Focus on Flushing Triggers
A Neural Link to Understanding Rosacea

Also in this issue:
Adult-onset Multisystemic Langerhans Cell Histiocytosis
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# Table of Contents

**JAOCD Editors** ............................................................................................................................................................................................4  
**Letter from the President** ..............................................................................................................................................................................5  
**Letter from the Executive Director** ...............................................................................................................................................................6  
**Letter from the Editor-in-Chief** ...................................................................................................................................................................7  

**FEATURE ARTICLE:**  
A Neural Link to Understanding Rosacea: Focusing on Flushing Triggers ................................................................................................11  
B.D. Gray, DO, K. Metzler-Wilson, PT, PhD, K.W. Dawes, MD, T.E. Wilson, PhD  

**EDITOR’S PICKS:**  
Adult-onset Multisystemic Langerhans Cell Histiocytosis: A Case Presentation and Discussion..........................................................17  
Shabrzad Akhary, BS, Adam Sorensen, DO, Richard Barmert, MD, FAASDP, Joseph Machuzak, DO, FAOCD, Stephen Kessler, DO, FAOCD  
A Rare Case of Unilesonal Follicular and Syringotropic Mycosis Fungoides: A Case Report and Review of the Literature.........................20  
Kevin Svancara, DO, Vernon T. Mackey, DO, FAOCD, FASMS  
Secukinumab for the Treatment of Plaque Psoriasis: A Review of Phase III Testing..................................................................................23  
Aline Babikian, DO, Kouros Beroekbhim, BS, Catherine Nguyen, BS, John Koo, MD  

**ORIGINAL ARTICLES AND CASE REPORTS:**  
Case of Persistent Regrowth of Blond Hair in a Previously Brunette Alopecia Areata Totalis Patient .......................................................28  
Karla Snider, DO, John Young, MD  
A case of chronic lichenoid dermatitis manifesting as hypopigmented, flat-topped papules ........................................................................31  
Ann Mazor Reed, DO, Jennifer David, DO, Stanley Skopit, DO, MSE, FAOCD  
Diffuse Dermal Angiomatosis of the Breast: A Case Presentation and Discussion...................................................................................33  
Gina M. Caputo, DO, Roxanne Rajaii, MS, DO, Gary Gross, MD, Daniel S. Hurd, DO  
Laser Improvement of Permanent-makeup Eyebrows: A Case Report .......................................................................................................35  
Jonathan Crane, DO, FAOCD, David George Jackson, PhD  
Christopher Hixon, DO, Collin M. Blattner, BS, Daniel Hurd, DO  
Topical Ivermectin for the Treatment of Papulopustular Rosacea: A Review ..............................................................................................38  
Sean McGregor, PharmD, John Minni, DO, FAOCD  
Lymphoepithelioma-like Carcinoma of the Skin: A Case of One Patient Presenting with Two Primary Cutaneous Neoplasms ...............40  
Jacqueline C. Fisher, DO, Rachel M. White, BA, Daniel S. Hurd, DO, FAOCD  
Primary Cutaneous Carcinosarcoma: A Case Report and Discussion of a Histological “Chimera”.............................................................43  
Joseph Dyer, DO, Kaylan Pustover, DO, Prasanna Sinkre, MD, Richard Miller, DO, FAOCD  
Case report: Eccrine porocarcinoma of the scalp in an immunosuppressed patient ...................................................................................45  
Claire Otteni, BS, Richard Limbert, DO, Joseph Dyer, DO, Richard A. Miller, DO, FAOCD  
En Coup De Sabre: A Case Report .............................................................................................................................................................47  
Ashvin Garlapati, DO, Ramya Tripuraneni, MBBS, Stanley Skopit, DO, MSE, FAOCD  
Sickle Cell–Associated Leg Ulcers: A Case Presentation and Discussion ..................................................................................................50  
Jessica Bernstein, DO, Kristen Stewart, MD, FAAD, Stanley Skopit, DO, MSE, FAOCD  
Twenty-nail Dystrophy in a 42-year-old Woman: A Case Report ..............................................................................................................53  
Chelsea Duggan, DO, Kristin Rongstad, BS, Matthew Elias, DO, FAOCD  
Urticaria Pigmentosa: A Case Report and Review of Current Standards in the Diagnosis of Systemic Mastocytosis ..............................55  
Riddhi J. Shah, DO, Mark A. Kuriata, DO, FAOCD
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<table>
<thead>
<tr>
<th>Name</th>
<th>Location, State</th>
</tr>
</thead>
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<th>Name</th>
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Dear Readers,

Welcome to another issue of the JAOCD. This publication has become one of the cornerstones of our organization. I want to thank Dr. Karthik Krishnamurthy for another fine issue and for his hard work and dedication. I also want to extend my thanks to Dr. Jay Gottlieb for his vision in starting the JAOCD. In addition, the national office staff, led by Executive Director Marsha Wise, has helped make this scientific publication a reality.

Many things have happened since the last issue of the JAOCD was published. The AOCD Delegation to the AOA, led by Drs. Lloyd Cleaver and David Grice, represented the College at the AOA House of Delegates this summer in Chicago. There was a lively discussion on the House floor on resolutions concerning gun control, mental healthcare for medical students and physicians, rules for prescribing pain medication to the elderly, and adopting a reversal for a federal ban on sperm donation by homosexual men. I want to thank Drs. Cleaver and Grice for representing our college at such an important event.

As my presidency comes to a close, I want to use this as an opportunity to thank all my mentors and advisors for guiding me through the year. I look forward to Dr. Alpesh Desai continuing to lead our beloved College and taking it to great heights. Although I will be stepping down from the presidency, I look forward to serving as the Immediate Past President and continuing my contribution to the Board of Trustees.

In addition, I will be focusing on the next stage of my professional and academic career. I have assumed the position of Program Director for the recently established Rio Grande Valley Dermatology Residency that is part of the Corpus Christi Medical Center. I am excited and humbled to be able to contribute to the education of future osteopathic dermatologists during this turbulent time of the Accreditation Council for Graduate Medical Education merger. I sincerely believe that with the continued contributions of our members, we will thrive as a profession in this era of uncertainty. As an organization, we will never lose sight of our goals to provide osteopathic dermatologic care and education to patients and physicians. We will always strive to do what is best for our patients.

Looking back to the vision of Dr. Gottlieb and the continued efforts of Dr. Krishnamurthy, I am touched and moved by the contributions of our members in bringing this journal to fruition. I can only imagine what the future holds for the AOCD. I look forward to seeing our future leadership in action and the increased active participation of our membership.

Rick Lin, DO, MPH, FAOCD
President, American Osteopathic College of Dermatology
Hello, Everyone,

In June, the AOCD Office welcomed a new member to the staff. Ms. Kristin Ayer was hired as our Administrative Assistant. She takes over for Jami Johnson, who left in May 2014. Look for Kristin’s article of introduction in the next issue of Dermline.


We had a very successful and well-attended Spring Conference in Charlotte, NC. We were most appreciative of Dr. Nicole Owens, Immediate Past Chair of the ACGME Dermatology Review Committee. Dr. Owens gave a presentation on the Single Accreditation system as well as took the time to sit down with our program directors to discuss the system and listen to their concerns.

Exciting changes are in store for our Fall Conference. Our meeting is scheduled for October 16-19, 2015, in Orlando at the Loews Royal Pacific Resort. An information packet with further details was mailed to our members about the changes happening with this meeting. Hotel Reservations can be made online at http://uo.loewshotels.com/en/Royal-Pacific-Resort/GroupPages/AOCD.

If you will be attending the Sunday session at the Orange County Convention Center, you will need to register through the AOCD office for a Day Pass. Please register by September 30, 2015. Please also let us know if you will be taking advantage of our shuttle service from Loews to the convention center.

The new CME cycle will begin on January 1, 2016. The AOA is updating the CME Guide for Physicians. As soon as the AOA makes it available to us, we will forward it to you. Please monitor your CME report, as the AOA will no longer provide this information to the AOCD office due to the AOA’s privacy policy.

Many AOCD members have been inquiring about OCC and OCAT. For those whose board certificates expire in 2020, you will need to complete two PPA Modules prior to sitting for the exam. One module must be completed in this CME cycle ending December 31, 2015, and one in the next CME cycle. If you have not already done so, you must register at https://www.osteopathic-cat.com/register.php. This is all mandatory for recertification. If you have any questions, please refer to the website at http://aobd.org/aobd/occ/aobd-occ-faqs. There are OCC updates at the annual AOCD meeting as well, where you can ask questions.

As always, should you have questions or concerns, please do not hesitate to call the AOCD office (800-449-2623). If we cannot answer your question, we will direct you to the person(s) who can.

Thank you for allowing me to be your Executive Director. I hope to see you in Orlando.

Sincerely,

Marsha Wise
Executive Director, American Osteopathic College of Dermatology
Dear Readership,

I am proud to report that the JAOCMD continues to flourish thanks to our hard-working editorial board and all of the submissions from our members and residents. We are committed to publishing quality manuscripts, and I think everyone can agree that we take meaningful pearls away from each issue.

During the ACGME/AOA single-accreditation transition, it remains important for us to be vigilant in incorporating those core Osteopathic Practices and Principles that we trained with. It is this identity that will ensure our survival as a unique profession within dermatology and protect our ability to deliver osteopathic care to our patients. This is why the journal has been showcasing osteopathy-focused articles on our covers whenever possible.

The JAOCMD’s Volume 29 original feature article, “An osteopathic approach to Raynaud’s Phenomenon,” was the No. 1 most-accessed article in 2014 by osteopathic physicians (not just dermatologists) across all journals (osteopathic and non-osteopathic), according to the American Academy of Osteopathy. Osteopathic dermatologists represent about 10% of the graduating dermatologists in the United States, mirroring the overall percentage of all osteopathic physicians among all U.S. physicians from all specialties. Osteopathy-focused literature will be especially vital in establishing the uniqueness of our core values during the merger, and the JAOCMD is distinctive in addressing this need. The journal may also eventually play a role in endowing required osteopathic credits toward continued certification. We already offer AOA Cat 2-B CME credit for readership.

I ask, then, that our members start incorporating osteopathic principles into more submissions. In addition to reflecting the uniqueness of our profession, it will contribute to a successful bid for Medline indexing, as we can fill a significant void in Medline’s current offerings. Indexing is paramount in validating the hard work of our students and residents.

With your help, we look forward to publishing more osteopathy-focused articles in the future.

Fraternally,

Karthik Krishnamurthy, DO, FAOCD

Editor-in-Chief, Journal of the American Osteopathic College of Dermatology
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A Neural Link to Understanding Rosacea: Focusing on Flushing Triggers

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**Assistant Professor of Neuroscience & Pharmacology, Marian University College of Osteopathic Medicine, Indianapolis, IN
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****Professor of Physiology, Marian University College of Osteopathic Medicine, Indianapolis, IN

Abstract
Facial erythema in rosacea can be triggered by events that do not normally cause sustained flushing. This review discusses why flushing was evolutionarily conserved, how facial blood flow increases, and how the process can go awry in rosacea. Known mechanisms of increased facial-skin blood flow associated with thermal/environmental, social/emotional, pharmaceutical/topicals, dietary, and physical-exercise trigger events are explored. Flushing triggers begin with neural (sympathetic, cranial nerve, axon reflex, or sensory afferent) responses inducing vasodilation (active vasodilation and/or reduced tonic vasoconstriction), fluid extravascularization, and increased vascular volume. Local inflammatory mediators can augment responses, but it is neural responses that initiate the process. We theorize that mechanistically understanding erythema will allow rosacea to be better tolerated and controlled.

Introduction
Rosacea is a chronic skin disorder most commonly characterized by erythema and inflammatory lesions in the central face region, which affects many people worldwide, including an estimated 16 million people in the United States.1 Disease classification often includes both subtypes and variants. Subtypes include erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea; variants include granulomatous and neurogenic rosacea.2,3 Regardless of classification or whether all patients can be adequately classified, most patients present at some point with induced or permanent facial flushing.4

Rosacea erythema, especially in the erythematotelangiectatic subtype, can change in intensity and is activated by trigger events. Erythema triggers vary among patients but can be grouped into categories related to thermal/environmental, social/emotional, pharmaceutical/topicals, dietary, and exercise (Table 1). In a recent National Rosacea Society survey, more than 50% of North American participants reported that hot weather and baths, sun and wind exposure, emotional stress, alcohol consumption, and exercise all trigger flushing and associated symptomatology.5 Besides acute erythema, these episodes can cause local inflammation, edema, and painful burning or stinging sensations. Chronic and repeated bouts of flushing and associated inflammation can induce structural changes in the vasculature (e.g., telangiectasias) and connective tissue, which add to disease signs and symptoms.

This review addresses what is known about the neural mechanisms underlying rosacea erythema trigger events. We discuss why flushing was evolutionarily conserved, how blood flow mechanistically increases in facial skin, and how it can go awry in disorders such as rosacea. A review with this particular focus, neural mechanisms of rosacea erythema triggers, has not been previously completed. Most mechanistic evaluations of rosacea have almost exclusively focused on the inflammatory aspects of the disease; while these are important, it is the neural events (sympathetic, cranial nerve, axon reflex, and sensory afferent) that initiate the trigger. We refer the reader to a number of excellent reviews and source material that cover general information about rosacea, inflammatory and pathological changes associated with it, and its potential treatment.6-12 Although etiology is unknown, current FDA-approved treatments in the United States include metronidazole, azelaic acid gel, and doxycycline, which decrease inflammation associated with rosacea but do not generally improve the erythema. In contrast, neural (ganglionic, cholinergic, and α-adrenergic) antagonism strategies have been reported to reduce rosacea erythema.13-15 One interesting approach is the use of an α1-adrenergic agonist (brimonidine gel), which has recently been approved for treatment of rosacea erythema. This class of drug can directly cause some vasoconstriction via post-synaptic α1-

Table 1. Common rosacea triggers

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Stimulus/Mechanism</th>
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<tbody>
<tr>
<td>Thermal/Environmental</td>
<td>Sun</td>
<td>UV,* local and whole-body heating</td>
</tr>
<tr>
<td></td>
<td>Hot weather</td>
<td>Local and whole-body heating</td>
</tr>
<tr>
<td></td>
<td>Wind</td>
<td>Local heating and cooling, irritation, AVAs,** blood-pressure effect</td>
</tr>
<tr>
<td></td>
<td>Hot bath, sauna</td>
<td>Local and whole-body heating</td>
</tr>
<tr>
<td></td>
<td>Cold</td>
<td>Local and whole-body cooling, AVAs, blood-pressure effect</td>
</tr>
<tr>
<td>Social/Emotional</td>
<td>Embarrassment</td>
<td>Mental stress</td>
</tr>
<tr>
<td></td>
<td>Psychological stress</td>
<td>Arousal, blood-pressure effect</td>
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<tr>
<td></td>
<td>Anxiety</td>
<td>Mental stress, blood-pressure effect</td>
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<tr>
<td></td>
<td>Sexual arousal</td>
<td>Arousal, whole-body heating</td>
</tr>
<tr>
<td>Pharmaceutical/Topical</td>
<td>Medications</td>
<td>Variable</td>
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<tr>
<td></td>
<td>Skin-care products</td>
<td>Irritation, allergic</td>
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<tr>
<td></td>
<td>Cosmetics</td>
<td>Irritation, allergic</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td>Direct effect, gustatory reflex</td>
</tr>
<tr>
<td>Dietary</td>
<td>Spicy food</td>
<td>Gustatory reflex</td>
</tr>
<tr>
<td></td>
<td>Heated foods and beverages</td>
<td>Gustatory reflex</td>
</tr>
<tr>
<td></td>
<td>Certain fruits and vegetables</td>
<td>Variable, unknown</td>
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<td></td>
<td>Dairy</td>
<td>Unknown</td>
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<tr>
<td>Exercise</td>
<td>Aerobic exercise</td>
<td>Whole-body heating</td>
</tr>
<tr>
<td></td>
<td>Resistance exercise</td>
<td>Arousal, blood-pressure effect</td>
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* UV - ultraviolet
** AVA - arteriovenous anastomosis
Skin Blood Flow

To understand the erythema associated with rosacea, an understanding of the physiology of skin blood flow and its measurement is required. The advent of many noninvasive indices of skin blood flow (e.g., laser-Doppler flowmetry with both fixed probes and scanners, transcutaneous tissue oxygenation, in vivo video microscopy, photoplethysmography) has allowed measurements of indices of facial blood flow.16-18 The ease of use of these devices has allowed for increased utilization, but most dermatology-focused studies do not appropriately control for factors that affect skin blood flow independent of their treatment paradigm. For instance, not expressing laser-Doppler measures as cutaneous blood flow changes to improve the body's ability to dissipate heat during an embarrassing task corresponds to an increase in an index of skin blood flow in that area.20 It is thought that embarrassment, and in part blushing, may be a remnant of appeasement display that is observed in some social animals.21 In sum, flushing should be considered a normal physiological response that can aid in providing social cues and conveying emotion.

Facial flushing can also participate to a minor extent in heat dissipation. Humans can lose heat from the face and head but primarily rely on hairy skin of the rest of the body for heat dissipation. Both in glabrous skin (e.g., nose, ears) and other facial areas (e.g., forehead, cheek), blood flow can increase during times in which heat dissipation is necessary, but because of hairy skin's sheer surface area and large blood flow capacity (up to 8 L/min), there is a much greater potential to offload heat in hairy skin.22-24 In addition to differences in skin blood flow, there are also neural, anatomical, and functional differences between the types of skin (Table 2). Notably, there is vasomotor cranial-nerve involvement in facial mucosa and skin but not in peripheral glabrous and hairy skin.25 Thus, for primary heat dissipation, humans rely not on facial flushing but on blood-flow changes in non-facial hairy skin.

If facial flushing is normal during embarrassment and heat-stress conditions, what constitutes a flushing disorder? There are a number of factors and disorders that can cause flushing.26 The differential diagnosis of the rosacea patient who presents with flushing, sensitive skin and facial edema can be difficult.27 Rosacea's most visible sign, facial erythema that fluctuates in intensity with trigger events, is defined by its pathophysiology, which includes neurovascular dysregulation and inflammation.28 The subsequent sections of the review discuss the neural origins of these erythema triggers based on patient-frequency data and trigger categorization.

**Rosacea Erythema Trigger Mechanisms**

In rosacea, no erythema trigger is universal.5 In the current review, we refer to triggers as having major (>50% of survey respondents), moderate (25%-50%), and minor (<25%) incidence rates and will discuss only the major and moderate triggers.5 Rosacea erythema triggers can be roughly categorized into five groups (Table 1), with varied mechanisms of induction of facial flushing and associated symptomatology. The study of facial blood flow is made more difficult because certain mechanistic pharmacological procedures (e.g., intradermal microdialysis) cannot be completed in the human face for safety and ethical reasons. Glabrous skin also suffers transcutaneous drug delivery difficulties due to its thick epidermal layer. Thus, the majority of mechanistic in vivo studies are completed in the hairy skin of the forearm, calf, or thigh. Nonetheless, a discussion of erythema triggers as they relate to forearm, leg, and palm skin with the inclusion of face skin when available provides a framework to investigate flushing mechanisms in the face and in individuals with rosacea.

**The Thermal/Environmental**

Whole-body heat stress is a major rosacea flushing trigger that induces a number of physiological changes to improve the body's ability to dissipate

---

**Table 2. Characteristic differences between types of human skin**

<table>
<thead>
<tr>
<th>Type</th>
<th>Neural</th>
<th>Anatomical</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hairy</td>
<td>Adrenergic vasoconstrictor</td>
<td>Surface capillary loops</td>
<td>Heat dissipation</td>
</tr>
<tr>
<td></td>
<td>Cholinergic-related vasodilator</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholinergic sudomotor</td>
<td></td>
<td>Tissue insulation</td>
</tr>
<tr>
<td></td>
<td>Adrenergic pilomotor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glabrous</td>
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<td>Surface capillary loops</td>
<td>Grip and dexterity</td>
</tr>
<tr>
<td></td>
<td>Cholinergic sudomotor</td>
<td>Arteriovenous anastomoses (AVAs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cranial nerves</td>
<td>Surface capillary loops</td>
<td>Display</td>
</tr>
<tr>
<td></td>
<td>Adrenergic vasoconstrictor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial</td>
<td>Cholinergic-related vasodilator?</td>
<td>Arteriovenous anastomoses (AVAs)</td>
<td>Heat dissipation</td>
</tr>
<tr>
<td></td>
<td>Cholinergic sudomotor</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Adrenergic pilomotor?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
heat. Notably, there are sympathetically mediated increases in heart rate and cardiac output; vasconstriction of renal, splanchic, and skeletal muscle vasculatures; and vasodilation of the skin to facilitate environmental heat transfer. Glabrous, hairy, and facial skin are under tonic sympathetic vasconstrictor tone, as evidenced by the release of vasconstriction with ganglionic blockade or presynaptic release inhibitor and the existence of basal skin sympathetic nerve activity. All skin types appear to utilize a release of vasconstrictor tone to increase skin blood flow during a whole-body heat stress. Peripheral hairy but not glabrous skin also employs a cholinergic-related active vasodilator that releases vasoconstrictor tone to increase skin blood flow.46 Local-heating due to an axon reflex and the later vasodilation to a skin, where the initial vasodilation is primarily occurs in a biphasic manner in peripheral hairy skin.47

A greater nerve-fiber densities in all subtypes of channel in erythematotelangiectatic rosacea and transient receptor potential vanilloid-1 (TRPV1) with an upregulation of the heat-activated substance(s) or the origin(s) thereof.42 Additional research is needed to determine whether changes in facial vasodilator mechanisms are implicated in rosacea during whole-body heating.

Local skin heating, also a major rosacea flushing trigger, induces vasodilation that is sympathetically independent but requires adrenergic innervation for complete expression.43-45 This vasodilation occurs in a biphasic manner in peripheral hairy skin, where the initial vasodilation is primarily due to an axon reflex and the later vasodilation to a nitric-oxide-mediated response.46 Local-heating-induced vasodilation occurs in facial skin but is not consistently observed in peripheral glabrous skin. Facial (i.e., forehead and cheek) axon reflex responses follow hairy skin's biphasic vasodilation pattern but are unique in that standard topical anesthetic protocols are not successful in blunting the initial, axon-reflex-associated vasodilation.47 Guzman-Sanchez identified increased local heat sensitivities in both erythematotelangiectatic and papulopustular rosacea.48 This result is consistent with an upregulation of the heat-activated transient receptor potential vanilloid-1 (TRPV1) channel in erythematotelangiectatic rosacea and greater nerve-fiber densities in all subtypes of rosacea.49-52 Thus, it is possible that the face has a greater axon-reflex component compared to peripheral hairy and glabrous skin and that this response is heightened in rosacea-affected areas.50

Ultraviolet (UV) exposure associated with sunlight is another major rosacea flushing trigger. This stimulus is likely multifactorial, involving whole-body and local heating mechanisms resulting from UV-induced heat gain in addition to the unique activity of UV radiation itself. It is unclear whether UVA (320-400) or UVB (290-320 nm) triggers symptoms. Although UVA is the dominant component of solar radiation, it requires greater energy to induce a minimal erythema dose.51 DNA is a chromophore, a UV-photon absorber, and in response to UVB-photon bombardment it creates a number of proinflammatory photoproducsthes, such as DNA-repair enzymes, TNF-α, and other cytokines.52,53 Photoproducsthes associated with tropothen, another chromophore, increase expression of COX-2 and thereby catalyze erythema, producing PGE2 and PGE, during UVB exposure.54 UVA travels deeper into the skin and thus affects the dermal layer to a greater extent. UVA damage is perfusion- and O2-dependent, which heavily implicates a reactive oxygen species (ROS) mechanism.55 Finally, both UVB and UVA exposures upregulate both vascular endothelial growth factor and toll-like receptor (TLR) pathways, which could mediate angiogenesis and cytokine synthesis and secretion.56,57 This latter effect may sensitize the skin for subsequent UV-exposure responses. Whether these UV processes are altered in facial compared to peripheral hairy and glabrous skin or in rosacea, however, remains to be determined.

Whole-body cold stress, a moderate rosacea flushing trigger, induces a number of physiological changes to increase tissue insulation and decrease environmental heat loss.5 Passive cold stress does not change cardiac output but causes systemic vasconstriction, thereby increasing vascular resistance and arterial blood pressure.58,59 Despite this pressure increase, both peripheral hairy and glabrous skin undergo pronounced decreases in cutaneous vascular conductance during whole-body cooling. Peripheral hairy skin normally remains vasconstricted throughout a cold stress; however, skin with arteriovenous anastomoses (e.g., glabrous skin) can oscillate between constricted and relaxed states.58 This cyclical response has been termed the “hunting reaction,” as it is thought to increase flow to aid in dexterity and prevent tissue freezing without losing extraordinary amounts of heat.59 Thus, in response to whole-body cooling, arteriovenous anastomosis-rich areas such as the nose, ears, and lips can increase blood flow, although responses in other areas of the face are less clear. Facial skin's absolute vasconstriction in response to cooling may also be blunted or absent because many facial locations such as the forehead do not appear to contain a high density of cutaneous vasconstrictor nerves.58 Thus, it is possible that there are regional arteriovenous anastomosis responses and less opposition to the increases in arterial blood pressure. This could be a mechanism to decrease blood flow in some facial skin while increasing skin blood flow to other facial areas during whole-body cooling. It is possible that the arteriovenous anastomosis response is altered in patients with rosacea, possibly due to changes in the neural control of this response.

Local cooling can also be a moderate rosacea flushing trigger. In peripheral hairy skin, locally applied cold produces biphasic vasomotor responses. An initial vasconstriction is followed by a transient vasodilation and then a prolonged vasconstriction.46 The mechanisms by which local cooling causes these vascular changes, with the exception of α2-adrenergic receptor translocation, are unclear but likely involve local sensory afferents. Under thermoneutral conditions, α2-adrenergic receptors are located in the Golgi apparatus membrane. Then, with mitochondrial ROS stimulation, such as during local cooling, the Golgi apparatus migrates to the cell surface and fuses with the existing cell membrane. This increases α2-adrenergic receptor density, which allows for greater vasconstrictor per quanta of norepinephrine released from sympathetic nerves. To our knowledge, the local cooling response in facial skin has not been described. Facial skin could be different in that it has a higher density of sensory afferents, which could lead to an augmented counteracting of vasodilation depending on pain and other sensory afferent vasoactive releases.42,59,60 Whether sensory afferent or other neural control of facial blood flow during local cold stress is altered in rosacea needs further clarification.

Wind is listed as a distinct and major rosacea flushing trigger, but the specific temperature is not accounted for in most surveys. Cold-wind responses may be related to local and whole-body cooling responses. Wind causes direct skin-temperature changes via convective cooling and may also cause irritation and thus induce sensory afferent responses similar to local cooling. Wind may also dry superficial skin layers, leading to a disruption of the skin barrier. If a hot or cold wind causes a great enough skin-temperature change, it may locally exacerbate or attenuate skin-blood-flow responses per change in internal temperature.51 Another possible cold-wind outcome, if applied directly to the face, is a “diving” reflex response that results in decreased heart rate and increased arterial blood pressure.62 Experimental “diving” reflex procedures decrease skin sympathetic nerve activity to peripheral glabrous and hairy skin; this reduction in vasconstriction coupled with increased arterial pressure could lead to increased skin blood flow.63,64 Little is known about wind or convective cooling, outside the “diving” reflex, in facial skin. Similarly, possible changes in rosacea have yet to be determined.

Social/Emotional
Emotional stress and anxiety are both major rosacea flushing triggers.5 Embarrassment is often not precisely delineated in rosacea surveys, but it is a very common cause of increased blood flow in facial skin (see Facial Flushing section) and is likely related to emotional stress. The precise mechanisms of emotional-stress-induced flushing are poorly understood. One theory relates to a catecholamine surge (likely neural due to timing) and associated b-adrenergic vasodilation. Peripheral hairy skin also possesses b-adrenergic receptors but not in a great enough density to induce erythema in these areas.65 Sudomotor activity to peripheral glabrous skin increases during embarrassment, but less is known about the response in skin blood flow. Validating these observations, mental stress increases peripheral glabrous and hairy skin sympathetic nerve activity.66,67 Mental stress also increases supraorbital-skin sympathetic nerve activity, and this increase is accentuated in those with erythematotelangiectatic rosacea.68

GRAY, METZLER-WILSON, DAWES, WILSON
However, Drummond and Su did not observe differences in an index of forehead-skin blood flow in those with rosacea while performing embarrassing tasks; this is despite those with rosacea reporting greater embarrassment and intensity of blushing compared to controls.48 There may be differences in neural responses to mental stress vs. embarrassing tasks, but it is possible that rosacea symptoms are due in part to supraorbital-nerve overactivity or altered issues of perception.

**Pharmaceutical/Topical**

Certain cosmetics, skin care products, and topical medications applied to the face are classified as moderate rosacea flushing triggers.5 Defining this category's mechanism of action is difficult because of the plethora of potential skin care products, but it most likely results from either skin irritation or an allergic reaction to the product. Sensory afferent nerves sense skin irritation, while the wheal and flare response of a typical allergic reaction involves an axon reflex. It is also possible that these irritations could not only increase skin blood flow but also compromise the skin barrier, leading to increased transepidermal water loss and inflammation. This disrupted and inflamed facial skin barrier in rosacea appears to be involved in the increased susceptibility to contact dermatitis and a more vigorous response to cutaneous irritation.49 Issues associated with rosacea-induced disruption of the facial skin barrier and how this relates to topicals require further research.

**Dietary**

Consumption of alcohol (ethanol) is a major rosacea flushing trigger.5 Alcohol is associated with small amounts of cutaneous vasodilation, especially in the face and periphery.70 The vasodilation effect is thought to be due to the direct effect of ethanol on vascular smooth muscle.71 Facial flushing is pronounced in individuals with aldehyde dehydrogenase inactivation due to a point mutation, but this mutation likely does not account for alcohol's potential trigger effect in most individuals with rosacea.72 It is possible that either individuals with rosacea are more sensitive to cutaneous vasodilation or that the ethanol induces a gustatory flushing response similar to that of hot drinks or spicy foods.

Hot drinks are classified as a moderate rosacea flushing trigger.1 Originally it was thought that the trigger was related to the caffeine in coffee or tea, but more recent investigations identified an oral-cavity heat effect.72 Wilkin suggested that heat draining from the oral cavity into the jugular vein heats carotid-artery blood via a countercurrent system.73 While some heat exchange occurs between vessels, it is more likely that the very warm temperatures (60 °C) cause a reflex vasodilation as occurs in other gustatory reflexes.25 This level of heat stimulates TRPV1 receptors on warm sensory afferents, which could lead to a cranial-nerve reflex response. It is unclear to what extent individuals with rosacea have abnormal gustatory reflexes.

Spicy-food consumption is also classified as a moderate rosacea flushing trigger and may utilize a TRPV1-channel mechanism similar to that of the oral sensation of heat.5 The classic response to spicy products is capsaicin-mediated, although other chemicals that are perceived as spicy could also be involved.74,75 Kashima and Hayashi observed increases in an index of skin blood flow throughout the face with oral capsaicin administration.74 Capsaicin-induced vasodilation occurs via TRPV1-receptor stimulation, which causes flushing through the gustatory parasympathetic vasodilator pathway.10 This reflex response via a cranial nerve is different from acute or chronic topical capsaicin administration5,76. As described previously, the increase in TRPV1-receptor gene expression in erythematotelangiectatic rosacea could provide a potential mechanism whereby rosacea may result in hyperactive gustatory-reflex responses.49

**Physical Exercise**

Physical exercise is another major rosacea flushing trigger.7 On surveys, this concept is often referred to as “carrying and lifting” (resistive exercise) or “walking, running, bicycling” (aerobic exercise). Physical stress increases arousal, which increases skin sympathetic-nerve activity to peripheral glabrous and hairy skin as well as facial areas independent of changes in metabolism.36,61,77-80 The level of effort, but not the amount of muscle mass engaged in the effort, determines the increase in peripheral skin sympathetic-nerve activity in response to resistive exercise.79,81 Exercise task visualization and direct motor-cortex stimulation increase peripheral skin sympathetic-nerve activity, indicating that feedback from the exercising muscle is not needed to increase sympathetic activity.81,84 Individuals with rosacea have augmented supraorbital skin sympathetic-nerve activity to resistive exercise.87 Thus, it is possible that this sympathetic-outflow increase is part of the reason for erythema in these patients. The responses of peripheral skin sympathetic-nerve activity in rosacea are unknown, and thus it is unknown if the augmented responses are limited to the face or reflect a global response.

Aerobic exercise causes an internally generated heat stress. Thus, similar to whole-body heat stress, widespread sympathetically mediated increases in skin blood flow conduct heat to the skin for dissipation. A few caveats associated with aerobic exercise-induced heat stress vs. environmental or passive heat stress: 1) There is an anticipatory or feed-forward aspect of exercise, where peripheral skin sympathetic-nerve activity increases prior to the generation and sensation of heat stress; and 2) internally generated heat (exercise heat stress) can occur more rapidly than passive heat stress.54,65 Further research is needed to determine whether changes in sympathetic or parasympathetic responses are involved.36,61,77-80 While this inflammatory cascade is important, the neural responses to erythema triggers may help to focus future rosacea treatments on mechanistically stopping disease progression earlier and potentially in a more individualized manner by targeting mechanisms of each patient’s specific triggers, allowing rosacea to be better tolerated and controlled.

**Perspectives and Conclusions**

Flushing is a normal facial physiologic process that becomes hyperactive in individuals with rosacea, often resulting in exaggerated responses; over time, persistent erythema, inflammation, and telangiectasia can develop. Highlighting these blood-vessel changes, using capillaroscopy, Rosina and colleagues described increases in vessel diameters, vessel tortuosity, and telangiectasia in rosacea-affected areas.46 Flushing triggers are numerous and individualized but can be grouped into thermal/environmental, social/emotional, pharmaceutical/topical, dietary, and exercise-related items. These erythema triggers begin with neural events such as sympathetic nervous system, cranial nerve, axon reflex, or sensory afferent responses. The nervous system, in addition to affecting inflammation, both directly and indirectly controls blood-vessel diameter and thus blood flow. The facial vasculature is innervated by post-synaptic sympathetic fibers and cranial nerves and is affected by axon reflexes, sensory nerves, and locally released paracrine substances. Because ganglionic blockade, intradermal botulinum toxin A, and adrenergic blockade have been reported to reduce flushing, potential roles for the sympathetic nervous system are implicated.15,30,11,37-49 Individuals with rosacea appear to have overactive supraorbital sympathetic responses to mental and physical stress, which further implicates this mechanism. Cranial nerves participate in cutaneous vasodilation via such responses as axon and gustatory reflexes.47 Individuals with rosacea may also have altered facial axon reflexes, which could contribute to these augmented reflex responses.46 When activated, sensory nerves release local vasodilator agents (e.g., CGRP and ATP) and can stimulate keratinocytes, sweat glands, and mast cells, releasing substances such as prostaglandins, bradykinin, and histamine.

Prostaglandins, bradykinin, and histamine are potent vasodilators, increase vascular permeability, and produce edema. Although still unknown, it is possible that individuals with rosacea release more of these or are sensitized to inflammatory substances. The current understanding of the pathophysiology of rosacea, including the inflammatory cascade involving TLR2 and serine protease KLK5 expression and abnormal forms of cathelicidin peptides (LL-37 and FA-29), is described in detail elsewhere.3,42,50 While this inflammatory cascade is important, the neural events initiate these processes. Over time, these erythema triggers can also lead to structural and functional adaptations that characterize the disease. Understanding these neural links and physiological responses to erythema triggers may help to focus future rosacea treatments on mechanismistically stopping disease progression earlier and potentially in a more individualized manner by targeting mechanisms of each patient’s specific triggers, allowing rosacea to be better tolerated and controlled.

**Acknowledgements**

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Adult-onset Multisystemic Langerhans Cell Histiocytosis: A Case Presentation and Discussion

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Abstract
Langerhans cell histiocytosis (LCH) is a rare, systemic disease characterized by the clonal proliferation and infiltration of CD207-positive (Langerin) dendritic cells in various organ systems.1 Historically, LCH has been classified into several categories based on clinical presentation, including Letterer-Siwe disease, Hand-Schüller-Christian syndrome, eosinophilic granuloma, and Hashimoto-Pritzker disease. The current understanding, however, describes these entities merely as possible presentations on the spectrum of the LCH disease process.2

The etiology of LCH is incompletely understood. While the pathologic Langerhans cells in LCH are known to be clonal, there has long been a debate in the literature regarding whether LCH is a neoplastic or a reactive proliferation. However, the recent discovery in 2010 of oncogenic BRAF-V600E mutations in 57% of archived LCH specimens lends support to the idea that LCH may in fact be a neoplastic process and may respond to antineoplastic therapy such as BRAF-pathway inhibitors.3

Due to the rarity of the disease, much that is known about LCH is a result of individualized case studies. More commonly recognized in the pediatric population, LCH affects children at a rate of one in 200,000, usually occurring between 1 and 3 years of age.4 In adults, the incidence is roughly one to two cases per million, predominantly affecting those between the ages of 20 and 35 years.5 Here, we present a rare case of LCH presenting in a patient well outside the typical age of onset.

Case Presentation
A 60-year-old Caucasian male presented to the dermatology clinic with a chief complaint of a pruritic, mildly tender scalp along with scaling and scabbing of 10 years' duration. During that time, he had been evaluated by several physicians, including dermatologists, with diagnoses ranging from eczema and seborrheic dermatitis to folliculitis and alopecia.

Previous treatments had included use of clobetasol shampoo, oral minocycline, and betamethasone valerate cream off and on for over many years, none of which had resulted in long-term relief of scalp changes. Past medical history was significant for long-standing central diabetes insipidus, type-II diabetes mellitus, hypertension, hyperlipidemia, low testosterone, iatrogenic hypothyroidism secondary to papillary carcinoma of the thyroid, anti-mitochondrial antibody (AMA)-negative primary biliary cirrhosis, and primary sclerosing cholangitis. Of note, the patient denied any history of smoking or pulmonary symptoms.

Physical exam showed multiple scattered, crusted papules and several vesicles over a nearly confluent erythematous, scaly base distributed diffusely over the scalp; there was also evidence of some follicular dropout and alopecia (Figure 1). Due to the progressive and prolonged nature of his disease as well as its refractoriness to prior treatments, two 4-mm punch biopsies of the left and right parietal regions were obtained. Differential diagnosis at the time included folliculitis decalvans and another cicatricial alopecia.

Both biopsies revealed a neoplastic, folliculocentric, extensive Langerhans cell infiltrate diagnostic of Langerhans cell histiocytosis (Figures 2, 3). Extensive positivity for Langerin (CD-207), staining for CD-31, and lack of immunoreactivity for CD-31, and CD-83 further confirmed the diagnosis.

Multisystemic Work-up
In light of the patient's history of central diabetes insipidus and hepatobiliary disease, we suspected multisystemic LCH. Systemic work-up revealed normal CBC and CMP with the...
exception of known and chronically elevated alkaline phosphatase and transaminases. A chest radiograph concerning for bibasilar changes prompted a high-resolution chest CT without contrast to be ordered. This revealed severe coalescing fibrotic and cystic lung disease in bilateral lower lobes with mild centrilobular emphysema and bilateral upper-lobar pulmonary fibrosis. Tiny calcified and uncalcified nodules were also noted throughout. A skeletal radiographic survey showed several tiny punctate luencies scattered in the right and left humeral heads as well as the humeral shafts. As these findings were consistent with multisystemic Langerhans cell histiocytosis with involvement of high-risk organs, the patient was referred to the Mayo Clinic in Scottsdale, Arizona for further evaluation and treatment. There, a follow-up bone-marrow biopsy and PET scan were not found to be consistent with hematologic malignancy.

**Treatment**

For scalp symptoms, the patient was prescribed 0.05% clobetasol spray and instructed to use it twice daily. After one month, he reported significant improvement in symptoms (Figure 4). However, seven months after initial presentation the patient presented with new, scattered erythematous papules on bilateral cheeks and jawline; these were biopsied and found to be consistent with LCH (Figure 5). It is interesting and gratifying to note that despite the above multisystemic findings, the patient insists he feels healthy and is not experiencing any shortness of breath, bone pain, or a lessened quality of life other than his skin complaints. However, due to the severe findings on imaging and persistent skin lesions, the patient was initiated on a regimen of methotrexate at Mayo Clinic, Scottsdale, where treatment is ongoing.

**Discussion**

In order to better classify LCH, the Histiocyte Society stratifies disease based on the number of organ systems involved (single-system versus multi-system) and whether or not disease activity is unifocal or multifocal in each organ system (Table 1). They also classify disease based on involvement of high-risk organs, defined as the hematopoietic system, liver, spleen, and lungs.

Once a biopsy-proven diagnosis of cutaneous LCH is made, investigation into multisystemic manifestations is of utmost importance to determine prognosis and guide treatment. Guidelines for diagnosis and treatment are well established for the pediatric population; however, the approach to management for adult patients is less well defined. In 2009, the Histiocyte Society published guidelines for recommended baseline laboratory and radiographic evaluation (Table 2). This proposed work-up investigates the hematopoietic system, liver, bone, lung, and endocrine system.

While Langerhans cell histiocytosis can affect any organ system, the skin is often the first identifiable manifestation of disease. In adults, cutaneous involvement is extremely variable in presentation. Lesions may present as small papules, pustules, and/or vesicles with accompanying yellow crust and erythema; these classically occur in intertriginous areas or, as with our patient, on the scalp. On examination, the cutaneous manifestations can be easily mistaken for common dermatologic conditions such as eczema, seborrheic dermatitis,

### Table 1. Clinical Classification of LCH

<table>
<thead>
<tr>
<th>Type</th>
<th>Involvement</th>
</tr>
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<tbody>
<tr>
<td>Single-system LCH</td>
<td>Bone: unifocal (single bone) or multifocal (&gt;1 bone)</td>
</tr>
<tr>
<td>(one organ/system involved, uni-or multifocal)</td>
<td>Skin</td>
</tr>
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<td></td>
<td>Lymph node (not the draining lymph node of another LCH lesion)</td>
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<tr>
<td></td>
<td>Lungs</td>
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<td></td>
<td>Hypothalamic-pituitary/central nervous system</td>
</tr>
<tr>
<td>Multisystem LCH</td>
<td>With or without involvement of “risk organs” (hematopoietic, liver, spleen, lung)</td>
</tr>
<tr>
<td>(two or more organs/systems involved)</td>
<td></td>
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</tbody>
</table>

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### Table 2: Recommended baseline evaluation upon diagnosis/reactivation of LCH

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
</tr>
<tr>
<td>Hemoglobin, white-blood-cell and differential count, platelet count</td>
</tr>
<tr>
<td>Blood chemistry</td>
</tr>
<tr>
<td>Total protein, albumin, bilirubin, ALT, AST, alkaline phosphatase, GGT</td>
</tr>
<tr>
<td>BUN, creatinine, electrolytes</td>
</tr>
<tr>
<td>Ferritin</td>
</tr>
<tr>
<td>Coagulation studies</td>
</tr>
<tr>
<td>INR/PT, APTT/PTT, fibrinogen</td>
</tr>
<tr>
<td>Early-morning urine sample</td>
</tr>
<tr>
<td>Specific gravity and osmolality</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
</tr>
<tr>
<td>Size and structure of liver and spleen</td>
</tr>
<tr>
<td>Chest radiograph (CXR)</td>
</tr>
<tr>
<td>Skeletal radiograph survey*</td>
</tr>
</tbody>
</table>

*Functional imaging such as bone scan is optional and can be performed in addition to skeletal survey. PET scan has proven to be the most sensitive functional test used in the identification of LCH lesions and in evaluating patient response to therapy. However, PET scan is currently expensive and not widely available.
dermatophytosis, and folliculitis. This mimicry, coupled with the rarity of adult LCH, often leads to a delay in biopsy and diagnosis. Central diabetes insipidus (DI) is the most common endocrine manifestation of LCH and is caused by Langerhans cells infiltrating the posterior pituitary. A retrospective analysis by Arico et al. reported DI to occur in 29.6% of patients; however, incidence as high as 40% in adult patients has been reported. Magnetic resonance imaging (MRI) is the most sensitive diagnostic tool for LCH-associated DI and will often show thickening of the pituitary stalk with “loss of bright spot,” which corresponds to loss of anti-diuretic hormone (ADH)-containing granules. Once this infiltration occurs, it results in the irreversible sequelae of central DI, and patients must receive lifelong supplementation with desmopressin acetate. Diabetes insipidus patients must receive lifelong supplementation in the irreversible sequelae of central DI, and portal hypertension. Bile-duct destruction and can lead to sclerosing cholangitis, biliary cirrhosis, and subsequent portal hypertension.

In adults, pulmonary LCH is more commonly seen as an isolated disease rather than a manifestation of multisystemic LCH, and it is strongly associated with smoking. When the lungs are affected in adult multisystemic LCH, as in our patient, the disease is classified as high-risk. The pathogenesis of pulmonary LCH is thought to be the infiltration and excessive activation of Langerhans cells in the lung parenchyma. While definitive diagnosis cannot be established without a biopsy demonstrating these abnormal Langerhans cells, imaging modalities can be highly suggestive of disease in the proper clinical context. Presence of nodules, cystic changes, and honeycombng on high-resolution CT are signs of advanced disease and increase the risk of pneumothorax, which occurs in up to 15% of patients. Dyspnea and a non-productive cough may also occur; however, as in our case, many patients may be asymptomatic, making imaging and subsequent pulmonary-function testing vital for patient diagnosis and monitoring.

As exemplified in our case, hepatobiliary and splenic involvement in Langerhans cell histiocytosis is not uncommon, occurring in up to 20% of patients. As Langerhans cells progressively infiltrate these organs, they cause bile-duct destruction and can lead to sclerosing cholangitis, biliary cirrhosis, and subsequent portal hypertension. Therefore, a metabolic panel with work-up of any abnormalities is always warranted in this patient population. Treatment for adult LCH is variable and depends largely on the extent of disease and its impact on the patient’s quality of life. Typically, patients with skin-limited disease will respond to high-potency topical steroids and require no further treatment. However, in patients with multisystemic disease, approach considerations may include a combination of systemic steroids along with a single-agent chemotherapeutic -- either vincristine or vinblastine. For these patients, response during the six-week induction phase with these therapies has been shown to be the single most important long-term prognostic indicator.

Conclusion
Adult multisystemic Langerhans cell histiocytosis is a rare, though likely under-recognized, disease that requires a high index of clinical suspicion to diagnose. LCH should be considered in adults with refractory lesions on the scalp. Once diagnosed, it requires an appropriate multisystem work-up both for risk stratification and to guide subsequent therapeutic decision-making. While patients often first present to the dermatologist, adults with multisystemic LCH require a multidisciplinary approach to manage disease manifestations and guide treatment.

References

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A Rare Case of Unilesional Follicular and Syringotropic Mycosis Fungoides: A Case Report and Review of the Literature

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Abstract

Mycosis fungoides (MF) is the most common cutaneous lymphoma. It has three newly classified variations, one of which is follicular mycosis fungoides. Follicular mycosis fungoides (FMF) can further be divided into the rare variants unilesional follicular mycosis fungoides and syringotropic mycosis fungoides. We present a case with overlapping unilesional follicular mycosis fungoides and syringotropic mycosis fungoides. These rare variants can often appear clinically as benign inflammatory skin conditions and are frequently misdiagnosed for years. Close follow-up with repeated biopsies can lead to a diagnosis as the disease progresses. The disease has a poor prognosis compared to similar-staged diseases of classic mycosis fungoides. This is attributed to the location of the pathology, deep in the dermis and subcutaneous tissue, which requires more aggressive treatments to reach the depth of the disease.

Introduction

Mycosis fungoides (MF) is the most common cutaneous lymphoma, estimated to occur in approximately 0.55 per 100,000 person-years.1 This cutaneous T-cell lymphoma (CTCL) is characterized by a T-cell lymphocytic infiltrate in the papillary dermis, the presence of atypical lymphocytes with cerebriform nuclei, and evidence of epidermotropism.2 MF has multiple variants presenting with different clinical and vastly different histologic presentations. The etiology of MF is unclear, with infectious, occupational, and genetic mutations presenting possible causes.1,3 It has been noted to be a challenging diagnosis histologically, as there can be a significant overlap between MF and benign inflammatory conditions.1,4 Many of the clinical and histopathological features of MF can be absent in early disease, often causing a delay of diagnosis and treatment.1 While multiple clinical and histological variants have been described over the years, MF has recently been divided into three variants. The World Health Organization and World Health Organization for Research and Treatment of Cancer held consensus meetings in 2003 and 2004 to align the classifications of cutaneous lymphomas by resolving controversy over definitions and terminology between the two organizations.3

MF variants reclassified during the meeting include the most common Alibert-Bazin type and three variants including folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin.2 Folliculotropic mycosis fungoides (FMF) is characterized by the presence of medium to large, hyperchromatic T-cell infiltrates within the follicular epithidium known as folliculotropism. The disease most often spares the epidermis of the surrounding skin. While classic MF is often reported with follicular manifestations representing follicular mucinosis, FMF reveals involvement of the hair follicles and eccrine glands by lymphoma cells.1,5,6 Clinically, the lymphoma is most commonly found on the head and neck.1 Patients often present with acneiform lesions, indurated plaques, or follicular-centered papules, with occasional tumors. Most often, patients can be found with multiple plaques throughout the body. There have been few published cases of FMF to date.8 Infiltrated plaques of the eyebrows with alopecia are common and highly characteristic findings with severe pruritus.1,9 In multiple cases, infiltration of the eccrine sweat glands is also present.1 Further classifications exist within each variant, including rare forms of unilesional FMF and syringotropic MF.5,9 Unilesional FMF is characterized by a single area of involvement of less than 5% body surface area. Syringotropic MF is characterized by prominent involvement of the eccrine glands with syringolymphoid hyperplasia.9 There is significant overlap between folliculotropic and syringotropic MF, causing difficulty for clinicians as the two have shown variations in prognosis (Table 1).9,10 We report a complicated case of unilesional follicular and syringotropic MF.

Table 1. Comparison of overall 5-year and 10-year survival rates1,2,4,18

<table>
<thead>
<tr>
<th>Classification</th>
<th>Overall survival rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 year</td>
</tr>
<tr>
<td>Mycosis fungoides (MF)*</td>
<td></td>
</tr>
<tr>
<td>Folliculotropic mycosis fungoides (FMF)</td>
<td>62-68</td>
</tr>
<tr>
<td>Syringotropic mycosis fungoides (SMF)</td>
<td>100</td>
</tr>
</tbody>
</table>

*Limited patch/plaque stage

Case Report

A 45-year-old Caucasian male presented to our office for a second opinion of a localized, indurated plaque over the right eyebrow with alopecia (Figure 1). The patient had no significant past medical or family history. The lesion started four months prior as a pimple with symptoms of itching and burning. The lesion progressed over the next two months into a firm plaque with alopecia. No lymphadenopathy or further plaques were noted on physical exam.

The lesion was biopsied prior to presenting at our office and read as follicular mucinosis. Prominent adnexal involvement within the follicular epithelium was noted. Superficial and deep perivascular infiltrates were also present. Follicular mucin was noted within the follicular epithelium, as well as prominent eosinophils. No significant lymphoid atypia was noted at that time. The patient was informed that the T-cell dyscrasia had the potential to be attributed to benign as well as malignant causes.

The patient presented to our office, and two further biopsies were performed. The patient's lab work showed a mild leukocytosis with all other labs within normal limits. The patient was started on clobetasol 0.05% cream twice a day after the initial visit. The slides (Figures 2, 3, 4) were reviewed by multiple dermatopathologists as well as a dermatopathologist specializing in cutaneous lymphomas. A marked atypical, cerebriform, lymphocytic infiltrate was noted surrounding as well as permeating the hair follicles. Eccrine ducts and glands were also affected, with sparing...
of the surrounding epidermis. Close examination of the infiltrate demonstrated marked nuclear irregularity with hyperchromasia. An admixture of histiocytes and eosinophils were present. The lymphocytic infiltrate was also present in the intrafollicular dermis and subcutaneous fat. An Alcian blue stain confirmed the presence of mucin within the hair follicles. The findings were suspicious for incipient tumor-stage development.

Phenotypic studies were performed, demonstrating a T-cell infiltrate represented by an almost exclusive CD4+, CD8+, CD7- phenotype. This pattern is characteristic of FMF as well as MF. Other positive T-cell markers included CD3 and CD5. A CD68+ marker representing macrophages was also present. PD-1 was negative and most often found in small/medium-sized (pleomorphic) T-cell infiltrates. PD-L1 was negative and most often found in small/medium-sized (pleomorphic) T-cell infiltrates. CD4/8 ratio was noted to have an absence of CD8 within the hair follicles and eccrine glands. However, an admixture of CD8 lymphocytes was noted within the intrafollicular dermis, adnexal dermis, and subcutaneous fat. Gene rearrangement studies were negative for both the biopsy specimen and peripheral blood.

Considering the extent of lymphoid atypia, degree of lymphocytic infiltration of the dermis and subcutaneous tissue, and the abnormal phenotypic profile, the patient was diagnosed with unilesional follicular and syringotropic mycosis fungoides. He was referred to a tertiary clinic that specializes in cutaneous lymphomas for treatment. The lesion had slightly decreased with topical clobetasol 0.05% cream. The patient was continued on clobetasol twice daily on Tuesday, Thursday, Saturday and Sunday. He was also instructed to apply bexarotene 1% gel, a retinoid, on Monday, Wednesday, and Friday mornings. This was paired with clobetasol in the evenings. For treatment, the lesion had no further progression, but the plaque persisted. The site was again biopsied, demonstrating persistence of the follicular and eccrine involvement. The patient was then referred for radiotherapy with follow-up pending.

Discussion

Our patient presents a rare case of unilesional follicular and syringotropic mycosis fungoides. The diagnosis of FMF or SMF can be very difficult, often requiring multiple biopsies over time. The clinical and histopathological presentation is often mistaken for follicular mucinosis (FM). Some debate exists on whether FM represents a precursor to FMF or a benign variant of MF with a non-aggressive clinical course. It should be noted that follicular mucinosis in younger patients most often is characterized by spontaneous regression after two months to two years, without any further progression to MF. Cerroni attempted to review the clinical and histopathological differences between FM and malignant FMF. He noted that despite looking at the age of the patient, location of lesions, number of lesions, amount of mucin deposited within the follicles, as well as gene rearrangement studies, significant overlap exists between the two disease states. This leads most often to delays in diagnosis averaging two to five years. Early diagnosis is important considering the poor five-year overall survival rate of 62%. The overlap between FM and FMF shows the importance of close follow-up and the need for multiple biopsies for persistent and changing lesions not responding to conventional treatments.

The histology of our patient’s lesion also demonstrated prominent involvement of the eccrine-duct epithelium, known as syringotropic involvement. SMF is described as atypical lymphocytes surrounding the eccrine ducts and glands and infiltrating the eccrine epithelium, with associated syringolymphoid hyperplasia. Some authors consider SMF and FMF to be closely related, but with separate disease processes. Other authors believe it to be a variation or progression of the same disease process. The current WHO-EORTC guidelines place SMF and FMF in the same group as a single variant of MF. Many articles describe FMF also affecting the eccrine ducts and cases of SMF demonstrating follicular involvement. Our case demonstrates an overlap of FMF with SMF.

FMF has multiple differences from MF, including head and neck involvement, which is typically spared in MF and often SMF. The pathogenesis and cause of accumulating lymphocytes within and around the follicular epithelium and eccrine glands, and sparing of the surrounding epidermis, is poorly understood. However, multiple studies have noted an increased expression of ICAM-1 within follicular keratinocytes, which is thought to be induced by neoplastic T lymphocytes. This is hypothesized to lead to the obstruction of follicular orifices by neoplastic T-cells. Pereyo explains the relationship of FMF to MF as one similar to that of lichen planopilaris to lichen plans. The immunohistochemical analysis of FMF and MF are similar, most commonly demonstrating a CD4+ T-cell dyscrasia with a common loss of CD7 and often clonal T-cell gene rearrangements. However, T-cell gene rearrangements can be conflicting, as they can be negative in many malignant cases and positive in benign conditions such as spongiotic dermatitis, further confusing the diagnosis. A few studies have required positive monoclonal gene rearrangements to make the diagnosis of FMF. Cerroni demonstrated that monoclonal gene rearrangements were noted in six out of 11 cases of idiopathic FM and only nine out of 19 cases of lymphoma-associated FM. This shows that gene rearrangements, although helpful if found, cannot be heavily relied upon to make the diagnosis.

FMF was reclassified as a separate entity from MF due to its distinctive clinical and histological features, as well as its worse prognosis and resistance to standard treatments. Fewer than 10% of patients with classic MF will progress to more advanced stages, and less than one third of those patients will develop extracutaneous disease with disease-related death in the first 10 years after diagnosis. Most FMF patients are clinically classified as stage IA or IB; however, they demonstrate worse five- and 10-year survival rates, more similar to survival rates of patients with tumor-stage MF. Multiple studies have noted disease-specific survival rates at five years and 10 years averaging 68% and 26%, respectively (Table 1). Many studies stress the importance of close follow-up and the need for multiple biopsies for persistent and changing lesions not responding to conventional treatments.
of treating all FMF patients as tumor-stage regardless of the clinical appearance.18 This demonstrates the need for early diagnosis with more aggressive treatments.17

Effective treatment options for FMF vary compared to classic MF, which often responds to phototherapy (PUVA) and topical creams including mechlorethamine, nitrogen mustard, retinoids and steroids.5,14 Although no standard treatment exists, many case reports have demonstrated the ineffectiveness of these more superficial treatments.14,15 It is thought that deep follicular involvement allows the disease to persist beyond their reach. Common, more aggressive treatments with beneficial results include radiotherapy for localized lesions and total–skin electron-beam therapy (TSEBT) for diffuse lesions, leading many to claim them as the treatment of choice.16,17,19

Conclusion
Our case demonstrates a rare presentation of MF with unilesional follicular and syringotropic mycosis fungoides. Debate continues regarding whether FMF and SMF are distinct entities or variations of the same disease process. Our patient had prominent, marked follicular involvement as well as eccrine–duct involvement with syringohyperplasia. As noted, FMF has a worse prognosis compared to classic MF. This is in contrast to SMF, which has a prognosis similar to early-stage classic MF.10 Both FMF and SMF have higher fail and recurrence rates with topical and superficial treatments, as was noted in this case. The case demonstrates the importance of follow-up in patients presenting with plaques or rashes consistent with benign inflammatory conditions that fail to respond to conventional treatments. Oftentimes, these processes can represent early stages of MF, requiring repeated biopsies with further cytological and serum testing in order to make the diagnosis. Most cases with unilesional plaques are associated with an indolent course; however, our case demonstrates that rarely they can be due to more aggressive forms such as FMF, requiring aggressive treatments. Further studies and case reports are required to better classify the differences and similarities between FMF and SMF.

References
Secukinumab is currently the only FDA approved biologic that acts by inhibiting the interleukin (IL)-17 cytokine. IL-17 is a proinflammatory cytokine that has been detected in psoriatic lesions and is strongly implicated in psoriasis pathogenesis. It is a downstream product of interleukin-23, which is targeted by another currently approved biologic, ustekinumab. In particular, IL-17A, one of the six homodimers of IL-17, is considered the most important in this family for psoriasis development. Secukinumab is a fully human monoclonal IgG1 antibody that specifically binds to and inhibits IL-17A, which normally acts on keratinocytes to promote changes culminating in the clinical manifestation of psoriasis. Additionally, IL-17 plays a role in the recruitment and activation of neutrophils, the blockade of neutrophil apoptosis, and the stimulation of psoriasis angiogenesis.

In addition to treating psoriasis, secukinumab is currently under investigation for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, Crohn’s disease, and non-infectious uveitis. The purpose of this article is to review the five phase III studies for secukinumab. Two clinical trials assessed the clinical response to secukinumab, with co-primary end points of at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) and scores of 0 (clear) or 1 (almost-clear) based on a five-point investigator’s global assessment (IGA) by week 12 of treatment. IGA is a tool used by clinicians to document their impression of disease severity, with scores ranging from 0 (clear) to 4 (severe disease). An additional phase III trial compared secukinumab to ustekinumab in a head-to-head study, with a primary end point of PASI 90 at week 16.

Methods

We reviewed the published phase III clinical trial results involving the clinical efficacy of secukinumab. An English language literature search was carried out on PubMed with the following word combinations: “secukinumab” and “psoriasis” or “IL-17” and “psoriasis.” Citations within these publications were also reviewed for pertinent data. Additionally, information on these topics was collected from oral presentations from the 73rd Annual Meeting of the American Academy of Dermatology.

Results

Two major clinical trials were conducted to investigate efficacy and safety of different doses of secukinumab. The first study compared secukinumab against placebo, and the other against placebo and etanercept. In addition, two minor studies evaluated the efficacy of two different delivery methods of the medication. Another study directly compared secukinumab to ustekinumab with a head-to-head design.

ERASURE

Study design. In this clinical trial, a total of 737 patients were randomized in a 1:1:1 ratio to either secukinumab 300 mg, secukinumab 150 mg, or placebo. The two co-primary endpoints were achievement of PASI 75 and IGA 0 or 1 at week 12. Patients who received secukinumab 300 mg and 150 mg were followed for another 40 weeks of maintenance. Those assigned to secukinumab received dosages at baseline, and then weekly for four weeks, followed by every four weeks for the remainder of the study.

Efficacy. By week 12, significantly higher percentages of those in both secukinumab 300 mg and secukinumab 150 mg groups achieved PASI 75 (81.6% and 71.6%, respectively) and IGA 0 or 1 (65.3% and 51.2%, respectively) than those who took placebo, of whom 4.5% reached PASI 75 and 2.4% reached IGA 0 or 1 (P<0.001). Additionally, greater efficacy was demonstrated with 300 mg than with 150 mg. Similar patterns were also noted for PASI 90 during the maintenance period and improvements of QoL, as assessed by the Dermatology Life Quality Index (P<0.001) (Table 1).

Adverse events. There was an overall higher incidence of adverse events with the secukinumab 300 mg and 150 mg groups than with placebo (55.1%, 60.4%, and 47.0%, respectively). Infections were more prevalent with the secukinumab 300 mg and 150 mg groups versus placebo (29.4%, 26.9%, and 16.2%, respectively). The most common adverse events were nasopharyngitis, headache, and upper respiratory tract infection. The clinical presentations and rates of serious adverse events were similar with secukinumab 300 mg, 150 mg, and placebo (6.3/100, 6.4/100 and 7.4/100, respectively, in patient-years).

FIXTURE

Study design. A total of 1,305 patients were randomized in a 1:1:1:1 ratio to either secukinumab 300 mg, secukinumab 150 mg, etanercept 50 mg, or placebo. This clinical trial evaluated secukinumab against placebo with co-primary endpoints of PASI 75 and IGA 0 or 1 at week 12. Those assigned to secukinumab received dosages at baseline, and then weekly for four weeks, followed by every four weeks for the remainder of the study; etanercept was
administered twice at baseline, twice a week until week 12, and then weekly through week 51.

**Efficacy.** By week 12, the percentages of patients taking secukinumab 300 mg and 150 mg that achieved PASI 75 (77.1% and 67.0%, respectively) and IGA 0 or 1 (62.5% and 51.1%, respectively) were greater than with placebo (4.9% reached PASI 75 and 2.8% reached IGA 0 or 1) (P<0.001). Secukinumab at 300 mg produced superior results compared to 150 mg (P<0.001). Additionally, secukinumab 300 mg showed superiority over etanercept for the percentage of patients achieving PASI 75 (77.1% and 44.0%, respectively) and PASI 90 (54.2% and 20.7%, respectively) (**Figure 1**).

**Adverse events.** Overall, the incidence of adverse events was similar among secukinumab 300 mg and 150 mg and etanercept during induction (55.5%, 58.4%, and 57.6%, respectively), and was higher than placebo (49.8%). However, statistical analysis for significance was not performed. The most common adverse events with secukinumab were nasopharyngitis, headache and diarrhea. Infections were noted for secukinumab 300 mg and 150 mg, etanercept and placebo as follows: 26.7%, 30.9%, 24.5% and 19.3%, respectively. While more patients with secukinumab (33 out

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**Table 1. Primary and secondary end points in ERASURE, FIXTURE, FEATURE, and JUNCTURE***

<table>
<thead>
<tr>
<th>End Point (category)</th>
<th>STUDY</th>
<th>Secukinumab 300 mg</th>
<th>Secukinumab 150 mg</th>
<th>Placebo</th>
<th>Etanercept 50 mg**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PASI 75</strong>&lt;br&gt;Week 12 (1°)</td>
<td>ERASURE</td>
<td>81.6% (200/245)</td>
<td>71.6% (174/243)</td>
<td>4.5% (11/246)</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>FIXTURE</td>
<td>77.1% (249/323)</td>
<td>67.0% (219/327)</td>
<td>4.9% (16/324)</td>
<td>44.0% (142/323)</td>
</tr>
<tr>
<td></td>
<td>FEATURE</td>
<td>75.9% (44/58)</td>
<td>69.5% (41/59)</td>
<td>0% (0/59)</td>
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</tr>
<tr>
<td></td>
<td>JUNCTURE</td>
<td>86.7% (52/60)</td>
<td>71.7% (43/60)</td>
<td>3.3% (2/61)</td>
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</tr>
<tr>
<td>**IGA 0 or 1 Week 12 (1°)</td>
<td>ERASURE</td>
<td>65.3% (160/245)</td>
<td>51.2% (125/244)</td>
<td>2.4% (6/246)</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>FIXTURE</td>
<td>62.5% (202/323)</td>
<td>51.1% (167/327)</td>
<td>2.8% (9/324)</td>
<td>27.2% (88/323)</td>
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<tr>
<td></td>
<td>FEATURE</td>
<td>69.0% (40/58)</td>
<td>52.5% (31/59)</td>
<td>0% (0/59)</td>
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<tr>
<td></td>
<td>JUNCTURE</td>
<td>73.3% (44/60)</td>
<td>53.3% (32/60)</td>
<td>0% (0/61)</td>
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<tr>
<td><strong>PASI 90</strong>&lt;br&gt;Week 12 (2°)</td>
<td>ERASURE</td>
<td>59.2% (145/245)</td>
<td>39.1% (95/243)</td>
<td>1.2% (3/246)</td>
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<td>FIXTURE</td>
<td>54.2% (175/323)</td>
<td>41.9% (137/327)</td>
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<td>60.3% (35/58)</td>
<td>45.8% (27/59)</td>
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</tr>
<tr>
<td></td>
<td>JUNCTURE</td>
<td>55% (33/60)</td>
<td>40% (24/60)</td>
<td>0% (0/61)</td>
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</tr>
<tr>
<td><strong>PASI 75</strong>&lt;br&gt;Weeks 12-52 (2°)</td>
<td>ERASURE</td>
<td>80.5% (161/200)</td>
<td>72.4% (126/174)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>FIXTURE</td>
<td>84.3% (210/249)</td>
<td>82.2% (180/219)</td>
<td>--</td>
<td>72.5% (103/142)</td>
</tr>
<tr>
<td></td>
<td>FEATURE</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td>JUNCTURE</td>
<td>--</td>
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</tr>
<tr>
<td><strong>DLQI Absolute Change</strong>&lt;br&gt;(2°)</td>
<td>ERASURE</td>
<td>-11.4</td>
<td>-10.1</td>
<td>-1.1</td>
<td>--</td>
</tr>
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<td>FIXTURE</td>
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<td>-9.7</td>
<td>-1.9</td>
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<tr>
<td></td>
<td>JUNCTURE</td>
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</tr>
</tbody>
</table>

*These studies were not conducted head-to-head. Studies had P<0.001 for ERASURE and FIXTURE and P<0.0001 for FEATURE and JUNCTURE. **PASI 75 and IGA data for etanercept are considered secondary end points but are included for comparison.

PASI: Psoriasis Area and Severity Index; values indicate percentage improvement of cutaneous symptoms.
IGA: Investigator’s global assessment.
DLQI: Dermatology Life Quality Index; an absolute decrease notes an improved individual assessment of a disease’s impact on life.

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Figure 1. Percentages of patients achieving PASI 75, IGA 0 or 1, and PASI 90 at week 12. P<0.001 for all comparisons. Studies were not conducted in a head-to-head manner.
of 946) over etanercept (4 out of 333) developed candida infections, none of those associated with secukinumab were classified as “severe,” while two cases associated with etanercept were classified as “severe.” Nine patients in both secukinumab groups were determined to have Grade 3 neutropenia without associated infection, while one patient on etanercept was diagnosed with Grade 4 neutropenia. Serious adverse events associated with etanercept were classified as “severe,” while two cases of candida infections, none of those associated with secukinumab, were classified as “severe,” while two cases associated with etanercept were classified as “severe.”

**FEATURE and JUNCTURE**

**Study design.** In the first study, 177 patients were randomized 1:1:1 to secukinumab 300 mg, secukinumab 150 mg, or placebo. Medication administration was carried out using a pre-filled syringe (FEATURE). In a second study, 182 patients were randomized 1:1:1 to the same groups, but medication was administered by autoinjector/pen (JUNCTURE). Primary end points were again achievement of PASI 75 and IGA 0 or 1 among the three groups, whereas secondary end points included medication-administration dynamics.

**Efficacy.** Efficacies of the three treatment groups were similar to former studies, despite small sample sizes (Table 1). Both the pre-filled syringe and autoinjector/pen delivery methods were shown to be successfully learned and employed by the first week of use (Table 1).

### Table 2. Primary and secondary end points of secukinumab vs. ustekinumab phase III head-to-head study*

<table>
<thead>
<tr>
<th>End Point (category)</th>
<th>Secukinumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 90 at Week 16 (1*)</td>
<td>79.0% (264/334)</td>
<td>57.6% (193/335)</td>
</tr>
<tr>
<td>PASI 100 at Week 16 (2*)</td>
<td>44.3% (148/334)</td>
<td>28.4% (95/335)</td>
</tr>
<tr>
<td>PASI 75 at Week 4 (2*)</td>
<td>50.0% (167/334)</td>
<td>20.6% (69/335)</td>
</tr>
</tbody>
</table>

*P<0.0001 for all comparisons. PASI values indicate percent improvement of cutaneous lesions.

**Figure 2.** Percentages of patients achieving PASI 90 and 100 at week 16 and PASI 75 at week 4. *P<0.0001 for all comparisons. Dosage of ustekinumab depended on a patient’s body weight: Patients <100 kg (220 lbs) received 45 mg, whereas patients >100 kg (220 lbs) received 90 mg.

**Adverse events.** Nasopharyngitis was a common adverse event. There were no new safety concerns of note that deviated from the former major studies.28,30

**Head-to-face Against Ustekinumab**

**Study design.** In this head-to-face phase III trial, 676 patients were randomized 1:1 to either secukinumab 300 mg or to either 45 mg or 90 mg of ustekinumab, depending on their weight. In line with FDA dosage guidelines, ustekinumab dosing was based on each patient’s weight such that patients weighing <100 kg (220 lbs) received 45 mg, and patients weighing ≥100 kg (220 lbs) received 90 mg at each appropriate visit. Secukinumab was administered once at baseline and then weekly at weeks 1, 2, 3, and 4, and then every four weeks through week 48. Ustekinumab was also administered at baseline, then at weeks 4, 16, 28, and 40. The primary end point for this study was achievement of PASI 90 at week 16. Secondary end points included PASI 100 at week 16 and PASI 75 at week 4.

**Efficacy.** Of 334 secukinumab and 335 ustekinumab patients evaluated, 79.0% and 57.6%, respectively, reached PASI 90 at week 16. Secukinumab was shown to be superior to ustekinumab in all secondary end points, including: PASI 100 at week 16 (44.3% and 28.4%, respectively), PASI 75 at week 4 (50.0% and 20.6%, respectively), and PASI 75 and IGA 0 or 1 at week 16 (Table 2, Figure 2).

**Adverse events.** There were no new substantial safety findings that deviated from other major phase III clinical trials. Total incidents of adverse events were similar for secukinumab and ustekinumab, 64.2% and 58.3%, respectively, and infection rates were 29.3% and 25.3%, respectively. Both groups were notable for 3% serious adverse events. Headache, nasopharyngitis, diarrhea, arthralgia, and fatigue were the most common events for both groups.31

**Discussion**

The clinical efficacy of IL-17 inhibitors such as secukinumab in phase III clinical trials further supports the importance of IL-17 (particularly IL-17A) in the pathogenesis of plaque psoriasis. A significant portion of patients who received this anti-IL-17 medication achieved PASI 75 and IGA scores of 0 or 1 – far greater than the portion that received placebo. Secukinumab performed considerably better than etanercept and ustekinumab, which were used as active comparators in these studies. Within the confines of these studies, there was no substantial difference noted in the safety profiles of these three medications.

Two other biologic agents targeting IL-17 are currently in development. While IL-17A is thought to be the most important of the IL-17 homodimers involved with psoriasis, IL-17F is also thought to play at least a small part.15,32 Brodalumab, a humanized antibody that blocks the receptor subunit (IL-17RA) to which both IL-17A and IL-17F bind, is thought to have a more powerful effect against psoriasis because of a wider blockage of IL-17 subsets. While there has been no head-to-head comparison, and dosages and schedules of administration were noted to be different, in phase II trials the percentage achieving PASI 90 was higher with brodalumab 210 mg (75%) than with secukinumab 150 mg (52%), while the PASI 75 was comparable (P=0.001).34 Similar to the studies on secukinumab, the most common side effects in studies involving brodalumab were infectious in nature – though there was one case of serious neutropenia with brodalumab, leading to discontinuation of the medication in this patient.34 One potential concern with brodalumab is that the broader blockage might prove to have negative clinical implications. For instance, in asthma studies, IL-17F deficiency (which would occur with brodalumab targeting the IL-17 receptor) led to higher expression of T helper type 2 (Th2) cytokine with more eosinophil function.35 The clinical relevance of this information was not established.

Another drug in development is ixekizumab, a humanized IgG4 monoclonal antibody that also specifically targets 17A.36 Secukinumab, on the other hand, is fully human. An increased humanness score is theoretically associated with a decreased extent of immunogenicity, as there is less deviation from the recipient species.37 Therefore, the fully human secukinumab may pose less of an immunologic risk than the humanized ixekizumab. However, studies suggest that the fully human and high-scoring humanized antibodies share relatively similar
immunogenicity.\textsuperscript{15,16} In the FIXTURE study, 7 of 19 patients who had anti-secukinumab antibodies at baseline continued to test positive for the antibodies. There were no associated decreases in efficacy or adverse events noted in these patients. Additionally, two patients on placebo and four patients on etanercept in the FIXTURE study, and two of 702 patients receiving secukinumab in the ERASURE study, tested positive for anti-secukinumab antibodies following the initiation of treatment.\textsuperscript{21}

Likewise, there is a difference in the isotype used by the two medications. Ixekizumab uses the isotype IgG4, which has been shown to act as a bispecific molecule in vivo, with the ability to interact with two separate antigens. This bispecificity may potentially lead to unknown drug reactions. However, this isotype is thought to be functionally monovalent. IgG1, used for secukinumab, is the most common isotype that is selected for the manufacture of therapeutic antibodies. This isotype of integral importance when an active antibody is necessary for complement activation and antibody-dependent effector-mediated cell killing, in the cases of certain cancer treatments. In contrast, IgG4 does not activate complement -- though when these criteria are not pertinent, killing, in the cases of certain cancer treatments.

Conclusions
The phase III trials of secukinumab have demonstrated positive results in the treatment of plaque psoriasis. While the drug has a satisfactory initial safety profile, long-term phase IV surveillance and registries are needed.

References


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Case of Persistent Regrowth of Blond Hair in a Previously Brunette Alopecia Areata Totalis Patient

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Abstract
We present a case of a brunette, 64-year-old female with no previous history of alopecia areata who presented to our clinic with diffuse hair loss over the scalp. She was treated with triamcinolone acetone injections and experienced hair re-growth of initially white hair that then partially re-pigmented to blond at the vertex. Two years following initiation of therapy, she continued to have blond hair growth on her scalp with no dark hair re-growth and no recurrence of alopecia areata.

Introduction
Alopecia areata (AA) is a fairly common autoimmune disorder of non-scarring hair loss. The disease commonly presents as hair loss from any hair-bearing area of the body. Following hair loss, it is not rare to see initial growth of depigmented or hypopigmented hair in areas of regrowth in the first anagen cycle. However, sustained and widespread hypopigmented hair regrowth in a patient with alopecia areata totalis is a rare phenomenon.

Case Report
A 64-year-old Caucasian, brunette female presented to our office complaining of two weeks of diffuse loss of hair from her scalp. The patient denied previous history of alopecia areata, autoimmune disease, recently beginning new medications, anemia, or a precipitating adverse event. The patient denied any history of dermatological diseases and had no family history of AA or autoimmune disease. She admitted to attempting treatment with OTC treatment regimens for her hair loss but was unable to recall specific details. Her past medical history was significant for hypertension and simvastatin, respectively.

Physical exam revealed diffuse thinning of hair over the entire scalp without scarring. No other body areas were affected. Over the next six months, her alopecia worsened to involve complete hair loss over her scalp (Figure 1).

Initial workup included a complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid stimulating hormone (TSH) test and antinuclear antibody (ANA) test. All values were unremarkable, and the ANA was negative. The patient declined a biopsy.

A clinical diagnosis of alopecia areata was made. The patient was treated with 5.0 mg/mL intralesional triamcinolone injections that were repeated every four to six weeks for 24 months. She concurrently used OTC minoxidil 5% solution as well as B12 and biotin supplements. She reported no side effects of treatment.

During the course of treatment, she began to see steady scalp regrowth of white hair within six months. Following initial growth of completely depigmented hair, she began to see growth of blond hair. Two years after treatment was initiated, complete scalp-hair regrowth had occurred, with blond-colored hair on the scalp vertex. Visual inspection demonstrated no demarcation line of color change, but blond hair was observed down to the root of the hair along the periphery of the occipital, parietal and temporal scalp, sisaipho pattern (loss of hair in the frontal parietotemporal scalp), patchy hair loss (reticular variant) and a diffuse thinning variant. Often, “exclamation point hairs” can be seen in and around the margins of the hair loss. The distal ends of these hairs are thicker than the proximal ends, and they are a marker of active inflammation.

A high percentage of patients experience remission of the disease and have hair re-growth. It is common to have initial hypopigmentation or de-pigmentation of hair re-growth during the first anagen phase. Most patients experience repigmentation to original hair color or even slight hypopigmentation of original hair color with subsequent growth.

Epidemiology
Alopecia areata is one of the most common autoimmune diseases, with a lifetime risk of 1.7 percent. AA affects both sexes equally. It is commonly encountered by dermatologists, representing from 0.7 percent to 3.8 percent of dermatological patient visits.

As with many autoimmune diseases, there tends to be a higher predilection of occurrence in patients afflicted with other autoimmune disease. In particular, thyroid disease, including Grave’s, Hashimoto’s thyroiditis and simple goiter has a high disease association with AA, with a co-presence of 8 percent to 28 percent. Vitiligo is also seen in a higher percentage of AA patients compared to the general population. It should be noted that there is often no concurrent vitiligo in distinct areas affected by alopecia areata because melanocytes within the epidermis express different antigens than those expressed by melanocytes within the hair follicle.

In patients with alopecia areata, there is also a high association with psychiatric morbidity, especially anxiety and depression. AA patients have a lifetime risk of 74 percent of developing one or more psychiatric illnesses.

Etiology
Hair color is determined by the type and amount of melanin within the keratinocytes of the hair.
Melanocytes situated in close proximity to the hair bulb transfer melanosomes containing melanin to newly formed keratinocytes within the hair bulb. The amount, type and density of pigment found within the keratinocytes in the cortex of the hair determine the color and tone of the hair.1 Pigmented hair in alopecia areata is targeted over depigmented hair, often with characteristic sparing of white and grey hair.1.2

The underlying etiology and pathophysiology are still unclear, but it is known that alopecia areata occurs due to an autoimmune assault to the hair follicle that results in hair loss.9 Hair follicles under non-pathological conditions have immune privilege, meaning there is an environment around the hair follicle that protects it from the immune system. One of the first steps in the development of alopecia areata is loss of hair-follicle immune privilege. Some individuals are genetically predisposed to lose of hair-follicle immune privilege due to expression of specific HLA class II alleles.3 Genetic studies have linked HLA-DQ3 to alopecia areata.3 Once immune privilege is lost, inflammatory cells attack pigment-producing anagen hair bulbs, and autoantigens are produced through autoreactive T cells with a TH1 cytokine profile (both CD4+ and CD8+). These autoantibodies are rumored to have experienced "overnight whitening."11 This phenomenon only describes the underlying etiology of total scalp whitening. Our patient suffered alopecia areata totalis of the scalp and then grew back depigmented hair that eventually gained some pigmentation, resulting in blond hair.

Histopathology
Histologically, the acute phase of AA is characterized by an infiltrate of mononuclear T-cells (both CD8+ and CD4+) and eosinophils around the lower portion of anagen follicles. It has been described histopathologically as a "swarm of bees."1,3 Chronically, there is a decrease in the number of mononuclear cells with miniaturization of hair follicles within the superficial dermis. Melanocytes are found within the hair bulb in decreased numbers, and they contain a decreased amount of melanin.12

Differential Diagnosis
The differential diagnosis for alopecia areata includes other non-scarring alopecias such as androgenic alopecia, trichotillomania, telogen effluvium, loose anagen syndrome, secondary syphilis (consider RPR) and non-active cicatricial alopecia.1

Treatment/Management
Several therapeutic modalities have been utilized in the treatment of alopecia areata. To date, there is no cure or prevention method for AA, and current therapies are aimed at ceasing hair loss and inducing hair regrowth. Therapy should be tailored and adjusted to the patient’s response. It is not uncommon for practitioners to utilize multiple therapies concurrently.

First-, second- and third-line therapies are listed in Table 1. Our patient responded well to intralesional corticosteroid injections, so we will discuss this treatment modality in detail.

The injection of intralesional corticosteroids, namely triamcinolone acetonide, is one of the most commonly used therapies for alopecia areata, resulting in hair regrowth in 64 percent to 97 percent of treated areas.1 To date, this is considered a first-line therapy in adult AA patients with less than 50% scalp involvement.10,14,15 The most commonly utilized concentration is 5 mg/ml, with no more than 3 mL injected into the scalp every four to six weeks to minimize side effects.13 Common side effects are atrophy of tissue at injection sites, skin hypopigmentation at injection sites, and telangiectasias. Relapse rates vary based on the type of AA being treated. In limited alopecia areata, the reported relapse rate at three months following therapy is 29%, while the reported rate in alopecia totalis is 72%.13

Patients with AA often experience significant psychological and psychosocial impacts. Treatment should be aimed at alleviating these effects. As mentioned previously, AA patients tend to have high rates of psychological comorbidities such as anxiety and depression, and practitioners should be sure to screen for and address these issues.

Conclusion
Alopecia areata is a common autoimmune condition that causes non-scarring hair loss in any hair-bearing area. Most patients experience hair regrowth, and it is common for hair growth in the first anagen cycle to be hypopigmented or depigmented. Our patient demonstrated an unusual case of AA totalis in which previously dark-pigmented hair regrew as blond hair. The exact etiology of this rare occurrence remains unknown, but we speculate a loss of hair-follicle autoimmune privilege and autoantibody production against melanocytes may be responsible. This may have led to reduced numbers of melanoblasts, incomplete melanogenesis and partial destruction of the mechanism of melanin production and/or transfer of melanin to keratinocytes within the hair follicle.

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A case of chronic lichenoid dermatitis manifesting as hypopigmented, flat-topped papules

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Abstract
We report a case of a 65-year-old African American female with chronic lichenoid dermatitis that manifested as hypopigmented, flat-topped papules. The lesions were initially thought to be flat warts based on their clinical appearance. Histology of a lesion revealed resolving lichenoid dermatitis with some features suggesting a possible histological differential diagnosis of cutaneous T-cell lymphoma. However, molecular studies showed oligoclonal results, which was insufficient to meet the criteria of a clonal process. We present a possible new subtype of lichen planus, the hypopigmented variant. After previous therapy with topical corticosteroid cream, our patient improved with clobetasol ointment twice daily, an intramuscular triamcinolone injection and narrowband UVB (NB-UVB) three times a week for six weeks.

Introduction
Lichen planus (LP) is an idiopathic inflammatory disease of the skin, nails, hair, and mucous membranes.1 The pathogenesis and etiology of LP is uncertain, although many believe it occurs secondary to T-cell-mediated autoimmune damage. Classical LP is characterized by small, pruritic, violaceous, flat-topped papules that favor the flexor surfaces of the extremities.2 Typically, the lesions are symmetric and bilateral. LP is a common inflammatory cause of hyperpigmentation.3 The hypopigmented variant of lichen planus has been hypothesized as a new subtype of lichen planus.

Case Report
A 65-year-old African American female presented to our outpatient dermatology clinic complaining of asymptomatic “white bumps” on her hands and feet that began three years prior to presentation. She stated that these lesions first developed on the dorsal surface of her hands and gradually spread to her forearms and elbows, eventually affecting her ankles as well. The patient had been under the care of another dermatologist for the past three years. Per patient history, prior treatment for this condition included a “steroid cream” with no improvement. The patient’s past medical and surgical history were non-contributory. She had no known drug or environmental allergies and denied taking any medications, including over-the-counter medications.

The findings on physical exam included multiple, white, hypopigmented, flat-topped papules on the bilateral dorsal hands, forearms, and lateral ankles (Figure 1). The patient had no oral or nail lesions nor did she exhibit any lymphadenopathy.

A shave biopsy was obtained from a papule on her right elbow and sent for histologic examination. Analysis of the biopsy revealed a focally lichenoid infiltrate with thinning of the epidermis, some irregular, jagged epidermal rete, and prominent fibrosis in the papillary dermis (Figure 2). Immunohistochemical studies were performed to further characterize the process. Lesional cells showed a CD3+, CD5+ and CD7+ phenotype (Figures 3, 4). The CD4 to CD8 ratio was approximately 1:1. CD20 staining was very focal and CD30 staining essentially negative. Melan-A staining highlighted focal loss of melanocytes at the dermoepidermal junction (Figure 5). Some features raised the possibility of a histological differential diagnosis of cutaneous T-cell lymphoma. However, molecular studies showed oligoclonal results, which was insufficient to meet the criteria of a clonal process. The patient’s lipid panel, complete metabolic panel, and complete blood count were all within normal limits. These findings along with her clinical presentation were highly suggestive of a long-standing and resolving lichenoid inflammatory process such as resolving lichen planus.

The treatment plan included clobetasol 0.05% ointment twice daily to affected areas on hands, forearms and ankles for two weeks per month, an intramuscular injection of 40 mg triamcinolone, and narrow-band UVB three times a week for six weeks. On two-month follow-up, the patient admitted to improvement of her skin condition.

Discussion
Lichen planus has numerous variants, including actinic LP, acute LP, annular LP, atrophic LP, bullous LP, LP pemphigoides, hypertrophic LP, inverse LP, LP pigmentosus, lichen planopilaris, linear LP, LP-lupus erythematosus overlap syndrome, nail LP, oral LP, ulcerative LP,
vulvovaginal LP, and lichenoid drug eruption. However, a hypopigmented variant has not been described. There is a subset of vitiligo patients that have some “lichenoid characteristics,” including analogous locations and, in the initial phase, pathological features similar to those of LP. This subtype of vitiligo is termed “lichen planus depigmentosus” and is considered by some to be the counterpart of lichen planus pigmentosus. Due to the normal melan-A stain and clinical findings, we do not believe our patient had lichen planus depigmentosus.

Although the pathogenesis and etiology of LP remain unknown, it is thought to be related to an autoimmune process in which CD8+ T lymphocytes attack basal keratinocytes. There are various triggers thought to be associated with the initiation of lichen planus. These include but are not limited to infections, vaccines, drugs, and contact allergens. Exposure to these triggers can initiate an autoimmune cascade and the generation of effector T cells with cytotoxic potential.

There are many drugs commonly implicated in lichenoid drug eruptions. The most common ones include ACE-inhibitors, thiazide diuretics, antimalarials, quinidine and gold.

In its classical form, LP is characterized by small, polygonal, violaceous, flat-topped papules that favor the flexor surfaces of the extremities. Because lichen planus most commonly presents as hyperpigmented or violaceous papules, other diagnostic possibilities were considered for our patient as well. Part of the differential diagnosis for hypopigmented flat-topped papules includes flat warts. However, because the histopathology did not reveal characteristics consistent with a wart, hypopigmented lichen planus was favored as our diagnosis.

Treatment
Formulating a treatment plan for lichen planus can be difficult, as there are some cases that remit spontaneously and others that are resistant to treatment. Additionally, it is important to rule out a drug-induced form, as withdrawal of the offending agent may lead to resolution of the lesions without additional treatment. Topical corticosteroids remain the first-line therapy for localized LP. For severe cases, immune-modulating therapies such as cyclosporine may be effective. In our case, the patient improved with topical clobetasol ointment twice daily for two weeks per month, one intramuscular corticosteroid injection, and NB-UVB therapy three times a week for six weeks.

Conclusion
Lichen planus has many variants, but a hypopigmented variant has not been described. The numerous subtypes of LP are differentiated from classic LP by distribution and morphology. The morphology of the lesions in our patient was hypopigmented, whereas the most commonly described lesions of LP are violaceous or hyperpigmented. The clinical differential for the described lesions included flat warts, but there were no koilocytes on histology. In our patient, clinical findings and histopathologic clues pointed to a case of hypopigmented LP.

References

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Diffuse Dermal Angiomatosis of the Breast: A Case Presentation and Discussion

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Abstract
Diffuse dermal angiomatosis (DDA), a rare dermatological disorder and variant of reactive cutaneous angioendotheliomatosis, is characterized clinically by the presence of erythematous and violaceous lesions that have the potential to ulcerate. Although it classically presents in the extremities, a few cases have been reported of DDA involving the breast (DDAB). DDA has often been linked to vaso-occlusive and cardiac co-morbidities, and treatment has therefore usually targeted these underlying conditions. This case presents a patient with DDAB who was successfully treated with isotretinoin therapy, supporting previous reports of its benefit in the management of this patient population.

Introduction
In 1994, Krell et al. initially recognized diffuse dermal angiomatosis (DDA) as a rare but distinct variant of reactive cutaneous angioendotheliomatosis. Clinically, it presents as erythematous, violaceous, indurated plaques that are often ulcerated and tender. It generally involves the lower extremities, although only a total of 14 cases of DDA have been cited in the current literature to date. A form of DDA has also been reported that is localized to the breast (DDAB). Only five documented cases of DDAB have been cited. Patients with DDAB often present with intractable breast pain along with these cutaneous lesions.

Due to its rarity, the pathogenesis of the disease is not fully understood, but it is thought to be a result of tissue ischemia. Numerous studies have reported an association with severe peripheral vascular disease among other co-morbidities. Histologically, diffuse dermal vascular- and endothelial-cell proliferation between collagen bundles is seen, and uniform positivity is achieved with immunoperoxidase stains CD31 and CD34, vascular markers characteristic of DDA.

The management of DDA and DDAB is centered on improving the underlying ischemia and achieving revascularization. The modalities in current practice include the use of oral corticosteroids, isotretinoin, reduction mammoplasty, and stent placement in extreme cases of vaso-occlusive disease. In this case report, we present an adult patient with a classic presentation of DDAB who was successfully treated with isotretinoin for a duration of four months.

Case Report
A 60-year-old Caucasian female presented with a three-month history of exquisitely tender, ulcerating and bleeding breasts, with a tremendous amount of exuded material bilaterally. This eruption started approximately six weeks after cardiac surgery. During the procedure, the patient received heparin, but was not placed on coumadin. She denied exacerbating or alleviating factors. Past medical history was significant for cardiovascular disease, transient ischemic attack, hypertension, and hypercholesterolemia. The patient was a smoker when she was evaluated for this eruption. Her medications upon evaluation included atorvastatin, clopidogrel, lisinopril, metoprolol, and topical lidocaine. Family history was noncontributory. All labs were found to be within normal limits.

Physical exam revealed livedo reticularis on the breasts, bilaterally. The left breast (Figure 1) was much more affected than the right (Figure 2), with associated healed punctuate ulcerations and changes of healed infarcts. The rest of her
Histologic sections of a punch biopsy from the left breast revealed a diffuse capillary proliferation within the dermis and extending into the subcutis in a patchy distribution (Figures 3 [5x], 4 [10x], 5 [20x] p. 33). There was no evidence of vasculitis or a thrombotic vasculopathy to suggest either cocomain or hepatitis necrosis. There was also no evidence of endothelial atypia or malignancy. This pattern was consistent with diffuse dermal angiomatosis, a form of reactive angioendotheliomatosis. Treatment included pain control and isotretinoin at a dose of 40 mg PO twice daily for a duration of four months, to which the patient responded positively.

Discussion
First described in 1994 by Krell et al., diffuse dermal angiomatosis (DDA) is a rare skin condition primarily affecting females and characterized by erythematous, violaceous, indurated plaques that are often ulcerated and tender and are commonly localized to the lower extremities. Although the pathogenesis is unknown, it is often noted in patients with severe peripheral vascular disease among other co-morbidities. A few authors have reported a correlation between DDA and trauma, namely from surgery. While DDA is rare, with 14 total cases reported, involvement of the breast is even less frequently diagnosed. To date, only five cases of DDA of the breast (DDAB) have been described. Although often affecting large pendulous breasts bilaterally, these patients presented in an otherwise atypical fashion without relevant medical history or vaso-occlusive disorder. Histologically, however, they demonstrated diffuse dermal vascular and endothelial cell proliferation between collagen bundles and uniform positivity with immunoperoxidase stains CD31 and CD34, vascular markers characteristic of DDA. HHV-8 is also often used to aid in diagnoses and is uniformly negative in DDA.

The exact process underlying the development of DDA has yet to be determined, but tissue ischemia is often cited. According to Bauer et al., the current hypotheses regarding the pathogenesis of the disease are as follows: (1) atherosclerotic plaques may emblazon to distal small vessels and create endothelial hyperplasia; (2) vascular steal syndromes can give rise to ischemic necrosis with subsequent ulceration; or (3) ischemia leads to increased vascular endothelial growth factor and subsequent endothelial proliferation. Given this understanding, it is believed that reversing ischemia and achieving revascularization can be beneficial in improving the clinical signs of disease. Several associations have been made between DDA and other co-morbid conditions. Many authors have reported associations between DDA and peripheral vascular atherosclerosis, arteriovenous fistulas, anticoagulant antibodies, hypercoagulable states, and breast ulceration. The most common and widely accepted association, however, has been with vascular occlusive disease. Smoking and DDA have also been found to be strongly associated, with patient's often having a significant clinical history of long-term tobacco use. Hypertension has also been reported to be associated with DDA. As noted previously, the management of DDA and DDAB is centered on improving the underlying ischemia and achieving revascularization. Many modalities have been implemented in the treatment of DDA and DDAB, including the use of oral corticosteroids, isotretinoin, reduction mammaplasty, and stent placement in extreme cases of vaso-occlusive disease. Morimoto et al., as well as other authors, have described successful revascularization procedures facilitating the healing of DDA ulcers. In this case report, we describe successful treatment with isotretinoin at a dose of 40 mg PO twice daily for a duration of four months. Isotretinoin is a retinoid compound most often used to treat severe acne. Its antiangiogenic properties, however, have proved to be beneficial in the treatment of DDAB as well. A similar response to isotretinoin therapy was reported by McLaughlin et al. This study found that treatment with a dose of 1 mg/kg of isotretinoin over two months resulted in complete resolution of the ulceration in this patient with DDAB. Although the exact mechanism of action of isotretinoin in the treatment of DDAB is unknown, it has been postulated that it may involve the inhibition of angiogenesis and/or protease production, stimulation of fibrinolysis, and possibly enhancement of keratinocyte migration.

Although the use of isotretinoin in the treatment of DDAB has proved promising, the drug is not without risk. It must be highly regulated due to its effect as a teratogen. Other possible side effects include dry skin, chapped lips, epistaxis, cheilitis, severe depression, and suicidal ideation. Therefore, although found to be effective in this patient population, all the risks and benefits of isotretinoin therapy must be thoroughly considered on a case-by-case basis.

Conclusion
DDA is a rare variant of reactive cutaneous angioendotheliomatosis, classically described on the lower extremities but occasionally involving the breast (DDAB) and presenting as unbearable breast pain. Although few cases of DDAB have been reported, its recognition and discussion is paramount in identifying the appropriate treatment for this patient population. Evaluation of these patients should be focused on symptoms and relevant medical history, with particular emphasis on vaso-occlusive and hypercoagulable co-morbidities. Management should be patient-dependent, and we believe that isotretinoin therapy should be considered in patients with a classical clinical and histological presentation of DDAB. In addition, due to the strong correlation of DDA and tobacco use, smoking cessation should always be encouraged in conjunction with medical treatment and strict control of cardiovascular risk factors.

References

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Abstract
With the growing use of permanent cosmetics, dermatologists are increasingly seeing patients who want to fix or remove their treatments. Many permanent-cosmetics tattoos can be treated with laser. When selecting a laser, wavelength and pulse duration are important considerations. It is also important to inform the patient that permanent-cosmetics tattoo removal typically requires multiple treatments, that the tattoo may not completely resolve and that treatment may cause color alterations. This case demonstrates laser treatment of a black permanent-cosmetics eyebrow tattoo that ultimately resulted in a brownish color.

Case Report
A 31-year-old Caucasian female presented to the office stating she was unhappy with the appearance of her permanent-makeup eyebrows. She felt they were too black. Prior to presenting to our office she had returned to the permanent-makeup artist to have brown added to lighten them, but she felt they were still too dark and wanted them lightened further. We decided to treat her with a 1064-nm Q-switched Nd:YAG laser, a laser often used for tattoo removal. We treated the eyebrows for a total of three treatments, with treatments spaced at three-month intervals. Settings were: 1064-nm wavelength, 2-mm spot, 8 J/cm², 5 Hz, and 5-ns pulse. By the end of the third treatment, the patient felt she was 60% to 70% improved and was very happy with the results.

Discussion
Many permanent-eyebrow procedures are attempting to fill gaps or address thinning of the eyebrows. They can be done by tattoo artists or permanent-makeup artists and are primarily administered by two related techniques. One method currently used by permanent-makeup artists is a derivative of traditional Japanese tattooing. The procedure, called “dermatography,” was developed by Dutch dermatologist Eddy van der Velden and involves applying varying colors in a small number of administration periods. The apparatus used is the Van der Velden Derminjector, which has a needle holder that moves up and down within a stainless-steel tube.1 Speed of the needle varies between 500 rpm and 3500 rpm. The needles of choice are entomological needles, which are 36 mm long and 0.36 mm or 0.41 mm in diameter.4 Some permanent-makeup artists use an alternate procedure that entails using a tattoo pen to insert pigment drops into the superficial dermis.1

The inks and pigments are considered “cosmetics and color additives” and are not regulated by the FDA. Some are “not approved for skin contact.”1 The ink colors in permanent eyebrows are usually of a darker hue.1 One issue is fading of the dark brown tint to a color more similar to red. A chemical change in these inks may alter the compound from ferrous oxide (FeO) to ferric oxide (Fe₂O₃), which results in a color change to brownish-red.4 Various lasers may be employed to remove permanent makeup, including lasers with wavelengths between 500 nm and 570 nm, which are easily absorbed by red and pink colors.3 This 500-nm range works well for reds and pinks but may actually darken some pigments, including those often used in permanent-eyebrow procedures. The longer-wavelength (1064-nm) Q-Switched Nd:YAG laser has been demonstrated as more effective than the frequency-doubled Q-Switched Nd:YAG laser in lightening permanent eyebrows.1 The 1064-nm wavelength is both useful for removing darker hues and less absorbed by melanin when compared to its 532-nm counterpart, making it ideal for darker permanent makeup and for patients with darker skin.2

Conclusion
When selecting a laser to use for permanent-makeup removal, it is important to consider the ink color and select the laser wavelength that will be most effective with that pigment. The patient needs to be well informed that the color could change. Since we are seeing an increase in permanent makeup and tattooing as a beauty trend, we as dermatologists should be prepared for patients seeking alterations or removal.

References

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Graham-Little-Piccardi-Lassueur Syndrome: A Case Report

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Abstract
Graham-Little-Piccardi-Lassueur syndrome is a variant of lichen planopilaris characterized by the triad of patchy cicatricial alopecia of the scalp, noncicatricial alopecia of the axilla and groin, and follicular spinous papules on the body, scalp, or both. The disease is most commonly seen in women 30 to 70 years of age. We present a case of this rare syndrome in a 68-year-old female with madarosis and provide a discussion about the disease and treatment options.

Introduction
Graham-Little-Piccardi-Lassueur syndrome (GLPLS) is a rare subtype of lichen planopilaris (LPP) that presents with the triad of multifocal cicatricial alopecia of the scalp, noncicatricial alopecia of the axilla and groin, and a follicular lichen planus (LP) eruption on the body, scalp, or both. It is four times more likely to affect women and is characteristically seen in those who are middle-aged to post-menopausal. Although the exact etiology of GLPLS is unknown, it is thought to be an immune-mediated disorder that causes an inflammatory reaction against the bulge region of hair follicles. The disease is non-familial, although one case with a familial origin has been reported.

Case Report
A 68-year-old female presented with a one-year history of a mildly pruritic, erythematous, scaly frontal scalp and alopecia involving her head, eyebrows, eyelashes, axillae, legs and arms. Her eyebrows and eyelashes experienced the most rapid progression of hair loss, with complete madarosis over six to eight months. However, her main areas of concern at the time of her initial visit were the frontal scalp and temporal regions. The patient reported that her hair was previously grey, but as her hairline receded, black pigmented hairs developed despite never coloring her hair. Previous treatment included triamcinolone ointment prescribed by her primary care physician for presumed scalp psoriasis, which reduced scaling but failed to arrest the hair loss. The patient then visited her beautician, who recommended over-the-counter selenium-sulfide shampoo for seborrheic dermatitis and tea tree oil shampoo and conditioner. These products caused mild reduction in scale, but she again noted an increasingly receding hairline. The patient had an otherwise unremarkable 12-point review of systems and had no known drug allergies except for gabapentin sensitivity, which caused nausea. Past medical history included hypothyroidism, aortic regurgitation, mitral regurgitation, hypertension, migraines, depression, seasonal allergies, and toxoplasmosis that had been treated 58 years prior. The patient's medications included levothyroxine, losartan, bupropion, sertraline, acetaminophen/butalbital/caffeine, sumatriptan, fish oil, and calcium with vitamin D. The only medication change in the past 18 months was from lisinopril to losartan. Family history revealed hypothyroidism in the patient’s father and son. Social history revealed a 25 pack-year smoking history but no tobacco use in the last 30 years. She denied any alcohol or illegal drug use.

Dermatological exam revealed cicatricial alopecia of the frontal scalp and temples with associated perifollicular scalp erythema and hyperkeratotic follicular scaling; also noted were a few residual tufts of black, normal-looking terminal hair (Figure 1). Noncicatricial alopecia of the eyebrows, eyelashes, axillae, forearms, and legs was present in addition to multiple follicular, keratotic, and spinous papules over the remainder of the scalp (Figures 2, 3). Differential diagnosis included GLPLS, classical LPP, frontal fibrosing alopecia (FFA), lichen spinulosus, alopecia mucinosa, discoid lupus erythematosus, pityriasis rubra pilaris, pseudopelade of Brocq, and sarcoidosis. Two 4 mm punch biopsies taken from the frontal scalp revealed scarring alopecia with dermal fibrosis, a perifollicular lymphohistiocytic infiltrate, and the absence of interface dermatitis in the overlying epidermis (Figures 4, 5). Histologic findings were consistent with a diagnosis of lichen planopilaris (LPP). The clinical picture of LPP, noncicatricial alopecia and keratotic papules is consistent with the rare variant of LPP known as GLPLS.

Treatment was initiated with topical high-potency steroids with consideration for systemic steroids or antimalarials pending punch-biopsy results and clinical course. At two-week follow-up, our patient demonstrated noticeable improvement in scalp erythema, scaling and pruritus. At one-month follow-up, scalp erythema was no longer present, scaling had improved, and hair loss had ceased. Systemic medications were not initiated given the significant clinical improvement, and she will continue to be monitored regularly.

Discussion
The name GLPLS comes from the names of the physicians who first described this condition. The disease was originally defined in 1913 by Piccardi, who described a case of progressive cicatricial scalp alopecia, noncicatricial alopecia in the axillae and pubic area, and follicular spinous papules on the trunk and extremities, to which he gave the name cheratosi spinulosa, or keratotic spinulosa. In 1915, Graham-Little published a case of a similar condition in a 55-year-old woman who was referred by Lassueur, describing it as “folliculitis decalvans et atrophicans.” In addition to the classical triad of cicatricial alopecia of the scalp, noncicatricial alopecia of the axillae and groin, and a follicular keratotic eruption, GLPLS can affect the eyebrows and lateral face.
GLPLS is a rare type of LPP that typically presents in women who are 30 to 70 years old, although the condition has been reported in males and younger individuals. GLPLS may have a positive pull test for anagen hairs due to the same altered integrin expression seen in active LPP. Histopathological findings of GLPLS are similar to those seen in LPP, but the absence of interface dermatitis of the overlying epidermis can help differentiate the two. Early lesions of LPP reveal a perifollicular lymphocytic infiltrate at the level of the infundibulum and the isthmus, along with vacuolar changes of the outer root sheath. More advanced cases show perifollicular fibrosis and epithelial atrophy at the level of the infundibulum that give rise to a characteristic hourglass configuration. As the disease progresses, vertically oriented elastic fibers replace the destroyed hair follicles.

The exact etiology of GLPLS is unknown, but it is likely similar to the T-cell-mediated immunological mechanism that triggers the clinical expression of LP. GLPLS has not been associated with underlying systemic disease, but it may cause stress and anxiety due to its presentation. Isolated cases describing a familial pattern (HLA DR1), association with hepatitis B vaccination, and a female (genetically XY) patient with complete androgen insensitivity syndrome have been reported.

Unless GLPLS is recognized early, treatment is usually only mildly effective. Once scarring occurs, hair regrowth will not occur. Treatment is directed at halting the progression of disease, preventing further alopecia, and providing symptomatic relief. Various therapies including intralesional and systemic corticosteroids, retinoids, PUVA therapy, topical tacrolimus, and antimalarials have all produced varying results. Isolated reports have demonstrated anecdotal success with cyclosporine and thalidomide. The disease is often progressive, with little potential for hair regrowth once complete destruction of the follicle occurs. Early, accurate diagnosis is imperative to prevent progression.

Conclusion

GLPLS is an uncommon entity that has been reported fewer than 50 times in the literature. It has a classical clinical presentation and is not associated with systemic disease. Although its pathogenesis is unknown, the T-cell-mediated immune response in GLPLS is similar to that in LP. There is no universally effective treatment, so therapy should be directed at halting disease progression.

References


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Topical Ivermectin for the Treatment of Papulopustular Rosacea: A Review

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Abstract

Rosacea is a common inflammatory skin disorder that affects many Americans. Currently, oral and topical antimicrobials are among the most effective medications used. Ivermectin 1% cream was recently approved for the treatment of papulopustular rosacea. The primary objective of this article is to provide a clinical review of the efficacy and safety of ivermectin 1% cream.

Introduction

Rosacea is estimated to affect nearly 16 million Americans. Patients with lighter skin types are most often affected by rosacea. However, those of darker skin types are not entirely exempt from this diverse disorder. Rosacea is defined as an inflammatory skin disorder characterized by the presence of inflammatory papules and pustules, erythema, and telangiectases distributed in the central facial region. Phymatous and ocular manifestations are also characteristic findings seen in rosacea.

The National Rosacea Society Expert Committee classifies rosacea into four distinct subtypes. However, patients do not always conform to one specific subtype, and there may be significant overlap between groups. Erythematotelangiectatic rosacea (ETR) is characterized by flushing and erythema of the central facial region with or without telangiectases. Papulopustular rosacea (PPR) is characterized by persistent central facial erythema with transient inflammatory papules and pustules. Phymatous rosacea (PhR) is characterized by thickened, nodular skin and rhinophyma. Finally, ocular rosacea (OR) is characterized by the presence of ocular dryness, conjunctivitis, and blepharitis in addition to burning and stinging sensations in the eye.

Rosacea is hypothesized to be the result of vascular dysregulation and abnormal inflammatory responses ultimately resulting in chronic vasodilation and inflammation. Additionally, a variety of triggers including stress, heat, hot liquids, spicy foods, and alcohol exacerbate the underlying vasodilation and inflammation and are associated with flares of rosacea. Innate immune mechanisms like antimicrobial peptides, serine proteases, and toll-like receptors (TLRs) have been implicated in the inflammatory and vasodilatory processes responsible for rosacea.

Specifically, elevated levels of cathelicidins (i.e. LL-37) and kallikrein 5 (KLK5) have been found in the skin of patients with rosacea. Additionally, patients with rosacea have been found to have an increased density of Demodex mites, specifically D. folliculorum and D. brevis, associated with their pilosebaceous units, and antigenic proteins from Bacillus sierosus isolated from Demodex mites may play a role in the underlying pathophysiology of rosacea. As such, rosacea may be the result of an abnormal innate immune response to environmental and/ or infectious stimuli.

Oral and topical antimicrobials have been used successfully for the treatment of rosacea, and ivermectin 1% cream was recently approved for the treatment of papulopustular rosacea. The primary objectives of this article are to review the current literature surrounding the use of topical ivermectin in the treatment of rosacea and to provide further insight with regard to administration and adverse effects.

Mechanism of Action

Ivermectin is an avermectin antiparasitic agent that is used orally for the treatment of strongyloidiasis, demodicism, pediculosis, and scabies, in addition to other parasitic/helminthic infections. It exerts its effect by binding to parasite glutamate-gated ion channels, resulting in increased permeability to chloride ions. Hyperpolarization of the cell ensues, ultimately resulting in the death of the parasite. Additionally, ivermectin has been shown to display anti-inflammatory properties through inhibition of lipopolysaccharide-induced inflammation. Specifically, a reduction in TNF-α and interleukin-1b (IL-1b) has been documented along with a corresponding increase in interleukin-10 (IL-10), an anti-inflammatory cytokine.

Clinical Trials

The Ivermectin Phase III Study Group reported the results of two, 12-week, randomized, double-blind, parallel-group, vehicle-controlled studies in 2014. The primary objective of each study was to determine efficacy based on the improvement in Investigator’s Global Assessment (IGA) of severity scores and the reduction in inflammatory lesion count. Approximately 700 patients were enrolled in each study, and patients were allocated to receive either ivermectin 1% cream or vehicle in a 2:1 ratio. Patients were then instructed to apply either ivermectin 1% cream or vehicle once daily. The patient population was primarily Caucasian (96.2% and 95.3%) and female (68.2% and 68.7%) with an mean age of approximately 50 years old (50.4 +/- 12.09 and 50.2 +/- 12.29). Mean inflammatory lesion counts upon initiation of the trial were 31 and 33 (SD +/- 14.33, 13.7), and the majority of patients had moderate rosacea as defined by an IGA score of 3 (82% and 72.9%).

Following 12 weeks of therapy, the percentage of patients able to achieve an IGA grade of clear or almost clear in the ivermectin groups were 38.4% and 40.1%, compared to 11.6% and 18.8% in the vehicle groups (p<0.001). Additionally, a significant difference in IGA scores was appreciated as early as four weeks in each study. The mean reduction in inflammatory-lesion counts were 75% and 76% with a mean difference of -8.16 [-10.12, -6.13] and -8.22 [-10.18, -6.25] in comparison to vehicle for each of the ivermectin groups (p<0.001). In comparison, a 50% reduction in inflammatory-lesion counts was observed in the vehicle groups from both trials (p<0.001). Additionally, quality-of-life assessments, as measured by Dermatology Life Quality Index (DLQI) and RosaQoL, were significantly improved in the ivermectin group in comparison to vehicle.

Both trials were then extended for an additional 40 weeks in order to assess long-term safety. Patients initially allocated to receive ivermectin 1% cream were continued on a once-daily topical-application regimen. Patients in the vehicle group were then assigned to receive azelaic acid 15% gel applied topically twice daily. A total of 622 and 636 patients continued the trial into its extension phase, and approximately 80% of the patients completed the study. Dermatologic adverse effects were noted in 7.8% and 9.8% of the patients in the ivermectin groups in comparison to 12.9% and 16.3% in the vehicle/azelaic-acid groups. Notably, no serious or severe adverse events were related to either study medication. While it was not the primary objective of the extension phases of the trials, efficacy at 52 weeks was addressed. A total of 71.1% and 76% of patients in the ivermectin groups were able to achieve IGA grades of clear or almost clear.

Another 16 week, randomized, investigator-blinded, parallel-group study was conducted on behalf of the Ivermectin Phase III study group in Europe. The study compared once-daily application of ivermectin 1% cream with twice-daily application of metronidazole 0.75% cream. The primary objective of this study was to determine whether ivermectin 1% cream was superior to metronidazole 0.75% cream with regard to reductions in inflammatory-lesion...
counts in patients with papulopustular rosacea. A total of 962 patients with moderate to severe papulopustular rosacea and inflammatory-lesion counts between 15 and 70 were randomized in a 1:1 ratio to receive either ivermectin 1% cream or metronidazole 0.75% cream. The mean number of inflammatory lesions at baseline was 32.46 (p=0.001). Additionally, 84.9% of patients had moderate rosacea based on IGA scores. The percent reduction in inflammatory-lesion counts in the ivermectin group was 83% in comparison to 73.7% in the metronidazole group, with an absolute difference of 9.3% (p<0.001). Additionally, 84.9% of patients in the ivermectin group were able to achieve IGA grade clear or almost clear in comparison to 75.4% in the metronidazole group (p<0.001). Similar findings were observed in each group with regard to patient-reported outcomes.

Adverse Effects

The most commonly reported adverse effects associated with ivermectin 1% cream were burning sensations, dry skin, skin irritation, pruritus, skin pain, and eye pain. Ivermectin 1% cream should be applied topically once daily to the affected areas of the face, typically the forehead, nose, chin, and cheeks. A pea-sized amount should be used and spread as a thin layer, avoiding the eyes and mouth.

Discussion

Ivermectin 1% cream is a novel antimicrobial agent for the topical treatment of papulopustular rosacea. Its efficacy and safety are well documented in the aforementioned clinical trials. Additionally, it has favorable patient-reported outcomes and a minimal side-effect profile.

Metronidazole, azelaic acid, and doxycycline are the most effective medications available for the treatment of papulopustular rosacea. Their anti-inflammatory effects are the proposed mechanism of action in papulopustular rosacea. Likewise, ivermectin has been shown to possess anti-inflammatory properties, in addition to effectiveness against demodidosis. This dual-action property might explain its effectiveness in the treatment of papulopustular rosacea. However, the exact role that Demodex mites play in the underlying pathogenesis of rosacea has yet to be fully elucidated.

Conclusion

There is documented evidence that ivermectin 1% cream is superior to metronidazole 1% cream with regard to percent reduction in inflammatory-lesion counts. However, it is difficult to conclude that this is a clinically significant difference. Additionally, it is difficult to determine whether this difference is applicable to metronidazole gel as well. Likewise, ivermectin 1% cream is likely better tolerated than azelaic acid. However, it is not possible to say that it is superior with regard to efficacy, as this was not the primary objective of the trial.

As with all new medications that come to market, cost will likely be the largest barrier to its use. However, ivermectin 1% cream should be considered in patients who fail or are unable to tolerate more affordable modalities.

References


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Lymphoepithelioma-like Carcinoma of the Skin: A Case of One Patient Presenting with Two Primary Cutaneous Neoplasms

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Abstract
Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare cutaneous neoplasm most frequently found on the head and neck of elderly patients. Debate exists regarding its histogenesis, but it’s believed to be of epithelial origin. Histologically, LELCS is remarkably similar to undifferentiated nasopharyngeal carcinoma, a neoplasm associated with Epstein-Barr virus (EBV) infection. EBV reactivity is the main distinguishing factor between these two cutaneous neoplasms, with LELCS rarely documented to test positive for EBV. In general, those diagnosed with LELCS are advised to undergo evaluation of the nasopharynx as well as other internal organ systems that may harbor a lymphoepithelioma-like carcinoma to exclude cutaneous metastasis. Current treatment guidelines recommend wide local excision or Mohs micrographic surgery to prevent local recurrence of LELCS. To the best of the authors’ knowledge, this case is the first to report a patient with two separate lymphoepithelioma-like carcinomas of the skin presenting simultaneously.

Introduction
Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare cutaneous neoplasm with low malignant potential. It is currently classified as a variant of squamous-cell carcinoma (SCC), although historically, its etiology has been debated. LELCS demonstrates nearly identical histologic features to undifferentiated nasopharyngeal carcinoma, also known as metastatic lymphoepithelioma of the nasopharynx, classically differentiated from LELCS by positive reactivity for an associated infection with Epstein-Barr virus (EBV). Therefore, an evaluation of the nasopharynx with an ear, nose, and throat (ENT) examination is advised to exclude undifferentiated nasopharyngeal carcinoma. LELCS generally is a slow-growing neoplasm with a good overall prognosis. However, due to multiple cases of recurrence after initial surgical excision, the gold standard of treatment for LELCS is wide local excision or Mohs micrographic surgery.

Case Report
An 83-year-old Caucasian female was referred to our dermatology clinic for surgical excision of a previously biopsied lesion on her left neck reported initially as a nodular basal-cell carcinoma with focal morpheaform features. The patient also complained of an asymptomatic, slowly enlarging lesion to her left parietal scalp believed to be present for at least three months. The patient’s past medical history was non-contributory, and she denied any constitutional symptoms at the time of clinical presentation.

Clinical examination revealed a solitary, 2.0 cm x 2.2 cm, tan to pink, indurated ulcerative plaque. There were no nasal or oropharyngeal abnormalities or regional lymphadenopathy. A shave biopsy was performed to the left parietal scalp to exclude both basal-cell carcinoma and squamous-cell carcinoma. The histopathological findings for both the left neck and left parietal scalp neoplasms showed a dermal proliferation of atypical epithelioid cells forming well-defined nests invested by a dense lymphocytic infiltrate. The atypical epithelioid cells were basophilic and featured enlarged nuclei with prominent nucleoli. A central ulceration was present under microscopic examination of the cutaneous biopsy on the patient’s left parietal scalp. The overlying epidermis appeared uninvolved in both samples. Each specimen stained positive for cytokeratin (CK) 5/6 and epithelial...
membrane antigen (EMA), suggesting tumors of epithelial origin. Staining for CK7 and CK20 yielded negative results, excluding Paget's disease and Merkel-cell carcinoma (MCC), respectively, from the differential diagnosis. Due to the concern for an underlying metastatic undifferentiated nasopharyngeal carcinoma or lymphoepithelioma-like carcinoma (LELC) of another internal organ, an in situ hybridization for Epstein-Barr virus-encoded RNA (ISH/EBER) was performed for detection of an active or latent EBV infection (Figure 3). The patient's histologic slides were compared to a control ISH/EBER immunohistochemical stain (Figure 4). The negative ISH/EBER stain for both lesions strongly favors two primary LELCS in our patient and does not favor a metastatic disease related to an EBV-driven undifferentiated nasopharyngeal carcinoma or internal LELC.

Our patient was referred to an oncologist for medical evaluation to exclude cutaneous metastasis of an undifferentiated nasopharyngeal carcinoma or lymphoepithelioma-like carcinoma of other internal organs. Given the patient's advanced age and frail status, the patient refused oncologic examination as she planned to decline systemic treatment if an underlying internal malignancy was discovered. Per initial consultation with the patient, the oncologist remarked that it was highly unlikely that an internal carcinoma was metastasizing to her skin. She was also referred to a plastic surgeon for evaluation and surgical removal of both LELCS.

Our plan is to undergo surgical excision of both cutaneous neoplasms and remains free from systemic symptoms, which supports the diagnosis of two primary lymphoepithelioma-like carcinomas of the skin.

**Discussion**

Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare primary cutaneous neoplasm initially described in 1988 by Swanson et al. Since this first report, close to 80 cases have been described in the English literature. LELCS occurs most often in elderly individuals on sun-exposed areas, primarily the head and neck. However, there has been a report of LELCS occurring on the trunk and upper extremity. The incidence is equal in men and women. LELCS often presents as a solitary, flesh-colored to red, firm papule, plaque, or nodule. The average size is fairly large, measuring about 2 cm to 3 cm in diameter. Typically, LELSC is asymptomatic and slowly enlarges over a period of months to years.

**Histology**

On histology, LELCS presents as a dermal proliferation of atypical polygonal epithelioid cells arranged in nests, cords, or sheets surrounded by a peripheral dense lymphocytic infiltrate. Cellular atypia includes vesicular hyperchromatic nuclei and prominent nucleoli with scant amphophilic-to-eosinophilic cytoplasm. The reactive lymphoid stroma is comprised of small B- and T-lymphocytes, staining positive for CD3 and CD20, with an occasional plasma cell present. LELCS generally extends into the reticular dermis with occasional involvement into the subcutis and even skeletal muscle. LELCS stains positively for pancytokeratin, CK5, CK6, p63 and EMA reactivity, likely indicating a neoplasm of epithelial origin. These markers also indicate that LELCS may derive from an epidermal, follicular, glandular, sudoriferous or neural origin. In fact, the histogenesis of LELCS is controversial. Historically, LELCS was thought to derive from adnexal origin, supported by the fact that LELCS is located in the dermis and usually lacks a connection with the epidermis. Also, within LELCS, there is often sebaceous, eccrine and trichilemmal differentiation. In more recent literature, some consider LELCS to be a variant of squamous-cell carcinoma (SCC). For instance, Wang et al. presented a case of LELCS occurring below a scar from removal of multiple recurrent, well-differentiated and subsequent moderately differentiated SCC. However, SCC is typically located in the superficial dermis and maintains connectivity with the epidermis; usually lacks a connection with the epidermis. Finally, others believe that LELCS is a morphologic pattern as opposed to a distinct clinicopathologic entity.

**Differential**

The differential diagnosis is fairly extensive and includes cutaneous metastasis of undifferentiated nasopharyngeal carcinoma, a lymphoepithelioma-like carcinoma of another internal organ, basal-cell carcinoma, squamous-cell carcinoma, keratoacanthoma, Merkel-cell carcinoma, melanoma, malignant lymphoma, Hodgkin's lymphoma, cutaneous lymphadenoma, and follicular dendritic cell tumor. Histologic features and immunohistochemical staining distinguish LELCS from the possible differential diagnosis.

**Merkel-cell carcinoma** (MCC) can present clinically similar to LELCS but will stain positive for neuroendocrine markers such as synaptophysin, neuron-specific enolase, and CK20. In addition, peripheral lymphocytic infiltrate is usually absent in MCC. Clarke and Ioffreda report a case in which LELCS demonstrates spindle-shaped cells that resemble the spindle-cell variant of melanoma. However, unlike LELCS, melanoma is positive for S100 and other neuroectodermal markers such as HMB-45 and melan-A. LELCS should be distinguished from malignant lymphoma by the absence of atypical lymphocytes in LELCS. Epithelial markers such as epithelial-membrane antigen and cytokeratins will react positive in LELCS and negative in malignant lymphoma. LELCS has shown the presence of occasional bunucleated cells resembling Reed-Sternberg cells; however, Hodgkin lymphoma is negative for cytokeratins and positive for CD30 and CD15. Basal-cell carcinoma will demonstrate neoplastic basophilic cells extending downward from the epidermis, whereas LELCS does not typically have an epidermal connection and lacks peripheral palisading. Inflamed, poorly differentiated squamous-cell carcinoma (SCC) strongly resembles LELCS. However, LELCS typically does not involve overlying epidermis, and poorly differentiated SCC usually has an area of well-differentiated carcinoma or overlying SCC in situ. Cutaneous lymphadenoma demonstrates a similar dense lymphocytic infiltrate as LELCS, but these lymphocytes appear benign and monomorphic. Follicular dendritic-cell tumor (FDCT) is similar to LELCS by way of syncytial-appearing plump cells surrounded by reactive lymphoid cells, but FDCT stains negative for cytokeratin markers. FDCT will demonstrate positive reactivity to Ki-M4, CD21, and CD35. Histologically, LELCS is remarkably similar to metastatic lymphoepithelioma of the nasopharynx, also known as undifferentiated nasopharyngeal carcinoma. Epstein-Barr virus (EBV) reactivity is the main distinguishing factor between LELCS and undifferentiated nasopharyngeal carcinoma. In general, LELCS is negative for EBV reactivity, whereas undifferentiated nasopharyngeal carcinoma will test positive for EBV. There has been only one reported case, that of a Japanese woman, of LELCS in a patient who tested EBV positive, but no related neoplasms were found elsewhere in the patient's body. In situ hybridization for EBER, the most reliable, specific, and highly sensitive method for detecting latent EBV, was used in this case report and yielded a negative result for EBV in our patient. Metastatic lymphoepithelioma of the nasopharynx is rare, but aggressive when it does occur. LELCS secondary to metastasis of undifferentiated nasopharyngeal carcinoma appears to be very rare, as there are fewer than 20 cases currently reported in the literature. Nonetheless, it is highly recommended to evaluate the patient for possible undifferentiated nasopharyngeal carcinoma by a complete otolaryngologic exam including indirect laryngoscopy of the nasopharynx. A review of symptoms is recommended when LELCS is confirmed to exclude metastasis from a variety of internal organ systems. Lymphoepithelioma-like carcinoma can be found in many organs besides the skin, including salivary glands, thyroid, thymus, lungs, stomach,
kidney, breasts, uterine cervix, prostate, vagina, and urinary bladder.\textsuperscript{6,7,16,17,23,27} Histologically, EBV reactivity has been associated only with lymphoepithelioma-like carcinoma of the stomach, salivary glands, lungs, and thymus.\textsuperscript{4,5,22,24}

### Treatment

The prognosis for patients with LELCS is generally good despite its categorization as a poorly differentiated neoplasm.\textsuperscript{2,3,6,22,27} It is a low malignant tumor with rare reports of metastasis to lymph nodes at presentation and to internal organs such as, liver, lung, and bone.\textsuperscript{9,27} There are only two reported deaths from metastatic LELCS.\textsuperscript{6} There are multiple reports of local recurrence after incomplete excision.\textsuperscript{4} Therefore, most LELCS are treated by wide local excision or Mohs micrographic surgery to lower the risk of recurrence.\textsuperscript{4,24} LELCS and undifferentiated nasopharyngeal carcinoma are both radiosensitive, and this treatment modality should be used for recurrent cases, nonsurgical candidates, and those with lymph-node metastasis.\textsuperscript{3,8} There are also a few reports of perineural invasion, in which Mohs micrographic surgery, radiation, and chemotherapy were used in combination therapy without evidence of recurrence on follow-up evaluation.\textsuperscript{4,27}

### Conclusion

In conclusion, lymphoepithelioma-like carcinoma of the skin is a rare, slowly growing neoplasm with low malignant potential. LELCS is believed to be of epithelial origin based on immunohistochemical reactivity, although its exact histogenesis remains debatable. There are multiple dermatologic neoplasms that can clinically resemble LELCS. Therefore, it is important to conduct a histologic examination from a biopsied specimen to exclude other dermatologic entities. Undifferentiated nasopharyngeal carcinoma demonstrates identical histologic characteristics, and although it rarely occurs, it is a very aggressive neoplasm that requires a thorough otolaryngologic examination and CT scans of the head and neck if suspected. A thorough review of systems is recommended to exclude other possible organ systems that may have a lymphoepithelioma-like carcinoma metastasizing to the skin. Wide surgical excision or Mohs micrographic surgery are the recommended treatments for non-aggressive forms of LELCS to prevent local recurrence. To the best of our knowledge, this is the first case demonstrating two primary lymphoepithelioma-like carcinomas of the skin presenting in different anatomic locations on the same patient without evidence of a metastatic source.

### References


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Primary Cutaneous Carcinosarcoma: A Case Report and Discussion of a Histological “Chimera”

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Abstract
Primary cutaneous carcinosarcoma is a rare and aggressive biphasic malignant neoplasm that exhibits both epithelial and mesenchymal components. This malignancy is more commonly described arising from organs such as the uterus, breast, bladder, and lung, and is rarely seen on the skin. The histopathogenesis of this neoplasm is unknown, but a prevailing divergence theory exists. It is imperative that this neoplasm be diagnosed and treated, as it can be fatal. Here we report a case of primary cutaneous carcinosarcoma presenting on the skin of an 86-year-old male.

Introduction
Primary cutaneous carcinosarcoma (PCC) is a rare neoplasm not commonly found on the skin. To our knowledge, fewer than 100 cases of PCC have been reported in world literature. Carcinosarcoma is most often observed in organs other than the skin including the uterus, breast, urinary bladder, and lungs. When it does occur on the skin, it is typically found on an elderly male in sun-exposed areas of the head, neck, and upper extremities. Clinically, the lesion is often exophytic and ulcerated and develops rapidly.

Case Report
An 86-year-old male presented with a lesion on his left cheek of 3 months’ duration. On physical exam, there was a 1.0 cm x 1.2 cm, ill-defined, red, friable nodule on the patient’s left cheek. The clinical impression was of basal-cell carcinoma. After a shave biopsy, routine H&E stains of the lesion revealed a poorly differentiated, biphasic malignant neoplasm comprised of trabecular arrangement of pleomorphic cells with considerable cytoplasm juxtaposed with atypical cellular hyperchromatic malignant stroma (Figure 1). Immunohistochemical stains revealed the pleomorphic cells with considerable cytoplasm were positive for cytokeratin (Figure 2) and p63 (Figure 3), while the intervening atypical stromal cells were positive for vimentin (Figure 4) and CD10. Both cell populations were negative for neuroendocrine markers. Computed tomography of the neck and chest was negative for locoregional lymphadenopathy. This microscopic and radiographic analysis was consistent with primary cutaneous carcinosarcoma. The mesenchymal component may be of osseous, cartilaginous or, more rarely, skeletal- or smooth-muscle lineage.

Discussion
Primary cutaneous carcinosarcoma is an aggressive tumor composed of carcinomatous and sarcomatoid cells. The epithelial component is most commonly a basal-cell carcinoma or squamous-cell carcinoma, but it can also be associated with adnexal-derived tumors including spiradenocarcinoma, porocarcinoma, proliferating trichilemmal cystic carcinoma, and metrical carcinoma. The mesenchymal component may be of osseous, cartilaginous or, more rarely, skeletal- or smooth-muscle lineage.

Immunohistochemical stains are important for the diagnosis of carcinosarcoma. Cytokeratin highlights the epithelial elements, while vimentin highlights the mesenchymal elements. Two studies emphasize the role of p63, a homologue of the tumor suppressor gene p53, in confirming epithelial derivation of poorly differentiated or metaplastic carcinomas. It is thought that p63 is involved in the prevention of terminal squamous stem-cell differentiation and can be the key to establishing an epithelial presence in a tumor. Pure sarcomas and carcinomas are negative for p63, thus p63 staining is highly specific for diagnosing metaplastic carcinomas like PCC.
CD10 in the mesenchymal component, but the significance of this is unclear as this pattern is recognized in both basal-cell carcinomas (epithelial lineage) and atypical fibroxanthomas (mesenchymal lineage).2

Treatment of PCC is predominantly surgical with wide local excision and, as in the case of our patient, Mohs micrographic surgery. Adjuvant radiotherapy is not currently recommended.4

Regular clinical follow-up is paramount.

Cutaneous carcinosarcomas typically have a better prognosis than carcinosarcomas arising in visceral organs, but nonetheless these tumors can be aggressive. Prognosis seems to be most closely linked to the origin of the epithelial component. One meta-analysis found that PCCs containing a basal- or squamous-cell carcinoma had a five-year survival rate of 70%.8 Conversely, PCCs with an epithelial element of adnexal origin have a poorer prognosis, with a 25% five-year disease-free survival rate.5 Other poor prognostic factors include age younger than 65, tumor size greater than 2 cm, a recent growth pattern, longer duration of existing skin tumor, and metastasis to lymph nodes.3,5 Even after surgical excision, 7% to 19% of PCCs recur.1,9 Diagnosis and treatment is necessary, with locoregional and distant metastases documented in 19% and 26% of cases, respectively.1 PCC can also be fatal, with one report documenting PCC with cerebral metastases resulting in death.10

Conclusion
PCC is an admixed malignancy of epithelial and mesenchymal components. The diagnosis of this rare neoplasm is critical given its high rate of recurrence, metastases, and occasional mortality. These risks are especially notable when the lesion clinically resembles an unexceptional basal-cell carcinoma, as in our case. It is necessary to increase knowledge and awareness of this uncommon and aggressive histologic “chimera.”

References

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Case report: Eccrine porocarcinoma of the scalp in an immunosuppressed patient

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Abstract
Eccrine porocarcinoma (EPC) is an extremely rare malignancy of the eccrine sweat glands. They arise from the intraepidermal portion of the eccrine glands and are locally aggressive, with a high propensity to metastasize. Compromised immunity may be a contributing risk factor for developing EPC. We report a case of EPC presenting on the scalp in a patient on immunosuppressive therapy for bilateral lung transplants.

Introduction
Eccrine porocarcinoma (EPC) was first described in 1963 by Pinkus and Mehregan. They used the term “epidermotropic eccrine carcinoma” to describe this tumor due to its origin from the intraepidermal portion of the eccrine sweat glands. EPC is a very rare type of skin cancer, representing 0.005% to 0.01% of all skin tumors.1-5 EPC tumors occur most commonly in older age groups, with peak incidence at age 67, and have a slight female predominance.3,4,6 They have various clinical appearances, presenting as an ulcerated nodule, plaque, polypoid or verrucous papule.4 The most common location is the lower extremities, but EPC can occur on the upper extremities, trunk and abdomen. EPC arising in the setting of immune compromise is rare. Here, we report a case of EPC presenting on the scalp in a patient on immunosuppressive therapy for bilateral lung transplants.

Case Report
A 49-year-old Caucasian male presented with a rapidly enlarging tumor on his left posterior scalp for five weeks. The lesion was mildly tender to palpation but was otherwise asymptomatic. No regional lymphadenopathy was palpable. Past medical history was significant for cystic fibrosis resulting in bilateral lung transplant. Medications included mycophenolate mofetil 1.5 g twice daily, prednisolone 5 mg daily, and tacrolimus 1 mg twice daily. Family history was noncontributory.

Clinical exam revealed a 2.7 cm, exophytic, pink, keratotic nodule on the left posterior scalp (Figure 1). Upon initial examination, squamous cell carcinoma was suspected, and excision with Mohs micrographic surgery (MMS) was planned for the following week. The patient was prophylaxed with cephalexin 500 mg twice daily due to his immunosuppression. The tumor was first debulked with a flexible blade, and a specimen was sent for permanent sections. Deep and peripheral margins were examined during MMS, and squamous cell carcinoma was present in the first two stages. The tumor was cleared after removal of the third stage. The resulting defect was 4 cm, and the patient was sent to plastic surgery for closure immediately following MMS.

Histopathological evaluation of the permanent sections revealed additional findings beyond what was seen during MMS. Low-power microscopy revealed a proliferation of atypical epithelium emanating from the intraepidermal portion of the eccrine sweat glands, extending into the dermis (Figure 2). Areas of epithelioid cells with intercellular bridges and keratinization were present. However, cells with ductal differentiation were present (Figure 3) and were highlighted with both carcinoembryonic antigen (CEA) (Figure 4) and cytokeratin 7 (CK7) (Figure 5). No areas of lymphovascular or perineural invasion were identified. Depth of involvement was at least 6.5 mm, Clarks level IV. A diagnosis of eccrine porocarcinoma with squamous differentiation was made.

Subsequently, the patient was sent to medical oncology for evaluation and recommendations for further workup. The consultant endorsed only close clinical surveillance. At the time of publication, this patient has been recurrence-free for two months.

Discussion
Pinkus and Mehregan first described the tumor as epidermotropic eccrine carcinoma in 1963, and it was later termed eccrine porocarcinoma (EPC) by Mishima and Morioka in 1969. 2

Eccrine porocarcinoma (EPC) is an extremely rare malignancy of the eccrine sweat glands. The tumors arise from the intraepidermal portion of
the eccrine glands and are locally aggressive, with a high propensity to metastasize. EPCs most commonly occur in adult life, with various reports of peak incidence ranging from 67 to 74 years. A majority of authors report no difference in incidence between genders; however, Riera-Leal et al. recently described a slight female bias (64%). The most frequent location of presentation is the lower extremities (50%), followed by the trunk (24%), head (18%), and upper extremity (8%).

Our case involved an atypical presentation on the scalp in an immunosuppressed patient.

Clinically, eccrine porocarcinomas can have a variety of appearances, such as ulcerated nodule, verrucous plaque, or polypoid papule. Due to their protean clinical presentations, these tumors are often misdiagnosed preoperatively and can be mistaken for pyogenic granuloma, basal cell carcinoma, seborrheic keratitis, amelanotic melanoma, and, as in our case, squamous cell carcinoma.

Histologically, EPCs are located in the epidermis and dermis, as they arise from the intraepidermal portion of the eccrine sweat glands. The tumor is characterized by epithelioid cells with ductal lumen associated with pleomorphic, hyperchromatic nuclei and mitotic figures. When confined to the epidermis, they are termed “in situ.” They can also invade the dermis with a pushing or infiltrative pattern. In our case, there was involvement of atypical cells extending into the dermis. There was no evidence of cutaneous or systemic metastases (no palpable lymphadenopathy); however, due to the aggressive nature of the lesion (and the patient’s immunosuppressed state), our patient was referred to medical oncology.

EPCs are locally aggressive with a high likelihood of metastasis. Twenty percent of cases have reported local and lymph-node metastases (even though margins were free on pathological exam), while 10% of cases have reported further metastases to viscera and bone. With metastases, prognosis is poor, with reports of mortality rates ranging from 67% to 80%. Prognosis has been associated with clinical characteristics such as multinodularity, ulceration, and rapid growth. Histologic features also correlate with prognosis: A mitotic index of more than 14 mitotic cells/hpf, lymphovascular invasion, and a tumor depth greater than 7 mm indicate a worse prognosis.

High-risk features in our patient’s tumor included ulceration, rapid growth, and a possible depth of greater than 7 mm.

In addition, compromised immunity may be a contributing risk factor for developing EPC. Six previous cases of EPC in immunosuppressed patients have been described: three patients with renal transplants, two patients with human immunodeficiency virus (HIV), and one patient with chronic lymphocytic leukemia (CLL). Our patient, on treatment after bilateral lung transplant with cystic fibrosis, is the seventh reported case of EPC with immunosuppression.

Due to the rarity of this lesion, as well its aggressive nature, an optimal treatment plan has not been defined. A variety of treatment options are used for EPCs and include wide local excision (WLE), chemotherapy, radiation therapy and Mohs micrographic surgery (MMS). While most cases have been treated with wide excision, Song et al. proposed that MMS has proven success and should be considered. MMS allows for examination of 100% of peripheral margins vs. traditional bread-loaf sections with WLE.

Conclusion

Eccrine porocarcinoma (EPC) is a rare skin malignancy presenting with a variety of clinical appearances, making identification difficult. In our case, an exophytic, pink, keratotic nodule was located on the scalp and initially thought to be squamous cell carcinoma. EPC recognition is important due to its aggressive growth, propensity for recurrence and spread, and resultant poor prognosis. No concise guidelines have been established for the treatment of EPC due to the paucity of reports in the literature. We report the 22nd case of EPC treated with MMS. It is a unique case of eccrine porocarcinoma due to its uncommon location on the scalp, as well as its presentation in an immunosuppressed patient. To the best of our knowledge, there have been fewer than 10 cases of porocarcinoma involving the scalp reported in the literature. Our patient is also only the seventh reported case of EPC with compromised immunity, and, to our knowledge, the first case in a patient with lung transplantation.

References


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Introduction
Scleroderma is a rare connective-tissue disorder of unknown etiology. It is characterized by increased collagen production resulting in dermal thickening and hardening of the skin. Scleroderma involves a wide range of disease. It can include systemic involvement of the internal organs, referred to as systemic sclerosis, or it can be confined to the skin in a localized form, referred to as morphea or localized scleroderma. En coup de sabre is a rare craniofacial subtype of localized scleroderma.

Case Report
A 16-year-old female presented to our clinic with a one-year history of hair loss involving the right side of her scalp. She denied any associated symptoms such as headaches, vision changes or trauma to the scalp. The patient had no medical history and no significant family or drug history.

On physical examination, there was a hyperpigmented, atrophic plaque extending from the vertex of her scalp down to the right side of her forehead (Figure 1). The patient’s complete blood count (CBC) and comprehensive metabolic panel (CMP) were unremarkable, but the vitamin D level was decreased at 16 ng/ml. Autoimmune serology was performed, and patient was negative for ANA, DSDNA, SSDNA, SCL-70, anti-centromere, SS-A, SS-B, C3, and C4.

A biopsy was taken from the vertex of the scalp. Histopathology showed thick, dense hyalinized collagen bundles in the dermis (Figure 2). There was a sparse, deep lymphocytic infiltrate that did not extend into the subcutaneous fat (Figure 3). The patient’s clinical history, physical examination, laboratory results and histopathologic findings were consistent with linear scleroderma en coup de sabre, a rare subtype of localized scleroderma.

Our patient received a prednisone taper, which began at 60 mg daily and eventually tapered down to 10 mg daily over a period of one month. Concurrently, the patient began methotrexate...
15 mg once a week with folic acid 1 mg every day except the day methotrexate was taken. Vitamin D supplementation was not given to our patient. Our clinic did not have UVA/PUVA or narrowband UVB therapy available, but the patient was referred to a clinic that did have these modalities. The patient refused these therapeutic options. This treatment plan yielded good results, with the patient and physician both noting less induration of the lesion after three months of methotrexate. The patient’s lesion did not show much improvement visually (Figure 4, p. 47), but on palpation there was significant softening of the plaque.

Discussion
Scleroderma is a rare connective-tissue disorder in which increased collagen production leads to thickening and hardening of the skin. In systemic sclerosis, there is systemic involvement of internal organs; in morphea, or localized scleroderma, the disease is confined to the skin. Both localized and systemic forms are characterized by fibrosis of the skin. Localized scleroderma is further divided into five main subtypes on the basis of clinical appearance and distribution.1 These include plaque, bullous, generalized, deep, and linear scleroderma.

The incidence of localized scleroderma ranges from 0.4 to 2.7 per 100,000 people.2 Though all races may be affected, there is an increased prevalence among Caucasians, accounting for 72% to 82% of patients.2 There is a female predominance in all subtypes of localized scleroderma except for linear scleroderma, in which males and females are equally affected.1 There is a similar distribution among children and adults. In adults, the incidence peaks in the fifth decade of life. In children, 90% of patients are diagnosed between the ages of 2 and 14 years.3,4 Though the pathophysiology of scleroderma has yet to be fully elucidated, it is postulated that the fibroblasts of patients with scleroderma produce increased levels of extracellular matrix components including collagen, elastin, fibronectin and glycosaminoglycans.7 This elevated fibroblast activity can also lead to increased levels of signaling and transcription molecules, including IL-6, pro-IL-1 alpha and ICAM-1.7 This culminates in increased deposition of extracellular matrix components, resulting in hardening of skin.

En coup de sabre is an unusual variant of linear scleroderma and is defined by its distinct location involving the frontoparietal region of the forehead and scalp. The term “en coup de sabre” was originally coined by the French to depict the wounds inflicted on foot soldiers who were struck on the head with a sword, which resulted in a thickened scar on one side of the forehead.

Clinically, the lesion presents as a linear, band-like, ivory-colored, sclerotic plaque with violaceous borders. The violaceous border often surrounds the indurated plaque and has been described as a lilac ring. En coup de sabre is also characterized by atrophy and furrowing of the skin. Alopecia may be present in the area of involved scalp, which can be the presenting complaint. Typically, the lesions are confined to the skin and subcutaneous tissue; occasionally, underlying muscle, cartilage and bone can also be involved, resulting in facial atrophy. When hemifacial atrophy occurs, Parry Romberg syndrome (PRS) should be in the differential diagnosis. It has been reported that PRS coexisted in 20% to 37% of patients diagnosed with en coup de sabre.4 There have been many discussions as to whether these are two distinct diseases or clinical variants of the same disease. The ailments have comparable ages of onset and disease progressions. PRS may have dermatologic findings similar to those seen in en coup de sabre, but they are typically more prominent and do not exhibit cutaneous sclerosis at any stage of the disease.

On rare occasions, localized scleroderma has been associated with multisystemic involvement, including rheumatologic, ophthalmologic and neurologic manifestations, which occur in about 20% of cases.5 Onset of cutaneous disease precedes extracutaneous manifestations. Neurologic abnormalities occur most commonly in association with en coup de sabre, and of these, complex partial seizures occur most frequently.10 Radiologic anomalies are predominantly ipsilateral to the skin lesion. Neuroradiologic abnormalities can involve white-matter lesions, cerebral atrophy, intraparenchymal calcification, meningoencephalomalacic changes and skull atrophy.11 CT scan of the brain can show thinning of the skull under the cutaneous lesions. MRI of the brain may show focal cerebral atrophy and blurring of the gray-white matter. A gadolinium-enhanced MRI of the brain has been recommended for all patients with neurologic symptoms.12 Amaral et al. suggest that all patients, regardless of symptoms, should be considered for neuroimaging studies at the time of diagnosis given that a subset of patients will have neurological damage without displaying clinical signs.8

The pathogenesis of scleroderma is not entirely known. Evidence suggests it is autoimmune in nature and initiated by a provocative event, most commonly local trauma to the skin. Subsequent endothelial-cell damage leads to an increase in fibroblast activity and ischemia secondary to narrowing of the lumen and alteration in collagen production.11 There have been reports of a positive association between Borrelia infection and scleroderma, but there has been no evidence of Borrelia infection in scleroderma lesions.15 Patients may also have elevated autoantibodies, most frequently anti-nuclear antibody and anti-single stranded DNA (ssDNA) antibody. Rheumatoid factor, anti-histone antibody, anti-phospholipid antibody and anti-topoisomerase IIB antibody may also be elevated, but these are seen more commonly in generalized morphea.13 There is no autoantibody that correlates with disease activity.14,15

It has also been noted that patients with scleroderma have lower serum levels of vitamin D. It is not entirely clear whether this is an incidental finding or reflects a true association between vitamin D levels and clinical manifestations of scleroderma. Recent studies, however, have shown that individuals with vitamin D deficiency are at a higher risk of developing autoimmune diseases.16 It is postulated that the relationship between vitamin D and autoimmune disease has to do with vitamin D’s immunomodulating activity on vitamin D receptors present on antigen-presenting cells and activated T cells.17 In 2011, a study conducted in Hungary to find a link between scleroderma and serum vitamin D levels concluded that patients with scleroderma do have considerably lower serum concentrations of vitamin D when compared to controls, and that cutaneous fibrosis is inversely related to serum vitamin D concentrations.18 This relationship between vitamin D and autoimmune disease suggests that vitamin D may be a modifiable environmental factor in patients with scleroderma.

Treatment and Prognosis
En coup de sabre is typically a self-limited disease in children. There can be softening or regression of skin lesions, but complete resolution seldom occurs and reactivation is always possible.19 The long-term prognosis of en coup de sabre in children is generally excellent. In most cases, the cosmetic defect is minimal and can be covered by the patient’s hair. Adults tend to have a more variable course, with some patients clinically deteriorating over time. This may result in severe contractures.

Studies have found that early intervention during the active phase of the lesions is most beneficial. For initial management, it has been recommended to use methotrexate and systemic glucocorticoids, followed by UVA1 with or without psoralens, narrow-band UVB, or mycophenolate mofetil.20,21 Other treatment options include topical and intraslesional glucocorticoids, vitamins E and D3, D-penicillamine, antimalarials, retinoids, and immunosuppressive agents such as cyclosporine and cyclophosphamide.11 Ultraviolet A light (UVA), with or without psoralens, is an effective therapeutic option. UVA1, which is a specific wavelength range of UVA, offers particularly deep skin penetration and is believed to soften the plaques by two mechanisms: causing systemic immunosuppression, and inducing enzymes that degrade the collagen matrix in the skin.

In cases where the lesions are disfiguring and the patient pursues cosmetic improvement, surgical repair is a corrective option. Narrow lesions can be treated with simple excision followed by primary closure. Wider lesions may necessitate a more elaborate reconstruction, which can include an array of flaps, implants or autologous fat or bone transplantation. Due to the invasiveness of these procedures, the use of fillers, such as hyaluronic acid, have been employed as an alternative.21

Conclusion
En coup de sabre is a rare connective-tissue disorder which may have a variable clinical course. The pathogenesis of the disease is not entirely understood, but it is postulated that it is autoimmune in nature. Early intervention during the active phase of the lesions is most beneficial. For initial management, it has been recommended to use methotrexate and systemic glucocorticoids, followed by UVA1 with or without psoralens, narrow-band UVB, or mycophenolate mofetil. Other treatment options include topical and intraslesional glucocorticoids, vitamins E and D3, D-penicillamine, antimalarials, retinoids, and immunosuppressive agents such as cyclosporine and cyclophosphamide. Ultraviolet A light (UVA), with or without psoralens, is an effective therapeutic option. UVA1, which is a specific wavelength range of UVA, offers particularly deep skin penetration and is believed to soften the plaques by two mechanisms: causing systemic immunosuppression, and inducing enzymes that degrade the collagen matrix in the skin.
disorder, identified by its distinct location on the frontoparietal scalp and forehead. Early intervention during the active phase of the disease has shown maximum benefit in overall outcomes in these patients. Scleroderma has been associated with low levels of vitamin D. Further studies are needed to elucidate whether there is a causative relationship between vitamin D deficiency and scleroderma. This could give insight into whether normalizing vitamin D levels would modify the disease progression, potentially presenting a new therapeutic focus.

References

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Sickle Cell-Associated Leg Ulcers: A Case Presentation and Discussion

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Abstract
This case describes a 46-year-old female with a history of sickle-cell disease and a non-healing ulcer on her lateral malleolus. Etiology, clinical presentation, and management of sickle-cell ulcers are discussed.

Introduction
Sickle-cell leg ulcers are a frequent complication of sickle-cell disease. While the pathogenesis of these ulcers is not completely understood, many factors are believed to contribute, including trauma, mechanical obstruction, venous incompetence, bacterial infections, abnormal autonomic control, thrombosis, anemia with decreased oxygen carrying capacity, and decreased nitric oxide bioavailability. Although management is often difficult, it should always include three key objectives: treatment of current ulcers, managing complications, and prevention of future lesions.

Case Report
A 46-year-old black female with a history of sickle-cell anemia treated with hydroxyurea presented to the dermatology clinic complaining of a non-healing wound on her right ankle for 10 to 12 weeks. She complained of a moderate, dull, constant pain and recalled wearing an ill-fitting shoe that had rubbed the area prior to the development of the wound. The patient had previously seen her internist, an infectious-disease physician, and a wound-care specialist for this condition. Previous treatments, including anti-gout medications, a six-day oral-prednisone taper, topical lidocaine and collagenase ointment, failed to improve symptoms. She was otherwise healthy and had no history of tobacco use or previous non-healing skin lesions.

On physical exam, there was a 4 cm x 3 cm ulcer overlying the right lateral malleolus with white-yellow adherent discharge centrally, undermined borders, and 1 cm of surrounding erythema (Figures 1, 2). The site was tender to palpation. No edema was present, and dorsalis pedis pulses were 2+ bilaterally. A biopsy was taken to rule out an underlying squamous-cell carcinoma and vasculitis.

The pathology revealed vaso-occlusion of superficial dermal blood vessels with overlying epidermal necrosis (Figures 3, 4). A bacterial culture taken after the biopsy demonstrated Pseudomonas aeruginosa, which was treated with ciprofloxacin. The patient was prescribed a trolamine emulsion for local wound care and zinc-sulfate supplementation, and her pain was adequately managed with a lidocaine patch and oral gabapentin. She was referred to vascular surgery for evaluation of possible venous insufficiency. Doppler ultrasound and MRI were negative for venous insufficiency and osteomyelitis, respectively.

Considering the patient’s history and negative supplementary tests, the differential diagnosis included sickle-cell ulcer versus hydroxyurea-induced ulcer. Due to concern for potentially severe vaso-occlusive crisis, discontinuation of hydroxyurea was not recommended by hematology. She was referred to wound care, who reported positive improvement in size, depth and pain with a combination of weekly surgical debridement and alternating topical collagenase gel and a triple antibiotic gel containing amikacin, levofloxacin, and vancomycin.

Discussion
Sickle-cell disease (SCD) is an autosomal-recessive inherited blood disorder characterized by bone-marrow production of red blood cells with defective, sickled hemoglobin (hemoglobin S). This occurs due to a point mutation in the DNA of the β-globin subunit of adenine for thymine.1 The resulting translated protein contains a substitution of the amino acid valine for glutamic acid in the beta-hemoglobin chain.2 When the defective hemoglobin becomes deoxygenated, polymerization occurs, leading to misshapen, sickled, rigid red blood cells. Leg ulcers are the most common cutaneous manifestation of SCD and are a long-recognized complication of SCD, dating back to the first documentation of a sickle-cell patient by Herrick in 1910.3,4 Reported prevalence is 2.5% in the United States, 1.5% to 13.5% in Africa, and >40% in Jamaica, with homozygous SS and SS β-thalassemia patients having the overall highest prevalence rate of all genotypes.3,5,6 Sickle-cell-associated leg ulcers (SCU) are often painful and disabling, with slow healing times and frequent recurrence. Limiting mobility, they often become a hindrance to education and employment. For these reasons, they have a profound effect on patients’ quality of life and can lead to mood disturbances.7

The pathogenesis of these ulcers is not completely understood, but it is generally believed to be a multifactorial process. Proposed potential contributing factors include mechanical obstruction by dense, sickled red cells, venous incompetence, bacterial infections, abnormal...
autonomic control with excessive vasoconstriction when in the dependent position, in situ thrombosis, anemia with decrease in oxygen carrying capacity, and decreased nitric oxide bioavailability leading to impaired endothelial function. Trauma is also believed to contribute to the development of these ulcers by triggering sickling of the red blood cells. Areas with less subcutaneous fat, thin skin, and decreased blood flow (such as the malleoli, anterior tibia, dorsal foot, and Achilles tendon) are frequently involved, with the medial malleolus being the most common location for sickle-cell ulcers. Other risk factors include age greater than 20 years old, male gender, hemoglobin less than 6 g/dL, lower fetal hemoglobin, antithrombin III deficiency, and HLA types B35 or Cw4.

Clinically, SCU appear as round, punched-out ulcers with raised borders, deep bases, necrotic slough, and at times surrounding hyperpigmentation and scaling. These surrounding changes are also frequently seen with venous ulcers. Having an active ulcer carries a 146-fold increased risk of developing further ulcers, so nearby additional ulcers or scarring from previous ulcers may be observed. Biopsies are often nonspecific; however, vascular obstruction of superficial dermal blood vessels by the rigid, inflexible, sickled red blood cells with overlying tissue necrosis may be seen. Additional work-up of a patient with suspected SCU includes venous and arterial studies to assess underlying peripheral vascular status, peripheral blood smear, complete blood count, folate, iron, vitamin B₁₂, homocysteine, liver enzymes, renal function, urinalysis, D-dimer, and hemoglobin electrophoresis to measure the levels of hemoglobins A, S, and F.

Management of SCU includes three key points: treatment of current ulcers, managing complications, and prevention of future lesions. Preventative measures include maintaining the skin barrier function with liberal use of emollients, evading trauma by wearing properly fitting shoes and using insect repellent, and promoting good venous drainage and minimizing stasis through compression stockings, leg elevation, and salt restriction. Patients should be educated regarding these preventive measures as well as on how to recognize early signs of skin injury. Treatment of existing ulcers can be challenging, and thus far there is no general consensus as to the gold standard of therapy. Treatment options include local wound care, surgical interventions, and systemic medications. Topical therapies for local wound care include triple antibiotic ointment, arginine-glycine-aspartic tripeptide bound to hyaluronate, and topical oxygen with a tent. In addition, various wound-care dressings have been used, such as wet-to-dry dressings, Unna boots, hydrocolloid dressings, collagen matrix dressings, hemodialysate, and hydrophilic polyurethane film.

Compression and activity restriction can be critical to healing. Surgical interventions include debridement to remove non-viable tissue as well as myocutaneous flaps and split-thickness skin grafts for extensive or recalcitrant ulcers. Unfortunately, most allografts fail due to the preexisting cutaneous changes. A bilayered skin-equivalent graft manufactured from neonatal foreskin was reported to cause rapid healing without recurrence. Reported systemic treatments for SCU include zinc sulfate, pentoxifylline, antithrombin III, L-carnitine, arginine butyrate, hydroxyurea, and transfusions. Oral zinc sulfate improves the anemia of SCD and is also a key element in wound healing. Pentoxifylline, an effective medication for decreasing vaso-occlusive crises in SCD, was reported successful in one case of SCU. It is thought to work by decreasing sickling of red blood cells, increasing erythrocyte deformability, increasing leukocyte flexibility, inhibiting platelet aggregation, reducing blood viscosity, and decreasing plasma fibrinogen levels. In a case of concomitant antithrombin III deficiency, heparin and antithrombin III concentrate successfully treated a patient’s ulcer. L-carnitine, an efficacious treatment for ischemic heart disease, peripheral arterial disease, and vasculopathic leg ulcers, has been demonstrated to aid in healing of SCU in case reports. Arginine butyrate, which increases fetal hemoglobin synthesis, rapidly healed one patient’s ulcer.

Hydroxyurea (HU) is an antimetabolite that inhibits ribonucleotide reductase, thereby inhibiting DNA synthesis. It increases fetal hemoglobin levels and red-blood-cell water content while decreasing deformability and adhesion to vascular endothelium. Its efficacy in treating SCD was first demonstrated in 1990 and has decreased the number of vaso-occlusive crises in severe cases. It is currently the only FDA-approved drug for SCD. While some authors report improvement of leg ulcers with hydroxyurea, others state development or worsening of leg ulcers with this drug. Theoretically, the increase in fetal hemoglobin should be beneficial, as populations of sickle-cell patients with high spontaneous rates of hemoglobin F (such as in Saudi Arabia) have a low incidence of leg ulcers. However, it has been hypothesized that the reduced susceptibility of erythrocytes to deformation caused by HU may impair blood flow in the microcirculation, leading to anoxia and consequent cutaneous ulceration after a minor trauma.

Average healing time for a hydroxyurea ulcer after discontinuing the drug is four months, which coincides with the known 120-day survival of the circulating red blood cells. While definitive, randomized controls are still needed to further elucidate the relationship between this drug and SCU, careful attention should be given to skin changes during HU treatment in patients with SCD. Adding recombinant human erythropoietin aided in ulcer healing in one case study and may be an option for patients who are unable to discontinue HU. Transfusions of packed red blood cells are commonly used to prevent and treat many complications of SCD, including anemia, acute chest syndrome, and pulmonary hypertension. Despite a lack of controlled trials, they have also been utilized as a mode of therapy for recalcitrant SCU. However, the procedure has several risks including iron overload and alloimmunization. Other recent, developing advances in therapy include topical granulocyte-macrophage colony-stimulating factor, negative-pressure therapy, low-level laser therapy, oral bosentan, and heparin sulfate. Additional randomized, controlled
Anticonvulsants. However, there are anecdotal reports of topical opioids offering total pain relief for SCUs. Balls described two patients, one treated with one tablet of oxycodone dissolved in 1 mL to 2 mL of water mixed with debride ment ointment, the other with one 100 mg tablet of meperidine dissolved in water and applied with xylocaine ointment. Both patients reported almost immediate pain relief and an ability to significantly reduce their consumption of oral opioids.

**Conclusion**

Sickle-cell ulcers are a common and difficult complication of sickle-cell disease. They present as round, punched-out ulcers on areas with thin skin and decreased blood flow, most commonly the medial malleolus. Their pathogenesis is not yet fully elucidated but seems to be multifactorial. Management consists of preventing, controlling complications, and treating existing wounds. Treatment of the ulcers is difficult and often requires a combination of topical medications, dressings, compression, debridement and even systemic therapies. The role of hydroxyurea is not yet fully determined; it could possibly help, worsen, or have no effect on patients’ ulcers. The risk-to-benefit ratio must be considered when initiating or discontinuing this medication in a patient with sickle-cell disease.

**References**

Twenty-nail Dystrophy in a 42-year-old Woman: A Case Report

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Abstract
Twenty-nail dystrophy is a nail disorder that commonly affects all 20 nails. We report a case affecting a 42-year-old female with co-existing alopecia areata.

Introduction
Twenty-nail dystrophy (TND), also known as trachyonychia, is a nail disorder commonly affecting all 20 nails. It may present as an idiopathic finding, a familial condition, or occurring in association with other dermatologic conditions, most commonly alopecia areata, psoriasis, or lichen planus. Here we present a case of a 42-year-old female with TND and co-existing alopecia areata (AA). Although TND is often self-limiting, many patients seek treatment secondary to the cosmetic appearance. There is not a well-known and universally accepted treatment for TND. Our patient was successfully treated with the daily application of flurandrenolide tape and urea 45% topical gel to all of her nails, along with biotin 5,000 mcg daily.

Case Report
A 42-year-old female with an unremarkable past medical history originally presented with a chief complaint of hair loss to the scalp, onset four months prior. During this initial encounter, the patient also had a secondary complaint that all of her fingernails and toenails had been painful and thinning for the past year. She stated that she had tried treating the nail problem with terbinafine, as well as fluconazole ointment, neither of which had improved her symptoms.

On physical exam, she was found to have an annular area to the scalp that was devoid of hair, as well as thinning of the nail plates to all of her fingernails (Figure 1) and toenails. The exam was otherwise unremarkable.

After diagnosing the patient with alopecia areata (AA) of the scalp and discussing options with the patient, a 3 mm punch biopsy was performed to the third digit of the left hand to further investigate her nails. Dermatopathology results showed a diagnosis of onychauxis with intraungual serum deposition (Figure 2). The changes in the sections were subtle and consistent with nail lichen planus. A dermatopathology consultation was also obtained, and again, nail changes most consistent with lichen planus were found. These findings, along with the concurrent AA, confirmed a diagnosis of trachyonychia and nail lichen planus. Had we not done a nail-matrix biopsy, it would have been assumed that the nail changes were secondary to the alopecia areata.
The patient was instructed to take biotin 5,000 mcg daily and apply flurandrenolide tape daily to all of her nails. She was also prescribed urea 45% topical gel to be applied to the nails daily. She opted to have triamcinolone acetonide injected to the annular area of the scalp. In her follow-up appointments, she reported that she had been compliant with our treatments and was found to have marked improvement of the pain and thinning of the nails, as well as re-growth of hair to her scalp lesion.

**Discussion**

Twenty-nail dystrophy, also known as trachyonychia, is a disorder that most commonly affects all 20 nails. It is a well-known disease and diagnosed based on clinical features and confirmed via biopsy.1 The causes of twenty-nail dystrophy (TND) can either be congenital, as in familial TND, or acquired in association with various dermatologic conditions.2 It was first described in 1950 by Alkiewicz.3 Twenty-nail dystrophy is characterized by a rough, sandpaper-like, lackluster appearance of the nails. Other possible nail findings include elevation/pitting, splitting, thinness, brittleness and/or a mushy-grayish color. A less common form of TND is characterized mostly by pitting and a “shiny” grayish color. A less common form of TND is usually bilateral and symmetric.1

TND is thought to have an autosomal-dominant mode of inheritance and often presents during childhood or at birth.5 The condition tends to have a slow progression.1 TND has been described occasionally in adults but most commonly affects children 3 to 12 years of age.6 TND has an equal predilection for males and females.7 TND is thought to be idiopathic, but occasionally an associated etiology is found.8 There is some question of a relationship with various other dermatologic conditions, such as vitiligo, psoriasis, eczema, lichen planus, alopecia areata/universalis, ichthyosis vulgaris, sarcoidosis, immunoglobulin (Ig)A deficiency, sarcoidosis, and graft-versus-host disease, among others.9,8,9 The most common associations and causes of TND are alopecia areata, psoriasis, and lichen planus.3 The strong association of TND with dermatologic conditions that have an autoimmune etiology has raised the suspicion that the nail changes could be immunologically mediated.10 In a study by Tosti et al., 40 of the 1,095 patients with AA had been diagnosed with trachyonychia.1,7 They found that trachyonychia occurs in approximately 3% of adults.7,11 Tosti et al. also noted that while nail changes may precede or follow the onset of alopecia, the two conditions often arise simultaneously.7,11 There was also found to be no association between the course of AA and the course of TND.7 In a study by Grover et al., AA was found to be the most common abnormality associated with trachyonychia.5

To confirm the diagnosis of TND, a nail biopsy is often performed. The specimen should be a longitudinal biopsy or a nail-matrix punch biopsy.1,5

The pathology often shows these subtypes: eczematous/dermatitis, lichen planus-like, and/or psoriasiform histopathology.1 The microscopic examination of the eczematous form may show spongiosi inflammatory changes of the nail matrix (most common), lymphocytic infiltrates, and exocytosis of the lymphocytes in the nail epithelium.1,9 The lichen planus-like morphology sections may show widespread hyperkeratosis, hypergranulosis, or a lymphohistiocytic infiltrate and degeneration of basal keratinocytes.1 Lastly, the psoriasiform histology sections may show acanthosis and parakeratosis with grouping of polymorphonuclear leukocytes along the nail plate.1

There is no generally accepted first-line treatment for TND. Treatment modalities range from intralesional injections to intramuscular injections as well as systemic and topical preparations. Some of the treatment modalities that have been used are PUVA (psoralen plus ultraviolet A light), acitretin, tazarotene gel 0.1%, triamcinolone acetonide IM injection, triamcinolone intralesional injections, oral prednisolone, topical 5-fluorouracil 5% cream, intra-matrix steroids with or without griseofulvin (10mg/kg for six months), and oral biotin therapy.1,8,9 Sakata et al. found in a follow-up study of 12 trachyonychia patients that regardless of treatment modality, 50% of the patients had resolution or significant improvement of their nail disease within six years.1,3

**Conclusion**

In summary, trachyonychia is a nail disorder commonly affecting all 20 nails. It may present as an idiopathic finding or along with other dermatologic conditions, most commonly AA, psoriasis, or lichen planus. Our patient did have an associated etiology of AA. The most common histopathological findings are spongiosis and lymphocytic exocytosis, although the disorder is usually diagnosed based on clinical appearance.1,13 Many treatment modalities have been tried, as there is not a universally accepted treatment regimen. However, depending on the cause of the TND, treatment may not be necessary, as it is a self-limiting disease that usually improves spontaneously, especially in children.5

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Urticaria Pigmentosa: A Case Report and Review of Current Standards in the Diagnosis of Systemic Mastocytosis

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Abstract

Mastocytosis is a group of diseases that is characterized by mast-cell infiltration of the skin. The cutaneous forms of the disease are most identifiable, yet it is important to recognize the progression to systemic disease due to the effect on morbidity and mortality. We Our goal is to describe a case of cutaneous mastocytosis as well as review the current standards in diagnosis and management of systemic mastocytosis.

Introduction

Mast-cell disease is a rare disorder, primarily of childhood, that is usually self-resolving. Approximately two-thirds of cases are limited to the skin. The most common forms of cutaneous mastocytosis include: mastocytoma, urticaria pigmentosa, telangiectasia macularis eruptiva perstans, maculopapular cutaneous mastocytosis, and diffuse cutaneous mastocytosis.1 Our case report presents a patient with a history of urticaria pigmentosa (UP) that had not resolved as expected. Furthermore, she started to develop symptoms that raised concern for possible systemic mastocytosis (SM). Based upon our literature search, systemic mastocytosis is an extremely rare diagnosis, but a potentially life-threatening one. This paper will help Uthas dermatologists become more familiar with worrisome signs/symptoms, diagnostic criteria, and treatments for systemic disease.

Case Report

A 20-year-old Caucasian female with a history of urticaria pigmentosa since childhood presented to our office for initial evaluation of worsening symptoms involving multiple organ systems. She complained of bone pain often localized to the bilateral knees. In addition, the patient had several bouts of loose stools. This was accompanied by bloating and indigestion, which occurred 30 minutes after a meal. A colonoscopy was performed one year prior at an outside facility, and it was within normal limits. However, no biopsies were performed to look for mast-cell infiltration of the digestive tract. Our patient also had sharp, intermittent, left upper quadrant abdominal pain that radiated to the left chest and shoulder. Remaining review of systems was negative except for occasional mild headaches and lightheadedness. She admitted to mild generalized pruritus for which she took hydroxyzine and cimetidine as needed. In addition, she experienced easy flushing, which was more pronounced while exercising and drinking alcohol.

The patient had a past medical history of mild asthma and attention deficit hyperactivity disorder. Social history included rare alcohol use, smoking one1 pack of cigarettes per day, and no illicit drugs. She was also exposed to different cleaning solvents daily as a carpet cleaner. Family history was non-contributory.

The physical examination revealed a subtle but diffuse, reddish-purple, motiled, reticular, macular discoloration involving the bilateral upper and lower extremities, chest, abdomen, and back (Figure 1–4, p. 55/56). The head and neck were uninvolved. Upon stroking lesions on the bilateral forearms, the areas became swollen, itchy, and red, eliciting a positive Darier’s sign. Examination of the liver and spleen did not reveal any organomegaly. Muscle strength and tone appeared to be within normal limits. There were no palpable lymph nodes in the neck, axillae or groin regions.

Our differential diagnosis included systemic mastocytosis as well as carcinoid syndrome, pheochromocytoma, inflammatory bowel disease, urticaria, and myeloproliferative disorder.

Through a collaborative effort between dermatology and hematology/oncology, an extensive workup to rule out SM was performed. Initially, punch biopsies of the right shin and left dorsal forearm revealed cutaneous mast-cell disease. Stains were positive for mast-cell tryptase and CD117 (Figure 5, p. 56). Complete blood count with differential, comprehensive metabolic profile, lactate dehydrogenase, fractionated catecholamines, IgE level, and uric acid were all within normal limits. Serum tryptase level was 14.8. Additionally, she underwent imaging studies including a CT scan of the chest, abdomen, and pelvis, abdominal ultrasound, and skeletal survey, which were all unremarkable. A bone-marrow biopsy was performed and showed that showed at least 15 clusters of dense mast-cell aggregates (Figure 6, p. 56). Flow cytometry did not reveal expression of CD2 or CD25 on CD117+ mast cells. Additionally, only about 10% of the mast cells were spindle-shaped within the bone marrow smear as opposed to greater than 25%. Furthermore, our patient tested negative for KIT D816V mutation.

Taking into account the clinical presentation, positive histopathology, and laboratory and bone-marrow findings, our patient did not meet the full criteria for the diagnosis of SM. For UP,
the patient was started on histamine H2-receptor antagonists, ranitidine 150 mg by mouth twice daily and famotidine 20 mg by mouth daily, as well as a mast-cell stabilizer, cromolyn 200 mg by mouth three times daily to control mast-cell activation. Additionally, she was given an epinephrine autoinjector in case of anaphylactic reactions. We suggested she also minimize exposure to cleaning solvents as this may be a potential aggravating factor. On follow-up, our patient's symptoms had improved. Cetirizine, a histamine H1-receptor antagonist, was also added to the regimen. In addition, we are considering phototherapy as an adjuvant treatment.

The patient continues to be closely monitored by both dermatology and oncology for potential risk of full-blown SM in the future. There is a likelihood that her disease will continue to progress. As a result, the patient was advised to follow up every four to six months for repeat labs.

Mastocytosis is more common in children than adults. Over 50% of children are diagnosed prior to two years of age, and disease is usually limited to the skin. Most children will spontaneously resolve by adolescence. In contrast, initial diagnosis of cutaneous mastocytosis as an adult increases the likelihood of developing systemic disease. The median age at diagnosis of SM in adults is 55 years, with a slight male predominance. The incidence of systemic disease is extremely rare. Neither cutaneous nor systemic forms of mastocytosis appear to be inherited.

Mutations of KIT have been implicated in the pathogenesis of both cutaneous and systemic mastocytosis. Mast cells express c-kit tyrosine kinase receptor on their surface, which serves as a site for attachment of stem-cell factor (SCF). SCF is a growth factor needed for the normal development and expansion of mast cells. In mastocytosis, there is a pathologic activation of the c-kit receptor, leading to unregulated clonal expansion and activation of mast cells. The most common mutation in systemic mastocytosis is on codon 816 replacing aspartic acid for valine. This is seen in up to 93% percent of patients with systemic mastocytosis. Recently, additional mutations have been identified.

Initial workup for SM involves a thorough history and physical examination looking for clinical clues to indicate an excess release of mast-cell mediators in cutaneous and extracutaneous tissues. Symptoms that may raise suspicion include rhinitis, vomiting, abdominal pain, bloating, diarrhea, flushing, pruritus, bone pain, fever, chills, weight loss, tachycardia, headaches, syncope, difficulty concentrating, anxiety, and depression. Physical assessment may reveal organomegaly, predominately involving the liver or spleen, lymphadenopathy, gastroesophageal ulcers, and signs of end-organ liver disease such as elevated transaminases, ascites, and portal hypertension in advanced disease forms.

In addition, one should investigate for skin findings consistent with reddish-brown, maculopapular, plaque-like, bullous or nodular lesions, diffuse skin involvement, solitary mastocytoma, telangiectasias, and positive Darier’s sign. These findings may indicate a new or prior diagnosis of cutaneous mastocytosis and will help with the workup for systemic disease.

The next step involves obtaining a skin biopsy. Special stains including Wright-Giemsa, Toluidine blue, tryptase, and CD117 should be ordered. In addition, laboratory investigation should include complete blood count with differential. The peripheral blood picture can show anemia, thrombocytopenia, and leukocytosis. Some patients with SM may also present with elevated eosinophils, basophils, and/or platelets. Myeloproliferative or myelodysplastic changes can also be seen.

Occasionally, it may be feasible to obtain imaging studies in order to identify the extent or stage of disease. For example, computed tomography scan, endoscopy/colonoscopy, or abdominal ultrasound may be considered in patients who present with primarily gastrointestinal complaints. Skeletal surveys and dual-energy X-ray absorptiometry scans may be helpful in patients with suspected bone involvement such as osteoporosis, osteolysis, and evaluation for pathological fractures. However, it is not necessary to evaluate extramedullary tissues for the presence of mast cells to make the diagnosis of SM if the bone marrow is being examined.

Bone-marrow analysis is of crucial importance in the diagnosis of SM. The presence of multiple aggregates of mast cells in bone-marrow aspirate is the major diagnostic criterion for SM as determined by the World Health Organization (WHO). Each aggregate should contain greater than 15 mast cells. The cells are usually located paratrabecularly, but they can also been
seen around vessels and adnexal structures. In addition, there are several bone-marrow findings in the WHO minor criteria for SM, which include the following: 1) more than 25% of mast-cell infiltrates demonstrating an abnormal spindle-shape; 2) flow cytometry of bone-marrow preparation demonstrating mast cells that express CD2 and/or CD25; and 3) polymerase-chain-reaction evaluation of bone-marrow cells detecting a positive mutation of KIT D816V. This mutation can also be evaluated via a blood test. Along with a serum tryptase level greater than 20 ng/mL, these four findings account for the WHO minor criteria for SM. In order to make a diagnosis of SM, an individual must present with one minor and one major criterion or three minor criteria.

The treatment of mast-cell disease is multifaceted. First and foremost, patients should avoid triggers such as excess heat, intense exercise, insect and snake bites, medications like aspirin and non-steroidal anti-inflammatory drugs, and alcohol. In addition, some muscle relaxants and inducing agents used during surgery for general anesthesia may cause mast-cell mediator release and potentially cause anaphylactic reaction. Radiocontrast media may cause a similar reaction.

H1 histamine-receptor antagonists (H1) such as loratadine and hydroxyzine are the first-line treatments for symptoms caused by mast-cell mediator release. These help control urticaria and pruritus. Psoralen plus ultraviolet A (PUVA) therapy can also improve pruritus by reducing histamine release. Gastrointestinal symptoms respond better to H2 histamine-receptor antagonists (H2) like cimetidine and ranitidine. Cromolyn sodium helps decrease diarrhea, malabsorption, and bloating.

Individuals who demonstrate signs of osteoporosis benefit from calcium and vitamin D supplementation and may need bisphosphonates depending on the severity of disease. In addition, all patients should be given an epinephrine autoinjector and instructed on its use in case of anaphylaxis. Patients with more aggressive subvariants of SM may qualify for cytoreductive therapies such as imatinib mesylate, interferon alpha, and cladribine. These treatments are not curative but are intended to improve symptoms and quality of life.

**Conclusion**

This case highlights the important role that dermatologists play in the recognition of cutaneous mastocytosis progressing to systemic disease. It is imperative to perform a thorough history, physical, and review of systems in all patients with cutaneous mastocytosis to help initiate a comprehensive work up. Systemic disease can be quite aggressive and potentially life-threatening. Timely diagnosis and early treatment can decrease morbidity and mortality.

**References**


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**REFERENCES:**
1. Blecker, J. Double-blind comparison between two new topical steroids, halcinonide 0.1% and clobetasol propionate cream 0.05%. *Curr Med Res Opin.* 1975;3:225-228.

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Ronald R. Brancaccio, M.D.
Receives Dermatology Foundation Practitioner of the Year Award

At its recent annual meeting of membership in San Francisco, the Dermatology Foundation recognized the many contributions that Ron R. Brancaccio, M.D. has made to dermatology by honoring him with the 2014 Practitioner of the Year Award. The award honors the exemplary clinical care Brancaccio provides for his patients as well as his significant contributions to the field through leadership and teaching.

A close colleague lauds Dr. Brancaccio for his “years of service to his many grateful patients, and to our specialty for sharing his expertise in contact dermatitis.” For Dr. Brancaccio, it is primarily about his patients. “It is amazing how much personal satisfaction I experience every day from my patients. There is nothing comparable to it,” he says.

Dr. Brancaccio became interested in dermatology in medical school. “It is very visual, and just seemed to click with the way my brain processes information.” And after he traveled west from George Washington University School of Medicine to take dermatology electives at Stanford and then Oregon Health Sciences University (OHSU), “I knew this was the direction I wanted to go in.”

He completed his residency at OHSU where—he explains—he benefited tremendously from the mentorship of Dr. Frances Storrs, an early prime mover in contact dermatitis. Then Dr. Brancaccio returned to NYC and spent three years working with another early leader in contact dermatitis, Dr. Alexander Fisher.

Dr. Brancaccio's overarching goal was to open his own practice while also maintaining an academic presence. He began in the late 1970s with a small office in Brooklyn in the neighborhood where he grew up. Then several years later he added a location in Greenwich Village in Manhattan, where he lived. Dr. Brancaccio has been affiliated with the NYU Medical School for nearly 40 years, where he is now Clinical Professor of Dermatology, teaching residents in the contact dermatitis clinic. Dr. Brancaccio has also shared his expertise through his many lectures and publications over the years, and ran patch testing courses at the AAD meetings until the technique finally became widespread.

Longtime friend and colleague, Dr. Frances Storrs, presented Dr. Brancaccio with this year's award and noted that Dr. Brancaccio “has published 49 articles, almost always with a resident, young faculty member, or medical student. As a mentor and roll model, he is superb.”

Dr. Brancaccio has held a variety of leadership positions, including president of the New York Dermatological Society, the Dermatological Society of Greater New York, and the American Contact Dermatitis Society. Other honors have included Clinical Attending Physician of the Year in Dermatology at NYU (1994), and numerous appearances among the “Best Doctors in New York.”

For Dr. Brancaccio, his patients of all ages (his oldest is 106) have always been his central focus. “I try to bring to each one my expertise and compassion, and help them understand their problem. Some of the most satisfying moments in my career involved the successful detective work that identifies an elusive allergen, which changes a patient’s life when they avoid it—and even when I can’t solve a case, it’s always an interesting journey. I love my work,” Dr. Brancaccio reiterates. “I am so proud and fortunate to be a dermatologist.”

The Dermatology Foundation was established in 1964 and is the leading private funding source for skin disease research. It provides funding that helps develop and retain tomorrow’s teachers and researchers in dermatology, and enable advancements in patient care. For more information visit dermatologyfoundation.org
Alan M. Menter, M.D. 
Receives Dermatology Foundation Clark W. Finnerud Award

At its recent annual meeting of membership in San Francisco, the Dermatology Foundation presented Alan M. Menter, M.D. with the prestigious 2014 Clark W. Finnerud Award. The award recognizes Dr. Menter’s many contributions to the field as both an exceptional clinician and highly effective teacher and mentor to new generations of dermatologists.

“Alan Menter is an exemplary clinician, a leader in the world of psoriasis, and an exceptionally capable teacher,” a colleague observes. “I have benefitted directly from his wisdom.”

Dr. Menter is a noted practicing dermatologist in Dallas, a highly respected teacher, and a widely recognized psoriasis expert. He came to the U.S. from South Africa, where he grew up and completed medical school and then his residency. Ironically, neither dermatology nor a move to the U.S. had been his plan. But near the end of his medical studies, “I met a highly erudite Scottish professor of dermatology” with a forward-looking grasp of skin biology. Dr. Menter was hooked. After his residency at the University of Pretoria General Hospital and two dermatology fellowships in London, Dr. Menter returned to Johannesburg with plans to begin his practice. Unexpectedly, he was offered a two-year dermatology fellowship at the University of Texas Southwestern Medical Center. He accepted and, before his fellowship had ended, made Dallas his home.

Dr. Menter’s decision to dedicate his efforts to improving the understanding and care of psoriasis grew from his family’s history with this disease. “Psoriasis is a very tough disease that often shows up in people at a really young age,” he points out. “Imagine being 30 or 35, trying to make your way in the world, and having unsightly patches all over your body. It is really important to get these patients clear.” Dr. Menter has an extensive clinical practice, and is known for the attentive care he gives each of his many patients.

His academic pursuits began at the University of Texas Southwestern Medical Center, where he is now clinical professor of dermatology. Dr. Menter began teaching at Baylor University Medical Center as well in the mid-1980s, which became the focus of his academic activities. He was eventually appointed chair of dermatology. His research there has included more than a hundred clinical trials, and he has published extensively.

Over his 40-year career in Dallas, Dr. Menter has worked continuously to stimulate solutions for psoriasis patients. He created the first gene bank for psoriasis and participated in identifying the first psoriasis gene. He also founded the International Psoriasis Council, a collaborative, innovative forum for those who work with psoriasis to improve knowledge and advance patient care.

The Dermatology Foundation was established in 1964 and is the leading private funding source for skin disease research. It provides funding that helps develop and retain tomorrow’s teachers and researchers in dermatology, and enable advancements in patient care. For more information visit dermatologyfoundation.org
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March 29 - April 2
LIVE IN COLORADO SPRINGS!

This area is the gem of the Rocky Mountain Front Range with over 300 days of sunshine, a dry climate, ready access to all outdoor activities, and a safe environment in which to enjoy life and raise a family. From the Garden of the Gods to the Olympic Training Center, this town is incredible, just an hour outside of Denver and a couple hours’ drive to numerous ski resorts including Breckenridge and Vail. Colorado Springs is a perfectly situated outdoor paradise.

Colorado Dermatology Institute (CDI) provides full-service medical, surgical (including Mohs micrographic surgery), and cosmetic care. CDI is designed to change patients’ expectations of the level of personalized care they can, and should, receive when seeking medical service. Our group currently consists of three dermatologists, three PAs, and three dermatology residents. We strive to remain on the leading edge of patient-centered medical care and to be actively involved in promoting the future of dermatology. Please visit our website at www.coderm.com.

We are looking to hire a BC/BE dermatologist, part- or full-time, with a demonstrated passion for excellence and patient care who wants a path to partnership in the rapidly expanding Colorado Dermatology Institute. We offer a relocation allowance, guaranteed salary, and comprehensive benefits package.

**Direct Contact Information**

For immediate consideration, please contact our practice manager:

Jeff Anderson       719-531-5400       pm@coderm.com