. As the disease progresses, hemorrhagic bullae with ulcerations manifest. The disease can become fulminant as ecchymoses with irregular borders appear on the extremities. The lesions may form necrotic centers. The disease progresses rapidly and is the only meningitis with skin manifestations, and it can be fatal if not treated and recognized early in its course (24,29). Since the patient has a history of recent outdoor activities, Rocky Mountain spotted fever should also be in the differential. This disease manifests with small, pink macules that evolve into petechiae and purpura starting on the palms and soles, later migrating inward toward the trunk. The disease occurs secondary to a tick bite from Dermacentor, Rhipicephalus or Amblyomma species. It is caused by the gram-negative bacterium Rickettsia rickettsii and occurs in the eastern two-thirds of the United States, Rocky Mountain states, Pacific coast, and southwestern United States. It most commonly affects children between the ages of 5 and 10. If the disease becomes too severe, it may present with extensive cutaneous necrosis due to DIC, requiring amputation. The patient will also have other associated symptoms including fever, headache, myalgia, and photophobia (30,31). Toxic shock syndrome secondary to Staphylococcus aureus can present clinically indistinguishable from meningococcemia. It also manifests with desquamation, particularly on the palms and soles, which can occur one to two weeks after onset of the illness (32).

The purpura in scurvy is usually found on the lower extremities and manifests as perifollicular petechiae that coalesce to form ecchymoses, especially on the thigh and buttock regions. The disease also presents with phlebothrombosis. Hemorrhaging can also occur in the joints, organs, and nail beds. Other skin manifestations include scaly dermatitis, pallor, dry mouth, and poor wound healing (34). A diet history may allow you to diagnose vitamin B12 and/or folate deficiencies, both of which can cause thrombocytopenia. Both syndromes present with megaloblastic anemia, but
vitamin B12 deficiency also has neurological symptoms (35).

Allergic purpura can appear secondary to foods such as wheat, eggs, milk, and chocolate. The most common cause of allergic purpura is streptococcal infection triggering an autoimmune reaction against the vasculature. Allergic purpura affects males more often and is most common in children from 3 to 7 years of age. It’s usually preceded by an upper respiratory infection. As of yet, there are no lab tests to diagnose this disease. It does, however, present with elevated WBC and ESR counts. Patients will have a positive tourniquet test, while coagulation panels and platelet-function tests are normal (36). A tourniquet test determines capillary fragility using an inflated blood pressure cuff for five minutes. The test is considered positive if there are 10 or more petechiae per square inch (37). UA and stool guaiac usually test positive for blood. A small bowel X-ray may show areas of transient edema as well. This disease is a diagnosis of exclusion (36,38).

Medication-induced purpura manifests within 24 hours of exposure and disappears following discontinuation of the drug. Warfarin administered on its own can cause painful areas of erythema that become purpuric and necrotic with a darkened eschar. Auto-erythrocyte sensitivity, which causes painful purpura and ecchymoses, appears either as a single lesion or as several lesions coalescing to form one lesion. The purpura and ecchymoses begin as pruritus, burning, or pain prior to their presentation. Furthermore, one must consider drug-induced thrombocytopenia as a causative factor for palpable purpura with medications such as quinidine, trimethoprim-sulfamethoxazole, and gold, among others (38-42).

A thorough physical exam should be performed initially. Amyloidosis can manifest with purpura that occurs most commonly on the eyelids and mucous membranes (43). Henoch-Schönlein purpura (HSP) is the most common form of vasculitis in children and is a form of immune-mediated vasculitis syndrome in which the platelet count is not affected and the diagnosis is made clinically. It manifests with a symmetric, palpable, purpuric rash of the buttocks and lower extremities. The disease affects males more often than females, and 50% of the time it appears after a URI (44). Other palpable purpuras include collagen vascular disease, Wegner’s granulomatosis, cryoglobulinemia and SLE immune-mediated thrombocytopenia (45).

Another diagnosis that can be made clinically is capillaritis, also known as pigmented purpuric dermatosis, which results in cayenne-pepper-like petechiae. There are several other clinical entities that fall under the umbrella of capillaritis: Schamberg disease, purpura annularis telangiectodes of Majocchi, eczematid-like purpura of Doucas and Kapetanakis, lichenoid purpura of Gougerot and Blum, and lichen aureus. Schamberg disease is characterized by yellow-brown patches with petechiae. Purpura annularis telangiectodes of Majocchi is characterized by annular lesions, commonly reddish and brown, that can become atrophic. Lichenoid purpura of Gougerot and Blum is characterized by symmetric purpuric papules and plaques on distal legs. Both Schamberg’s disease and lichenoid purpura of Gougerot and Blum can be pruritic. Eczematid-like purpura of Doucas and Kapetanakis presents with scale and erythema with petechiae. Lichen aureus can present with solitary or multiple lesions (46).

The dysproteinemias that cause purpura include multiple myeloma and cryoglobulinemia (hyperglobulinemic purpura of Waldenström). Multiple myeloma manifests with purpura, petechiae and ecchymoses, as well as gum bleeding and excessive bleeding after surgery (47). Waldenström is characterized by recurrent crops of petechiae and purpura on the dependent areas of the body. Patients may be positive for IgG or IgA rheumatoid factor titers, antibodies to Ro(SS-A) and La(SS-B), and elevated ESR (48).
Case 6: Purpura secondary to vasculitis/autoimmune disease

A 47-year-old female presents complaining of a one-week history of rash involving both lower extremities. She also reports oral ulcers and hematuria. Her past medical history is unremarkable, she denies a family history of bleeding disorders, and she takes no medications. Vital signs are normal. Physical examination shows small, palpable, punctate purple lesions involving bilateral lower extremities. CBC and coagulation studies are all within normal limits. What is the diagnosis?

Differential Diagnosis:
- Leukocytoclastic vasculitis (LCV)
- Microscopic polyangiitis (MPA)
- Cutaneous polyarteritis nodosa (CPAN)
- Cryoglobulinemia
- Wegener’s granulomatosis (WG)
- Churg-Strauss syndrome (CSS)
- Cocaine levamisole toxicity (CLT)
- Antiphospholipid antibody syndrome (AAS)

Algorithm 6:

Purpura secondary to vasculitis can be caused by leukocytoclastic vasculitis (LCV) or systemic vasculitis syndromes including Wegener granulomatosis (WG), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MPA) and cutaneous polyarteritis nodosa (CPAN) \(^{(49)}\). Based on the history, physical exam findings and the algorithm above, the patient has WG.

Nearly half of the cases of LCV are idiopathic and self-limited. The other half are due to drugs or infection. Cutaneous vasculitis may be the first initial symptom in CSS, MPA, and WG. Cutaneous vasculitis most commonly presents as palpable purpura, but can also present as other morphologies including livedo reticularis, nodules and ulcers \(^{(49)}\).

The first test that should be conducted when suspecting LCV is a punch biopsy. The histology of leukocytoclastic vasculitis is identified by the presence of fibrin deposits, fragmented nuclei and neutrophils disrupting postcapillary venules and intravascular fibrin. HSP is restricted to the superficial dermis. Purpura secondary to a drug reaction will have severe fibrinoid necrosis of vessel walls but will have tissue eosinophilia. Sometimes a spongiform interface dermatitis may also be present \(^{(50)}\).

Once LCV is confirmed, systemic involvement must be analyzed with a thorough history, CBC with differential, urine analysis, chemistry panel, erythrocyte sedimentation rate, antiphospholipid antibodies, immunoglobulin (IgG, IgA, and IgM) levels, chest X-ray, fecal occult blood test and DIF. After a vasculitis is confirmed, infectious and rheumatologic etiologies can be ruled out by ordering ANA, anti-neutrophilic cytoplasmic antibody (ANCA), rheumatoid factor, anti-Ro, anti-La, complement levels, cryoglobulins, hepatitis B and hepatitis C serology \(^{(49,51,52)}\).

WG, CSS, and MPA are small-vessel vasculitides and have an absence of immune complexes (ICs). WG most commonly affects the upper respiratory tract, lungs and kidneys. Patients may also present with hemoptysis and hematuria. IgG, IgM, and/or C3 in or around the vessels characterizes IC-mediated vasculitis, which includes cryoglobulinemic vasculitis, connective-tissue disease vasculitis, and LV \(^{(52)}\). In MPA and CSS, p-ANCA is seen; in WG, c-ANCA is commonly seen. However, these markers are not diagnostic \(^{(53)}\). The histology of WG will have the presence of palisaded and neutrophilic granulomatous dermatitis. CSS patients will present with asthma, blood eosinophilia, and eosinophilic-rich and “red” necrotizing extra-vascular granulomas. MPA does not have granulomas, eosinophilia or asthma \(^{(49,51)}\).

Cutaneous PAN demonstrates a starburst appearance on physical exam. Secondary changes that may present include tender nodules, livedo reticularis or ulceration. Cutaneous PAN does not have peripheral gangrene, which is seen in systemic PAN. Histology will demonstrate neutrophilic muscular-vessel vasculitis in the dermal-subcutis junction or in the subcutis \(^{(49,51)}\).

Cryoglobulinemia vasculitis is characterized by the triad of purpura triggered by cold exposure or prolonged standing, weakness, and arthralgia. DIF will demonstrate deposits of IgM and/or complement \(^{(49)}\).

Retiform purpura is a non-blanching purpura seen with antiphospholipid antibody syndrome (AAS) and cocaine levamisole toxicity (CLT). AAS is an autoimmune disease characterized by elevated autoantibodies including the cardiolipin antibody,
purpura can be due to coagulation-factor deficiencies, including hemophilia A/B; von Willebrand disease; liver disease; or coagulopathic diseases including DIC and Kasabach-Merritt syndrome. Purpura can present secondary to an acquired thrombocytopenia caused by viral infections, vitamin B12 and folate deficiency, or a drug reaction. Purpura may also be the result of thrombocytopenia secondary to platelet destruction in diseases such as immune thrombocytopenic purpura, connective-tissue disease, leukemia, drugs, DIC, and thrombotic thrombocytopenic purpura. Finally, purpura can be due to abnormal platelet function, observed with aspirin ingestion, kidney and liver dysfunction, and thrombocytosis.

Conclusion

Purpura, a very common and non-specific term used in medicine, has a considerable number of possible underlying etiologies. Since the differential diagnosis can be very extensive, we have presented six case scenarios with algorithms to review the history and physical exams, lab findings, and work-up necessary to determine the underlying causes of purpura. In summary, purpura can be due to coagulation-factor deficiencies, including hemophilia A/B; von Willebrand disease; liver disease; or coagulopathic diseases including DIC and Kasabach-Merritt syndrome. Purpura can present secondary to an acquired thrombocytopenia caused by viral infections, vitamin B12 and folate deficiency, or a drug reaction. Purpura may also be the result of thrombocytopenia secondary to platelet destruction in diseases such as immune thrombocytopenic purpura, connective-tissue disease, leukemia, drugs, DIC, and thrombotic thrombocytopenic purpura. Finally, purpura can be due to abnormal platelet function, observed with aspirin ingestion, kidney and liver dysfunction, and thrombocytosis.

References


**Dermatofibroma-Like Glomus Tumor On The Knee**

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

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

**ABSTRACT:** Glomus tumor is a rare benign neoplasm and usually occurs under the fingernails. It can be misdiagnosed as other diseases when occurring in other body area. We reported a case of glomus tumor occurring on the knee. It was difficult to differentiate from dermatofibroma.

A German male, 66 years old, complained of a firm, pinkish nodule on his right knee. This protuberance had been visible for three years, grew slowly and was not itchy. However, it felt painful when bumped against hard surfaces. There had been no history of trauma to the knee. He'd had gout for 28 years and was taking allopurinol. His hypertension was under good control for five years through the use of ramipril. The patient was diagnosed with diabetes type 2 one year prior and had since been taking metformin. He had also suffered from hyperthyroidism 15 years ago, was previously treated with radioactive iodine and was currently taking levothyroxine. He worked as a public transit driver for 28 years. Family history was non-contributory.

**Physical Examination**

There was a solitary pink nodule on the medial side of the right knee, about 6 mm in diameter and 3 mm in height. It was well-defined without hyperpigmentation in the periphery. It felt firm and tender when pressure was applied on the top of the nodule. There was no dimpling or pain when the nodule was squeezed from the sides.

**Pathological Examination**

Within the dermis, there was a tumor consisting of small vessels surrounded by several layers of small cuboidal cells, which are typical of glomus cells (Figures 1,2).

**Treatment:** Surgical excision.

**Discussion**

Glomus tumor is a rare, benign neoplasm arising from the glomus body. It usually occurs as a solitary reddish spot under the fingernail, sometimes with a distal fissured nail plate or nail bed elevation. It often manifests with a classic triad of symptoms: pain, tenderness and temperature sensitivity. The pain can usually be reproduced when the lesion is immersed in cold water.

Glomus tumour may rarely occur in other body areas. In 1985, Macaluso et al. reported a U.S. case of glomus tumor on the glans penis.1 Park et al. reported another case of glomus tumor on the glans penis of a 19-year-old man in Korea in 2004.2 Lorber et al. reported a case of glomus tumor in gastric antrum in 2005.3 Clark et al. and many other authors reported several cases of glomus tumor causing knee pain in other years.4 They all concluded that glomus tumor can be a rare cause of knee pain.

This case of glomus tumor occurred on the right knee without pain. Its location, appearance, tenderness, and lack of temperature sensitivity made it difficult to differentiate from dermatofibroma. The only diagnostic clue was the lack of dimpling.

**References**

**Day Spa Disasters: Patients’ Injuries on the Rise**

Jonathan Crane, DO, FAOCD,* Richard Flexner, JD,** David Jackson, BS***

*Atlantic Dermatology Associates, P.A., Wilmington, NC
**The Law Offices of Richard Flexner, Wilmington, NC
***University of North Carolina at Wilmington, Wilmington, NC

**Abstract:** Procedures including laser hair removal and chemical peels, termed “non-surgical medical procedures,” have increased 749% from 1997 to 2008.1 Between 2005 and 2006 alone, injury from mishaps related to procedures at these “medical spas” rose 41% in clients of a Southern California law firm.1 Some of these injuries include burns from hair-removal lasers, scarring from chemical peels, and even death.1,2,3,4 From bodily harm caused by improperly-done procedures, lawsuits have dramatically risen as clients seek monetary repayment after suffering tremendously.5 Here, we review the increase in day-spa related injuries stemming from this new and problematic beauty trend.

**Introduction**

Recently, there has been a boom in the business of “day spas”.1 Originally, day spas offered traditional spa procedures such as massages and pedicures, but have recently grown to provide “non-surgical medical procedures” or “small plastic surgery procedures.”1,5 These procedures include laser treatments, chemical peels, filling agents and the use of neurotoxins. Day spas providing these treatments are the most rapidly-growing portion of the spa industry as noted by the International SPA Association, and have quadrupled in number from 2004 to 2009 alone.5 Many of these businesses may seem official and similar to physicians’ offices, but are generally much less regulated, if at all.5 Some of these businesses call themselves “medical spas” or “med spas,” which in some states is allowed by law provided that certain criteria, most importantly medical supervision, is met. Many states do have laws allowing surgical procedures to be performed at a spa with a supervising physician, but in practice the physician is often not present during the procedure, and may not even be present on-site. Moreover, even with regulatory laws on the books, they are not uniformly enforced.6

In other states where the law is silent (such as in North Carolina), some businesses present themselves as “med spas” without any supporting basis in law. In these cases, the purported “med spas” are unregulated by medical boards, and may in fact be wholly medically unsupervised, which would constitute a fraud upon the patient and be actionable, along with other theories of legal liability such as negligence and medical malpractice, in lawsuits filed to seek compensation for injuries caused by these procedures. Thus, as a result of patients sustaining bodily harm from insufficiently supervised medical procedures, litigation is increasing; in particular, a spike in laser-related lawsuits has been noted.5,6

**History of Cosmetic Surgery**

Cosmetic surgery in some form has been done historically for thousands of years. Ancient Egyptians and Romans both managed to use compounds such as fermented grape leaves and sour milk for chemical peels.5 Sanding of the skin was also done as an older form of dermabrasion.6 In 1905, Kromayer invented a technique called “surgical planing,” which later became dermabrasion.7 Kurtin and Robbins created standardized dermabrasion in 1959 in order to treat “traumatic tattoo injuries” that patients acquired in World War II.7 In 1972, Baker and Gordon showed that phenol is beneficial in chemical peeling. Recently, plastic surgeons and dermatologists have improved upon chemical-peel methods in both safety and effectiveness.7 Currently, the usual chemical peel in a day spa is a “superficial or lunch-time variety,” which means that the penetration is not deep.4 In the 1980s, the process of laser resurfacing emerged and was initially done with continuous-wave carbon-dioxide lasers.9 New techniques have since emerged that have fewer side effects. Some of these techniques include nonablative resurfacing, which injures the dermis “to improve rhytides and photodamage” without affecting the epidermis; and fractional resurfacing, which works over a fraction of the skin surface in order to shorten recovery time.9

**History of Day Spas**

Around the beginning of the 21st century, medical spas were few and far between.10 However, around 2003, the medical spa industry began to rapidly develop.11 This growth has been so massive that between 2006 and 2007 alone, medical spas increased by 50% to 1,250 businesses.10 Numerous reasons have propelled these businesses to develop, but one main reason seems to be demand by clients, especially for anti-aging procedures.10,12,13 This is especially prevalent among the aging “baby boomer” generation, and these spas are in turn offering anti-aging treatments including botulinum toxin type A and laser hair removal.10 These medical spas have attempted to move away from the “disease treatment” model to create a more hospitable environment with “memorable experiences” for clients, along with combining various medical practices that range from alternative and preventive medicine to “mind-body” views.11 Also, physicians have been attracted to working in this field due to the promise of a large profit that will boost income even with “declining insurance reimbursements.”10

**Processes and Problems in Day Spas**

Numerous medical procedures done at day spas can result in serious injury. Acid peels can result in atrophic scars, hypertrophic scars, and keloids. Postinflammatory hyperpigmentation (PIH) and hypopigmentation may occur from acid peels in spas. Superficial peels, including salicylic acid and glycolic acid, are commonly used in day spas. Some spas use more aggressive peels, such as trichloroacetic acid. Day spas using trichloroacetic acid may injure and burn patients.

This is an example of a patient injured in a day spa in Wilmington, North Carolina. She received a deep chemical peel from an esthetician, licensed only by the North Carolina Board of Cosmetology, which licenses barbers and hairstylists as well. This esthetician and the day spa were completely unprepared to deal with the second and third degree burns caused by the procedure that was being provided. Following the disastrous procedure, the esthetician involved a dentist friend who was not on scene and not apparently involved in any way in the supervision of either the day spa or the esthetician. The dentist undertook to
prescribe medication for the burned patient without ever seeing her to establish a doctor-patient relationship, and without even speaking with her. The dentist took no steps to refer the patient to a qualified medical specialist to treat her burns, thereby delaying the patient obtaining qualified medical care for her serious burns (Figure 1).

**Other examples include:**

A Southern California woman who visited a day spa in a mall near her home was treated with a laser and suffered third-degree burns, which resulted in severe scarring and nerve damage.1

A woman in Arizona sued a spa there in 2009 after having second-degree burns and scars from improperly-done laser hair removal.5

A man sued a different Arizona spa over a laser hair removal treatment done on his back and shoulders.5

One woman in North Carolina became septic after undergoing stomach fat reduction at a day spa.14

Three women in North Carolina developed kidney failure from receiving injections intended for buttocks enhancement.15 These injections were likely comprised of hCG (human chorionic gonadotropin) and phentermine.

A 22-year-old college student in North Carolina died from a “violent reaction” to a numbing lidocaine cream applied to her skin before a laser hair removal treatment.3 The lidocaine cream caused lidocaine poisoning in this student, and resulted in her death. This tragedy led to a shutdown of this spa, but not to additional regulation of the medical spa industry in North Carolina.

Due to the rising number of injuries from the greater number of medical spa procedures being performed, lawyers are filing more negligence and malpractice lawsuits seeking redress for injuries caused by improperly performed procedures. Claims have increased, especially related to injuries from laser hair removal and anti-wrinkle and acne scar treatments. In North Carolina, a claim was filed on behalf of three women who received un supervised injections for buttocks enhancement that resulted in kidney failure in all of them.5,15,16 Some of these cases can result in major monetary recoveries for the client, and corresponding losses for the businesses.16 In one case, a Chicago woman won $100,000 from a medical spa (Pure Med Spa) based on scarring on her neck from laser treatment that was supposed to remove age spots (Figure 2), and the spa went bankrupt as a result, which suggests that the spa did not carry liability insurance. This form of litigation is predicted to increase dramatically in the near future.5 Accordingly, many lawyers have advertised their field-related services and have won cases in the area of day-spa-related lawsuits.15,17

**Regulations**

One critical problem is that while the majority of states require physicians to supervise these medical procedures, many of the procedures nevertheless go unregulated.5 In some states, a person can perform deep chemical peels without having a medical degree.18,19 Due to this deficiency, Florida, New York, Illinois, and other states are attempting to enact laws that would impose tighter regulation on day spas that offer medical treatments.5

Various states have different laws pertaining to the use of lasers in a day spa setting.20 In California, state law provides that a registered nurse or physician's assistant is allowed to give injections of botulinum toxin type A, as well as perform laser hair removal, microdermabrasion, and an array of other “non-surgical treatments.”1 However, Senator Liz Figueroa (D-Fremont) proposed bill 1423, which would make constant physician supervision mandatory.
their procedures for laser hair removal "safe, guaranteed, and FDA endorsed," and others offer a doctor's office-like setting with the personnel in white coats, these claims are empty and may increase the risk to a patient.1,2,7

Conclusion

Injuries and deaths from procedures performed in day spas are on the rise. Related lawsuits are on the rise, as well.1 Lawsuits have been increasing so much that comparisons are frequently made between laser cases and asbestos-exposure cases.24 Some lawyers also forecast that the numbers of this form of lawsuit will balloon, and say that this is "the beginning of the industry being targeted."25 Day spas offering medical treatments may have only recently arisen, but closely-linked problems have haunted this industry since its beginning, most notably the lack of regulation of these procedures.5,10,11 However, some states are already in the process of intensifying current regulations, thereby beginning to address the severe problems associated with facilities with questionable staff offering procedures including chemical peels and laser treatments.5

References


ABSTRACT: Transient reactive aquagenic acrokeratoderma is a rare condition characterized by rapid development of white to translucent papules on the palms following immersion in water. Histopathologically, hyperkeratosis and dilated eccrine ducts are seen. We describe a case of a 62-year-old Caucasian female who presented with a 3-year history of pebble-like palmar eruptions following exposure to water. We discuss the clinical and histopathologic features, etiology, and treatment of the disease.

Introduction

In 1996, English and McCullough described the first case of transient reactive aquagenic acrokeratoderma in a report of two sisters with symmetric, flesh-colored to white papules on the palms and lateral fingers, which, upon re-exposure to water, evolved into translucent white papules with dilated puncta. Since then, more than 30 cases have been described under different names, including “aquagenic palmoplantar keratoderma,” “aquagenic syringeal acrokeratoderma,” “aquagenic keratoderma,” “aquagenic wrinkling of the palms,” and “aquagenic acrokeratoderma.” Herein, we report a case of transient reactive aquagenic acrokeratoderma arising on the palms of a 62-year-old female, and characterize the histopathological features and pathogenesis of the disease.

Case Report

A 62-year-old Caucasian female presented to our dermatology clinic for evaluation of a palmar eruption. She noted a three-year history of bumps under the skin of her hands after brief immersion in water. The lesions were associated with a burning sensation and resolved within minutes after drying her hands. She denied any concomitant hyperhidrosis. She had no family history of similar problems and denied any personal or family history of cystic fibrosis or atopy. Her past medical history was noted for hypertension and hypothyroidism. Her medications included hydrochlorothiazide, thyroxine and multivitamins.

Physical examination was remarkable for hyperlinearity of the palms as well as palmar erythema. Following exposure to warm water for a few minutes, she developed pebble-like papules with dilated puncta (Figures 1-2). The soles of her feet were not involved.

A shave biopsy of the right palm was performed. Histopathologic examination revealed acanthosis and hyperkeratosis (Figure 3). Focally, a discrete focus of orthokeratotic hyperkeratosis was identified with slight epidermal invagination. There were local fibrosis and lymphocytic infiltrate. The granular layer was intact, and no viral inclusions were identified.

Based on the clinical and histopathologic findings, a diagnosis of aquagenic acrokeratoderma was made. A trial of topical aluminum chloride was prescribed. Within one week, the patient noticed dramatic improvement. At the time of submission, we plan to continue to monitor her condition with the current therapy.

Discussion

Transient reactive aquagenic acrokeratoderma is a rare condition characterized by rapid development of white-to-translucent papules on the palms following immersion in water. It has a predilection for females, with a mean age of 22.1 years. Preferential involvement of the hands and not the feet, as in our patient, is unclear. The “hands-in-the-bucket” sign, which is not clearly visible until the hand is immersed in water, is considered to be pathognomonic. The lesions appear within a few minutes of exposure to water and subside with drying of the skin. A burning sensation, pain, tingling, or pruritus may be present, although the condition may be asymptomatic.

Histologically, aquagenic acrokeratoderma is characterized by orthokeratotic hyperkeratosis and dilated eccrine ducts. However, the dermis and epidermis may appear normal. In our patient, biopsy after water exposure showed acanthosis and a discrete focus.
of orthokeratotic hyperkeratosis with slight epidermal invagination.

The pathogenesis of the disease remains unclear. MacCormack et al. hypothesized that aquagenic acrokeratoderma develops as a result of a defect in the sweat duct due to friction or occlusion.8 Betlloch et al., on the other hand, proposed that a transitory structural or functional alteration of the stratum corneum elements (proteins, lipids, humectant substances, etc.) leads to the disease.7 Itin et al. suggested an increase in water absorption capacity due to a defect in barrier function of the stratum corneum as the etiology and pathogenesis of the disease.9 Aquagenic acrokeratoderma has also been reported in association with cystic fibrosis and as an adverse effect of cyclooxygenase-2 (COX-2) inhibitors.4

Several features help to differentiate transient reactive aquagenic acrokeratoderma from hereditary papulotranslucent acrokeratoderma (Table 1). HPA appears soon after puberty and is characterized by persistent, asymptomatic papules and plaques that appear on the pressure and/or trauma points of the hands and feet, and is associated with fine-textured scalp hair and an atopic diathesis. After puberty, new lesions fail to arise, but existing lesions do not disappear or decrease in size.1 The condition exhibits an autosomal-dominant pattern of inheritance. Histologically, the lesions show focal hyperkeratosis, acanthosis, and normal eccrine ducts.6 Males and females are equally affected.

Most treatment regimens for transient reactive aquagenic acrokeratoderma focus on decreasing the hyperkeratosis associated with the condition, or with providing a water barrier to prevent exposure. Topical treatment with aluminum chloride, iontophoresis, and botulinum toxin have been reported as effective options.5,9 Spontaneous amelioration or remission after water withdrawal has been described.3 Our patient responded well to topical aluminum chloride.

Table 1: Features differentiating transient reactive aquagenic acrokeratoderma from hereditary papulotranslucent acrokeratoderma.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Transient Reactive Aquagenic Acrokeratoderma</th>
<th>Hereditary Papulotranslucent Acrokeratoderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Females predominately</td>
<td>Females and males</td>
</tr>
<tr>
<td>Inheritance pattern</td>
<td>Sporadic in most cases</td>
<td>Autosomal dominant</td>
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<tr>
<td>Distribution</td>
<td>Hands</td>
<td>Edges of hands and feet</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Symptomatic translucent white papules after exposure to water, associated with burning, tingling or pruritus</td>
<td>Asymptomatic papules and plaques</td>
</tr>
<tr>
<td>Trauma associated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>History of atopy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal hair</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Course</td>
<td>Transient</td>
<td>Permanent</td>
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</table>

References

ABSTRACT: Erythema Induratum is a disease process that belongs to a group known as tuberculids; diseases caused by a silent or active focus of tuberculosis. We present a 49 year-old man from India who presented with recurring tender nodules on the posterior aspects of his legs. He had a BCG vaccination as a child and previously positive PPD. Initial lab work, and chest X-ray were all unremarkable. A skin biopsy resulted in findings consistent with Erythema Induratum and the patient was subsequently referred to infectious diseases to begin treatment and investigate any other possible evidence of TB.

Examination
Physical exam revealed multiple hyperpigmented patches and erythematous tender nodules on the posterior lower legs, and admixed areas of poorly defined violaceous-to-erythematous macules (Figures 1-2). No regional lymphadenopathy was identified. The remainder of the exam was unremarkable.

Laboratory
Laboratory work showed a negative quantiferon test. A PPD was not performed due to history of BCG vaccination and a positive PPD in the past. All other labs including CBC and CMP were normal. An AFB culture was performed on a tissue sample from the right leg and showed no growth of any bacteria.

Histopathology
A 1.0 by 1.0 cm excision biopsy of the posterior right leg and a punch biopsy of the right ankle were performed. Histopathology revealed a septal-lobular panniculitis consisting of a mixed infiltrate of acute supplicative and granulomatous inflammation with foreign body-type giant cells. The inflammation extended into the overlying deep reticular dermis. Focal fat necrosis was also observed. There was also involvement of large vessels.

Course And Therapy
The patient received a diagnosis of erythema induratum and was referred to infectious disease in an attempt to uncover any unseen tuberculosis infection and begin treatment. The patient began a rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) regimen and experienced a gradual resolution of symptoms within the first two months.

Discussion
Pierre-Antoine-Ernest Bazin from France first used the term erythema induratum (EI) nearly 150 years ago to represent the chronic disorder of painful, violaceous, indurated, and sometimes even ulcerated nodules found on the lower extremities of patients. Initially he classified the disorder as a scrofula or scrofulid. With the discovery of Mycobacterium tuberculosis years later and subsequent findings of...
mycobacteria in lymph nodes of patients with EI, the association between the two began. In 1898, fellow Frenchman Audry began to challenge such an association after encountering similar patients lacking tuberculosis granulomas on biopsy, acid-fast bacilli within lesions, and even a history of previous TB exposure (3). Whitfield reported similar cases in patients without evidence of tuberculosis and postulated that EI consisted of two entities dependent on the presence of TB or lack thereof (2). Thus, a Bazin and Whitfield variation respectively emerged. Montgomery and colleagues further described the Whitfield type as a non-tubercular nodular vasculitis (3). Various authors continue using the term erythema induratum to represent either variant rather than utilizing different names for the two distinct processes (4, 5, 6).

EI currently belongs to a group of diseases known as tuberculids, which are skin conditions thought to result from either a silent or active focus of tuberculosis. In some cases patients do not present with symptoms or positive test results consistent with a tuberculosis infection. Many authors would advocate the use of M. tuberculosis DNA PCR on skin biopsy of EI lesions to prove the association in this setting (7).

Along with the reported association with both active and latent TB, many possible etiologies have coexisted and have been thought to be triggers for EI. Cases of EI have been thought to be triggers for EI. Cases with both active and latent TB, many distinct processes (4, 5, 6). In addition, cases of EI have been reported in totally healthy individuals with no known underlying co-morbidities (3).

That there exists more than one single etiologic cause for EI, a diagnosis should rest on the clinical pathological correlation. Patients with EI present with recurrent flares of cold violaceous nodules on the posterior and anterolateral surfaces of the lower legs. These nodules may or may not be painful and can have a predisposition to centrally ulcerate, leaving behind scars and/or post-inflammatory hyperpigmentation. The nodules that ulcerate can also present as superficial crusts with rolled erythematous borders (1). This ulceration is thought to result from the caseous necrosis induced by vascular damage that progressively migrates to the overlying dermis and epidermis. The nodules can share similarities in appearance with other diseases such as erythema nodosum, polyarteritis nodosa, and perniosis (3). EI becomes chronic with recurrences taking place in 4-month intervals.

Workup includes testing for an active or latent TB infection, an incisional skin biopsy with H&E and stains for acid-fast organisms, and labs such as a complete blood count with differential, erythrocyte sedimentation rate, liver function tests, and hepatitis C serology.

Though 60% of patients with EI have a positive tuberculin skin test and/or evidence of TB exposure, lack of these findings does not in any way negate a diagnosis of EI. In contrast, more reliance should be placed on the combination of clinical and histological findings with M. tuberculosis DNA PCR results acting as a strongly supportive test (7, 4). The patient in this case presented with both the clinical and histological evidence consistent with EI. The negative quinolone gold test in this case points to a Whitfield variant. It could also represent a false negative or a rare true negative finding in the Bazin type of EI.

As mentioned previously, tuberculosis does not always represent the sole etiology. Nevertheless, multiple authors have found success utilizing the anti-tubercular regimen of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE). This combination was used by Schneider and colleagues in treating a group of 20 patients diagnosed with EI. They reported that only five of the group had positive PCR results for MTB DNA. Despite that, the entire group of patients experienced resolution of symptoms within one to six months (9). Alothman and colleagues successfully treated two different female patients with negative medical and family history of TB, negative mycobacterium tuberculosis cultures, and negative PCR for MTB DNA. They utilized the same anti-tubercular therapy and witnessed excellent clinical results as well as gradual declines in their respective erythrocyte sedimentation rate values (9). The current recommended regimen consists of either two months of RIPE with four subsequent months of isoniazid and rifampin, or two months of rifampin, isoniazid, pyrazinamide, with seven proceeding months of rifampin and isoniazid (9). Unfortunately, the possible adverse effects of these antitubercular drugs are well known (e.g. hepatotoxicity, agranulocytosis, drug-induced systemic lupus erythematosus, peripheral neuropathy, optic neuritis, gout, etc.) and have raised some debate as to whether or not such a treatment plan should wait for positive evidence of TB involvement. Some have even recommended the use of interferon-gamma release assays to aid in diagnosing patients with TB positive EI before beginning anti-tubercular treatment, especially in patients with previous BCG vaccination or known TB exposure (10).

Other efficacious treatment options exist as well. These include more supportive methods such as rest with spontaneous resolution, compression and supportive bandages, and NSAIDS.

Additionally, success has stemmed from potassium iodide, dapsone, gold salts, colchicine, and doxycycline (1, 5, 8). Pegylated interferon and ribavirin use have also demonstrated the ability in treating patients with concomitant hepatitis C. (4). Unfortunately, a prospective comparison of RIPE therapy versus such alternatives has not been conducted.

References
Important Safety Information for ZIANA Gel

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

To learn more, contact your Medicis, The Dermatology Company representative.

See reverse side for a Brief Summary of the Full Prescribing Information.

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

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

Ultraviolet Light and Environmental Exposure

Exposure to sunlight, including sunlamp, should be avoided during the use of ZIANA® Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with ZIANA® Gel.

ADVERSE REACTIONS

Clinical Studies Experience

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

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

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ZIANA® Gel N=1853</th>
<th>Clindamycin N=1428</th>
<th>Tretinoin N=846</th>
<th>Vehicle N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENTS WITH AT LEAST ONE ADVERSE REACTION</td>
<td>842 (45)</td>
<td>342 (24)</td>
<td>225 (27)</td>
<td>91 (22)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>65 (4)</td>
<td>64 (5)</td>
<td>16 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Pharyngotonsillitis pain</td>
<td>29 (2)</td>
<td>18 (1)</td>
<td>5 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (1)</td>
<td>7 (1)</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (1)</td>
<td>21 (2)</td>
<td>9 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (1)</td>
<td>19 (1)</td>
<td>15 (2)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Baseline N=1835</th>
<th>End of Treatment N=1014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>636 (35)</td>
<td>416 (26)</td>
</tr>
<tr>
<td>Scaling</td>
<td>237 (13)</td>
<td>280 (17)</td>
</tr>
<tr>
<td>Itching</td>
<td>189 (10)</td>
<td>70 (4)</td>
</tr>
<tr>
<td>Burning</td>
<td>38 (2)</td>
<td>56 (4)</td>
</tr>
<tr>
<td>Stinging</td>
<td>33 (2)</td>
<td>27 (2)</td>
</tr>
</tbody>
</table>

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and 2, 1,277 subjects enrolled with moderate to severe acne, 854 subjects treated with ZIANA® Gel and 423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were slightly higher for the ZIANA®-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA® Gel showed a similar adverse reaction profile as seen in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.
**Plaque of the Glans Penis: Differential Diagnosis**

Melinda F. Greenfield, DO,* Joseph M. Dyer, BS**
*Board-certified dermatologist, Albany Dermatology Clinic, Albany, GA
**OMS-III, Philadelphia College of Osteopathic Medicine – Georgia Campus, Suwanee, GA

**Abstract:** We offer the case of an erosive penile plaque in an elderly male that follows a relapsing and remitting course and discuss the differential diagnosis.

**Case Report**

A 77-year-old African American male complained of a sore on his penis for several years. The lesion appeared intermittently, healed, then recurred, always on the glans. He stated it was irritated by sexual intercourse. Of note, the patient uses a vacuum erection device (VED) to achieve tumescence. When present, the lesion lasted two to three months. The patient reported an initial blister that would subsequently "bust and stay raw." He stated that the lesion did not itch but was tender. The patient had sampled a variety of creams, none of which gave relief.

Review of systems was non-contributory except for osteoarthritis. The patient reported taking non-steroidal anti-inflammatory drugs (NSAIDs).

Past medical and surgical history was unremarkable except for prostatectomy. The patient was a non-smoker and non-drinker, with no known drug allergies.

Additionally, the patient provided a pathology report from a penile biopsy of a similar lesion taken six months prior. The report described fibrosis involving subcutaneous tissue and corpus spongiosum. It characterized the specimen as having mild epithelial hyperplasia and focal dystrophic calcifications. Further, the report noted a moderate number of pigmented cells consistent with either melanophages or hemosiderophages. No significant inflammatory component was apparent. No dysplasia or malignancy was identified. This original biopsy was read by a general pathologist.

Physical examination of the lesion revealed an erythematous, scaly, eroded plaque of the right penile tip (Figure 1). The penis was circumcised. Inguinal lymphadenopathy was not appreciated. The plaque was moderately tender to palpation.

The initial assessment was chronic dermatitis. The patient was treated with clobetasol 0.05% cream BID for one week. The patient was asked to follow up in one week. If there was no clinical improvement, another biopsy might have been indicated.

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Fixed drug eruption</td>
</tr>
<tr>
<td>Psoriasis inversus</td>
</tr>
<tr>
<td>Zoon's balanitis</td>
</tr>
<tr>
<td>Erythroplasia of Queyrat</td>
</tr>
<tr>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>Syphilitic chancre</td>
</tr>
<tr>
<td>Chancroid</td>
</tr>
<tr>
<td>Herpes genitalis</td>
</tr>
<tr>
<td>Erosive lichen planus</td>
</tr>
<tr>
<td>Lichen sclerosus et atrophicus</td>
</tr>
<tr>
<td>Vacuum-associated penile injury</td>
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</tbody>
</table>

**Discussion: Differential Diagnosis**

Fixed drug eruption (FDE) is a special type of drug sensitivity where exposure to an inciting medication causes recurrent lesions at the same location. Any area of skin or mucous membrane may be involved, although the glans penis is a typical site. Lesions begin as solitary or multiple dusky-red, demarcated plaques and may become bullous or erosive. Characteristically, the affected area appears hyperpigmented after healing. Lesions vary from asymptomatic to pruritic and painful. Offending medications include tetracyclines, sulfonamides, NSAIDs, anticonvulsants, quinine, and phenolphthalein. Limited anecdotal evidence suggests that an FDE may be elicited in an individual after sexual contact with a partner who has taken a sensitizing drug.

Psoriasis inversus (PI) is the most common noninfectious dermatosis occurring on the glans penis. Distribution of PI includes intertriginous areas, such as the submammary folds, axillae, gluteal cleft, and genital region. Examination reveals erythematous, fissured plaques with clearly delineated margins. Lesions may appear macerated, lacking the typical scaling of psoriasis, due to increased moisture content of these areas. Microscopically, psoriasis demonstrates parakeratotic hyperkeratosis, where cornified cells in the thickened epidermis retain pyknotic nuclei. The dermis displays swollen, tortuous capillaries that are grossly evident through bleeding when the superficial layer of the plaque is scraped away (Auspitz’s sign).

Zoon’s balanitis (ZB) is a rare, idiopathic dermatosis occurring almost exclusively in the uncircumcised penis. It presents as a mildly pruritic, mildly tender, red-orange plaque on the glans or prepuce. Histologically, plasma cell infiltration of the dermis attests to ZB’s alternate name, plasma cell balanitis. Although calcineurin inhibitors and carbon dioxide lasers have been reported as beneficial therapies, circumcision is usually curative.

Erythroplasia of Queyrat (EoQ) is squamous cell carcinoma in situ (Bowen’s disease) that presents on the penis. It appears as a glistening, velvety, red plaque on the glans, prepuce, or urethral meatus of elderly males. The lesion gradually enlarges over time. Symptoms include bleeding, pain, and itching. Management of EoQ involves 5-fluorouracil, Mohs micrographic surgery, or partial penectomy.

Contact dermatitis occurs after physical exposure to an irritating or sensitizing substance. There are several categories of
common materials that may induce a skin reaction: metals, such as nickel; preservatives, such as formaldehyde; rubber ingredients, such as thiurams; plants, such as poison ivy; or medications, such as topical steroids. With regard to the glans penis, latex condoms and diaphragms are common culprits. Clinically, pruritus and edema are significant features of allergic contact dermatitis, and expression of symptoms is especially florid when this entity affects the genitalia.

Three sexually transmitted infections deserve mention. First, a syphilitic chancre is the primary manifestation of the disease caused by the spirochete Treponema pallidum. This lesion is described as a painless ulceration with an elevated border and scanty serous exudate. Discrete, rubbery lymph nodes may be palpated regionally and are commonly unilateral. Chancres develop around three weeks after inoculation and persist for approximately three to six weeks before resolving. Syphilis progresses with serious systemic and neurologic sequelae, if untreated. Another infectious consideration is chancroid, a painful genital ulcer caused by Haemophilus ducreyi. Tender, suppurative lymphadenopathy occurs in 50% of patients. Chancroid is most common among young males in tropical and subtropical developing countries. Finally, herpes genitalis classically manifests as grouped vesicles on an erythematous base. More commonly, though, it progresses from plaque to vesicles, with erosions and fissuring culminating in ulcerations. These lesions heal in two to four weeks. Again, inguinal and femoral lymph nodes are usually enlarged and firm.

An inflammatory condition of skin and mucous membranes, typical lichen planus (LP) presents as pruritic, purple, polygonal, planar papules. Close inspection of papules frequently reveals pathognomonic Wickham striae, a whitish reticular pattern on a circumscribed, pale base. LP papules are often nonspecific, less shiny, poorly demarcated, and may instead appear erosive. Erosive LP may mimic FDE, but a chronic rather than recurrent course suggests the former. Biopsy submission to a dermatopathologist may be necessary to yield a definitive diagnosis.

Lichen sclerosus et atrophicus (LSA) is a cutaneous disorder affecting the anogenital region of females ten times as often as men. Involved areas may appear as ivory-white plaques, indurations overlain with skin that is thin and fragile like tissue paper. Purpura and telangiectasia may also be associated. When present on the penis, LSA is renamed balanitis xerotica obliterans (BXO). Lesions of BXO are usually confined to the glans and prepuce. Symptoms include pruritus, pain, and, in the uncircumcised male, phimosis. Complaints may be heightened by intercourse. Once irritated, plaques may erode and heal with contraction. BXO occurs most frequently in uncircumcised, middle aged men and shows no racial predilection. Potent topical glucocorticoid preparations, such as clobetasol, are effective treatments.

Vacuum-associated penile injury bears special consideration in this case. Common side effects from VED use include numbness, pain, penile bruising, and petechiae. Anecdotally, penile hematoma, hyperpigmentation, and Fournier’s gangrene have been reported. Surprisingly, penile blister formation is not a known complication of vacuum therapy in erectile dysfunction, although it remains a theoretical concern. Although VEDs vary considerably among manufacturers, time required to achieve a suitable penile erection ranges from 30 seconds to 7 minutes at negative pressures of 100 to 225 mm Hg. Deliberate induction of suction blisters in vivo takes at minimum 1 to 2 hours at negative pressures of 300 mm Hg. Thus, without gross misuse, VEDs would seem incapable of generating suction blisters.

Case Follow-Up

After one week, the patient returned for evaluation. The penile plaque demonstrated improvement after applying the clobetasol. The patient stated that his symptoms were resolving. Re-biopsy was deemed unnecessary at that time.

Conclusion

A recurrent penile plaque in an elderly patient warrants a thorough investigation into the differential diagnosis.

If the initial assessment and treatment had proved inadequate in our case, the patient’s history would have been re-visited. Does he always have sexual intercourse with the same partner? Is contraception employed, such as condom, sponge, diaphragm, spermicide, or intrauterine device (IUD)? Contact dermatitis may be implicated by accelerators used in latex condom manufacture or metallic ions eluted from an IUD. Has the patient had any known exposure to a sexually transmitted infection? Is his partner taking any medications? What brand of vacuum erection device does he use? How does he use it? Was he circumcised at birth? Late circumcision confers risk for balanitis xerotica obliterans. Does he self-administer any medications or creams before coitus? What medications does he take for osteoarthritis? Does the patient take any other over-the-counter drugs, prescription medications, or supplements?

If the lesion had persisted, a repeat biopsy would have been necessary, with evaluation by a dermatopathologist.

In general, the goal in this situation is to rule out malignancy (erythroplasia of Queyrat), treat infections (syphilitic chancre, chancroid, and herpes genitalis), avoid inciting substances or scenarios (fixed drug eruption, contact dermatitis, and vacuum-associated penile injury), manage other conditions (psoriasis inversus, Zoon’s balanitis, erosive lichen planus, and lichen sclerosus et atrophicus), and allay the patient’s anxiety.

References


26 PLAQUE OF THE GLANS PENIS: DIFFERENTIAL DIAGNOSIS
Advancement Flap for Distal Nasal Defects

Albert E. Rivera, DO, FAOCD,* Roger I. Ceilley, MD,** Andrew K. Bean, MD,* Joshua B. Wilson, MD*

*Dermatology P.C., West Des Moines, Iowa
**University of Iowa Department of Dermatology, Iowa City, Iowa

ABSTRACT: Skin cancers involving the distal one half of the nose are commonly encountered in dermatology. Herein we present an example of a nasal advancement flap to expand the dermatologic surgeon’s alternatives for restoring both the aesthetic and functional characteristics of such a surgical site after tumor removal. The following technique provides a simple, single-stage option with a high survival rate that maximizes use of cosmetic unit borders and minimizes functional concerns.

Intro

Skin cancers involving the distal half of the nose are commonly encountered in dermatology. Herein we present an example of a nasal advancement flap to expand the dermatologic surgeon’s alternatives for restoring both the aesthetic and functional characteristics of such a surgical site after tumor removal. Mohs micrographic surgery is often the treatment option chosen for tumor clearance due to its tissue sparing properties. Once a tumor is totally resected, the repair of the resulting defect must be addressed. Various techniques exist depending on the defect location, cosmetic concerns, patient tolerance of procedures, comorbidities and previous interventions. Being familiar with the range of reliable repair alternatives is essential. The following technique provides a simple, single-stage option with a high survival rate that maximizes use of cosmetic unit borders and minimizes functional concerns.

Repair Concerns

There are several factors that deserve consideration when surgically restoring the functional and cosmetic aspects of a patient’s nose. The primary concern is to maintain the nasal valve function. Cosmetically, symmetry is also essential due to the midfacial location of the nose. Respect for the cosmetic units is a key component in achieving an optimal result and minimizing suture line visibility. Sites that are of particular concern include the nasal tip, nasal dorsum, bilateral nasal alae, bilateral nasal sidewalls and the soft triangle. Depending on patient preference or physician recommendation, a single- or multi-staged procedure might be favored. If considering a graft, the color, adnexae, thickness and skin quality (ultraviolet exposure or damage) are variables. Other relevant considerations include the overall healing time, wound care required, anatomic variations, functional deficits, size of the defect, patient comorbidities and prior procedures (or tumors) at or near the same location.

Surgical Technique

Figure 1 illustrates a representative defect that is well suited for this repair. Figure 2 shows the appropriate design. From the most lateral margin of the defect, an incision down to the subcutaneous tissue, or submuscularly if the defect allows, is made running cephalad along the junction of the nasal sidewall and the nasal dorsum. This location allows for camouflage of the suture line once healed. At the junction of the nasal dorsum, nasal root and sidewall, the incision is carried laterally, again hiding the line within the cosmetic unit borders. A Burrow’s triangle is taken from this location to allow for the later caudal advancement. A second Burrow’s triangle is then removed from the primary defect, contralateral to the original incision to allow optimal approximation of the original defect. Both pieces of removed skin are placed in sterile saline should an unexpected need for tissue arise. Extensive undermining of the entire flap in the subcutaneous or, as allowed, submuscular plane is then performed. Meticulous hemostasis is achieved to ensure prevention of hematoma or ecchymoses. The cephalad secondary defect is closed using subcutaneous dissolvable sutures, essentially
Discussion

The described advancement flap is best suited for defects of the distal nose less than approximately 2 centimeters in diameter. Benefits of this particular flap variation include a robust random vascular supply and thus excellent survival. Also, the incision lines tend to respect the cosmetic units, allowing for better cosmetic results, and the local tissue is a superb match for color, adnexae and quality. It is a favorable option to patients since it is a single stage procedure. Slight lateral or upward pull can occur, but it usually returns to baseline within a few weeks. Overall, it is an easily performed and tolerated procedure with good cosmetic and functional outcomes.

There are a number of other options for repair of the type of lesion discussed. Secondary intention could be considered but is usually reserved for more superficial defects and primarily on concave areas rather than convex sites. Primary linear closure is another proposed option for repair of smaller defects. If the lesion is not centrally located, there can be lateral nasal deviation or sometimes alar flaring. Defects of great size that are closed primarily can very commonly result in a “saddle nose” deformity where the central area of the incision line is depressed.

Full thickness grafts may also be utilized. Burrow’s grafts tend to match the local skin more closely but often alter or cross cosmetic units. The survival rate is lower because a new, viable blood supply must develop to sustain the metabolic needs. Grafts from other locations demonstrate these same difficulties in addition to creating an additional secondary donor defect. Also, the thicker sebaceous skin of the nose is a difficult match when using remote tissue. With delayed grafts, there is a higher chance of survival and usually a smaller size requirement because of wound contraction and granulation. It is still burdened by occasional graft failure, cosmetic unit disruption, matching difficulty and donor defect. In addition, it is a multi-staged procedure and requires additional visits and wound care by the patient.

Other flaps could be considered. One would include the dorsal nasal rotation (Hatchet) flap. It has excellent survival, but it crosses multiple cosmetic units. The bilobed flap utilizes similar local tissue but can often develop “pincushioning” at the suture lines. Though more commonly used for alar defects, the nasolabial flap has good survival, but it is a multi-staged procedure. Island pedicle flaps (unilateral or bilateral) have been suggested due to use of adjacent tissue. The Rintala flap is a good skin match but is for midline lesions only and can distally necrose. A horizontal advancement flap is more difficult to utilize for smaller noses or defects that are too far lateral. Use of a rhombic flap usually does not utilize the cosmetic units. A less frequently encountered option would be the orbicularis oculi musculocutaneous flap. The survival is improved because of the infraorbital artery supply, but the multi-staged nature makes it a less attractive option.

In summary, there are multiple designs to consider when repairing a defect of the distal nose. Any consideration will have positive and negative aspects. Our suggestion is a simple, single-stage procedure with a high survival rate that maximizes use of cosmetic unit borders and has minimal cosmetic or functional concerns. The addition of this flap to the dermatologic repair arsenal will hopefully expand the possibilities and improve outcomes within the appropriate surgical patient population.

References

**AMELANOTIC SPINDLE CELL MELANOMA IN A HISPANIC MALE**

**Case Presentation**

An 83-year-old Hispanic male from the Dominican Republic presented with the chief complaint of a growth on his face for approximately 5-6 months. His past medical history was significant for hypertension and prostate cancer. Review of systems was non-contributory; the patient denied pain, neuropathy, and bleeding or constitutional symptoms. He was not on any medications and had no known drug allergies. Family history was non-contributory, and he denied smoking or alcohol use. Physical examination revealed a 2 x 2 cm erythematous nodule with rolled border, telangiectasias and a central keratotic plug (Figure 1). An incisional biopsy was performed with clinical suspicion of keratoacanthoma versus squamous cell carcinoma. Histopathology showed a tumor comprised of a highly cellular proliferation of plump spindle cells arranged in nests, intersecting fascicles and confluent sheets. Cells had large, hyperchromatic nuclei with frequent mitoses present. The adjacent dermis had severe actinic elastosis, and there was no melanin pigment present (Figure 2). The tumor cells were strongly and diffusely positive for S100 protein and vimentin, and negative for specific melanoma markers HMB 45 and MelanA. There was strong reactivity with CD68, a macrophage marker, and neuron specific enolase, which can label melanomas as well as other neural crest tumors. Histochemical staining in addition to histopathology allowed us to make the diagnosis of spindle cell melanoma. The patient was referred for immediate surgical excision and metastatic workup. ACT PET scan showed no evidence of metastatic disease, and labs including complete blood count, comprehensive metabolic panel and lactate dehydrogenase were all within normal limits. The mass was excised, and the defect was closed with a rotational Z plasty flap. Final diagnosis of the specimen revealed a Breslow’s depth of 6.35 mm with a Clark’s level of V and a mitotic count of 12 per mm2. Blood vessel, lymphatic and neural invasion were not identified; however, ulceration was present and measured greater than 1 centimeter.

**Discussion**

Spindle cell melanoma is an uncommon variant of melanoma that is locally aggressive and tends to have a high recurrence rate. The clinical appearance can be highly variable and may mimic a variety of lesions. In this case, a Hispanic male presented with a lesion clinically resembling a keratoacanthoma. The diagnosis of amelanotic melanoma of the spindle cell type was achieved via histopathology and histochemical markers. Melanomas are less common and often under recognized in patients of color. This case demonstrates the need to maintain a high index of suspicion for melanoma even in non-pigmented lesions and especially in patients of color.

**ABSTRACT:** Spindle cell melanoma is a rare form of melanoma that is locally aggressive and tends to have a high recurrence rate. The clinical appearance can be highly variable and may mimic a variety of lesions. In this case, a Hispanic male presented with a lesion clinically resembling a keratoacanthoma. The diagnosis of amelanotic melanoma of the spindle cell type was achieved via histopathology and histochemical markers. Melanomas are less common and often under recognized in patients of color. This case demonstrates the need to maintain a high index of suspicion for melanoma even in non-pigmented lesions and especially in patients of color.
Histologically, lesions are usually large, poorly circumscribed and can extend to the subcutaneous tissue, fascia and nerves. Desmoplastic melanomas show a lentiginous melanocytic proliferation with atypia and pleomorphic spindle cells in the dermis. There are dermal and/or subcutaneous infiltrates of spindle-shaped cells arranged in fascicles or singly within a prominent collagenous or mixoid stroma. There is variability among tumors classified as desmoplastic melanomas. Desmoplasia can be prominent throughout the entire tumor, classified as a "pure" desmoplastic melanoma, or it can represent a portion of a non-desmoplastic melanoma, referred to as a "combined" desmoplastic melanoma. Some tumors have prominent nerve involvement, in which case they are termed desmoplastic neurotropic melanomas.

Immunohistochemical staining becomes important in these cases. S100 is a reliable marker with high sensitivity for identifying spindle cell melanomas and is often positive; however, its usefulness is limited by its low specificity. Newer studies reveal that p75 nerve growth factor receptor staining could prove beneficial in cases of S100-negative desmoplastic or neurotropic melanomas and should be used as well to increase diagnostic sensitivity. P75 nerve growth factor receptor is a member of the tumor necrosis family and is one of the earliest markers expressed by cells of the neural crest. Staining for HMB-45, a marker for premelanosomes and a more specific marker for melanoma, is often absent; however, when present, tumors tend to have more aggressive behavior.10,11,12 CD 68, a macrophage marker, has been demonstrated in a minority of cases and was positive in the case described.5 The tumor cells are positive for vimentin in all cases and for neuron-specific enolase in about 95% of cases.12

As with most forms of melanoma, surgery is the first line of treatment as this tumor is both highly infiltrative and locally aggressive. Optimal margins for excision have not been established owing to the smaller number of reported cases as compared with other types of melanoma. Metastasis to regional lymph nodes is uncommon, and elective lymph node dissection is not usually indicated. However, sentinel lymph node biopsy (SLNB) can be used to detect subclinical metastases to regional lymph nodes. Su et al. examined 33 patients with desmoplastic and neurotropic melanoma without clinical evidence of metastatic disease who underwent sentinel lymph node biopsy; 4 of the 33 patients had at least one positive sentinel lymph node.13 Some authors recommend adjuvant post-operative radiation therapy to control local recurrence. In a study of 49 patients with desmoplastic melanomas of the head and neck, the local recurrence rate was 4% (2 of 49 patients). Surgical margins greater than or equal to 2cm were obtained for head and neck lesions that measured > 1mm in depth. In this study, wide excision alone was found to produce excellent results without the need for adjuvant radiation.14

Desmoplastic melanoma is locally aggressive and often has an advanced Breslow’s thickness at the time of presentation, possibly due to late diagnosis. These tumors carry a high risk of local recurrence, while the incidence of distant metastasis is low. Desmoplastic neurotropic melanomas present at a more advanced stage locally and may be associated with a better survival than other forms of non-desmoplastic melanomas of equal Breslow’s depth of invasion. In an analysis of 28 cases of desmoplastic melanoma by Carlson et al., actual 5-year survival for tumors greater than 4mm thickness was 72%, which was greater than for other types of melanoma with greater than 4mm thickness.14 Although this particular type of melanoma does portend a better prognosis, it can be fatal if local invasion is deep enough.

As with all types of melanoma, close follow-up is recommended. The rate of local recurrence is higher with incomplete excision of the primary lesion, greater tumor thickness, and the presence of neurotropism.8

This particular type of tumor should be considered when faced with an elderly individual who presents with a tumor arising in a background of sun-damaged skin. Melanomas are less common in people of color when compared with Caucasians. Melanomas are also under-recognized in patients of color and often do not present the same way they would in Caucasian populations. Age adjusted incidence rates, per 100,000, for melanoma in Hispanics, Blacks and Asians are approximately 4.5, 1.0, and 21.6, respectively.15 Skin cancers in skin of color often present at a more advanced stage locally, with a history of excessive sun exposure. Perhaps better education of patients of lower socioeconomic status is needed to aid in diagnosis of melanoma in the non-white population.

References

Conclusion
Spindle cell melanomas are frequently mistaken for a non-melanocytic proliferation; diagnosis is often delayed, and presentation at an advanced stage is quite common. This case demonstrates the need to maintain a high index of suspicion for melanoma even in non-pigmented lesions and especially in patients of color, in whom melanoma is less common. This diagnosis should be kept in mind when faced with suspicious growths particularly in patients with a history of excessive sun exposure. Perhaps better education of patients of lower socioeconomic status is needed to aid in diagnosis of melanoma in the non-white population.

30 AMELANOTIC SPINDLE CELL MELANOMA IN A HISPANIC MALE
ABSTRACT: Persistent cutis marmorata and phlebectasia presenting at birth describe cutis marmorata telangiectatica congenita (CMTC). The etiology is unknown for this uncommon disorder. Associated anomalies are numerous and may include limb asymmetry, port wine stains, as well as glaucoma. The differential diagnosis includes physiologic cutis marmorata, capillary malformations, as well as vascular defects. The diagnosis is primarily ascertained clinically. Management involves careful evaluation for associated disorders, supportive care, and routine follow-up visits at least until age 3. This article presents a case of a young boy diagnosed with extensive cutis marmorata telangiectatica congenita. Following is a discussion including the hypothesized pathogenesis, clinical findings, potential associated abnormalities, differential diagnoses as well as management of CMTC.

Case Report

A 12-month-old Caucasian male was born full-term via Caesarian section at 39 weeks gestation without complications. At birth, he was sent to the neonatal intensive care unit for evaluation of a “skin condition” described as “diffuse ecchymosis” and areas of “skin necrosis.” Upon examination by hematology, the patient was thought to have protein C/S deficiency, and a disseminated intravascular coagulation panel was ordered. The patient was started on fresh frozen plasma for work-up, as well as ampicillin and gentamicin due to suspected sepsis. Dermatology was consulted on day 4 of life.

Physical exam revealed numerous reticulate purpuric plaques with central depression noted over the right upper extremity, trunk, left lower back, and bilateral lower extremities (Figures 1-3). Subcutaneous tissue was diminished over the right arm and leg, and erosions were noted within the purpuric areas. Faint linear purpura was noted over the forehead and cheeks. Skin biopsy was not performed, and the laboratory results from earlier work-up were non-contributory. He did not have protein C/S deficiency.

Based on the history and physical exam, the diagnosis of cutis marmorata telangiectatica congenita was established and supportive treatment instituted. For eroded areas, petroleum jelly and hydrocolloid dressings were applied, with healing occurring over the following months. At 12 months of age, the patient continues to show improvement with fading of the marmorated plaques.

Discussion

Cutis marmorata telangiectatica congenita (CMTC) was first described in 1922 by Maarten van Lohuizen, a Dutch pediatrician. It is a relatively uncommon congenital vascular malformation characterized by persistent cutis marmorata along with variable presence of telangiectasia, phlebectasia, cutaneous atrophy and ulceration.1,2,3 It is generally recognized as a sporadic condition, although there are case reports of familial associations, suggesting a possible genetic link.4 The pathogenesis is unknown; however, hypotheses regarding its etiology include genetic mosaicism, peripheral neural dysfunction, or an environmental teratogenic agent.5,6 There does
not appear to be any gender predilection.\textsuperscript{3}

Greater than 90\% of patients present at birth with reticulated blue-violet to red patches, but lesions can appear anywhere from 3 months to 2 years after birth.\textsuperscript{1} The livedo reticularis-like pattern preferentially affects the extremities (in particular the legs), followed by the trunk and face.\textsuperscript{2,3} Although the sharply demarcated reticular erythema can be generalized, it is more commonly localized, unilateral, and does not appear to cross the midline.\textsuperscript{2,3} The lesions are relatively fixed, and while more prominent with cooling and crying, the motting does not resolve with warming of the skin.\textsuperscript{6} These major features are often accompanied by focal areas of atrophy within the reticulated bands, resulting in limb circumference discrepancy as well as varying degrees of vein prominence, telangiectasia, and ulceration.\textsuperscript{7,8}

The rate of associated anomalies, both cutaneous and extracutaneous, range from 20-80%.\textsuperscript{7} The large discrepancy in reported rates may be due to an overestimation from purely coincidental findings.\textsuperscript{3,9} The most common finding associated with CMTC is body asymmetry, with limb hypoplasia or hyperplasia confined to areas affected by CMTC, often with overlying cutaneous atrophy.\textsuperscript{2} Also commonly seen are vascular anomalies, including port wine stains, angioectasias and hemangiomas. Although not exhaustive, other associations include underlying musculoskeletal defects (e.g., syndactyly, tendinitis stenosans, hip dysplasia, clubfoot, cleft palate), ocular malformations (glaucoma, especially in association with facial lesions), neurologic anomalies (e.g., macrocephaly, mental retardation, seizures), and cardiovascular, gastrointestinal and genitourinary abnormalities.\textsuperscript{3,4,10,11} There does not seem to be any correlation between the severity or extent of skin lesions and the presence of associated anomalies.\textsuperscript{12} Of note, a finding seen in many patients with Adams-Oliver syndrome is CMTC. These patients present with generalized CMTC, heart anomalies, limb defects, and calvarial malformations.\textsuperscript{9}

The differential diagnosis is extensive and must be differentiated from other reticulated vascular lesions. Physiologic cutis marmorata, a common benign neonatal response to cooling, can be differentiated from CMTC by the finer reticulated pattern, resolution with heat application as well as lack of atrophy and ulceration.\textsuperscript{3,6,9} Physiologic cutis marmorata, when persistent, often co-exists with genetic syndromes, including Down syndrome, Cornelia de Lange syndrome, homocystinuria, and Divvy-Van Bogaert syndrome.\textsuperscript{5} Bockenheimer syndrome presents in infancy and progresses to diffuse painful phlebectasia.\textsuperscript{2} Capillary malformations, such as port wine stains, may present in a reticulated pattern and be localized and unilateral without crossing the midline; however, they are not associated with atrophy and do not fade with time.\textsuperscript{7} Klippel-Trenaunay syndrome presents with port wine stains, prominent varicosities, and bony or soft-tissue hypertrophy.\textsuperscript{2} There is a questionable association between CMTC and neonatal lupus erythematous, wherein CMTC affects bilateral extremities symmetrically and the infant has the presence of anti-Ro antibodies, suggesting that CMTC may be a part of the cutaneous spectrum of neonatal lupus.\textsuperscript{11,12}

Finally, macrocephaly-cutis marmorata syndrome (previously known as macrocephaly-CMTC syndrome) must be considered when there is concomitant macrocephaly, as these patients are at significant risk for neurologic abnormalities.\textsuperscript{12} While initially believed to be associated with CMTC, this syndrome, which presents with neonatal hypotonia, developmental delay, segmental overgrowth, syndactyly and connective tissue defects, is in fact associated with a capillary malformation or persistent nevus simplex.\textsuperscript{7,8,11,14}

Diagnosis of CMTC is primarily clinical. Although a biopsy may be performed, the histopathologic findings are generally non-specific, revealing dilated capillaries in the deep dermis with hyperplasia and swollen endothelial cells.\textsuperscript{3} Performing a careful clinical examination is important to exclude possible associations. Along with a thorough medical history and cutaneous exam, the musculoskeletal system should be evaluated for body asymmetry, such as limb hypoplasia.\textsuperscript{2} When the head is affected, both an ophthalmologic and neurologic examination must be performed to assess for glaucoma, head circumference, and developmental delays.\textsuperscript{7}

Limb asymmetry, if present, tends to persist; however, in approximately 50\% of cases, the reticular pattern remits by the second year of life, conferring a favorable prognosis.\textsuperscript{3,7} Thus, treatment is primarily supportive, including wound care regimens for ulcerations and consideration of the pulsed-dye laser for persistent lesions.\textsuperscript{3} Patients should be seen annually for a minimum of three years, and long-term follow-up is indicated with associated abnormalities.\textsuperscript{2}

**Conclusion**

CMTC is a rare congenital vascular anomaly characterized by persistent cutis marmorata and phlebectasia, with variable presence of cutaneous atrophy, telangiectasias and ulcerations. Associated abnormalities may affect cutaneous, ocular, neurologic, musculoskeletal, hematologic, gastrointestinal or genitourinary systems. The differential includes physiologic cutis marmorata, capillary malformations such as port-wine stains, vascular defects such as Klippel-Trenaunay syndrome, and CMTC-inclusive syndromes such as Adams-Oliver syndrome. This entity carries a good prognosis and usually resolves within the first two years of life.

**References**

A Suspicious Lesion Arising in a 28-Year-Old Female After Administration of Melanotan II

ABSTRACT: Melanotan I and Melanotan II are synthetic peptides analogous to naturally occurring alpha melanocyte stimulating hormone (α-MSH). Despite potential benefits of these peptides with tanning and treatment of erectile dysfunction, the safety of such drugs has been questioned. We present a case of a 28-year-old female with history of frequent tanning and Melanotan II use that presented to our clinic with multiple irregularly hyperpigmented papules and plaques on her abdomen, back, chest, and breasts.

Case Report

A 28-year-old Caucasian female with no history of previous dysplastic nevi presented to our clinic with a suspicious lesion on her abdomen. The patient noticed the lesion began to enlarge, but denied any change in color or bleeding. Interestingly, she had a history of subcutaneous injection of Melanotan II, an analog of α-MSH, which she purchased without prescription from an Internet website. Over a period of five months, she injected doses of Melanotan II to increase her tan and improve her sexual performance. She initially injected the substance every other day during a loading phase and then subsequently every other week for a maintenance phase. She also visited the tanning salon every five days to accelerate her tan. During the months following the injections, she experienced marked darkening of her skin tone, ephelides, and nevi. The patient also reported a long history of visiting tanning salons with an estimation of biweekly visits over a 10-year period. A review of systems was negative for preceding illness, recent weight loss, or constitutional symptoms.

Histopathology

A biopsy of the patient’s left lower abdominal lesion was sent to a dermatopathologist for interpretation. According to the pathology report, the results displayed superficial spreading malignant melanoma, Clark’s level II. Both peripheral and deep margins were involved. Microscopic findings showed atypical melanocytes disposed as solitary units and in nests unevenly distributed within the epidermis and extending into the upper dermis. Single cells in a pagetoid array were noted in the upper layers of the epidermis as well. Melanocytes did not mature with progressive descent into the dermis, and melanophages were found in the upper layers of the epidermis as well. Melanocytes did not mature with progressive descent into the dermis, and melanophages were found in the upper layers of the epidermis as well. Melanocytes did not mature with progressive descent into the dermis, and melanophages were found in the upper layers of the epidermis as well. Melanocytes did not mature with progressive descent into the dermis, and melanophages were found in the upper layers of the epidermis as well. Melanocytes did not mature with progressive descent into the dermis, and melanophages were found in the upper layers of the epidermis as well. Melanocytes did not mature with progressive descent into the dermis, and melanophages were found in the upper layers of the epidermis as well.

Examination

Physical examination revealed a well-appearing patient with a darkened skin tone and multiple irregularly hyperpigmented papules and plaques on her abdomen, back, chest, and breasts, ranging in size from 0.5 to 1.5 cm. Axillary and inguinal lymph nodes were palpated and were not enlarged. On the left lower abdomen was a 1.2 cm hyperpigmented, multicolored plaque with irregular borders.

Course And Therapy

This patient returned to our clinic for excision of her lesion and has remained free from any sign of recurrence for two months. She continues to get full-body skin checks every three months, and has stopped the self-administration of Melanotan II and the practice of tanning.

Discussion

The synthetic peptides known as Melanotan I and Melanotan II are analogues of the naturally occurring alpha melanocyte stimulating hormone (α-MSH). These peptides are up to 1,000 times more potent than their endogenous counterpart. Initial clinical trials confirmed the assumed effects of these peptides on the tanning of the skin (Melanotan I) and the treatment of male erectile dysfunction (Melanotan II). The potential benefits of such drugs have caused an increase in the use of unlicensed melanotropic hormones, further complicating the presentation and diagnosis of nevoid lesions.

α-MSH is the most potent of the melanotropic hormones. Produced by an array of cells found in the body, including keratinocytes, it acts through activation of the melanocortin receptors. Melanocortin 1 receptor is present in virtually every cutaneous cell type and is the target of the synthetic analogues Melanotan I and II. Its activation leads to increased melanogenesis and pigmentation of the skin. This receptor has also been found to be over-expressed in melanoma.

Despite the initial belief that Melanotan actually had a protective role, inhibiting melanoma cell proliferation by reducing cell migration and invasion, evidence exists that may contradict the initial findings. α-MSH not only has been shown to have direct stimulatory effects on melanoma cells by inducing change in cell shape and increased dendrigicity but it also down-regulates adhesion molecules that would normally allow interaction of the immune cells with melanoma. This interaction may allow melanoma to escape immune detection and increase its survival. Studies have also suggested a decreased level of α-MSH is actually a good prognostic factor for response to immunotherapy of melanoma.

Recent reports of the appearance of atypical nevi and changing of appearance of pre-existing nevi in Melanotan users has called into question the safety of such drugs. One case of melanoma has been reported in a Melanotan user but with no clear evidence of the causative factor. Caution should be taken in pursuing the use of these potent melanocortins due to the possible serious unknown risks associated with them.

References

ABSTRACT: Herpes infections in immunocompromised individuals can demonstrate unusual clinical presentations. Herpes vegetans is an uncommon manifestation of herpes simplex infection that presents as an exophytic mass mimicking a large verrucous tumor or malignancy. We report a case of herpes simplex vegetans in a 54-year-old human immunodeficiency virus (HIV)-positive man caused by both herpes simplex virus (HSV) types 1 and 2.

Case Report

A 54-year-old Haitian man with HIV infection diagnosed two years prior presented with an asymptomatic, oozing growth on the left buttock present for at least six months. He had been treated by his primary care physician with oral antibiotics without improvement. The patient had no other relevant past medical or family history. He was married and denied tobacco, alcohol, or recreational drug use. He had no known drug allergies. His medications included darunavir 600 mg twice daily, ritonavir 100 mg twice daily, emtricitabine/tenofovir 200/300 mg daily, and a multivitamin daily, with which he was compliant. Review of systems was negative for fever, chills, night sweats, or weight loss.

Physical examination revealed a well-developed, well-nourished black man in no acute distress. Skin exam revealed a round, 4 cm x 4 cm x 1 cm, exophytic, pink and flesh-colored, nontender, partially-erosive, papillomatous tumor on the left lower buttock with serous drainage (Figure 1). There was no inguinal lymphadenopathy. A skin biopsy confirmed a diagnosis of herpes simplex vegetans with herpes simplex virus immunoperoxidase studies demonstrating both HSV-1 and HSV-2 infections (Figures 2-5). Other laboratory data included CD4 count of 382, HIV viral load undetectable at less than 48 copies/mL, non-reactive rapid plasma reagin (RPR), and unremarkable complete blood count, comprehensive metabolic panel and urinalysis. Recommended treatment was destruction or surgical debulking of the mass combined with long-term oral antiviral therapy and continued control of underlying HIV infection with highly active antiretroviral therapy (HAART) as managed by infectious disease team.

Discussion

Herpes virus infections can present in unusual ways in immunocompromised individuals, such as chronic ulcerations or erosions, hyperkeratotic lesions, or in non-traditional locations.¹ There have been few reports of herpes vegetans in the literature, with cases associated with HIV, B-cell chronic lymphocytic leukemia, common variable immunodeficiency, congenital T-cell immunodeficiency, and chronic cutaneous lymphoid leukemia.²,⁵ Unlike conventional genital herpes infections that present with painful grouped vesicles on an erythematous base, herpes vegetans presents as an exophytic, proliferative lesion that
resembles a verrucous or malignant growth, most often found on the digits, genitalia, or perioral skin. The differential diagnosis may include squamous cell carcinoma, giant condyloma of Buschke-Lowenstein variant of verrucous carcinoma, or pyoderma vegetans.

Histopathology of herpes vegetans may show a hyperproliferative epithelium with ulceration, virocytopathic changes at the periphery including multinucleated giant cells, and a dense mixed inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, histiocytes, and plasma cells. The presence of eosinophils may be secondary to the TH2 cytokine response characteristic of advanced HIV disease. Although the exact pathogenesis of these lesions is unknown, the hypothesized mechanisms include immune dysregulation related to concomitant HSV and HIV as well as immune reconstitution following HAART.

Prior cases of herpes vegetans in the literature were often partially resistant to acyclovir and thus responded more favorably to valacyclovir, foscarnet, cidofovir, or surgical removal. Imiquimod has also been proposed as an alternative treatment in resistant cases, effectively stimulating self-healing by increasing alpha interferon response.

Although a large, exophytic lesion would not normally prompt suspicion for HSV, HSV-2 seroprevalence is three times higher among HIV-infected adults than in the general U.S. population. Awareness of the possible unusual presentations of HSV in HIV and other immunocompromised states may broaden the differential diagnosis of such vegetative, exophytic lesions and facilitate early diagnosis and institution of effective antiviral therapy.

References
Microcystic Adnexal Carcinoma (MAC) is an uncommon locally aggressive neoplasm that tends to invade deeply and recur but rarely metastasizes. First described by Goldstein et al. in 1982, MAC tends to have a predilection for the left side of the face but may also present in sun-exposed or radiation treated areas. It can appear as a flesh-colored, red, or yellow papule or as an indurated plaque and is often misdiagnosed clinically. The pathogenesis of MAC remains unclear, but it is thought to arise from pluripotent keratinocytes capable of differentiating into sweat glands or hair follicles. It most commonly arises in older adults with less than a dozen pediatric cases reported to date. We present a case of MAC in a 7 year old female as well as a discussion of diagnosis and treatment for this rare tumor.

ABSTRACT: Microcystic Adnexal Carcinoma (MAC) is an uncommon locally aggressive neoplasm that tends to invade deeply and recur but rarely metastasizes. First described by Goldstein et al. in 1982, MAC tends to have a predilection for the left side of the face but may also present in sun-exposed or radiation treated areas. It can appear as a flesh-colored, red, or yellow papule or as an indurated plaque and is often misdiagnosed clinically. The pathogenesis of MAC remains unclear, but it is thought to arise from pluripotent keratinocytes capable of differentiating into sweat glands or hair follicles. It most commonly arises in older adults with less than a dozen pediatric cases reported to date. We present a case of MAC in a 7 year old female as well as a discussion of diagnosis and treatment for this rare tumor.

Case Presentation

In January 2008, a 7-year-old Caucasian female was referred to our dermatology clinic by her nurse practitioner for a lesion on her left lower lip. The patient's mother stated the lesion had been present for approximately four years. Previously it had been biopsied by a dermatologist with unknown results. Her mother had used various home remedies on the area with the thought that it might be a wart. The lesion was asymptomatic. The patient had no previous history of skin disease and her other medical, family, surgical, and social history were unremarkable. She took a multivitamin daily but otherwise used no medications and had no allergies.

On physical exam, a firm, flesh-colored plaque measuring approximately 0.8x0.5cm was identified on the left lower lip, near the vermilion border (Figure 1). No associated erythema or induration was appreciated surrounding the lesion. She had multiple benign-appearing nevi on her upper and lower extremities, along with a 4x2.3cm café au lait spot on her right lower back. The remainder of her skin and physical exam was normal. Given the lesion's persistence and resistance to any treatment, a biopsy was taken to rule out pilomatrixcoma based on the patient's age and clinical presentation. The clinical differential diagnoses included syringoma, desmoplastic trichoepithelioma or other adnexal tumors.

The biopsy showed an infiltrative, asymmetrical, epithelial neoplasm occupying all levels of the dermis. The neoplasm was disposed into cords, nests, and angulated glandular foci containing inspissated material, which was consistent with a diagnosis of a desmoplastic follicular neoplasm. Re-excision of the lesion to obtain clear margins and definitive diagnosis was recommended, and Mohs surgery was determined to be the best course of action.

The patient was brought back for Mohs micrographic surgery approximately one month later. The dermatologist took a first stage, and based on the microscopic findings, consulted pathology. The pathologist noted a follicular neoplasm with nests of uniform cells and central keratinous microcysts. In one section these cysts were broad, but in subsequent sections interconnected smaller nests were noted. Desmoplastic trichoepithelioma was still favored at this point, but a final diagnosis was deferred to dermatopathology. The margins of the first section appeared free of tumor, so the family agreed to defer further intervention until a more definitive diagnosis was reached. The defect site was closed primarily, and the procedure was well tolerated by the patient.

The Mohs specimen was re-sent to the original reporting dermatopathologist for further evaluation. After comparison with the initial biopsy slides, microcystic adnexal carcinoma (MAC) was the favored primary biopsy diagnosis. The final dermatopathology report indicated free margins with no residual MAC. The patient was to follow up with our dermatology clinic one month after her Mohs procedure and every three months thereafter for a year. Her surgical site continued to heal well with slight hypertrophy but no recurrence of the lesion. The patient regularly follows up with our clinic and remains tumor free.

Discussion

Microcystic adnexal carcinoma (MAC), also called sclerosing sweat duct carcinoma (SSDC), is an uncommon, locally aggressive tumor that may invade deeply and has the propensity to recur. Though the exact pathogenesis of MAC remains unclear, it is thought to arise from pluripotent keratinocytes capable of differentiation to either sweat glands or hair follicles. No gender predilection has been shown in studies, and the vast majority of reported MAC cases has been in Caucasians, although rarely it has been seen in other ethnicities. MAC typically involves the face of older adults but also has been
report on the scalp, axilla, trunk and extremities. Chiller et al. found a slight predominance for the left side of the face (specifically the lip) and postulated this to be from sun exposure to drivers on the left side of cars in the United States. MAC is extremely uncommon in children, making the case reported here very unique.

To date there are still very few reported cases of MAC in any age demographic. A total of 223 were identified by Surveillance, Epidemiology, and End Results registry from 1973–2004. A more recent case study done in 2011 reported still only 300 cases in the literature, with fewer than a dozen involving children under the age of 18. From the majority of accounts, the predilection site of MAC is still predominantly in the head and neck area (74%) in all ages. A review by Nelson and colleagues done in 2008 cited a lesion diagnosed as SSDC in the pre-auricular area of a 6-year-old African American girl. This had been the youngest known MAC patient until recently, when two congenital cases were reported in the literature. The first was from Smart et al., detailing a malar lesion diagnosed as MAC on a 3-day-old Caucasian female. The second was provided by Fu et al. and described a 1cm verrucous-like plaque on the temple of a 2-week-old female. In both cases, the tumor involved the nearby muscle and extended almost to the periosteal zygoma. As a result, re-excisions were necessary to ensure clear margins, and both patients have remained free of recurrence upon close follow-up. To date, formal pediatric management protocols for MAC do not exist.

One risk factor for MAC is postulated to be exposure to ultraviolet light, given the tumor’s common appearance in sun-exposed areas. Yet another risk factor seems to be related to prior radiation exposure, as several MAC cases have been reported in patients who have undergone radiation for acne or various cancers. Curiously, the tumors in patients with a history of radiation exposure have not been more aggressive or histologically more atypical than those in patients without prior radiation exposure. MAC has also been seen in immunocompromised patients and may possibly have a genetic link. Abbate et al. did report sibling cases of MAC, thus suggesting that there may be an increased risk in immediate family members for developing the tumor.

**Diagnosis**

Due to its varying presentation, micro cystic adnexal carcinoma is often misdiagnosed clinically and may be mistaken on physical exam for morphoform basal cell carcinomas, desmoplastic trichoepitheliomas, syringomas, cysts, squamous cell carcinomas, or even lichen simplex chronicus. MAC lesions may appear flesh-colored, yellowish, or red, are sometimes blanchable, and often are asymptomatic. In some instances MAC will present as a firm, indurated, slow-growing plaque, while other times it may be an ill-defined round papule. One case report described a verrucous plaque with peripheral telangiectasias. In the two congenital cases cited above, both lesions had firm, subcutaneous, nodular components along with the accompanying plaque/papule. The most consistent diagnostic feature has been its frequent location on the face. Due to its difficulty in diagnosis, MAC should always be considered in the differential for any slow-growing tumor of the head and neck region.

Microcystic adnexal carcinoma has a relatively bland microscopic appearance, especially in superficial biopsy specimens, which can also complicate the pathological identification and lead to misdiagnosis. Thin biopsy specimens are commonly inadequate as they capture only the superficial cystic or ductal component, which may be misinterpreted as a benign adnexal neoplasm such as syringoma or desmoplastic trichoepithelioma. Thus a deep shave, punch, or excisional biopsy is recommended if MAC is in the differential diagnosis.

Other diagnostic tools used with identification of MAC have included computed tomography or magnetic resonance imaging. Due to the infiltrative growth pattern and perineural invasion often seen with MAC tumors, these modalities have sometimes been implemented preoperatively to determine the extent of invasion. CT/MRI has also been utilized to detect the presence of metastatic disease, which is still relatively rare despite the infiltrative nature of MAC. Only five local and three distant metastases have been reported, and only one death has been attributed to MAC.

**Histopathology**

In 1982, Goldstein et al. first described MAC as a malignant appendage tumor with distinct histologic features that were necessary to distinguish it from benign tumors with a similar appearance. Histologically, MAC tends to exhibit a biphasic pattern of both eccrine and follicular structures, but apocrine and sebaceous differentiation have also been described. The tumor usually involves the dermis and subcutis, with paisyte-tadpole-shaped ducts and keratinous horn cysts common in the upper dermis, and small basoloid strands and nests with pilar differentiation and benign-appearing keratinocytes or squamous cells in the deeper dermis (Figures 2, 3). The stroma is densely pink-to-red and sclerotic. The tumor cells themselves are bland with minimal atypia or mitoses. As mentioned above, MAC is deeply invasive and tends to exhibit lymphoid aggregates along with perineural
invasion.

Histologically, the differential diagnosis of MAC includes desmoplastic trichoepithelioma (DTE), morphoeform basal cell carcinoma (MBCC), or syringoma. All have similar histologic features, including duct-like structures, round cells with high N:C ratio, and dense sclerotic stroma. However, DTE commonly shows micro-calculcations, rarely has lymphoid aggregates in the dermis, displays no perineural extension, and does not involve the deeper dermis as MAC does. MBCC can be histologically very similar to MAC but will only occasionally display the paisley-tie tadpole ducts and typically does not contain horn cysts. Syringomas display clear cell changes, show no perineural invasion, and do not exhibit a deep infiltrative growth pattern. The difficulties in identifying MAC both clinically and histologically may often lead to late diagnosis and the danger of a more infiltrative and potentially inoperable tumor.

Immunohistochemistry staining has shown MAC will stain most consistently with carcinoembryonic antigen stain (CEA), epithelial membrane antigen (EMA) with carcinoembryonic antigen stain shown MAC will stain most consistently with cytokeratin AE1/AE3 but not reactive to S100 and BerEP4. Thus these tumors frequently require extensive surgical resection, and even lesions treated with MMS can lead to a four-fold increase in defect size. However, simple wide excision can lead to equal if not greater overall defect sizes. Due to the locally aggressive nature of MAC and the often extensive surgery required to extricate it, radiotherapy may play an adjuvant role in treatment. Radiation as primary treatment has been reported in a small number of patients, but almost all cases reported recurrences of MAC. In fact, there has been a report of radiation possibly converting MAC to a more aggressive neoplasm. Another case study by Abbate et al. documented five cases of MAC on the face in which all patients had had prior radiation exposure. As a result, most literature recommends eliciting a careful radiation history from individuals diagnosed with MAC or if MAC is suspected in the differential.

The preferred method of treatment for MAC in children has yet to be elucidated. In the few literature case reports available, both wide local excision and Mohs surgery have been performed. MMS has also been the most favored initial modality in children, but sometimes the need for anesthesia, the child's age, or lack of availability of a Mohs surgeon dictates the wide excision option over MMS. In either case, no recurrences in children have yet to be reported in the literature. Despite this, recommendation for follow-up in children has been inspection and palpation of the surgical site as well as regional lymph nodes every three months for several years. Overall survival in all patients with MAC has been excellent, and most have lived a normal lifespan.

References
Desonate Gel offers these benefits:

- Proven efficacy in clinical studies\(^1,3,4\)
- Approved for use in patients 3 months of age and older\(^1\)
  (For pediatric safety information, see ISI and the following page for Brief Summary)
- Helps maintain the stratum corneum barrier function\(^5\)
- Copay assistance programs that make the average cost comparable to or lower than generics\(^*\)

\(^*\)$0 copay with patient’s first prescription. Most patients pay $10 each for 3 refills. See eligibility requirements. Maximum benefit of $200 on each fill.

INDICATION AND USAGE
Desonate Gel is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

IMPORTANT SAFETY INFORMATION
Desonate is contraindicated in those with a history of hypersensitivity to any of the components of the preparation. Topical corticosteroids can produce reversible hypothalamic pituitary adrenal (HPA) axis suppression, Cushing’s syndrome and unmask latent diabetes. Systemic absorption may require evaluation for HPA axis suppression. Modify use should HPA axis suppression develop. Potent corticosteroids, use on large areas, prolonged use or occlusive use may increase systemic absorption.

Pediatric patients may be more susceptible to systemic toxicity when treated with topical corticosteroids due to their larger skin surface-to-body mass ratios. Unless directed by a physician, do not use on the underarm or groin area of children. Do not use to treat diaper dermatitis. Use in children less than 3 months of age is not recommended.

Local adverse reactions may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation and allergic contact dermatitis and may be more likely with occlusive use or more potent corticosteroids. The most common adverse reactions (incidence ≥ 1%) are headache, application site burning and rash. To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare at 1-866-463-3634 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Not for ophthalmic, oral or intravaginal use. As with other corticosteroids, therapy should be discontinued when control is achieved. Safety beyond 4 weeks has not been established.

See following page for Brief Summary of full Prescribing Information.
Use of more than one corticosteroid-containing product

Desonate is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older. Patients should be instructed to use Desonate for the minimum amount of time as necessary to achieve the desired results because of the potential for Desonate to suppress the hypothalamic-pituitary-adrenal (HPA) axis [see Warnings and Precautions (5.1)]. Treatment should not exceed 4 consecutive weeks [see Dosage and Administration (2)].

CONTRAINDICATIONS

Desonate is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

WARNINGS AND PRECAUTIONS

Effects on Endocrine System

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, 6 months to 6 years old, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosynopin stimulation test. As follow-up evaluation of the subject’s adrenal axis was not performed, it is unknown whether the suppression was reversible [see Use In Specific Populations (8.4) and Clinical Pharmacology (12.2)].

Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of Desonate due to their larger skin surface-to-body mass ratios [see Use In Specific Populations (8.4)].

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Cushing’s syndrome, hypergycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Local Adverse Reactions with Topical Corticosteroids

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include skin atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

Concomitant Skin Infections

If concomitant skin infections are present or develop during treatment, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Desonate should be discontinued until the infection is adequately controlled.

Skin Irritation

If irritation develops, Desonate should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies of 425 Desonate-treated subjects and 157 Vehicle-treated subjects, adverse events occurred at the application site in 3% of subjects treated with Desonate and the incidence rate was not higher compared with vehicle-treated subjects. The most common local adverse events in Desonate treated subjects were application site burning in 1% (4/425) and rash in 1% (3/425) followed by application site pruritus in <1% (2/245).

Adverse events that resulted in premature discontinuation of study drug in Desonate treated subjects were telangiectasia and worsening of atopic dermatitis in one subject each. Additional adverse events observed during clinical trials for patients treated with Desonate included headache in 2% (8/425) compared with 1% (2/157) in those treated with vehicle.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, skin atrophy, striae, and miliaria.
Abstract: The carbon dioxide laser is utilized in a variety of situations for dermatologic use. Several complications can occur with these laser treatments; however, clinical manifestations of verruca plana are uncommon. We report a case of an elderly woman who presented to the clinic with verruca plana on the periocular regions of the face after a recent carbon dioxide laser resurfacing procedure. She was successfully treated with imiquimod 5% cream. The lesions were theorized to occur secondary to prior inoculation from latent human papillomavirus, the causative agent of verruca plana. Although the skin can appear without evidence of clinical infection, human papillomavirus can lie dormant and be reactivated secondary to the induced trauma by a laser procedure.

Case Report

A 69-year-old female presented with multiple, symmetric, bilateral, flesh-colored, 0.4mm flat-topped papules surrounding the periocular and temple regions of the face, present for several months. Evidence of mild pink erythema and inflammation was noted on the physical exam (Figure 1). They appeared shortly after a periocular carbon dioxide laser resurfacing treatment more than six months prior, which was performed at another location by an unknown medical professional. She fully healed from the carbon dioxide laser procedure, but the papules remained present. She denied a history of herpes simplex virus and did not remember taking an oral antiviral prior to the procedure. The differential diagnosis included lichen planus and scar tissue. The biopsy revealed verruca plana (Figures 2 and 3). The patient refused different laser treatments or liquid nitrogen. Treatment consisted of imiquimod 5% cream twice per week for 16 weeks. Two weeks later, the areas appeared flatter and smaller. The patient increased imiquimod 5% cream to three times per week for the remainder of the course of therapy. Four months later, the majority of the areas were clear; however, there were four small 0.2mm papules on the right malar crescent and one small 0.2mm papule on the left temple region near the hairline (Figure 4). The patient refused further treatment and was satisfied with the resulting outcome.

Introduction

Verruca plana (VP), also known as flat or plane warts, are caused by human papillomavirus (HPV) types 3 and 10. They are most often seen on sun-exposed areas of children, young adults and the immunosuppressed. Flat warts are typically asymptomatic, with cosmetic disfigurement being the only associated
morbidity. They are characteristically smooth, flat-topped, pink, light brown, or light yellow papules. VP warts vary between 0.1 to 0.5 cm in size and are generally numerous on the following typical sites: forehead, perioral, dorsal hands and shaved areas such as the beard region and the lower legs. Koebnerization may occur.

Once VP undergoes clinical manifestation, the papule can last for several weeks or for years. Regression is usually heralded by an erythematous change to the lesion, inflammation and sometimes the development of depigmented haloes.

**Histopathology**

VP lesions display hyperkeratosis and acanthosis without the papillomatosis or parakeratosis seen with verrucae vulgaris. The stratum corneum has a characteristic basket-weave appearance. Infected cells have a “bird’s eyes” appearance, containing large vacuoles and shrunken nuclei with condensed basophilic chromat in the upper malpighian layer. In cases where VP spontaneously resolves, a lymphocytic infiltrate, cell exocytosis and apoptosis occur.

**Transmission**

Transmission is through skin-to-skin contact, with an incubation period of one to six months. The source can be individuals experiencing clinical or subclinical infection or viral particles on fomites. HPV can resist desiccation, freezing and prolonged time outside of its host. Infections can be latent in normal-appearing skin.

There are a variety of cases found in the literature describing unusual transmission. In one case, VP developed over a port wine stain being treated with a pulsed dye laser. There are reported cases associated with tattooing and eyebrow threading as well.

**Differential Diagnosis**

There are multiple diseases that can mimic VP lesions. Epidermodysplasia verruciformis (EV) results from the same HPV subtypes as flat warts. EV lesions are more persistent and widespread, and plaques are present. Acrokeratosis verruciformis of Hopf, a genodermatosis associated with Darier’s disease, resembles plane warts on the dorsum of the hands. Histologically it contains papillomatous changes, hyperkeratosis and acanthosis causing a prominent granular layer that has a church spire appearance. Lichen planus has flat-topped papules that can be differentiated from verruca plana by the presence of lacy oral lesions and Wickham’s striae. In addition, scar tissue, seborrheic keratosis, nevi and lentigines should be considered in the differential.

**Skin Resurfacing with CO₂ Lasers**

Carbon dioxide (CO₂) lasers have been shown to be safe, precise and reliable, but complications can arise. One of the most common post-treatment infections is herpes simplex virus, found in up to 2% of cases. In patients without a prior history, this risk can be decreased to 0.5% with antiviral medications one day before treatment and continued for five to seven days following the procedure. Erythema is expected for several days after the procedure and can be reduced with a light-emitting diode. There is also the possibility of both hyperpigmentation and hypopigmentation from laser procedures. Fitzpatrick III-VI skin types have an increased risk for developing post-inflammatory hyperpigmentation. Acne, milia, ectropion formation, contact dermatisis and hypertrophic scarring have also been reported. Many complications can be avoided with patient education and preoperative and postoperative skin care.

In the case presented herein, VP appeared secondary to skin-resurfacing treatment with a CO₂ laser. There have been similar published case reports. One such study describes a patient who developed an exacerbation of plane warts to her nose, glabella and left perioral following treatment with a CO₂ laser to the same region for active VP and skin irregularities caused by acne. New-onset verruca vulgaris to the facial cheeks resulting from full-face CO₂ resurfacing has been reported. To these authors’ knowledge, no accounts of new-onset VP following periorcular CO₂ resurfacing have been reported in the English literature.

We theorize the virus disseminated from prior inoculation in the presented case. Evidence of HPV has been detected in random sites on healthy human skin. Animal models have demonstrated significant evidence for HPV latency and reactivation. HPV infects basal epithelial cells and can remain undetectable until triggered to differentiate for wound healing. Dormant HPV may have been reactivated by the CO₂ laser procedure. We conclude the breakdown of the epidermal layer allowed latent HPV to proliferate, rather than it resulting from direct inoculation from the laser system, operator or any other environmental source. Nanni and Alster found this to be the cause of many herpes simplex virus infections after resurfacing treatments.

**CO₂ Laser Plume Smoke**

The hazards resulting from plume of CO₂ laser treatments have been well documented. The thermal tissue breakdown is emitted in the smoke by-product, which contains intracellular components that were carbonized or underwent vaporization. This process produces gas contents including carbon monoxide, benzene and hydrogen cyanide. These substances can cause respiratory inflammation and have mutagenic potential. In addition, studies have confirmed the risk of HPV transmission from contaminated smoke.

A study conducted by the Mayo Clinic found CO₂ laser surgeons are at an increased risk of nasopharyngeal lesions, particularly those treating genital warts. The study concluded that inhalation of plume smoke carries infectious particles into the upper airway, displaying various levels of contagion.

Smoke removal is one of the best ways to decrease papillomavirus particle transmission. Smoke evacuators are 98.6% effective at removing the virus when placed 1 cm from the treatment site, with efficacy decreasing by half when moved to 2 cm from the treatment site. Several federal agencies, national societies and institutes have recommended measures to minimize particle transmission. Such measures include local exhaust ventilation procedures and wearing approved N-95 respiratory masks.

Management There are several approaches to VP therapy, including surgical destruction, topical treatments, and laser resurfacing procedures. When treating the patient, location and severity of the lesions along with patient compliance should be considered in choosing the appropriate management. Topical medications such as imiquimod, tretinoin and 5-fluorouracil can be applied. Kim et al. showed successful results in 73% of patients using 5% imiquimod cream for VP. Although imiquimod can initially cause severe inflammation, desirable clinical and cosmetic results are documented. A recent report showed glycolic acid 15% topical gel plus salicylic acid 2% was found to be effective within eight weeks of treatment.

Sun protection should be stressed due to phototoxic effects. Liquid nitrogen, an electrocautery needle or laser resurfacing may be performed for more immediate results. Nontraditional methods such as vitamin B12 acupoint injections and the Chinese herbal medication Qu You Ding have also been described in the literature.

**Conclusion**

Verrucae are rare complications from fractional CO₂ laser resurfacing. The specific etiology of this patient’s VP is undetermined.
Once the skin is damaged by the laser, a number of sources can be implicated in the HPV transmission: latent HPV, the laser operator, or plume smoke.

This case illustrates an unusual complication of CO2 laser resurfacing. Operators should be mindful of the potential for viral spread between patients if inappropriate handling of laser handpieces between patients occurs, although many handpieces do not make contact with the patient’s skin. Patients need to be thoroughly informed of the expected treatment outcome, anticipated recovery period, and treatment risks, including viral infection, prior to resurfacing. Pre-treatment antiviral therapy may reduce the chance of infection. It is important for patients to understand an opportunistic infection can result with any breakdown of the body’s natural protective system. Once the epidermis is exposed, it is susceptible to local spread or an outside element.

Acknowledgement
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References
ABSTRACT: Pinta is an increasingly uncommon disease that is characterized by polymorphic patches of hyper or hypopigmentation. The etiologic agent of pinta, Treponema carateum is not endemic to the United States, however due to increasing international travel this topical disease occasionally presents in the United States and should remain in the differential diagnosis of hypopigmented patches. We present a case of pinta in a young boy and his family members who were successfully treated with penicillin.

Case Study
A 12-year-old, healthy Columbian boy presented with several slowly enlarging, hypopigmented patches with faint erythema and scale that were located on the right cheek, chest and back (see Figures 1-3). The areas were asymptomatic, and he and his family denied any preceding illnesses, topical medication use, or prior treatments. His medical history and family history were unremarkable, and he was not taking any medications or supplements. Further inquiry of the patient's mother revealed that a few weeks prior to presentation, they had a biopsy performed in Columbia prior to immigrating to South Florida, for which the results were unknown. The biopsy report was recovered, and it revealed treponemes present within the epidermis, a finding compatible with a diagnosis of pinta. The patient was subsequently treated with penicillin G benzathine 1.2 million units intramuscularly (IM) for one dose and sent home. However, the patient's mother and brother returned three weeks later for evaluation of newly forming hypopigmented macules similar to the first boy's previous lesions. They were subsequently also treated with penicillin G benzathine 2.4 million units IM, with eventual resolution of the hypopigmented areas over the ensuing months.

Discussion
The onset of hypopigmented patches is often a disturbing event for patients, and the clinical differential diagnosis is broad (see Table 1). However, as in this case, a focused history combined with histopathologic analysis can often yield a correct diagnosis. Pinta is unique among the treponematoses in that it causes only skin manifestations.1 Pinta is one of the three non-venereal treponematoses, along with bejel and yaws. All three diseases' causative organisms closely resemble Treponema pallidum, the etiologic agent of syphilis. Treponema carateum, the species responsible for pinta, is morphologically and antigenically indistinguishable from T. pallidum.2 Interestingly, in recent attempts to sub-classify the treponemes, no differences were detected by either the Western or the Southern blot hybridization techniques.3 T. carateum cannot be cultured in vitro but can be transmitted to chimpanzees.4

Pinta's incidence over the last few decades has declined precipitously for unknown reasons, with some calling it extinct worldwide aside from a few scattered endemic areas in Central and South America, as well as a more recent case identified in Cuba.5,6,7,8 Also known as pururu or carate, the disease has been known to exist since the 16th century in Aztec and Carib Amerindians.8 Rural areas in Mexico,
Honduras, Venezuela, Bolivia, Peru, Colombia, Guatemala, and Brazil are believed to be endemic foci.

The mode of transmission is as yet unknown; however, most believe it to be spread by touch. As described in the case above, it is classically described as spreading between family members. Older case reports emphasize a variety of specific cultural customs, such as ritualistic whipping ceremonies among Indian tribes, as methods of transmission; however, insect bites or other physical factors which disrupt the natural skin barrier likely play a more pertinent role. Typically, children and young adults are affected, with a typical age of onset of 15-30 years. Both sexes are affected equally.

Clinically, pinta’s primary lesion is characterized by an erythematous papule surrounded by erythematous, squamous plaque or halo that appears one to eight weeks after inoculation. By direct extension or fusion of satellite lesions, the primary site may grow to a diameter of 12 cm or larger, forming an ill-defined erythematous plaque with hypopigmentation. Occasional local lymphadenopathy can be seen. Secondary lesions, or “pintids,” manifest as initially erythematous patches that turn brown, slate blue, gray or black. After several years, a mix of depigmented and hyperpigmented lesions may result. The tertiary stage is evident with the development of multiple hypopigmented, symmetric areas on the bony prominences over the wrists, elbows, ankles and knees, giving patients a “mottled” appearance. All three stages may result in hypopigmented patches; however, only within the first two stages can organisms (which are highly infectious) be found within lesions.

Dark-field examination of specimens will reveal numerous T. carateum organisms in early lesions, the number of which declines with the lesion’s overall age. Biopsy with visual microscopy of primary or secondary lesions by hematoxylin and cosin staining is relatively nonspecific. Acanthosis with spongiosis is seen in the epidermis, and there is a sparse dermal infiltrate of lymphocytes, plasma cells, and neutrophils scattered among dilated blood vessels within the dermis. Lichenoid inflammation with basal layer vasculopathy and pigment incontinence is also sometimes seen. Tertiary-stage lesions typically have numerous melanophages within the dermis, along with epidermal atrophy and perivascular lymphocytic infiltrates. Anti-treponemal immunohistochemical stains or silver stains may be employed to visualize organisms in all but late, chronic lesions. Treponemal laboratory tests (rapid plasma reagent [RPR], Venereal Disease Research Laboratory [VDRL] test) will be positive as in syphilis in all stages of disease and are not able to discriminate between species of Treponema. Confirmatory tests such as T. pallidum hemagglutination (TPHA), microhemagglutination T. pallidum (MHA-TP), and fluorescent treponemal antibody absorption (FTA-Abs) will also be positive.

The difficulty in differentiating treponemal species strictly by laboratory testing alone lies in the strikingly similar genetic sequences between T. pallidum and the non-venereal treponemal species. Clinical diagnosis with histopathologic confirmation currently remains the most practical means of differentiation.

Treatment of pinta is most easily accomplished with a single injection of penicillin G benzathine 2.4 million units IM for disease of less than 2 years duration. For those cases with duration >2 years, 2.4 million units of penicillin G benzathine is recommended IM, three times in one week for adults. The dose for patients under six years of age is 600,000 units IM, and for patients 6-15 years of age 1.2 million units IM for disease of less than two years duration. For those with penicillin allergy, tetracyclines or erythromycin can be used (tetracycline 500 mg four times a day for 15 days in adults, or erythromycin 250 mg four times a day in children <15 years old). Lesions become non-infectious 24 hours after treatment. Following treatment, treponemal titers will slowly decline, and pigmentary abnormalities typically resolve slowly in primary and secondary lesions.

The patient discussed herein presented with multiple hypopigmented patches that were a manifestation of a rare but still present tropical disease. With increased globalization, people in areas of the world that are not known to be endemic for this disease may have to be more wary. The astute clinician should continue to include this unusual, communicable, and easily treatable entity in the differential diagnosis of hypopigmented patches.

References

ABSTRACT: Reed Syndrome or Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is catalogued in the Online Mendelian Inheritance in Man Database (OMIM 150800) and was first reported in 1973. This condition is associated with significant, aggressive internal malignancies, and thus is an important genodermatosis for dermatologists and other clinicians to recognize. Herein, we present a characteristic clinical presentation of this syndrome and review pertinent treatment options and screening recommendations.

Case Report

Patient ML, a 54-year-old Caucasian male, presented to our dermatology clinic with a chief complaint of a few small painful “bumps” on the right upper back. He had noticed many similar small, persistent, pink papules which had first arisen in this same area years ago. It was only recently, however, that they had become more bothersome and symptomatic. His medical history was unremarkable other than remote past treatment for testicular cancer, now in remission. Family history revealed a father who was deceased after battling “some problem with his kidney.” The patient was unsure if this problem was kidney cancer. Physical exam showed numerous small, 5-10mm pink, firm, dermal-based papules, with no overlying epidermal change, segmentally clustered over the right upper back and shoulder (Figures 1-2). At this point, a punch excisional biopsy was taken around a representative symptomatic lesion and sent off for histopathological analysis, which revealed a leiomyoma (Figures 3-4). Taking into account the multi-focal nature of these leiomyomas, along with a possible family history of kidney cancer, it was decided that genetic testing for Reed syndrome (HLRCC) would be prudent. Whole blood samples were then sent for laboratory sequencing, which ultimately revealed the patient to be heterozygous for an A117P missense mutation in the fumarate hydratase gene, confirming the diagnosis. Genetic counseling was provided at length for the patient along with a discussion concerning the implications for any living blood-relatives. Baseline CT of the abdomen, with and without contrast, was negative for any kidney abnormality and will be repeated, per urology, at 1-2 year intervals. Finally, as to symptomatic treatment, the few particularly bothersome leiomyomas have been punch excised without complication, and the patient has been pleased.

Figure 1 – Numerous leiomyomas seen as small, skin-colored to pink, dermal-based papules grouped on the right upper back and shoulder.

Figure 2 – Close-up view of a representative skin-colored leiomyoma on the right upper back.

Figure 3 – 4x power H&E view of the biopsied leiomyoma from the right upper back. Note the poorly demarcated dermal-based proliferation of cells with pink cytoplasm, round nuclei and peri-nuclear vacuolization.

Figure 4 – 10x power H&E view of the same biopsied leiomyoma. Note the characteristic bundles of cells with pink cytoplasm, round nuclei and peri-nuclear vacuolization. Those cells in longitudinal section also nicely demonstrate the classic cigar-shaped nuclei seen in these benign smooth-muscle proliferations.
Discussion

First reported in 1973, Reed syndrome (HLRCC) has been linked to the fumarate hydratase gene on chromosome 1q42.3-q43.1,4 Mutations in this gene lead to short-ages of the fumarate hydratase enzyme, which is part of the Krebs cycle. The exact pathogenesis of how this defect leads to smooth muscle proliferation and renal cancer is unknown. In the autosomal-dominant, heterozygous form, it displays the typical findings of Reed syndrome, while the rare autosomal-recessive variety manifests as fumarate hydratase deficiency with severe neurological disease absent cutaneous signs.

Reed syndrome typically presents with multiple cutaneous or uterine leiomyomas starting in the third decade of life. In the skin, these benign cutaneous smooth-muscle neoplasms characteristically arise from the arrector pili muscle and are visualized as smooth, firm, pink to skin-colored papules or nodules that are symptomatically painful in the majority of patients. These recurrent painful episodes can be triggered by pressure, cold, or rubbing, or they may occur spontaneously.5,6 Uterine leiomyomas (fibroids) in these patients tend to have a slightly earlier age of onset (20-35) compared to the general population (35-44) and are more symptomatic, often needing hysterectomy.4,7-9 Cutaneous leiomyomas generally precede the uterine fibroids by about seven years.4

The kidney tumors associated with Reed syndrome tend to be very aggressive compared to other cutaneous-renal genodermatoses such as Birt–Hogg–Dubé syndrome. These tumors are thought to arise in around 15% of patients with HLRCC.7,10 The most common types that have been definitively linked are papillary renal cell carcinoma and collecting duct carcinoma. Rarely, leiomyosarcomas have been reported as well. Owing to the aggressive nature of these associated renal malignancies, periodic imaging with MRI or CT is suggested, while ultrasound alone is considered inadequate.4 There is currently no definitive consensus as to the optimum recommended screening interval.

Treatment of these leiomyomas is classically dependant on symptomatology. Options range from simple excision to numerous pharmacologic possibilities, all with varying degrees of success. Some reports have shown that excision to be associated with high recurrence rates approaching 50%.11,12 Other destructive modalities such as cryotherapy and electrocoagulation, however, tend to be even more disappointing.2,11 Drugs such as nifedipine, nitroglycerin, NSAIDS, analgesics, gabapentin, doxazosin, phenoxybenzamine, pregabalin, duloxetine, and even Botox injections have all been advocated.1,3,4,11 The effective dosing regimen for these medications varies and is anecdotal. Partial rather than complete resolution of symptoms tends to be the rule. Our patient, though not completely symptom-free, was more than satisfied with our procurement of a definitive diagnosis and partial relief of his pain.

Finally, comprehensive genetic counseling should be provided to the patient and family. Taking into account the autosomal-dominant nature of this condition, if possible, blood-relatives should be clinically examined and offered genetic screening as well.

References
Case Description

A 36-year-old Caucasian male with an unremarkable medical history presented to our clinic with a nodular plaque on his right nasolabial fold as well as an erythematous lesion on his left mid-back. The lesions arose spontaneously two and a half weeks prior to his visit. They began as flesh-colored papules and subsequently enlarged and transformed into firm, erythematous nodules. There was slight pain associated with the lesions. He denied any trauma or previous injuries to the areas. The patient also noted two patches of hair loss on his legs occurring over the past few years. He denied any previous treatment prior to his presentation. The patient had no personal history or family history of skin cancer. He also denied any history of fever, weight loss, night sweats, or fatigue.

On physical examination, a fairly tender, erythematous, nodular plaque in the right nasolabial fold was noted. In addition, there was a slightly tender erythematous papule on his left mid-back. Grossly, both lesions appeared aceniform and were presumptively treated as such. The lesions were each treated with a triamcinolone 10mg injection, clindamycin/benzoyl peroxide topical, as well as 0.1% tazarotene topical gel.

At his two-week follow-up appointment, the patient reported no significant relief of his symptoms. The papule on his back had decreased in size and had some clearing of erythema; however, the nodule on his nasolabial fold had developed marked induration and erythema. The lesion was incised and drained with minimal pus expression, and bacterial and fungal cultures were obtained. A course of cephalexin 500mg antibiotics four times a day was initiated for a presumptive facial cellulitis. A week later, the patient returned to the clinic with progression of erythema, ulceration, and marked swelling of the right nasolabial fold. At this time, he was started on a course of sulfamethoxazole and trimethoprim. In addition, the fungal cultures came back negative, and the bacterial gram stain showed gram-positive bacilli along with other polymorphonuclear leukocytes. In an effort to identify the nature of the lesion, the patient was referred to plastic surgery, where an excisional biopsy of the lesion was done and sent for pathology.

The pathology from the biopsy specimen is shown in Figures 1-3. The biopsy shows lymphocytes infiltrating into follicular epithelium where there is associated follicular mucinosis (Figure 1). The infiltrate is comprised of large lymphoid cells with vesicular indented nuclei as well as prominent nucleoli. There are numerous mitotic changes with atypia (Figures 2, 3). Also, the infiltrate shows the presence of eosinophils and neutrophils. Immunohistochemical stains showed positive labeling of the folliculotropic lymphocytes for CD2, CD3, CD4, CD5, and CD30 and negative for CD7 and CD8. Additional immunohistochemical stains were done and showed anaplastic lymphoma kinase (ALK-1) negative, epithelial membrane antigen (EMA) negative, and MUM1 and MIB1 positive. Given these findings, a subsequent diagnosis of CD30+/ALK- primary cutaneous anaplastic large-cell lymphoma was made.

With the diagnosis of PCALCL, the patient was referred to a cutaneous T-cell lymphoma clinic for treatment. A PET CT scan of the neck, thorax, abdomen, and pelvis was done to look for any metastatic lesions, and came back negative. A number of treatment options were discussed with the patient including bexarotene gel, intralesional corticosteroids, and radiotherapy. Due to its irritating properties, bexarotene was not used on the face. Since two sessions of intralesional corticosteroids offered no...
improvement to the lesions, localized radiotherapy was chosen. The patient successfully completed 20 treatments of local radiation therapy to the right cheek. He also denied any symptoms of pain, headache, drainage, or any new skin lesions. Since subsequent radiotherapy, the lesion on the patient’s face has regressed, and close follow-up has been maintained.

Discussion

The group CD30+ cutaneous lymphoproliferative disorders (CLPD) includes a spectrum of disorders such as lymphomatoid papulosis, borderline cases of CD30+ CLPD, and primary cutaneous anaplastic large-cell lymphoma (PCALCL). These lymphomas comprise the second most common group of cutaneous lymphomas after mycosis fungoides. Three variants of CD30+ anaplastic large-cell lymphoma (ALCL) include the common, lymphohistiocytic, and small-cell types. Primary cutaneous CD30+ T-cell lymphoproliferative disorders as a group are one of the more common types of T-cell lymphoma, comprising around 30% of the total number of cases. More specifically, PCALCL is the second most common cutaneous T-cell lymphoma.

Primary cutaneous anaplastic large-cell lymphoma is a rare anaplastic CD30+ large T-cell lymphoma originating in and usually confined to the skin, characterized by solitary or multiple, erythematous or brown nodules and tumors with a tendency to ulcerate. Typically, progression to extracutaneous sites is rare. In general, the prognosis of CD30+ cutaneous T-cell lymphoma (CTCL) is more favorable than that of its CD30- counterparts, and spontaneous regression is observed in up to 25% of cases of PCALCL. These disorders are more common in middle-aged males than in females. Typically, lesions present on the face, trunk, or extremities as rashes, plaques, nodules and/or tumors with central ulceration and may undergo spontaneous regression; however, they maintain a high recurrence rate.

Histology of ALCL typically shows diffuse, non-epidermotropic infiltrates with cohesive sheets of large CD30+ tumor cells, oval or irregularly shaped nuclei, prominent eosinophilic nucleoli and abundant cytoplasm with a high mitotic index. Immunohistochemistry is essential in determination of CTCL subtypes, and in the differentiation between primary and secondary disease. PCALCL more frequently expresses the cutaneous lymphocyte antigen (CLA) but lacks the epithelial membrane antigen (EMA), and ALK expression is negative in most cases, as in our patient’s case.

One particular PCALCL case study showed on histology a diffuse infiltration of lymphocytes and macrophages seen in the dermis associated with hypertrophied hair follicles, follicular mucinosis, and marked folliculotropism, leading to follicular disruption. Cohesive groups of CD30+ large, atypical lymphocytes with a high proliferative index were seen focally. Similarly, our patient’s biopsy showed the follicular epithelium to be expanded and containing mucin. The infiltrate showed large lymphoid cells with vesicular indented nuclei as well as prominent nucleoli. Lymphocytes were also noted in the expanding follicular epithelium, as well scattered mitoses. Consequently, PCALCL may present with different histologic features, including a follicular variant, that may mimic both benign and malignant conditions such as mycosis fungoides or Sézary syndrome. Histology of PCALCL typically shows cohesive sheets of neoplastic cells with anaplastic morphology, including round to irregularly shaped nuclei, prominent nucleoli, and abundant cytoplasm. When an ulcer is present, it is accompanied by an abundant inflammatory infiltrate consisting of reactive T-cells, neutrophils, eosinophils, and histiocytes, similar to the histology in our patient. PCALCL is difficult to recognize histologically, since it is characterized by variable histopathological presentations and a broad cytomorphologic spectrum. It can be classified according to histologic features (i.e., pleomorphic, immunoblastic, monomorphic, small-cell predominant, Hodgkin-disease related), immunophenotype, and clinical features, such as ALCL occurring after another lymphoproliferative disorder (i.e., mycosis fungoides or lymphomatoid papulosis) or arising in HIV-positive patients.

Clinically, physicians must be aware of differential diagnoses when approaching a cutaneous lesion similar to that seen in this patient. PCALCL can present in benign and malignant forms and appear similar to other common dermatological diagnoses. It can present like lymphomatoid papulosis, mycosis fungoides (MF), and Sézary syndrome (SS). It can also present similarly to the more common cases of cellulitis, eczema or even acne, as in our patient. Lymphomatoid papulosis is a self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a (CD30+) malignant lymphoma. Mycosis fungoides also presents with different stages including pre-MF, patch, plaque, and tumor, similar to the patch on our patient’s face. Other differentials include B-cell lymphoma, Hodgkin disease, metastatic carcinoma, granulocytic sarcoma, and even malignant melanoma. If detected early, as in our patient’s case, PCALCL typically has an excellent prognosis in the initial stage when it is confined to the skin; however, it carries a grim prognosis once systemic spread has occurred.

Management of primary cutaneous lymphomas often requires a multidisciplinary approach. Although one quarter of PCALCL cases resolve spontaneously, the vast majority require treatment. Choice of therapy depends on two factors: disease dissemination, and the presence of localized or multifocal lesions. For a solitary lesion, local radiotherapy is the preferred treatment. Surgical excision is an alternative approach for localized lesions and in conjunction with radiotherapy leads to an excellent prognosis. Single-agent therapy using low-dose methotrexate is effective for patients with multifocal disease or for those who do not respond well to surgical and radiation treatment. Consequently, physicians must be keen and clinically suspicious if patients present with non-healing recurring ulcers. Cutaneous lymphoma should be considered as a differential diagnosis in these instances, and further clinical workup should be initiated.

References

A CASE OF SEGMENTAL NEUROFIBROMATOSIS

ABSTRACT: Segmental neurofibromatosis is a rare variant of neurofibromatosis type 1 and is characterized by café-au-lait macules, freckles and/or cutaneous neurofibromas that are limited to a circumscribed body segment. This subset of neurofibromatosis type 1 is considered to be the result of a somatic mosaicism and is believed to be underreported. We report a case of localized segmental neurofibromatosis in a 54-year-old female who presented with a 10 year history of painful papules clustered in a dermatomal distribution on the right posterior shoulder. In this case study we will discuss the pathogenesis, clinical findings, and consequences of segmental neurofibromatosis.

Introduction

Segmental neurofibromatosis (SNF) is a rare variant of the common genodermatosis neurofibromatosis type 1 (NF1). SNF is characterized by café-au-lait macules (CALMs), freckles and/or cutaneous neurofibromas that are limited to a circumscribed body segment.1-5 Fewer than 150 cases have been reported in the literature since the first case was described in 1931 by Gammel,6 with a prevalence estimated to be 0.002%.2 SNF is thought to be underreported due to its absence of symptoms and complications in most patients.2-4 Here we present a 54-year-old female with SNF localized to the right scapula.

Case Report

A 54-year-old Caucasian female presented to the dermatology clinic complaining of painful lesions on her right posterior shoulder. She stated that the first lesion appeared more than 10 years ago and had gradually progressed into multiple lesions confined to the back of her right shoulder. She reported stinging, pruritus, and pain with palpation of the papules. She noted that her primary care physician had tried removing them with cryotherapy in the past. Her past medical history was significant for hepatitis C and bipolar disorder, but she denied any history of seizures or other neurologic disorders. Family history was non-contributory, and the patient had no children.

Examination revealed approximately 15 discrete, flesh-toned and pink papules on the posterior right shoulder in a dermatomal distribution (Figures 1 and 2). The papules ranged in size from 2mm to 8mm. Full body exam revealed no other significant lesions, including CALMs or axillary freckling. A 4mm punch biopsy
was performed on one of the lesions, which demonstrated proliferation of spindle cells in the superficial dermis surrounding eccrine ducts. The cytoplasm of the cells was pale, wavy and eosinophilic with no cytologic atypia or capsule present (Figures 3 and 4). The clinical and histopathological findings were consistent with neurofibromas in a segmental distribution.

**Discussion**

This patient demonstrates features that are consistent with localized segmental neurofibromatosis. This rare variant of NF1, in which lesions are confined to a circumscribed body segment, is a non-inherited form of NF1 caused by a postzygotic mutation of the NF1 gene resulting in mosaicism.3-6 Mosaicism is the consequence of a sporadic mutation that occurs in a single, genetically homogenous zygote, resulting in more than one genetically distinct cell line in an individual. The timing of the mutation (early versus late embryonic development) determines the clinical effect of the disease; early mutations lead to generalized disease, whereas mutations occurring later (after cell differentiation) give rise to segmental disease.2,6,9 Despite the sporadic nature of mutations, familial occurrence has been reported in several cases.6,10-12 This can be explained by germ-line mutations referred to as gonosomal mosaicism.6,9

Neurofibromatosis has been previously classified by Riccardi into seven different types.1 The segmental type, demonstrated by our patient, was referred to as NF-type 5 and was defined as the occurrence of cutaneous lesions (café-au-lait spots, freckling, and/or neurofibromas) restricted to a single side of the body, with no crossing of the midline, in a patient with no family history of neurofibromatosis.1 This definition has since been adjusted as different clinical subtypes continue to be reported.2,14 Roth et al. has proposed a new classification system to further encompass the different types of SNF,14 in which our patient is classified as true segmental (i.e., meets Riccardi’s criteria). True segmental neurofibromatosis is the form that is most commonly reported in the literature.2,5

SNF has a prevalence of 1 in 36,000 to 40,000 individuals in the general population,5 with the majority of cases occurring in white females.15-16 A review of 82 SNF patients by Hager et al. revealed the median age of onset to be 28 years (range, birth to 83) with a female predominance of 59%.17 A review of 124 SNF patients by Ruggieri and Huson in 2001 demonstrated a mean age of onset of 17.4 years (range, 4 to 70) with a slight male predominance of 53%.2 Neurofibromas are the most common manifestation of SNF and are most often unilateral and located on the right side of the body.2,17 The lesions tend to occupy a single dermatome,2 most commonly cervical or thoracic.17 Patients suffering from SNF are typically asymptomatic, and the lesions are discovered incidentally, with the exception of patients with spinal neurofibromas or lesions on major peripheral nerves. These patients often present with pain or neurologic deficits. Common dermal neurofibromas, as seen in our patient, lie within the dermis and epidermis and move passively with the skin. When they are on relatively superficial nerves, neurofibromas present as subcutaneous nodules that are often only painful when touched. They tend to have a characteristic violaceous color and may be pruritic.2

Extracutaneous manifestations of SNF are rare but have been described.2,17-19 A study of ophthalmological manifestations in 72 patients with SNF by Ruggieri et al. revealed no Lisch nodules or hypertelorism in any of their patients,18 findings commonly seen in NF1.20-21 One study reported a higher prevalence of short stature and macrocephaly.19 The review by Ruggieri and Huson demonstrated specific NF1
complications in 5.6% of their patients, which included learning difficulties, pleomorphic neurofibromas, optic pathway gliomas, and pseudarthrosis.\textsuperscript{2} SNF has been reported to occur in association with a variety of conditions, including renal agenesis,\textsuperscript{23} adenocarcinoma of the colon,\textsuperscript{25} partial unilateral lentigogenesis,\textsuperscript{24} agenesis of the corpus callosum,\textsuperscript{25} and nevus sebaceous of Jadassohn.\textsuperscript{26} Malignancies are rare, but reported cases include adrenal ganglionuroma\textsuperscript{17} and peripheral nerve sheath tumors.\textsuperscript{20}

Management of SNF is simple. Patients should be aware that disease-associated complications are very rare in localized SNF.\textsuperscript{2} Regardless, all patients suspected of having this disorder should undergo a thorough skin and ophthalmologic exam.\textsuperscript{29} If the neurofibromas cause discomfort, create cosmetic disfigurement, or compromise adjacent structures, they may be surgically removed.\textsuperscript{30} With regard to genetic counseling, those considering having children have a very small risk of having a child with generalized NF1, although the exact risk is unknown.\textsuperscript{2}

**Conclusion**

SNF is a rare but probably underreported disorder, as the majority of patients are asymptomatic.\textsuperscript{2} This condition is thought to be secondary to a sporadic postzygotic mutation resulting in mosaicism, making it incapable of spreading to offspring unless involving the germ-cell line.\textsuperscript{3,5,9,13} Our patient is an example of the most common presentation documented in the literature.\textsuperscript{2,17} Unilateral neurofibromas present in a dermatomal pattern on the right side of the body in an individual without a family history. Our patient does not currently suffer from any extracutaneous manifestations.

**References**

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ABSTRACT: A blue nevus with histological evidence of balloon cells is underreported and rare in scientific literature. This histological case report illustrates the rare occurrence of this combined nevus and discusses the importance of recognizing this change to avoid misinterpreting the lesion as malignant.

Case

A 68-year-old male with history of basal cell carcinoma presented to an outpatient office for routine screening. A shave biopsy of a well-defined blue papule on his right jaw was performed. The subsequent histological diagnosis of a combined nevus (blue nevus and balloon cell nevus) was made. (See histology photos.)

Discussion

The blue nevus was first described in 1906 by Tiesche and is clinically described as a well-defined blue papule or nodule. Histologically, it consists of a normal epidermis, and spindle-shaped, dendritic melanocytes in the dermis associated with abundant, fine granules of melanin, melanophages and sclerosis of collagen. Blue nevi are usually acquired and have their onset most commonly in childhood and adolescence, although up to one-fourth of cases arise in middle-aged adults. Blue nevi consist of benign tumors of dermal melanocytes. The melanocytes disappear from the dermis during the second half of gestation, but some residual melanin-producing cells remain. The scalp, sacral region, and dorsal aspect of the distal extremities are the most common sites for blue nevi. The blue coloration of these nevi is the result of the Tyndall phenomenon. The Tyndall effect modifies the color of skin and of lesions by the selective scattering of light waves of different wavelengths. This also explains why the brown melanin in the dermis appears blue-gray clinically.

The malignant form of the blue nevus is known as malignant blue nevus. Malignant blue nevi can arise in a previously benign cellular blue nevus, in a nevus of Ota or Ito, or de novo. Histologically, it is more densely cellular and contains atypical melanocytes, necrosis, and more inflammation compared to the non-malignant blue nevus.

There are many variations of the blue nevus, including cellular blue nevus (Jadassohn’s nevus or nevus coeruleus), deep penetrating nevus (Seab’s nevus), blue neuronevus (Mason’s nevus), amelanotic blue nevus (hypomelanotic blue nevus), epithelioid blue nevus, compound blue nevus, and combined nevus.

The term "combined nevus" is applied to the association of a blue nevus with an overlying melanocytic nevus or to other combinations of benign nevi. Histologically, one component is often a congenital pattern nevus in which pigmented spindle cells form a focal collection of fascicles among nests of ordinary nevus cells. The fascicles tend to be organized along the lines of a blue nevus, which may be either a common or a cellular blue nevus. The other component may be an overlying nevus of the junctional, compound, or intradermal type, or rarely Spitz.

The balloon cell nevus was first described in 1901 by Judalewitsh. Histologically, it consists of large, ballooned melanocytes with a central metastasis is the lymph nodes. Malignant blue nevi can arise in a previously benign cellular blue nevus, in a nevus of Ota or Ito, or de novo.
nucleus and a pale granular cytoplasm with or without ordinary nevus cells. Balloon cells are altered melanocytes with clear, vacuolated cytoplasm caused by a defect in the process of melanogenesis. Clinically, balloon cell nevi are indistinguishable from ordinary nevi. Balloon-cell change has been reported in cases of intradermal melanocytic nevi, large congenital melanocytic nevus, dysplastic nevi, and melanoma.

In 2006, McGowan reported a case of an 18-year-old female who presented with multiple nodules developing in a previously stable giant congenital nevus that involved the left side of her neck, shoulder, and upper back. Three of these nodules were biopsied, and two of the three were diagnosed as large congenital melanocytic nevi with balloon-cell change.

In 1992, Laaff reported seven cases of HMB-45 positive balloon cells in a combined nevus, which can make the differentiation between benign and malignant more challenging. In the balloon-cell melanoma, the nuclei are large and pleomorphic, mitotic figures are present, and there is an absence of intervening stroma.

In 1991, Requena reported a case of a combined nevus with malignant transformation. The clinical impression was blue nevus. Histologically, the lesion was composed of a cellular blue nevus in the reticular dermis and an overlying compound melanocytic nevus. The junctional component of the melanocytic nevus showed transition to malignant melanoma in situ.

Presence of the balloon-cell phenomenon is predominantly determined by the dermatopathologist. Treatment can vary from reassurance to surgical excision with appropriate margins, depending on the degree of atypia. The purpose of this case report is to convey an enhanced awareness of the combined nevus (blue nevus and balloon cell nevus).

References
A CASE OF TELANGIECTASIA MACULARIS ERUPTIVA PERSTANS (TMEP)

Samuel M. Wilson, DO,* R. Scott Thomas,** Allison K. Divers, MD,*** Daniel S. Hurd, DO, FAOCD****
*Dermatology Resident, PGY2, VCOM/LewisGale Hospital-Montgomery, Blacksburg, VA
**Medical Student, OMSIV, KCOM-ATSU, Kirksville, MO
***Clinical Professor of Dermatology, VCOM/LewisGale Hospital-Montgomery, Blacksburg, VA; The Art and Science of Dermatology, Roanoke, VA
****Program Director, VCOM/LewisGale Hospital-Montgomery, Blacksburg, VA

ABSTRACT: Mastocytosis represents a wide spectrum of disorders that result in the accumulation of mast cells in one or more organ systems. The organ most commonly involved is the skin. The spectrum of cutaneous mastocytosis includes; cutaneous mastocytoma, urticaria pigmentosa, diffuse cutaneous mastocytosis and telangiectasia macularis eruptive perstans (TMEP). TMEP is a rare form of mastocytosis that often presents in adulthood and carries an indolent course. Treatment is often focused on symptomatic relief and avoidance of exacerbating triggers. We describe a case of a 20-year-old Caucasian female that presented with a one-year history of multiple asymptomatic tan to pink telangiectatic macules. Darier’s sign was mildly positive. The cutaneous H&E biopsy confirmed the diagnosis of TMEP. Clinical and laboratory findings failed to demonstrate systemic involvement.

Case Report

A 20-year-old Caucasian female presented to the dermatology clinic for a one-year history of persistent “red spots” on her breasts, abdomen and upper thighs. The lesions were described as asymptomatic. The patient’s primary concern was that new lesions were appearing while the old ones were not “going away.” Review of systems failed to reveal any history of fevers, unintentional weight loss, reflux, diarrhea, flushing, bone pain, difficulty breathing, swelling of the lips, dysphagia, or anaphylaxis. Past medical history included: linear scleroderma requiring treatment with methotrexate at the age of 8, generalized anxiety, and occasional headaches. Medications included: alprazolam as needed and dextroamphetamine/amphetamine as needed. Family history was non-contributory.

Physical exam revealed a well-developed, well-nourished 20-year-old female with multiple 2-3mm, tan to pink, blanchable, telangiectatic macules scattered over the breasts, lower abdomen and upper thighs (Figure 1). The oral, genital, and ocular mucosa and face were uninvolved. Darier’s sign was mildly positive. No lymphadenopathy of the cervical, axillary, and inguinal regions was appreciated. A 4mm punch biopsy of the skin from the left lateral chest demonstrated a sparse paucicellular infiltrate consisting predominantly of mast cells around dilated vessels of the superficial vascular plexus. The immunohistochemical stain for mast-cell tryptase confirmed the presence of mast cells. The suggestive clinical findings combined with the histopathology findings confirmed the diagnosis of telangiectasia macularis eruptive perstans (TMEP). A serum tryptase level was entertained as part of the patient’s diagnostic evaluation due to the age of onset. Given the patient’s asymptomatic presentation and a pertinent negative review of systems, the initial work-up included only a CBC with differential. The laboratory findings failed to reveal any abnormalities. The diagnosis and disease course were discussed in detail with the patient. The patient was educated on the potential triggers and activators of her disease. This included the risk of cardiovascular collapse secondary to anesthesia. She was ultimately prescribed an epinephrine injector as a precautionary measure. Regular follow-up by the dermatologist and primary care provider was advised, as was a yearly CBC.

History

Having an increased number of mast cells in one or more organs indicates the diagnosis of mastocytosis.1 Mastocytosis represents a wide spectrum of disorders that are clinically very heterogeneous. The organ most commonly involved is the skin. The spectrum of cutaneous mastocytosis (CM) includes: solitary mastocytoma, diffuse CM (erythroderma), urticaria pigmentosa, and telangiectasia macularis eruptiva perstans (TMEP) (Table 1).2 TMEP is the rarest form of CM, originally described by F. Parkes Weber more than 80 years ago as a variant of urticaria pigmentosa.3

Epidemiology/Etiology

It has been estimated that TMEP occurs about 1 percent of all cases of CM.4 Adults represent the majority of patients with TMEP. Rare occurrences in infancy and childhood have been reported. The course is often indolent in nature, unlike other forms of CM (such as urticaria pigmentosa) that often resolve by adolescence.4,5 Familial cases have been reported as well, with a particular family exhibiting a possible autosomal-dominant form of inheritance.1,4,6

The exact etiology of CM has yet to be fully determined. Evidence has shown that multiple cell types, including epidermal keratinocytes, produce mast-cell growth factor (steel factor, stem-cell growth factor
Clinical Presentation

Skin findings usually consist of ill-defined erythematous telangiectatic macules/patches that range in size from 2-6 mm with an underlying tannish-brown color.9 These most often appear symmetrically arranged on the trunk and extremities, usually sparing the face, palms, and soles.1,2,5,14 The telangiectasia also exhibits a reticular pattern alignment when examined with a dermatoscope.15 Physical stroking or application of heat to the affected areas may illicit a local urtication response, a positive Darier’s sign. However, in TMEP, Darier’s sign is typically negative or only slightly positive compared to other forms of CM. This is demonstrated by the smaller number of mast cells involved.4,5,16

Histopathology and Diagnostic Evaluation

Skin findings resembling those of CM require a skin biopsy in order to establish a definitive diagnosis and to differentiate among the various types. While performing this, some authors suggest avoiding the use of local anesthetic containing epinephrine during skin biopsy due to the ability of epinephrine to stimulate mast-cell degranulation.16

TMEP usually possesses less apparent histopathological findings, as mentioned above. There usually exists a mild increase in mast cells, particularly in the interstitial collagen and around the superficial plexus blood vessels of the top third of the dermis.5,19 With TMEP, authors have found the value of mast cells per high-power field to be around 15-20, though a simple contrasting difference of mast cells when comparing normal and affected skin can suffice for diagnosis.5,16,20 Stains used to visualize mast cells and their cytoplasmic metachromatic granules include Giemsa and toluidine blue. Chloroacetate esterase (Leder stain) may also be used to identify mast cells.14 Additionally, monoclonal antibodies that recognize KIT (CD117) and/or trypase are more sensitive and useful in confirming the diagnosis of mastocytosis.16,21

It is also vital to rule out any systemic involvement. Serum tryptase is a reliable

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical evidence</th>
<th>Pathological evidence</th>
<th>Demographics</th>
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<tbody>
<tr>
<td>Telangiectasia macularis eruptiva perstans</td>
<td>2-6 mm irregular, red/brown telangiectatic macules/papules. Commonly found on trunk and extremities. Darier’s sign often negative.</td>
<td>Slight increase in mast cells perivascularly and in upper third of dermis, dilution of superficial capillaries.</td>
<td>Almost always affects adults, rare: less than 1% of patients diagnosed with mastocytosis.</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>0.5-3.5 mm red-brown macules and papules, associated flushing and pruritus, positive Darier’s sign and dermatographism.</td>
<td>Increase in mature mast cell population.</td>
<td>Most common type of cutaneous mastocytosis, bimodal peak distribution in childhood and 3rd decade but can be seen in any age.</td>
</tr>
<tr>
<td>Mastocytoma</td>
<td>1 cm or smaller reddish brown nodules/plaques with positive Darier’s sign.</td>
<td>Large group of densely packed mast cells.</td>
<td>Rarely seen in adults, usually present within first 3 months.</td>
</tr>
<tr>
<td>Diffuse cutaneous mastocytosis</td>
<td>Red/brown thick, edematous skin with orange peel texture, positive Darier’s sign and dermatographism.</td>
<td>Generalized mast cell infiltration, band-like.</td>
<td>Seen in infants and children before the age of 3.</td>
</tr>
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Table 1: Types of cutaneous mastocytosis

Adapted from Watkins CE, Bokor WB, Leicht S, Youngberg G, Krishnaswamy G. Telangiectasia macularis eruptiva perstans: more than skin deep. Dermatology Reports. 2011; 3(1)
initial test to investigate for systemic mastocytosis.23 Tryptase is the main protein component of mast-cell secretory granules.23 Those presenting with purely cutaneous disease process often demonstrate serum tryptase levels within normal ranges. Authors have found that most patients with systemic mastocytosis reveal tryptase levels greater than 20 μg/L.24,25 Another preliminary test is the 24-hour urinary histamine. Due to its non-specific nature, authors recommend the use of the more sensitive histamine metabolite N-methylhistamine.23

A bone marrow biopsy can also aid in uncovering a systemic process as well as provide evidence of mutations such as c-kit (D816V) and FIP1L1. While these provide evidence of mutations such as c-kit (D816V) and FIP1L1, they may often be confused with other skin disorders. At initial onset, and exam findings will often point to this heterogeneous group of disorders. Often, the lesions seen in mastocytosis are so characteristic that they are rarely mistaken for other skin disorders. At initial glance, lesions may appear similar to melanocytic nevi or lichen. Mastocytosis in children may be confused with pseudolymphoma, juvenile xanthogranuloma, or café-au-lait macules.21 The presence of systemic symptoms such as episodic flushing may necessitate the ruling out of disease processes such as carcinoid syndrome, endocrine tumors secreting vasoactive peptides, pheochromocytoma, and medullary thyroid carcinoma. Urinary 5-hydroxyindoleacetic acid (5-HIAA) and metanephrine concentrations within normal limits would help to differentiate carcinoid syndrome and pheochromocytoma from mastocytosis, as the latter usually has normal urinary concentrations.14,15,17,19

Treatment

Unfortunately, there is no cure or an established first-line therapy for TMEP. Symptomatic treatment, with the emphasis on avoidance of triggers, is the primary treatment goal. According to the literature, the combination of symptomatic treatment and avoidance of triggers minimizes the release of mast-cell mediators and helps block the effects of these mediators.16 Potential triggers and activators include: physical exercise, temperature extremes, bacterial toxins, bee stings/insect bites, ethanol intake, emotional and physical stress, Psychological/emotional stress, Bacterial toxins, Food allergens (e.g., shellfish, peanuts), Immunologic stimuli (e.g., IgE), Solar radiation, Hot/cold temperature extremes, Venoms (e.g., hymenoptera), Other insect bites. Pharmaceutical agents:

- Acetylsalicylic acid
- Amphotericin B
- d-tubocurarine
- Dextromethorphan
- Gallium
- Iodine-based contrast dyes
- Narcotics (e.g., morphine, meperidine, codeine)
- Nonsteroidal anti-inflammatory drugs
- Polymyxin B
- Polymeric eye drops
- Quinine
- Reserpin
- Scopolamine

If only CM is observed, then simple conservative management and observation are appropriate. When systemic symptoms are present, H1 antagonists can be used to alleviate pruritus and/or flushing.14 Oral disodium cromoglycate can aid with gastrointestinal symptoms and may be useful in patients who fail to respond to other forms of treatment.17,27 Some have demonstrated the efficacious use of psoralen plus ultraviolet-A light therapy in alleviating the cutaneous “stinging” sensations. This treatment works to inhibit the release of histamine by mast cells.16,17 Given that mast cells release a variety of pro-inflammatory mediators, cytokines, and signaling molecules, including cysteineyl leukotrienes, some authors have recommended a trial of leukotriene antagonists such as montelukast.27 Temporar

Differential Diagnosis

Other CM-related processes deserve consideration, especially due to the rarity of TMEP. Clinical presentation, age of onset, and exam findings will often point to this heterogeneous group of disorders. Often, the lesions seen in mastocytosis are so characteristic that they are rarely mistaken for other skin disorders. At initial glance, lesions may appear similar to melanocytic nevi or lichen. Mastocytosis in children may be confused with pseudolymphoma, juvenile xanthogranuloma, or café-au-lait macules.21 The presence of systemic symptoms such as episodic flushing may necessitate the ruling out of disease processes such as carcinoid syndrome, endocrine tumors secreting vasoactive peptides, pheochromocytoma, and medullary thyroid carcinoma. Urinary 5-hydroxyindoleacetic acid (5-HIAA) and metanephrine concentrations within normal limits would help to differentiate carcinoid syndrome and pheochromocytoma from mastocytosis, as the latter usually has normal urinary concentrations.14,15,17,19

Table 2: Known mast cell releasing triggers

<table>
<thead>
<tr>
<th>Trigger Type</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Ethanol</td>
<td>Psychological/emotional stress</td>
</tr>
<tr>
<td>Physical exertion</td>
<td>Physical exertion</td>
</tr>
<tr>
<td>Bacterial toxins</td>
<td>Food allergens (e.g., shellfish, peanuts)</td>
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<tr>
<td>Immunologic stimuli</td>
<td>Solar radiation</td>
</tr>
<tr>
<td>Hot/cold temperature</td>
<td>Venoms (e.g., hymenoptera)</td>
</tr>
<tr>
<td>Other insect bites</td>
<td>Other insect bites</td>
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</table>

Adapted from Watkins CE, Bokor WB, Leicht S, Youngberg G, Krishnaswamy G. Telangiectasia macularis eruptive perstans: more than skin deep. Dermatology Reports, 2011; 3(1).
of mast cells present, and therefore mainly improves cosmesis. Such an option may need a pretreatment with histamine-receptor blockers to prevent any laser-induced mediator release. Systemic therapy for aggressive/severe systemic mastocytosis may include interferon-α-2b, radiation and chemotherapeutic agents. Chemotherapeutic agents have been used with little success. Intravenous cladribine (2-chlorodeoxyadenosine) was reported to be effective in reducing bone-marrow mast cells and eliminating skin lesions in one patient. Imatinib mesylate, an oral tyrosine kinase inhibitor, has been used for the treatment of systemic mastocytosis. However, adults with the common D816V mutation often respond poorly to imatinib. Isolated case reports have shown that adults with mutations outside of the exon 17 (location of the codon 816V) were treated successfully with imatinib.

Conclusion

TMEP is rare form of cutaneous mastocytosis that often presents in adults. The course is often indolent in nature. The pathogenesis is not fully understood and requires further clinical studies. Treatment is often centered on controlling symptoms and avoiding triggers. Although rare, case reports of systemic involvement have been associated with TMEP, so a thorough history and physical exam are essential. In the aforementioned case, the patient presented without any concerning symptoms or laboratory findings to suggest underlying systemic involvement. Given the asymptomatic nature of her disease, the patient was advised on the importance of frequent examinations by her primary care provider and dermatologist along with a yearly CBC. If the patient develops any systemic symptoms, additional testing will be completed.

References


60 A CASE OF TELANGIECTASIA MACULARIS Eruptiva PeroSTANS (TMEP)
KENALOG SPRAY 100g
Triamcinolone Acetonide Topical Aerosol, USP
0.2% Triamcinolone

For dermatological use only
Not for ophthalmic use

63 g Still Available!

PRECAUTIONS
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Use as directed. Refer to full Prescribing Information. For more information go to www.kenalogspray.com

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
KENALOG® SPRAY
Triamcinolone Acetonide Topical Aerosol, USP (0.147 mg/g)
For dermatologic use only
Not for ophthalmic use

DESCRIPTION
The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. The steroids in this class include triamcinolone acetonide. Triamcinolone acetonide is designated chemically as 9-Fluoro-11β,17β,21-trihydroxy-16α,17-dihydroprogesterone-1,4-diene-3,20-dione cylic 16, 17-acetic acid with aceton. The structural formula is:

\[
\text{C}_{24}\text{H}_{24}\text{F}_{1}\text{O}_{4}\text{. MW 434.50}
\]

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

CLINICAL PHARMACOLOGY
Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

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

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS
Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifesting as Cushing’s syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression occurs or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, substitute a less potent steroid, or use a sequential approach.

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

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

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

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

Information for the Patient
Patients using Kenalog Spray should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. avoid contact with the eyes and inhalation of the spray.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be inclusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
6. Do not use Kenalog Spray on the underarms or groin areas unless directed by your physician.
7. If no improvement is seen within 2 weeks, contact your physician.
8. Do not use other corticosteroid-containing products while using Kenalog Spray without first consulting your physician.
9. Kenalog Spray is flammable. Avoid heat, flames or smoking when applying Kenalog Spray.

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

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

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

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

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

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

HPA axis suppression, Cushing’s syndrome, and intrasellar hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenocortical suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intrasellar hypertension include bony lentenolism, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

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

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

DOSAGE AND ADMINISTRATION
Directions for use of the spray can be provided on the label. The preparation may be applied to any area of the body, but when it is sprayed on the body, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided. Spray is flammable; avoid heat, flame or smoking when using this product.

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

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

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

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

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Revised
ABSTRACT: Superficial leiomyosarcoma (SLMS) is a rare sarcoma which is further classified into either cutaneous or subcutaneous based on dermal location and site of origin. Cutaneous SLMS has an excellent outcome with rare recurrence whereas subcutaneous SLMS has a high incidence of recurrence and metastases. Wide excision with 2-5 cm margins has historically been advocated for treatment for both subtypes. However, due to the low recurrence and metastatic potential of cutaneous SLMS more conservative excisional margins may be more appropriate and is supported by recent institutional based studies.

Case Report

A 74-year-old Caucasian man presented with an asymptomatic lesion of six months duration on his right upper back. Physical examination revealed a 5 mm, tan-colored papule. His past dermatologic history was significant for actinic keratoses, and his medical history was non-contributory. He denied a history of non-melanoma skin cancer or other cutaneous neoplasms. A shave biopsy was performed with dermatopathologic examination and immunohistochemistry staining. Histological examination revealed atypical spindle cells and fascicles present within the dermis (Figures 1 & 2). Cells contained hyperchromatic and pleomorphic nuclei (Figure 3). Immunohistochemical stain for desmin was strongly positive, and there was weak staining for smooth-muscle actin. A diagnosis of cutaneous SLMS was rendered. Treatment included wide local excision with 1 cm margins and en face histologic evaluation (Figure 4). Temporary wound closure was maintained with subcutaneous sutures (Figure 5). Histologic examination of the surgical specimen revealed the margins free of tumor, and the defect was then closed primarily with subcutaneous sutures and a running, interrupted subcuticular suture with excellent wound approximation and tissue eversion (Figure 6).

Discussion

Leiomyosarcomas are sarcomas of smooth muscle that are classified as superficial or metastatic depending on the site of origin (Table 1). Superficial leiomyosarcoma (SLMS) is an extremely rare sarcoma, and the incidence is not known or reported in the literature due to its rarity. If often arises on hair-bearing skin of middle-aged men. SLMS is often asymptomatic but may present with mild tenderness, pruritus, bleeding and slow growth. Clinically, the differential diagnosis includes many benign cutaneous tumors including irritated seborrheic keratosis, cysts, lipomas, neurofibromas, dermatofibromas, and carcinoma. Histologic examination is strikingly significant for a proliferation of pleomorphic fascicles of spindle cells in the dermis. Immunohistochemistry is necessary for diagnosis, as many spindle-cell neoplasms mimic SLMS, such as spindle-cell squamous cell carcinoma, atypical fibroxanthoma, and melanoma. SLMS is further subdivided into cutaneous and subcutaneous SLMS, and this distinction is based on the location in the dermis and presumed site of origin (Table 2). This classification is of prognostic significance, as the biologic behavior of these two subtypes diverges greatly. Cutaneous SLMS is postulated to arise from the arrector pili muscles and is located in the dermis, whereas subcutaneous SLMS arises from the endothelium of dermal vessels and extends into the subcutaneous tissues. Furthermore, cutaneous SLMS has an excellent prognosis with variable recurrence rates and only isolated reports of metastases, whereas subcutaneous SLMS has a grimmer prognosis, with reported recurrence of 50% and 30-40% reported incidence of metastases.

Surgical excision is the standard of care for SLMS; however, recommended excisional margins and follow-up are poorly defined. Historically, recommended margins ranged from 2-5 cm for both cutaneous and subcutaneous SLMS, with no criteria outlined for narrower verses wider margins. As the prognosis differs significantly between these two subtypes, excisional margins should be recommended for each separately. A recent analysis of 33 patients with cutaneous SLMS showed excellent outcomes with wide local excision with 1 cm margins and no reported recurrences nor metastases at a median follow-up time of 15.5 months. This observation is supported by other large, institution-based studies in the literature. We recommend pathologic evaluation...
using the en face technique of the peripheral and deep margin with immunohistochemical staining, as this would allow for more complete margin assessment.\textsuperscript{11} Although this was not performed in this case, it was requested. This should result in high cure rates and better margin control.

In conclusion, superficial leiomyosarcoma is a rare soft-tissue sarcoma with poorly defined treatment algorithms. Cutaneous SLMS has an excellent prognosis and low recurrence rates with narrow excisional margins. Dermatopathology-controlled surgical excision proves to be a viable approach to decrease recurrence and increase patient outcomes.

References