Metastatic Squamous Cell Carcinoma
Updated Staging Guidelines and Prognostic Factors for “High-risk” SCC

Also in this issue:
Delineating the Perforating Dermatoses
A Rare Case of Cogan’s Syndrome with Cutaneous Findings
Rhomboid Flaps and Their Modern Modifications
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAOC Editors</td>
<td>4</td>
</tr>
<tr>
<td>Letter from the Editor-in-Chief</td>
<td>5</td>
</tr>
<tr>
<td>Letter from the President</td>
<td>6</td>
</tr>
<tr>
<td>Letter from the Executive Director</td>
<td>7</td>
</tr>
<tr>
<td><strong>FEATURE ARTICLE:</strong></td>
<td></td>
</tr>
<tr>
<td>A Rare Case of Metastatic Squamous Cell Carcinoma: A Case Presentation and Discussion of Updated Staging Guidelines and Prognostic Factors</td>
<td>12</td>
</tr>
<tr>
<td>Steven Brandon Nickle, DO, Nicole Arnold, DO, J Ryan Jackson, DO, Tracy Favreau, DO, FAOCD</td>
<td></td>
</tr>
<tr>
<td><strong>EDITOR’S PICKS:</strong></td>
<td></td>
</tr>
<tr>
<td>Review of Rhomboid Flaps and Their Modern Modifications</td>
<td>16</td>
</tr>
<tr>
<td>Alexandra Grammenos, MS, Ana M. Rivas, BS, Jacqueline A. Thomas, DO, David L. Thomas, MD, JD, EdD</td>
<td></td>
</tr>
<tr>
<td>Delineating the Perforating Dermatoses: Case Reports and a Review of the Literature</td>
<td>20</td>
</tr>
<tr>
<td>Richard Lintert, DO, Rachel White, BA, Richard Miller, DO, FAOCD</td>
<td></td>
</tr>
<tr>
<td>Cogan's Syndrome with Cutaneous Findings: A Case Report and Review of Dermatologic Manifestations</td>
<td>25</td>
</tr>
<tr>
<td>Khasha Touloei, DO, Emily Tongdoo, BS, Brittanny Smirnov, DO, Tracy Favreau, DO, Leor Porges, DO</td>
<td></td>
</tr>
<tr>
<td><strong>ORIGINAL ARTICLES AND CASE REPORTS:</strong></td>
<td></td>
</tr>
<tr>
<td>Cutaneous Adenosquamous Carcinoma: A Case Study and Literature Review</td>
<td>30</td>
</tr>
<tr>
<td>Mayha Patel, DO, Anne Nguyen, BS, David Horowitz, DO, FAOCD, Paul Shitabata, MD</td>
<td></td>
</tr>
<tr>
<td>Bacterial Pseudomyces of the Skin: A Case Report</td>
<td>32</td>
</tr>
<tr>
<td>Robert Lin, DO, Alpesh Desai, DO, FAOCD</td>
<td></td>
</tr>
<tr>
<td>Favre-Racouchot Syndrome in a Unilateral, Perioral Distribution Associated with Tobacco Use: A Case Report and Review</td>
<td>34</td>
</tr>
<tr>
<td>Mitchell R. Marroay, DO, Joseph M. Dyer, DO, Joshua D. Gapp, MD, Melinda F. Greenfield, DO</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathic Form of Endemic Kaposi Sarcoma in an HIV-negative Gambian Male</td>
<td>36</td>
</tr>
<tr>
<td>Eugene Sanik, DO, Ryan Schuering, BS, Marcus B. Goodman, DO, FAOCD</td>
<td></td>
</tr>
<tr>
<td>Coexisting confluent and reticulated papillomatosis and terra firma-forme dermatosis</td>
<td>40</td>
</tr>
<tr>
<td>Claire Otteni, BA, Laura F. Sandoval, DO, Jonathan S. Crane, DO, FAOCD</td>
<td></td>
</tr>
<tr>
<td>A Case of Pili Annulati Following Resolution of Alopecia Areata</td>
<td>42</td>
</tr>
<tr>
<td>Karan Lal, BS, Charlotte Noorollah, DO</td>
<td></td>
</tr>
<tr>
<td>Two Cases of Pediatric Acral Cutaneous Calcinosis with Transepidermal Elimination Presenting as Skin-colored Papules</td>
<td>44</td>
</tr>
<tr>
<td>Gabriela Maloney, DO, Robini Chennuri, MD, Patricia Dymek, MD, Marylee Braniecki, MD</td>
<td></td>
</tr>
<tr>
<td>Recurrent Basal Cell Carcinoma with Perineural Invasion: A Case Report and Review</td>
<td>46</td>
</tr>
<tr>
<td>Shana Rissmiller, DO, Alecia Folkes, MS, Indira Krishnaraj, MD</td>
<td></td>
</tr>
<tr>
<td>Atypical presentation of Sézary Syndrome with CD4+/CD7+/CD26- T-cells and marked epidermotropism: A case report and literature review</td>
<td>49</td>
</tr>
<tr>
<td>Gabriela Maloney, DO, Sujata Gaitode, MD, Igor Altman, MD, Marylee Braniecki, MD</td>
<td></td>
</tr>
<tr>
<td>A Rare Case of Tumid Lupus Erythematosus Coexisting with Systemic Lupus Erythematosus: A Case Presentation and Discussion</td>
<td>52</td>
</tr>
<tr>
<td>Jennifer Moscoo Conde, DO, Simona Bartos, MPH, John Horward, DO, Jacqueline Thomas, DO, FAOCD</td>
<td></td>
</tr>
<tr>
<td>A Vesiculobullous Eruption Following Solid Organ Transplantation</td>
<td>54</td>
</tr>
<tr>
<td>Nadine George, DO, Ann Reed, DO, Frank Don, DO, FAOCD, Stanley Skopit, DO, MSE, FAOCD</td>
<td></td>
</tr>
<tr>
<td>A rare case of verrucous psoriasis in young female: A case report and review of clinicohistologic presentation and variable therapeutic response</td>
<td>56</td>
</tr>
<tr>
<td>John Moesch, BA, Jessica Mercer, MD, Jennifer B. Sissom, PA-C, Jonathan S. Weiss, MD</td>
<td></td>
</tr>
</tbody>
</table>
## Associate Editors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sami Abbasi, DO</td>
<td>Brownstown, MI</td>
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<tr>
<td>Marcus Goodman, DO</td>
<td>Roswell, GA</td>
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<tr>
<td>Scott Lim, DO</td>
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<td>Red Bluff, CA</td>
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<td>Albany, GA</td>
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<td>Chava Lustig, DO</td>
<td>Weston, FL</td>
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<td>Hilliard, OH</td>
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<td>Denise Guevara, DO</td>
<td>Weston, FL</td>
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<td>Jere Mammino, DO</td>
<td>Winter Springs, FL</td>
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<td>Igor Chaplik, DO</td>
<td>Aventura, FL</td>
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<td>Andrew Hanly, MD</td>
<td>Miami, FL</td>
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<td>John Minni, DO</td>
<td>Port St. Lucie, FL</td>
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<td>Michael P. Conroy, MD</td>
<td>Columbus, OH</td>
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<td>John Perrotto, DO</td>
<td>West Palm Beach, FL</td>
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</tbody>
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## Editorial Board

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
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<tbody>
<tr>
<td>Sami Abbasi, DO</td>
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<td>Mesquite, TX</td>
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<td>Hilliard, OH</td>
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<td>Weston, FL</td>
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<tr>
<td>Jere Mammino, DO</td>
<td>Winter Springs, FL</td>
</tr>
<tr>
<td>Amara Sayed, DO</td>
<td>San Marcos, TX</td>
</tr>
<tr>
<td>Igor Chaplik, DO</td>
<td>Aventura, FL</td>
</tr>
<tr>
<td>Andrew Hanly, MD</td>
<td>Miami, FL</td>
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<tr>
<td>John Minni, DO</td>
<td>Port St. Lucie, FL</td>
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<td>Joseph Brant Schneider, DO</td>
<td>Shawnee Mission, KS</td>
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<tr>
<td>Michael P. Conroy, MD</td>
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<td>Joel Harris, DO</td>
<td>Madison Heights, MI</td>
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<tr>
<td>Tony Nakhla, DO</td>
<td>Orange County, CA</td>
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<tr>
<td>Gregg Severs, DO</td>
<td>Scranton, PA</td>
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<tr>
<td>John Coppola, DO</td>
<td>Ormond Beach, FL</td>
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<td>Heather Higgins, DO</td>
<td>Troy, MI</td>
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<tr>
<td>Navid Nami, DO</td>
<td>Newport Beach, CA</td>
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<td>Sean Stephenson, DO</td>
<td>Troy, MI</td>
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<tr>
<td>Matthew Elias, DO</td>
<td>Lighthouse Point, FL</td>
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<tr>
<td>David Horowitz, DO</td>
<td>Torrance, CA</td>
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<td>Lexington, KY</td>
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<td>Jacqueline Thomas, DO</td>
<td>Fort Lauderdale, FL</td>
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<tr>
<td>Merrick Elias, DO</td>
<td>Delray Beach, FL</td>
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<tr>
<td>Mark Lebwohl, MD</td>
<td>New York, NY</td>
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<tr>
<td>Dimitria Papadopoulos, DO</td>
<td>Bellmore, NY</td>
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<tr>
<td>Jim Towry, DO</td>
<td>Ocala, FL</td>
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<tr>
<td>Michelle Foley, DO</td>
<td>Ormond Beach, FL</td>
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<tr>
<td>Angela Leo, DO</td>
<td>New York, NY</td>
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<tr>
<td>John Perrotto, DO</td>
<td>West Palm Beach, FL</td>
</tr>
<tr>
<td>Scott Wickless, DO</td>
<td>Dallas, TX</td>
</tr>
</tbody>
</table>
Dear Readership,

Medscape recently published its 2015 “Why Most Doctors Get Sued” report. As I clicked on the link in my email, I held my breath in anticipation of a report confirming what I already knew: Dermatologists get sued more than other specialties. As the slideshow loaded, I reviewed the anatomy of Erb’s point in my mind.

When it finished loading, I saw that 47% of all doctors had been named in a lawsuit during their careers. Okay… that’s bittersweet. Should we be relieved that there would be kindred spirits, or alarmed that there is a coin-toss chance of being sued?

At the next slide, I let out a sigh of relief. Dermatology was not in the list of the top seven specialties sued: OBs (85%), Surgery (83%), Orthopedics (79%), Radiology (72%), Anesthesiology (58%), IM/FM (46%), and Oncology (34%). If we’re below Oncology, I thought, we’re down to a one-in-three shot, at worst.

As the report continued, I was drawn in to find out the reasons why physicians were sued, and what effect it had on them. I continued to read, but with a different attitude… what could I be doing differently or better in order to avoid harm or potential harm to my patients? “Failure to diagnose” was the leading cause of suits (31%). “Poor documentation” and “consent” issues together made up about 10% of suits.

Then, I got worried again. More than 50% of responders had reported that the threat of malpractice influenced their care. Almost all responders reported that there are flaws in the way suits are handled in our legal system, with lack of peer review for merit. Seventy percent were surprised when they were sued; they weren’t expecting it. Most reported more than 100 hours in preparation, court, and trial-related meetings, and almost half the suits lasted longer than three years. More than half of responders stated that the long-term emotional and financial effects were severely disruptive.

Then things got a little brighter. About half of all cases were dismissed. Of the suits that were not settled before trial, only about 3% went against the physician. More than half the physicians who were sued stated that they would not have changed a thing in their care. More than half of the monetary awards for all cases were $0. Eighty-one percent of responders felt that saying “I’m sorry” would not have helped the outcome.

I went to bed ambivalent-to-slightly-relieved. When I woke up the next morning, I knew I could shift my focus back to prior authorizations, step-therapy, and automated 1-800 insurance operators.

Yours,

Karthik Krishnamurthy, DO, FAOCD
Editor-in-Chief, Journal of the American Osteopathic College of Dermatology
Greetings from Houston, Texas!

As President of the AOCD, I welcome you to another edition of the Journal of the American Osteopathic College of Dermatology. I would be remiss in not recognizing the Editor-in-Chief of this powerful publication, Karthik Krishnamurthy, DO. His commitment to the College and willingness to go above and beyond is admirable. Thank you, Dr. Krishnamurthy. I also want to express my appreciation to Dr. Lin, our Immediate Past President, for his tireless efforts on behalf of the College. His friendship and his willingness to continue participating in a meaningful way will only make this year more successful. I think it most important that we honor our heritage, and to that end, I want to express my deepest appreciation to Dr. Jay Gottlieb for his vision and wisdom in launching the JAOCDD.

I appreciated our time together in Orlando on a number of levels. First, the friendships that continue and the opportunity to develop new friendships and relationships are vital to our personal growth and development. Second, hearing new ways of doing things, discussing similar challenges, and hearing solutions to many old challenges was powerful. Finally, I believe there are no words to describe how special Orlando was personally to me. The attendees were so very caring! There is, inherent in this great organization, a camaraderie blended with the desire to help others. The kindnesses shown to me during this conference will linger long in my memory.

The year 2016 is upon us. It seems only yesterday I was entering the Kansas City University of Medicine and Biosciences, followed by my internship and residency. Soon another cycle will pass. New, excited doctors will emerge and enter residencies in dermatology. As Director of the South Texas Dermatology Residency Program in Houston, I have borne witness to fine physicians honing their skills and expanding their knowledge in anticipation of launching their medical careers. We need to be mindful that the future of our organization rests squarely upon the shoulders of these new physicians we train. It is to the great benefit of the AOCD that we serve not only as mentors but also remain active in their development in both practice and science.

Our future residents and fellows will be entering a new environment, working within a single accreditation system for graduate medical education programs in the United States. When the new system is fully implemented in July 2020, the graduates of osteopathic and allopathic medical schools will complete their residency and/or fellowship education in ACGME-accredited programs and demonstrate achievement of common milestones and competencies. No longer will there be a great divide in the practical training of DOs and MDs.

Clearly our world is changing! I suppose the greatest morsel I could share with you comes from one of my mentors, who said, “Today, at this moment, we are living in yesterday’s future.” The changes in our practice of dermatology and medicine in general are profound. We spend great swaths of time dealing with electronic medical records and ICD 10. My challenge to you is to pause and remember why you chose medicine, and particularly why you chose dermatology. Then look at your patients through a lens tinted with that memory. While we must tend to the busyness of EMRs, we must not forget our patients.

I look forward to serving you and the opportunity to meet all of you as you attend our meetings.

Alpesh Desai, DO, FAOCD
President, American Osteopathic College of Dermatology
Greetings, Everyone!
The year is quickly coming to an end, and it has been a very busy one. We had a great meeting in Orlando, with 550 registered! It was our highest attendance ever!

December 31, 2015, is the end of the current CME cycle. The new cycle begins January 1, 2016. I encourage everyone to check your CME reports and to monitor the AOA site for the new CME guide, which has not been published. We are hearing that there will be changes in the requirements for the new cycle. You can find that information here: http://www.osteopathic.org/inside-aoa/development/continuing-medical-education/Pages/default.aspx.

Many AOCD members have been inquiring about OCC and OCAT. If you have not already done so, you must register at http://www.osteopathic-cat.com (under “Register”). This is mandatory for recertification. **If you have any questions please refer to the AOBD website at http://aobd.org/aobd/occ/aobd-occ-faqs.**

The Foundation for Osteopathic Dermatology is accepting applications for research grants. For more information, visit the Foundation page at https://aocd.site-ym.com/?page=Foundation.

AOCD membership dues for 2016 are now due. The AOCD has made it easier for you to renew your dues by providing quick and secure renewal online. Just go to our web site, http://aocd.org, and log in. Your username is the email address you have on file with the AOCD, and your password is “Aocd” followed by your AOA# (case sensitive). Please contact our office if you have difficulty logging in.

Also on that page is a form to update your database information. This database is maintained on our web site so you can make changes to your membership information at any time. All changes you make will be recorded in the database and will also update the “Find a DO” section of the web site. Although you will see all of your information in your personal file, inquiries will only generate your office address, office telephone number and office fax number.

**Save the Dates!**
The 2016 Spring Meeting will take place from March 30th to April 3rd, 2016, at the Ritz Carlton Battery Park, New York, NY. The 2016 Fall Meeting will take place from September 15th to 18th, 2016, at the Loews Santa Monica, Santa Monica, CA. The 2017 Spring Meeting will take place from March 29th to April 2nd, 2017, at the Ritz Carlton Atlanta, Atlanta, GA.

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

Sincerely,

Marsha Wise
Executive Director, American Osteopathic College of Dermatology
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- US News – top 5% of American high schools
- US Census – top 30 fasting growing metros in Southeast
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- Progressive Policy Institute - #4 America’s high tech hot spots
- NerdWallet – top 10 US cities on the rise
- Google - digital capital of Alabama
- CNN Money – #7 great place to live and find a job in country
- NerdWallet – #3 best places for science, technology, engineering, math grads
- Family Circle – 10 best towns for families
- Policom – nation’s top 20 economies
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Contact Albert E. “Bo” Rivera, DO with any questions or to express interest in joining our team.

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A Rare Case of Metastatic Squamous Cell Carcinoma: A Case Presentation and Discussion of Updated Staging Guidelines and Prognostic Factors

Steven Brandon Nickle, DO,* Nicole Arnold, DO,** J Ryan Jackson, DO,*** Tracy Favreau, DO, FAOCD****

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**Traditional Rotating Intern, Sampson Regional Medical Center, Clinton, NC
***Dermatology Resident, 1st year, Beaumont Medical Center, Farmington Hills, MI
****Director/Chairman of Dermatology, Nova Southeastern University College of Osteopathic Medicine/Broward General Medical Center, Fort Lauderdale, FL

Abstract
Cutaneous squamous cell carcinoma (cSCC) is well recognized in the literature as a fairly common neoplasm that arises from a malignant proliferation of epidermal keratinocytes. Prognosis is typically favorable in cSCC, as it rarely metastasizes. However, the literature is unclear in regard to what defines “high risk” cSCC and what its prognostic indicators are. We report a case of a 68-year-old Caucasian female with metastatic cSCC and review the recent available guidelines regarding staging and major tumor characteristics associated with aggressive behavior and a poor outcome.

Introduction
Cutaneous squamous cell carcinoma (cSCC) is the second most common human cancer, with an estimated annual incidence of 186,157 to 419,843 cases in the United States. While tumor recurrence, metastasis, and death occasionally occur, prognosis is typically excellent, as these complications only occur approximately in 1% to 5% of cases. Current literature supports a correlation between certain pathological and clinical features, aggressive tumor behavior, and increased risk of metastasis. However, there are disputes over the definition of “high-risk cSCC” and its appropriate prognostic indicators. Without a prognostic model, clinicians lack evidence to guide decisions regarding appropriate nodal staging and adjuvant therapy. We report a 68-year-old Caucasian female with metastatic cutaneous SCC and review the most up-to-date guidelines regarding staging and major tumor characteristics associated with aggressive behavior and a poor outcome.

Case Report
A 68-year-old Caucasian female presented to the emergency room (ER) with a left scapular mass that had been present for approximately six months per patient recollection. The initially small, pruritic papule had enlarged, become tender and eventually ruptured. The rupture produced a malodorous purulent discharge that prompted her to seek medical attention.

Past medical history was significant for 10 or more blistering sunburns without sunscreen as a child, hypertension, dyslipidemia and diabetes mellitus. Family history was significant for melanoma in two out of her six sisters. Surgical history consisted of a hysterectomy and cholecystectomy. The patient lived at home and was cared for by her son. The patient denied any weight change, fever or chills.

On physical exam, temperature was 98.4 F (36.9 C), heart rate 66, respiratory rate 20, blood pressure 166/76 and oxygen saturation at 95% on room air. The patient had a firm, left axillary node that had been present for an unknown duration of time; a 12 cm x 10 cm fungating mass on her left scapula (Figure 1) that was tender to palpation and symmetrical with central erosion, surrounding erythema and malodorous discharge; and a single, 3 cm x 2 cm, variegated multi-toned brown to black, isolated patch with irregular borders, focal hyperpigmentation and slight elevation on the right upper back of unknown duration.

Infectious disease was consulted for potential superimposed infection of the left upper scapular mass. The patient was started on vancomycin and piperacillin/tazobactam with preliminary microbiology Gram stain for Gram-positive cocci and Gram-negative rods. We recommended a wide excision of the left upper-back mass to rule out angiosarcoma versus squamous cell carcinoma, along with an excision of the right upper-back mass to rule out melanoma.

Upon completion of the excisions, the histologic examination of the left upper-back wide-excision specimen revealed a necrotic, poorly differentiated neoplasm with epidermoid and sarcomatoid components with blood-vessel invasion. The following stains were performed on the left upper-back tissue specimen: p63 (+), p16 (+), Pan-K (+), HMB45 (-), MART1 (-), vimentin (+) (Figures 2, 3). The clinical and histopathologic exam favored a diagnosis of the left upper-back as sarcomatoid squamous cell carcinoma. Histologic examination of the right upper-back lesion demonstrated malignant melanoma in situ with benign margins. After surgery, it was recommended that the patient be followed by oncology for further adjunctive therapy.

Months later, the patient presented again to the ER due to extreme weakness and fatigue. The left axillary mass measured 16 cm in size and had become necrotic (Figure 4). A core biopsy of...
the left axillary mass was conducted and revealed metastatic squamous cell carcinoma with an H&E stain that demonstrated multiple spindle-shaped, atypical cells (Figure 5). The axillary mass most likely represented an enlargement of the initial left axillary node, which had now infiltrated into major blood vessels and other structures, making surgical treatment impractical. The patient elected at that time for palliative radiation therapy.

High-risk Characteristics

The American Joint Committee on Cancer (AJCC) substantially altered the staging of cSCC in 2010 with the 7th edition of its staging manual. The new edition aimed to create congruence by replicating the staging system for the mucosal squamous cell cancer variant. The TNM classification and staging system remains with many changes. Perhaps the most important of these components is the high- and low-risk designations. T1 and T2 are defined as a lesion < 2 cm or > 2 cm, respectively. However, if there are more than two high-risk characteristics, regardless of tumor size, it is designated as T2 and stage 2. These characteristics include: clinical tumor diameter 2 cm or greater, Breslow thickness greater than 2 mm, poor differentiation, perineural invasion, Clark level IV or higher, and primary location on the external ear or non-glabrous lip. However, in a prospective study, Veness et al. examined 266 patients with cSCC that metastasized to parotid or cervical lymph nodes and found that 70% of the lesions measured ≤ 2 cm, indicating that factors other than tumor size likely contribute to metastatic risk. A review by Matorell-Calatayud et al. suggests other high-risk cSCC characteristics to be included in the discussion of prognosis and treatment. These high-risk cSCC characteristics include: genetic disorders (xeroderma pigmentosum, epidermodysplasia verruciformis, oculocutaneous albinism, dyskeratosis congenita, and recessive dystrophic epidermolysis bullosa), cSCC arising at the site of a pre-existing lesion (scars, burn sites, ulcers that are slow growing, chronic radiation dermatitis), immunosuppression and transplantation, and molecular markers. For example, EFG overexpression has been linked to early metastasis, and lesions with p16 overexpression have shown aggressive metastasis.

Prognosis

Currently, the nodal classification used in staging is divided into N1, N2, and N3, with further subdivision of the N2 component into a, b, and c based on ipsilateral vs. contralateral nodes. From a retrospective study of 603 patients, Clark et al. found that stages N2a, N2c, and N3 of the AJCC staging system contained less than 10% of patients exclusive of any prognostic relevance. This assessment calls into question the validity of the classification and the overall utility of the system.

Further research on patient outcomes from cutaneous SCC will prove useful for verifying which adjustments to the AJCC staging system are indicated. Histologic features consisting of a poorly differentiated tumor, Breslow depth greater than 2 mm, and the presence of nerve involvement negatively influence the prognosis. Approximately 75% of recurrences or metastases of cSCC occur within two years after therapy, and approximately 95% occur within five years. Thus, close follow-up is indicated. The risks for local recurrence and distant metastasis are impacted by tumor characteristics and patient characteristics.

Discussion

Cutaneous squamous cell carcinoma (cSCC) is a fairly common malignancy with an average lifetime incidence greater than 10%. The majority of patients with cSCC present with a localized disease that is cured with local treatment; however, tumor recurrence, metastasis, and death from this disease occasionally occur. Tumors that are associated with an increased risk of aggressive behavior and demonstrate clinical or histological features have been termed “high-risk.” The mortality rate for disease-specific death from cSCC is 2.1%, with more deaths occurring annually from cSCC than melanoma due to the higher prevalence of the disease. Adequate classification and staging of cSCC is necessary in order to accurately predict a prognosis and appropriately develop a treatment plan. The difficulties lay in the controversy regarding the newest staging system and a lack of conclusive, evidence-based research regarding high-risk characteristics, prognosis, and treatment efficacy.

Table 1. AJCC tumor (T) staging and “high risk” features

<table>
<thead>
<tr>
<th>Designation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension with fewer than two high-risk features</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm in greatest dimension, or tumor of any size with two or more high-risk features</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with invasion of maxilla, mandible, orbit or temporal bone</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-risk Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designation</td>
</tr>
<tr>
<td>Depth/Invasion</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anatomic Location</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
</tr>
</tbody>
</table>
A CASE PRESENTATION AND DISCUSSION OF UPDATED STAGING GUIDELINES AND PROGNOSTIC FACTORS

Table 2. NCCN guidelines for "high-risk" cSCC

<table>
<thead>
<tr>
<th>Factors indicating &quot;high-risk&quot; cSCC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area M ≥ 10 mm**</td>
</tr>
<tr>
<td>Area H ≥ 6 mm***</td>
</tr>
<tr>
<td>Recurrence</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Site of prior RT or chronic inflammatory process</td>
</tr>
<tr>
<td>Rapidly growing tumor</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
</tr>
<tr>
<td>Moderately or poorly differentiated histology</td>
</tr>
<tr>
<td>Acantholytic, adenosquamous, or desmoplastic subtypes</td>
</tr>
<tr>
<td>Depth: ≥ 2 mm or Clark levels IV, V</td>
</tr>
<tr>
<td>Perineural or vascular involvement</td>
</tr>
</tbody>
</table>

*High-risk = ≥1 of 12 risk factors
**M = Medium risk: forehead, scalp, cheek, neck
***H = High risk: “masked areas” of face, central face, ears, periauricular, eyelids, periorbital, nose, temple, lips

Note: Low risk: trunk and extremities

Table 3. Alternative T-staging system by Jambusaria-Pahlajani, et al. 12

<table>
<thead>
<tr>
<th>Alternative T-staging System</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ SCC</td>
</tr>
<tr>
<td>T1</td>
<td>0 risk factors</td>
</tr>
<tr>
<td>T2a</td>
<td>1 risk factor</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 risk factors</td>
</tr>
<tr>
<td>T3</td>
<td>4 risk factors or bone invasion</td>
</tr>
</tbody>
</table>

Poorly differentiated histologic characteristics
Perineural invasion (of any caliber)
Tumor invasion beyond the subcutaneous fat (excluding bone invasion, which automatically upstages tumors to alternative stage T3).

This alternative T-staging system differs from 2010 AJCC tumor staging in the following regards:

- Stage T1 comprises tumors that have no risk factors.
- Stage T2 tumors are categorized into two substages based on number of risk factors.
- Stage T3 includes all cases of bone invasion as well as tumors without bone invasion but with all four risk factors.
- There is no stage T4 in the alternative staging.
- Location on the ear and vermilion lip are not considered risk factors.
- Breslow (millimeter) tumor depth was not used as a risk factor.
- Invasion beyond subcutaneous fat was the best prognostic cutpoint in this data set defining elevated risk of poor outcomes.
- Stage T2b tumors are responsible for most poor outcomes.

The proposed alternative tumor-staging system provides improved prognostic discrimination via stratification of stage T2 tumors. However, validation in other cohorts is still needed.

**Conclusion**

Cutaneous squamous cell carcinoma is a challenging neoplasm to classify and treat. This challenge is largely due to the lack of substantial prospective studies regarding disease-specific survival. It is necessary for practitioner to be vigilant regarding these high-risk characteristics by promoting close follow-up with these patients due to the higher risks of recurrence and metastasis.
References

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NICKLE, HACKERT, JACKSON, FAVREAU
Review of Rhomboid Flaps and Their Modern Modifications

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Abstract

Background: First proposed by Alexander Limberg in 1945, the rhomboid flap has been modified to accommodate a variety of different surgical settings. Rhomboid flaps have proven to be integral in a variety of sub-specialties. Objective: The aim of this review is to examine the rhomboid flaps of Limberg, Dufourmentel, Webster, and Quaba and report the appropriate surgical context and advantages of each flap type. Methods & Materials: A literature search was performed of PUBMED, SCOPUS, and MEDLINE for articles assessing the proper surgical context and subsequent outcomes of the Limberg, Dufourmentel, Webster, and Quaba/Sommerlad flaps. Results: The use of rhomboid flaps proved optimal for closure of large defects because of the reduced risk of distal-end necrosis. Conclusion: This review details a thorough examination of modification of rhomboid flaps and their effectiveness as an alternative to primary closure.

Introduction

Following the formation of a surgical defect, a closure type is chosen to suit the surrounding tissue characteristics and defect size. While primary closure is often the first choice, simple suturing may not be sufficient to appropriately close the defect. Size is the most common deterrent from primary closure, where the long or short axes of the defect are either too long or too wide, respectively.1,2 Rhomboid flaps maintain continuity of texture, color, and vascularity with the surrounding tissue, eliciting the most successful aesthetic outcome.3 Rhomboid flaps are most commonly used for tumor resection in head and neck surgeries but are widely applicable in fields such as general and plastic surgery, ophthalmology, and otolaryngology.1,3

In 1946, Alexander Limberg first designed a surgical protocol for transposition of a rhomboid flap 120° onto a proximal skin defect.4 This was innovative and successful due to the retention of local vascularity via the pedicle.5 Claude Dufourmentel later modified this in 1966, using a reduced angle size to ≤ 60° to limit the amount of disruption of healthy tissue during closure while increasing pedicle width.1,2 This closure is compared to that created by primary closure.5

The original Limberg flap was further modified by Richard Webster in 1960 to include a 30° transposition flap with an M-plasty closure.1,3 The addition of the M-plasty allowed for a better distribution of tension, reducing the strain on the distal tip of the flap. In 1987, Awf Quaba designed a modified rhomboid flap to address closing a circular defect with minimal healthy skin loss. While all four flaps are widely useful, it is imperative to not distort the anatomy or maintain skin laxity.3 Limberg, Dufourmentel, Webster, and Quaba flaps are types of transposition flaps that are generally smaller in size than both the advancement and rotational flaps.7,8

The varieties of rhomboid flaps provide superior results when compared to skin grafts of similar size and location because the sub-papillary and sub-dermal vascular plexuses are maintained through the flap's pedicle, which is absent in skin grafts.4,7 The enhanced vascularization established through the pedicle lends the rhomboid methods to successful treatment in post-burn defect treatment.7 Even when adequate blood supply is maintained, the surgeon must be cautious of the tension on the distal end of the flap in order to reduce the likelihood of necrosis.5 It is important to note that the maintenance of perfusion pressure is the critical aspect to flap success, as compared to the width-to-length ratio of the pedicle as traditionally thought.10 Vascular testing methods, such as dermal bleeding pricks and reperfusion time testing, are performed prior to closure to ensure adequate perfusion.11

Discussion

Limberg Flap

The simplicity and efficacy of the Limberg flap makes it versatile, allowing for adequate cosmesis with few complications. The excision is made up of two equilateral triangles with 60° and 120° angles, respectively. The flap is then created by extending a line of equal length from either of the 120° angles. At the end of this extended line, a second line is created at an angle of 60° (Figure 1a). It is important to ensure this line is parallel to the side of the rhomboid defect.10,12 The flap is then transposed and ready for closure (Figure 1b).

The placement of the Limberg flap greatly influences its survival and aesthetic appearance (Figure 1c). The flap should be positioned in the direction of minimal tension and maximum extensibility. The flexibility of the skin in the area to be excised can be inspected by pinching the skin with the forefinger and thumb.13 Placement

Figures 1a - 1c. Steps employed in the Limberg flap.
of the flap becomes more challenging on the face, where anatomical features may create boundaries. The incisions should not be placed on relaxed skin tension lines; instead, incisions should be made parallel to the relaxed skin tension lines. Placement of incisions parallel to Langer’s lines allows the resulting scar to fall within the creases of the skin. A reduction in tension on the flap decreases the likelihood of necrosis of the donor tissue. The parallelogram-shaped defects are ideal for the use of a Limberg flap.

Limberg flaps have been used in a variety of areas of the body. Particularly, this flap has been practical for defects on the face, neck, and back. However, the usefulness of the Limberg flap makes it easy to employ and modify for defects in other parts of the body, such as the oral mucosa, the floor and ala of the nose, and the lips.

**Dufourmentel Flap**

The design of a Dufourmentel flap allows for closure of rhomboid defects of differing angles, such as acute angle closure, when compared to closure with a Limberg flap. The angles of the rhomboid do not need to equal 60° as in the Limberg flap. Upon bisection of the parallelogram, a plumb line is placed at 90°. A second line is created parallel to one of the sides of the defect. The angle that is created from the two extended lines is bisected with a line that is the same length as a side of the rhomboid. The bisected line creates a smaller tip angle of the flap. From the end of the bisected line, another line is created that is parallel to the longitudinal axis of the parallelogram (Figure 2a). This parallel line must still be equal in length to a side of the rhomboid. The design of the Dufourmentel flap allows two flaps to be created from each of the four angles of a square defect. In the case of an asymmetrical rhomboid, four flaps can be created from a rhomboid defect (Figures 2b-c).

The ideal scenario for the use of a Dufourmentel flap is with an acute angle defect of greater than 60°. Other factors besides defect angle should be considered in the application of the Dufourmentel flap over other methods. The presence of laxity of the tissue favors the use of a Dufourmentel flap over the simpler Limberg flap. A Dufourmentel flap does not require as great of a transposition movement of the flap covering the primary defect as the Limberg method. If a defect is less than 60° and cannot be closed via primary closure, the defect angle is enlarged and a Limberg flap is employed.

Further alterations to the Dufourmentel flap were applied to address certain limitations of this type of transposition flap. One modification, a “diamond flap,” is used to decrease the amount of healthy tissue excised from a Dufourmentel flap. The diamond flap modified one of the acute corners of the rhomboid excision following initial completion of the Dufourmentel flap design. One of the acute corners is transformed into a circular shape. In order for the flap to close the new circular shape, an arc of the same dimension is created on the part of skin that is transposed.

**Advantages of Limberg and Dufourmentel Flaps**

Considering the tension of the skin, primary closure can cause an increase in delphiscence and infection in defects. A similar trend was observed comparing secondary-intention healing and the use of the Limberg flap. Secondary intention requires greater care and increases the risk of infection of the open wound compared to the closed sutures of a Limberg flap. In areas of the body where skin may not have great laxity, secondary-intention closure may be preferred over a rhomboid flap such as the Limberg method.

The Dufourmentel flap is advantageous with smaller defects because of the narrow flap. Application of the Dufourmentel flap has shown satisfactory cosmetic results with a decrease in flap rotation, compared to the Limberg flap, and adequate survival from vascularity from subdermal plexus.

**Rhomboid Flaps for Pilonidal Sinus Surgery**

The Limberg flap has shown to be one of the quickest and least complicated treatments for wound healing in pilonidal sinus surgery. Through placement of the most inferior angle of the rhomboid slightly lateral to midline, the recurrence and maceration of the defect was decreased. A slight disadvantage of this modification to the Limberg flap is the excess healthy tissue that is lost. A study conducted by Kaya proposed a modification to the Limberg flap that included a complete lateralization of the rhomboid from the intersgutal cleft.

The Dufourmentel flap is also used for the treatment of pilonidal sinus disease. Yildar et al. applied a modified Dufourmentel flap for wider defects of pilonidal sinus disease. This modification involved using an S-type oblique excision along with a modified Dufourmentel flap that placed the excision lateral to the midline of the intergluteal sulcus. A modified, asymmetrical Dufourmentel flap can be used to treat pilonidal sinus disease with low rates of necrosis and complications.

A literature review of pilonidal sinus surgery found the use of the Limberg flap to be the quickest and least complicated treatment for wound healing. Pilonidal surgical procedures that healed with tension-free primary closure had greater disadvantages than wounds that healed using the Limberg flap.

**Webster Flap**

The Webster flap was developed in 1960 as a further adaptation of the original Limberg flap,
Webster flaps retain good sensation as well as maintaining good oral competence and microstomia and poor aesthetic outcomes, as well as maintaining good oral competence and sensation.  

With the reduction of the flap's angle of rotation from 60° to 30°, there is less disruption and removal of healthy tissue when compared to the aforementioned flaps. Additionally, the utilization of the M-plasty closure allows for a more uniform distribution of tension across the flap. This reduction in tension promotes better revascularization to the most distal ends of the flap, ensuring a more rapid healing time with less chance of distal-flap necrosis.

There have been several modifications of the Webster flap technique described in the literature, all of which utilize the reduced angle of rotation for more favorable surgical outcomes. One such modification is the combination of the Webster and Johanson techniques for closure of defects greater than 80% with a staircase scar. The Johanson technique was originally designed as a staircase suture for a defect no larger than two thirds of the total area with improved scarring aesthetic when compared to the linear suture of Webster. As with rhomboid flaps, the step technique described by Johanson is of clinical importance due to maintenance of tissue texture between the donor and lesion sites, retention of intact muscle fibers and innervation, and better aesthetic outcomes along the lateral lower lip. The proposed modification allows for the combination of closure of a larger defect (Webster) with the more aesthetically pleasing staircase sutures (Johanson).

In 2011, Minagawa et al. further modified the Webster flap, altering the flap formation itself, including the formation of the flap on the contralateral side of the defect versus bilaterally in concert with a nasolabial flap. The combination of closure via the modified Webster method and nasolabial flap ensured optimal aesthetic outcome of the lower lip with good donor site matching in color and texture. The unaffected oral commissure remained untouched, and the formation of horizontal suturing between the mouth and nasolabial groove was avoided.

**Quaba/Sommerlad Flap**

The Quaba/Sommerlad flap was first described in 1987 as a rhomboid-flap modification for closure of circular defects (Figure 4a). Because circular defects are the most common types encountered in facial surgeries, their closure is of great clinical significance. This flap uses the basis of the Limberg flap with two key modifications: (1) no need to create a rhomboidal defect, and (2) a flap smaller than the defect size. The predominating advantage to this is a reduced sacrifice of healthy donor tissue. In the case of Quaba/Sommerlad, a diagonal is extended to be two-thirds the size of the defect (Figure 4b). Although most simple to achieve, the Quaba/Sommerlad flap taken from shortest diagonal does not always achieve the most aesthetically pleasing outcome. In contrast to the other rhomboid flap designs, the Quaba/Sommerlad flap is raised less than the size of the defect and donor tissue is allowed to contribute to the wound closer. Key stitch locations are integral to adequately distribute the tension to ensure good vascularization to the distal aspects of the flap.

The Quaba/Sommerlad method has been especially helpful in the closure of hand defects where the cutaneous branch of the dorsal metacarpal artery serves as the perforator artery supplying blood to the flap from the pedicle. In hand surgery, in order to increase flap vascularity, Bailey et al. prosed a modification that starts the perforator artery at the junction of the dorsal metacarpal artery and the dorsal communicating branch of the common digital artery. This increases the ability to cover the dorsal aspect of the finger past the proximal interphalangeal joint. The increased blood flow makes this technique especially helpful when treating defects on burned or grafted areas.

**Advantages of the Quaba/Sommerlad Flap**

There are numerous advantages to the Quaba/Sommerlad flap, the most obvious being the decrease in excision of healthy donor tissue when raising the flap. In addition, this protocol permits more variability of the donor site, allowing for better concealment of scarring.

**Ablation and Rhomboid Flaps**

Rhomboid flaps are commonly used for closure of defects following skin-cancer excision. One study by Murillo et al. examined the use of skin-cancer ablation in conjunction with flap transposition for complete resection of the malignancy while maintaining optimal aesthetic outcomes. Due to the variety of skin thicknesses and compositions throughout the head and neck region, this study mapped the anatomical areas and based closure protocols on where the cancer was located. For instance, a rhomboid flap was utilized in the medial aspects of the cheek because of the ease of transposition of the attached skin. Closure of these defects produced great aesthetic outcomes.

**Conclusion**

The extensive application and versatility of rhomboid flaps contributes to their success and popularity among physicians. Several different types of modifications to flaps better tailor this small surgical procedure for certain defects. The Limberg flap was the initial flap used for rhomboid defects, with effective healing and acceptable cosmetic appearance. The simple design of a Limberg flap gave rise to more advanced and complex flaps such as the Dufourmentel, Webster, and Quaba flap. Rhomboid flaps have shown great effectiveness over alternative methods of healing such as primary closure. Such advantages propel their use and are a common reason why these flaps are one of the first techniques used by surgeons. While certain closure techniques are invasive and involved, rhomboid flaps are associated with a good prognosis and rapid healing time. Continued modifications and advances in dermatologic surgery will further improve the outcomes of rhomboid flaps.
References


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Perforating dermatoses (PD) are a rare group of papulonodular skin diseases with a distinct central keratotic core representing the transepidermal elimination of an altered dermal substance. Diagnosis is established via biopsy and histopathologic evaluation. The primary PD are best categorized into four groups: reactive perforating collagenosis (RPC), acquired perforating dermatosis (APD), elastosis perforans serpiginosa (EPS), and perforating calcific elastosis (PCE). The primary PD can be differentiated based on the perforating substance, the distribution of the lesions, and their unique associations. Diagnosis of a PD should prompt screening for underlying systemic disease. Treatment of the PD is often difficult, but numerous reports have shown success. Here we present our case reports and a thorough literature review incorporating all identified case reports and studies found on PubMed as of July 2015.

**Abstract**

Perforating dermatoses (PD) are a rare group of papulonodular skin diseases with a distinct central keratotic core representing the transepidermal elimination of an altered dermal substance. Diagnosis is established via biopsy and histopathologic evaluation. The primary PD are best categorized into four groups: reactive perforating collagenosis (RPC), acquired perforating dermatosis (APD), elastosis perforans serpiginosa (EPS), and perforating calcific elastosis (PCE). The primary PD can be differentiated based on the perforating substance, the distribution of the lesions, and their unique associations. Diagnosis of a PD should prompt screening for underlying systemic disease. Treatment of the PD is often difficult, but numerous reports have shown success. Various classifications of the PD have been used in the literature, and various names have been reported for each entity. This has led to ambiguity and confusion. A useful classification scheme of all PD was proposed by Patterson in 1984:

1. Perforation as an incidental histologic finding
2. Perforation associated with other cutaneous and systemic disorders (secondary PD)
3. Disorders chiefly characterized by perforation (primary PD)

Even more numerous are the variations of the primary PD in the literature. The authors feel that the best classification is outlined in Table 1 and will be discussed in this review.

**Case Reports**

**Case 1**

A 17-year-old Hispanic male presented with a three-year history of spreading “warts.” He denied pain, pruritus, or manipulation of lesions and requested treatment for cosmetic concerns. Past medical history was significant for asthma, allergic rhinitis, and medulloblastoma. He had attempted numerous over-the-counter treatments, including topical salicylic acid and cryotherapy, with no improvement.

Physical exam revealed skin-toned, dome-shaped papules on the elbow. A punch biopsy of a representative lesion on the elbow was taken (Figure 1), and the margins were sent for histopathologic evaluation.

**Table 1. Primary perforating dermatoses**

<table>
<thead>
<tr>
<th>Perforating Substance</th>
<th>Location</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive perforating collagenosis</td>
<td>Collagen</td>
<td>Extremities, overlying sites of trauma</td>
</tr>
<tr>
<td>Acquired perforating dermatosis</td>
<td>Collagen, elastic fibers, or necrotic material</td>
<td>Lower extremities or generalized</td>
</tr>
<tr>
<td>Elastosis perforans serpiginosa</td>
<td>Elastic fibers</td>
<td>Lateral neck, flexures</td>
</tr>
<tr>
<td>Perforating calcific elastosis</td>
<td>Calcified elastic fibers</td>
<td>Abdomen, periumbilical, areolar</td>
</tr>
</tbody>
</table>

**Figure 1.** Dome-shaped papules with keratotic core overlying the knuckles.

**Figure 2.** Dome-shaped papules with keratotic core overlying the elbow.

**Figure 3.** Vertical section of the lesion from Figure 1 showing a plug of keratin, collagen, and inflammatory debris.
A punch biopsy was taken from the lower leg, screening labs were ordered, and the patient was started on desoximetasone 0.25% ointment bid. The biopsy revealed a channel through an acanthotic epidermis filled with a plug of amorphous, degenerated material with overlying parakeratosis and underlying neutrophils (Figure 6). Verhoeff-van Gieson stain failed to demonstrate perforating elastic fibers. Labs revealed a low hemoglobin and elevated alkaline phosphatase, AST, and ALT.

A diagnosis of acquired perforating dermatosis was established. The patient was referred to his gastroenterologist for evaluation and treatment of his anemia and hepatitis and was subsequently lost to follow-up.

**Discussion**

**Reactive Perforating Collagenosis**

RPC was first reported in a 6.5-year-old female by Mehregan et al. in 1967. It is a very rare, inherited disease thought to be caused by a genetic abnormality of collagen. Attempts to isolate the specific genetic defect have been unsuccessful to date. RPC occurs in an autosomal-recessive pattern, although there have been isolated reports of autosomal-dominant inheritance. Onset is in childhood, with a mean age of 5.3 years, and there is no gender or racial predilection.

Lesions present as 5 mm to 8 mm, flesh-colored papules with a central keratotic core. They grow over three to four weeks and may spontaneously resolve over six to 10 weeks, though some persist. Some lesions can grow up to 2 cm with increased age and a lack of treatment. There may be only a few localized lesions, or lesions can be more widespread and numerous. RPC can remain quiescent for long periods of time, but a relapsing-remitting course is common. RPC occurs in areas of superficial trauma and Koebnerizes more than any other PD. The most frequently affected areas include the dorsal hands, forearms, elbows, and knees. Some reports have associated exacerbations with cold weather in the winter months. It is postulated that the cold may induce degeneration of collagen and thinning of the epidermis. Pruritus is not prominent but has been reported in less than half of patients.

RPC is histologically characterized by a cup-shaped invagination of acanthotic epidermis containing a plug of vertically oriented collagen fibers, keratin, and inflammatory debris. The connective tissue surrounding the plug is typically unremarkable. After the plug falls off, the epidermis atrophies. There is no gold standard of treatment for RPC. Treatment is not necessary since lesions may spontaneously resolve and are largely asymptomatic. Yasmeen et al. compared treatment between 10 patients with RPC and report the most successful responses were with oral isotretinoin and topical tretinoin combined with emollients. Other treatments reported with varying levels of success include: topical steroids under occlusion, phototherapy, UVB phototherapy, cryotherapy, allopurinol, methotrexate, and electrical nerve stimulation. Despite all treatment regimens, RPC often recurs.

**Acquired Perforating Dermatosis**

APD is overwhelmingly the most common PD. This category includes all PD arising in adults that have been previously reported as acquired RPC, acquired EPS, Kyrle’s disease, and perforating folliculitis, among others. The splitting of this group reflects the variable histologic morphologies found in lesions of APD depending on the stage of development. A biopsy may reveal perforating collagen, elastic fibers, amorphous degenerated material, and/or altered follicular structures.

The classification of APD has changed over time, and disagreement remains amongst authors. Kyrle’s disease was first described by Kyrle in 1916 as “follicular et parafollicularis in cutem penetrans” in a diabetic female with generalized hyperkeratotic nodules. Kyrle’s disease is sometimes used synonymously with APD, and some describe it as the end stage of excoriated hyperplastic nodules of folliculitis. Patterson et al. propose that perforating folliculitis and acquired RPC are subsets of Kyrle’s disease. Others suggest perforating folliculitis is not a specific disease, as perforation of follicles can occur in any folliculitis regardless of the etiology. The term “acquired perforating dermatosis” was first used by Rapini et al. in 1989. Kim et al. characterize the various APD lesions in a study of 30 cases as follows: KD-like hyperkeratotic papules, PF-like follicular infiltrating papules, EPS-like serpiginous hyperkeratotic papules, or RPC-like keratotic plugged umbilicated papules (most common: 66.7%).

APD occurs in middle-aged adults, with no gender or geographic predilection. In the largest study to date, Kim et al. report a mean age of onset of 55.5 years. APD generally presents as umbilicated papules and nodules with a central white keratotic core. The core is sometimes picked and physically removed by patients. Giant variants have been reported where lesions are 2 cm. Lesions can be found on any cutaneous surface, but the extensor lower legs are most common, and many cases are generalized and diffuse. Koebner’s phenomenon is occasionally
CaCl₂ is used to treat dermatitis and pruritus. Membranes, palms, and soles are generally spared, failure, neurodermatitis, atopic dermatitis, and herpes zoster, tuberculosis, congestive heart (hypothyroidism, hyperparathyroidism), (Hodgkin's lymphoma, hepatocellular carcinoma, include liver disease (primary biliary cirrhosis, 

APD is most commonly associated with diabetes or chronic renal failure (CRF). APD is also associated with numerous other underlying systemic diseases, particularly ones that cause pruritus. 14 Saray et al. report that 86.4% of APD patients have at least one systemic disease. 14 An estimated 90.9% of diabetic patients with APD have an associated nephropathy, but non-diabetic CRF has been reported as well. Further, most patients with CRF are on dialysis, but it can occur earlier in the disease course prior to dialysis initiation. Approximately 10% of dialysis patients develop APD. 14 Other reported associations include liver disease (primary biliary cirrhosis, hepatitis, alcoholic cirrhosis), malignancies (Hodgkin’s lymphoma, hepatocellular carcinoma, thyroid cancer, acute leukemia), endocrinopathies (hypothyroidism, hyperparathyroidism), infections/infestations (scabies, aspergillosis, herpes zoster, tuberculosis), congestive heart failure, neurodermatitis, atopic dermatitis, and AIDS. 13 Kim et al. reported a pregnant APD case with no associated DM, CRF or previous cutaneous disease. 11 APD has also associated with TNF alpha inhibitors, bevacizumab, sirolimus, and indinavir. 10

An extremely rare variant of APD called verrucous perforating collagenomas is reported in the literature but not well understood. It is characterized by verrucous papules with transepidermal elimination of collagen. It occurs after severe trauma. 9 Acquired perforating calcific collagenosis is an APD variant that develops after topical calcium chloride (CaCl₂) exposure. In certain cultures, CaCl₂ is used to treat dermatitis and pruritus. Lee et al. reported two patients exposed to a CaCl₂-containing emulsion, used to produce bean curd, who developed coalescing umbilicated papules. 10 Histologically, the lesions show transepidermal elimination of calcified collagen and elastic tissue. The authors were able to experimentally induce a similar phenomenon in guinea pigs. Patel et al. report similar findings in a patient exposed to rock salts containing calcium chloride. 14-16 It also has been described in oil field workers exposed to the chemical. 11

Histologically, APD shows cup-shaped invagination of epidermis plugged with amorphous, degenerated material and inflammatory cell debris. 10 Rapini et al. originally proposed that the histologic findings represent different stages or different types of lesions within the same pathologic process. 9 They report elimination of both collagen and elastic fibers in four patients with APD. Schreml et al. agree that all APD have similar pathogeneses because all eliminated materials, including collagen, elastin and keratin, have been noted in one patient. 17 On the contrary, Saray et al. propose that APD represent a broad spectrum and are not variants of the same process. 13 Kim et al. also did not observe overlapping histologic features in the same patient. 13

There is also debate as to whether perforation actually exists. Schreml et al. point out that scratching may lead to epidermal gaps that expose subepithelial contents, which may appear as perforation. 17 Therefore, they advocate obtaining continuous imaging of the evolving lesions to guide understanding of the pathohistologic mechanism; however, that is not possible at this point. APD is proposed to originate from pruritus resulting in chronic scratching and epidermal hyperplasia. A similar process is seen in prurigo nodularis, a common concomitant condition seen with APD. 11 This theory is supported by the presence of Koebnerization. Fujimoto et al. propose that scratching exposes keratinocytes to advanced glycation end product (AGE)-modified extracellular matrix proteins, specifically collagen types I and III. 14 The interaction leads to terminal differentiation of keratinocytes via AGE receptor (CD36) and results in keratinocytes along with glycated collagen moving upward through epidermis.

Other studies suggest that the interaction of keratinocytes with altered structural proteins plays a role. Fibronectin is increased in both the serum and lesional skin of diabetic and renal-failure patients with APD. 19 Fibronectin is an extracellular matrix protein involved in epithelial cell signaling, movement, and differentiation. It binds collagen IV and keratinocytes and may induce epithelial proliferation and transepidermal elimination. 19 One study identified type IV collagen from the basement membrane as the specific type of collagen eliminated. 20 Other proteins overexpressed in APC include: transforming growth factor beta-3 (TGF-β3), matrix metalloproteinase-1 (MMP-1), and tissue inhibitor of metalloproteinase-1 (TIMP-1); however, this may simply reflect normal wound healing in these sites. 17, 21

An abundance of neutrophil remnants has been found in early lesions of APD, leading some to believe that proteolytic enzymes, such as collagenase and elastase, play a role. 17 The enzymes may transgress the epidermis and digest extracellular matrix components, leading to destruction of anchoring fibrils and collagen IV, ultimately resulting in their elimination. Another theory pinpoints diabetic microvascularopathy as the culprit. 11, 12 Microvascularopathy leads to dermal necrosis by hypoxia. This would incite the elimination of the necrotic dermal material. This mechanism is supported by positive periodic acid-Schiff staining of thickened blood vessel walls in the upper dermis in diabetic patients with APD.

Other proposed hypotheses involve deposition of substances such as calcium salts, uric acid, hydroxyapatite, or silicon, and metabolic disturbances leading to alteration of fibers, prompting their elimination. 11, 12 Another theory proposes a role of abnormal vitamin A or D. 4 Anecdotal success of antibiotics for treatment has led to the idea of a possible infectious etiology. 11, 24 There are also familial reports of APD. One family in India has 22 members afflicted with so-called Kyrle’s disease over five generations. 25 Unique features are also noted within the affected family members, including eye changes and palmoplantar lesions. There are no clinical studies conducted regarding treatment for APD, and therefore there is no gold standard. Conventional treatments have been derived from case reports. Kim et al. reported 93.3% of patients responding to topical steroids and 80% responding to antihistamines to decrease pruritus. 13 Control of pruritus and treating any underlying disease is the key to treatment. Other commonly reported treatments include intralesional steroids and topical retinoids. Other reported treatments include: UVB, PUVA, oral retinoids, and methotrexate. 11 Some dialysis patients have been cured of disease after transplant. 27

Allopurinol has recently emerged as a useful treatment of APD. Hoque et al. successfully treated four patients with a giant variant with allopurinol. 12 The theory behind the use of a xanthine oxidase inhibitor is that it reduces oxygen free radicals, which cause collagen damage and skin necrosis. Allopurinol is also reported to inhibit neutrophil activity. 28 Antibiotics have been used to treat culture-negative APD. Clindamycin is reported to have cleared a case after Kasiakou et al. noted the inflammatory histlogic findings and suspected an infectious cause, thought to be anaerobic bacteria. 24 Doxycycline has also been used successfully in cases of APD. 19 Metronidazole was successfully used in another case in which biopsy showed inflammatory infiltration in the lesion. As opposed to clindamycin, metronidazole does not have any anti-inflammatory properties, which supports an infectious etiology. 23 A vitamin D3 synthetic analogue, tacalcitol, used in the treatment of psoriasis has also been used to treat APD. 10 Tacalcitol inhibits the proliferation of keratinocytes and simultaneously modifies inflammatory mediators. Since APD lesions contain significant inflammation and epidermal hyperplasia-like psoriatic lesions, Escribano-Stable et al. decided to use this treatment on a case refractory to topical steroids and antihistamines. 30 They report achieving complete remission after two months.

Elastosis Perforans Serpiginosa

Lutz first described EPS in 1953 and termed the disease “keratosis follicularis serpiginosus” based on the unique configuration. 31 In 1955, Miescher characterized the specific pathologic finding of perforating elastic fibers and termed the disease “elastoma intrapapillare perforans verruciform.” 92 Dammert and Putkonen coined the current name in 1958. 31 EPS can either be idiopathic (most
common), drug-induced, or reactive. There are also few familial reports of EPS.34,35

It is reported that 40% of EPS patients have an underlying genetic disorder involving fibrous tissue including: Down syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, Marfan syndrome, pseudoxanthoma elasticum (PXE), scleroderma, Rothmund-Thomson syndrome, acrogeria, and Moyamoya disease.46 An extensive history and physical exam should be performed when establishing the diagnosis. However, pediatric dermatologists collectively do not routinely perform genetic testing on the sole basis of EPS in an otherwise healthy child.34

EPS has a predilection for males in a 4:1 ratio and most commonly occurs in the second decade of life.33,37 EPS is characterized by 2 mm to 5 mm, keratotic papules in a serpiginous or annular configuration.38 Rings of papules may be up to several centimeters in diameter. Lesions are most commonly located on the lateral neck but can also appear on the face and flexural extremitities.3 There are isolated case reports of EPS on the axilla and glans penis.39 EPS is typically asymptomatic.

Diagnosis is established through biopsy. EPS lesions show eosinophilic elastic fibers and other basophilic debris filling tortuous channels that span from the papillary dermis to the epidermis. In adjacent dermal tissue there are many inflammatory cells including lymphocytes, macrophages, and multinucleated giant cells and also altered elastic tissue.31 Elastic fibers are best highlighted by special stains like Verhoeff-van Gieson, which stains elastin black.

Most theories for EPS pathogenesis focus on altered elastic fibers. A hypothesis presented by Fujimoto et al. through in vitro studies demonstrated that elastic fibers interact with and influence the differentiation of keratinocytes.40 They propose that altered elastic fibers accumulate in the dermis and induce upward movement and differentiation of keratinocytes via elastin-receptor protein, 67 kDa. Expression of 67 kDa elastin-binding protein has not been reported in normal epidermal keratinocytes but is overexpressed in elastin-rich connective tissue. Other reports have implicated immunologic dysfunction like that seen in Down syndrome.33

Reports of EPS implicating dysfunctional epidermal barrier from mechanical trauma, chemicals like calcium chloride salt water, and scabies are best classified as APD.34 As with other perforating disorders, there are no clinical trials or gold standards for treatment. Several treatments are described with mixed efficacy and poor long-term success. Destructive modalities attempted include cryotherapy, curettage, electrocautery, dermabrasion, excision, tape stripping, topical salicylic acid, and CO2 laser.41 Caution is advised, as there is risk of scarring with these modalities. Furthermore, treatment is not necessary, as EPS remains localized and asymptomatic. Mixed results are also reported using topical and intralesional steroids, UVB, erbium-doped yttrium aluminium (Er:YAG) laser, and pulsed dye laser.42 Successful case reports are described using topical imiquimod, topical calcipotriene ointment, and systemic isotretinoin.43 Topical tazarotene was used with remission of lesions that recur when medication was discontinued. Phenotin was tried in one case with no success.39 There are also reports of successful treatment of resistant cases with photodynamic therapy and topical allium cepa-allantoin-pentagalycan gel.44

Perforating Calcific Elastosis

PCE is an exceedingly rare disease and is both histologically and clinically similar to PXE. Some authors argue PCE is a localized form of PXE, while others say it is a separate entity.45 PCE is acquired and localized, whereas PXE is an autosomal-recessively inherited, multi-organ systemic disease. PCE has also been reported as “peribulbar perforating PXE.”46 The first case of PCE was diagnosed as EPS with PXE by Schutt in 1965.47 Lund and Gilbert reported PCE as a separate entity in 1976, terms it “perforating PXE,” and Lever and Schaumburg-Lever coined the term “PCE” in 1989.48,49

PCE occurs most commonly in middle-aged, obese, multiparous African-American females.40 Woo and Rasmussen reviewed 22 cases of PCE and reported an 82% female preponderance with a mean age of onset of 43 years.50 PCE presents as yellowish verrucous plaques with keratotic papules scattered at the periphery. Lesions are usually exclusively distributed on the abdomen, especially periumbilically; however, there is a report of lesions on periareolar skin in one patient and on the axilla of another.44

Histologically, PCE shows short, thick, basophilic, calcified elastic fibers residing in the lower dermis. EPS, in contrast, reveals non-calciﬁed elastic fibers in the upper reticular and papillary dermis.48 The pathogenesis of PCE is unknown. Pruza et al. propose lesions originate from repeated stretching of the skin from multiparity, obesity, ascites, or surgery.46

No successful treatments have been identiﬁed for PCE. Failed treatments include topical tretinoin and topical steroids.45

Secondary Perforating Dermatoses

Secondary perforating dermatoses are a group of unrelated disorders in which a substance is transepidermally eliminated as a minor phenomenon of another disorder. As with the primary PD, the epidermis becomes hyperplastic, surrounds the substance being eliminated, and causes the upward extrusion via keratinocyte maturation.1 Secondary PD include substances that are endogenous (chondrodysplasias nodularis helicis, hematomas, calcinosis cutis, lichen nitidus, papular mucinosis, amyloidosis), exogenous foreign materials (silkia, wood, suture), infectious organisms (chromoblastomycosis, leprosy, schistosomiasis, tuberculosis, leishmanniasis), granulomas (granuloma annulare, necrobiosis lipoidica, sarcoidosis, rheumatoid nodules, leprous gout), and neoplastic cells (melanoma, Paget’s disease, mycosis fungoides, pilomatrixoma, nevus sebaceous).153 Perforation in these dermatoses is best considered an incidental finding.

Conclusion

The PD have been classified and named in numerous ways in the literature, which has led to confusion. This thorough literature review attempts to compile all available case reports and studies of the PD from PubMed. The primary PD are best organized into four groups. Diagnosis of a PD should prompt the evaluation for underlying disease. Further studies are needed to elucidate effective treatment options.

References

Abstract
Cogan's syndrome (CS) is a rare autoimmune disease characterized by ocular and vestibuloauditory symptoms, occasionally presenting with vasculitis. Although rare, dermatologic manifestations often compel patients to seek medical attention. Classically associated with vasculitis, cutaneous findings vary widely, making it vital for dermatologists, neurologists, rheumatologists, and primary care physicians alike to consider CS in any patient with ocular and vestibuloauditory symptoms, especially with dermatologic findings.

We report a rare case of CS with dermatologic findings, reviewing the literature for its classification, epidemiology, etiology, pathophysiology, and current therapeutic approaches. We emphasize the spectrum of cutaneous findings, which spans from non-specific skin rashes and urticarial vasculitis to palpable purpura and pyoderma gangrenosum.

Coexisting cutaneous conditions can delay diagnosis, affecting patient outcome particularly in reference to permanent sensorineural hearing loss. Irreversible loss of visual acuity can also result from delayed treatment. Dermatologic findings may direct physicians to CS and prevent severe negative outcomes.

Introduction
The first case of non-syphilitic keratitis in association with audiovestibular symptoms was reported in 1935 by Morgan and Baumgartner. In 1945, David Cogan reported four additional cases, and the syndrome was hence termed Cogan's syndrome (CS). CS is a rare vasculitis whose hallmark features are non-syphilitic interstitial keratitis and audiovestibular symptoms similar to Meniere's syndrome, including hearing loss, tinnitus, and vertigo. By 1980, Haynes et al. defined atypical CS, a variant wherein patients present with ocular and audiovestibular symptoms other than the interstitial keratitis and Meniere's-type symptoms characteristic of the typical variant.

The pathophysiology of CS is believed to be autoimmune in nature, initially supported by the positive response to corticosteroids. Western blots and immunofluorescence eventually revealed autoantibodies to the inner ear, including both anti-neutrophilic cytoplasmic antibodies (ANCA) and anti-endothelial antibodies.

CS has been described most commonly in Caucasians, with no reported sex predisposition. Pediatric Cogan's syndrome, however, affects males more than females by a ratio of 2:1. Both typical and atypical CS generally present between the second and fourth decades of life, although other sources suggest the first three decades. The age of onset of pediatric CS cannot be specified due to the low number of cases reported in the literature. Disease course varies, but it most often becomes chronic and slowly progressive following an initial flare.

This article will focus on both variants of CS and review the literature of dermatologic findings in CS.

Case Report
A 47-year-old Trinidadian male presented with a two-month history of progressive loss of visual acuity and bilateral hearing, as well as headache and a rash that developed over six days on the dorsum of his hands bilaterally (Figure 1). The patient reported that similar symptoms initially began one year prior, during which time he presented to and was discharged from the emergency room without intervention. The patient reports that the rash began as a single papule on the left lateral hand, enlarged and then eventually ulcerated to become what he described as looking like a “cigarette burn.”

Figure 1. Erythematous, crusted papules and plaques.

Figure 2. Light brown, reticulated hyperpigmentation with splinter hemorrhages and petechiae.
systems was positive for pruritus and vertigo. Physical examination revealed a Fitzpatrick 3 patient with erythematous, crusted papules and plaques on the dorsal lateral hands and digits and light brown, reticulated hyperpigmentation on bilateral lower extremities, with splinter hemorrhages on the right hallus and petechiae on the bilateral toes (Figures 1, 2). Ocular examination revealed bilateral inferior conjunctival erythema. Ophthalmologic consultation diagnosed the patient with anterior scleritis and scleromalacia.

Two biopsies were performed for hematoxylin and eosin (H&E) staining as well as a lesional direct immunofluorescence (DIF) to rule out Buerger’s disease or any other form of vasculitis. Biopsy revealed spongiosis dermatitis with overlying crust, and DIF was negative and thus non-diagnostic (Figure 3). An extensive workup was performed to rule out vasculitis, with all studies being negative. An autoimmune workup for lupus was negative. Additionally, the patient was negative for HIV and RPR. MRI scan of the brain revealed a right basal ganglia, left external capsule, and left central semioval infarct. The constellation of ocular inflammation (diagnosed as scleritis), bilateral hearing loss, thrombocytosis, pruritic skin lesions, and elevated ESR and CRP was consistent with CS.

Discussion
CS is a clinical diagnosis based on ocular inflammation, audiovestibular symptoms, negative serologic syphilis tests, and histological evidence of vasculitis. However, due to the variability of symptoms and lack of specific tests, CS is best retrospectively diagnosed after responsiveness to corticosteroid treatment. Dermatologic symptoms can be the impetus for CS patients seeking treatment, so the condition should be considered when certain dermatologic findings present along with the constellation of symptoms characteristic of CS (keratitis, scleritis, vertigo, and hearing loss). Although our patient presented with a biopsy indicating hemorrhagic crusts and scabs, other dermatologic findings have also been documented. The few skin manifestations reported among CS patients have varied from non-specific erythematous or urticarial rash, purpura, nodules or ulceration of the limbs, genitals or mouth, pyoderma gangrenosum, and limbal erythema. In an analysis of 24 pediatric cases, only three presented with cutaneous manifestations of skin rash and urticarial vasculitis. Although musculoskeletal, ocular, and vestibular symptoms improved throughout the disease course, cardiovascular and skin manifestations did not. In this study, a delayed diagnosis was related to a worse outcome. Additionally, among 50 case reports of CS, only four presented with dermatologic findings. These findings included a transient macular rash, a hemorrhagic, ulcerated vasculitis rash, and two cases complicated with pyoderma gangrenosum. One case emphasized the significance of an early diagnosis to prevent hearing loss, while another highlighted how isolated systemic manifestations may delay diagnosis if ocular and audiovestibular symptoms are absent.

A common problem in the diagnosis of CS patients is the variability of disease progression over time. As evidenced by Zulian et al., hallmark symptoms do not follow a chronological timeline. In that study, a 4-year-old Caucasian boy developed conjunctivitis 10 days prior to admission. Although hallmark symptoms may occur within years of one another, this patient developed sensorineural hearing loss soon after admission. However, in many cases it is not until much time has passed, often after many misdiagnoses, that the patient finally presents with the second of the two hallmarks. By that time, physicians may not associate the two symptoms, making it difficult to diagnose the symptoms as a syndromic event, let alone as a rare condition such as CS. Despite being an uncommon presentation, dermatologic manifestations can help clue physicians in to CS, especially when the patient does not have a history of both hallmark features. The significance of early diagnosis cannot be stressed enough, especially in pediatric cases of CS. This is due to the positive outcomes associated with early treatment via immunosuppression. Systemic symptoms tend to fully resolve upon treatment. Most important, though, vision and hearing loss can be reversible or irreversible depending on the extent of delay from illness onset to time of treatment. Orsoni et al. present a case report of two children with CS, both treated with corticosteroid-sparing immunosuppression. While both children’s systemic symptoms resolved, one child’s visual acuity and hearing loss improved whereas the second child had no ocular or auditory improvement. Given the devastating effects of irreversible deafness and vision loss, awareness of less-common presentations, such as those of the skin, can decrease the occurrence of not just negative outcomes, but permanent negative outcomes.

Pathophysiology
CS is mediated by lymphocytic and plasma-cell infiltration of the corneal and cochlear tissue. Autoantibodies targeting corneal, inner ear, and endothelial antigens have been found to be specific to CS. More specifically, IgG antibodies against the inner ear were identified in CS patients, in addition to IgG, IgM, and IgA antibodies against the cornea. Other autoantibodies, such as ANCA and rheumatoid factor (RF), have also been reported but remain non-specific due to their prevalence in other rheumatologic and autoimmune conditions. One study found an immunodominant autoantibody common among eight CS patients that showed similarities to antigens such as SSA/Ro and the reovirus III major core protein lambda 1. The autoantibody was also similar to cell-density enhanced protein tyrosine phosphatase-1 (DEP-1/C14D8), a protein expressed on sensory epithelia of the inner ear and on endothelial cells. In CS, IgG antibodies bind to cells expressing DEP-1/C14D8 and inhibit cell proliferation. Antibodies targeting heat shock proteins 70 and 68kDa derived from bovine inner ear have also been reported. All the aforementioned cochlear-targeting autoantibodies were originally thought to be specific for CS but were later found in children with idiopathic sensorineural hearing loss. Etiology
The exact etiology of CS remains unknown; however, various hypotheses have been proposed. It is possible that an infection may trigger CS, given that upper respiratory tract infections precede 21% of cases. CS may also be associated with Chlamydia infections or tuberculosis vaccination. In support of the theory of infection, some HLA loci, including HLA-B17, HLA-A9, HLA-Bw35, and HLA-Cw4, correlate with CS.

Presentation
CS primarily presents with bilateral interstitial keratitis with audiovestibular symptoms. In addition to its hallmark features, CS may also present with systemic, cardiovascular, neurologic, and gastrointestinal manifestations. Skin manifestations are not commonly seen but do occur rarely. The presentation varies slightly between typical and atypical CS. The clinical criteria for typical CS include non-syphilitic interstitial keratitis, audiovestibular symptoms similar to Meniere’s syndrome, and an interval between the onset of the first two criteria of less than two years. Ocular symptoms are usually bilateral. Audiovestibular symptoms can develop at any time throughout the disease course and commonly include hearing loss, vertigo, tinnitus, ataxia, and oscillopsia. Systemic manifestations may be present secondary to vasculitis of all vessel sizes, with complaints of headache, arthralgia, fever, arthritis, and myalgia being most common. Aortitis with aortic insufficiency is a major cardiovascular manifestation that occurs in 10% of patients. Neurological symptoms include sensorineural hearing loss but also extend to hemiparesis or hemiplegia secondary to a cerebral vascular accident and aphasia secondary to a transient ischemic event. Finally, gastrointestinal
manifestations may range from diarrhea and melena to abdominal pains, presumed to be due to mesenteric arteritis.26

The clinical criteria for atypical CS include various inflammatory ocular symptoms (with or without interstitial keratitis), audiovestibular symptoms unlike Meniere's syndrome, and more than two years between the onsets of the first two criteria.1 Ocular manifestations that separate atypical from typical CS include acute closure angle glaucoma, retinal vasculitis, papillitis, central vein occlusion, vasculitic optic neuropathy, and papilledema.23 The systemic vasculitis of atypical CS involves the cardiovascular, neurological, and gastrointestinal systems, unlike in typical CS.23 Differentiation between typical and atypical CS may be difficult due to variability in the progression of the disease. However, systemic manifestations occur more often in atypical CS and can thus be used to distinguish between the two.3

### Differential Diagnosis

CS needs to be diagnosed early to prevent the onset of severe hearing loss.29 The differential diagnosis of CS includes syphilis, Vogt-Koyanagi-Harada (VKH) syndrome, and Meniere's syndrome.24 Diagnosis may be difficult during the onset of CS due to audiovestibular similarities to Meniere's syndrome. The loss of balance and ataxia present in CS differ from the typical vertigo of Meniere's syndrome, which can help differentiate the two. Furthermore, Meniere's does not present with ocular symptoms. VKH is a multisystem disease that includes uveitis, leukokera,

### Table 1. Summary of prior case reports of CS with dermatologic manifestations.

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Dermatologic Findings</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Review of clinical features of CS among 23 children with CS (Paginini, et al.3)</td>
<td>Three of 23 patients had skin manifestations:</td>
<td>Of the various manifestations of CS, only skin and cardiovascular manifestations did not improve over time.</td>
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<td></td>
<td>1) 9-year-old female: maculopapular rash resembling marginated erythema of parvovirus B-19 infection on the lower limbs.</td>
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<td></td>
<td>2) Previously healthy 4-year-old Caucasian male: developed transient macular rash after admission to the hospital.</td>
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<td>3) Only one patient developed a skin rash over the course of the disease.</td>
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<tr>
<td>Case report of pediatric CS (Podder, et al.29)</td>
<td>A 4-year-old female developed cutaneous manifestations over the course of her diseases, characterized by a vasculitic rash on her buttocks that was initially hemorrhagic. The rash progressed to ulceration and was slow to heal.</td>
<td>Cutaneous manifestations need not appear at disease onset and may evolve as the disease progresses.</td>
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<tr>
<td>Case report of pediatric CS (Zulian, et al.29)</td>
<td>A 4-year-old Caucasian boy presented 10 days after an upper respiratory tract infection having developed bulbar conjunctivitis, fever, and arthralgias. After admission to the hospital, he developed sensorineural hearing loss and a transient macular rash and arthritis on his right, eventually diagnosed as CS.</td>
<td>CS can present as a constellation of systemic symptoms that do not necessarily appear simultaneously. The ability to recognize both common and rare symptoms despite separation through time can allow an early diagnosis and treatment – especially important in the prevention of loss of visual acuity and sensorineural hearing.</td>
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<td>Case report of atypical CS with urticarial vasculitis (Ochonisky, et al.34)</td>
<td>An 18-year-old black female with atypical CS presented with urticarial vasculitis as a new manifestation of atypical CS. Ochonisky further explains the significance of the patient's high levels of Chlamydia trachomatis antibodies in the pathogenesis of CS.</td>
<td>Urticarial vasculitis is reported as a new manifestation of atypical CS.</td>
</tr>
<tr>
<td>Case report of symptoms post-splenectomy in atypical CS (Wohlgethan, et al.30)</td>
<td>A patient with atypical CS was proposed to have developed palpable purpura and uveitis, with splenectomy as the trigger.</td>
<td>Wohlgethan discusses the importance of recognition of precipitating factors rather than CS as the sole primary cause of skin manifestations.</td>
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<td>Two cases of pediatric CS (Orsoni, et al.23)</td>
<td>A 13-year-old presented with limbal hyperemia and edema in one knee. A 9-year-old presented without skin manifestations. Both patients had a history of ocular and vestibulococlear symptoms that presented at separate times throughout the disease progression. Other symptoms included headache, asthenia, arthritis, and splenomegaly. Following corticosteroid-sparing immunosuppressive drug therapy, symptoms (excluding ocular inflammation and hearing loss) resolved in both patients. Hearing loss and visual acuity improved significantly in the 13-year-old, with best-corrected visual acuity improving from 21/200 to 21/100. The 9-year-old, however, incurred irreversible ocular and otolegic damage.</td>
<td>This case emphasizes the importance of early diagnosis and treatment to prevent permanent amblyopia and profound deafness. The commonality of the underdiagnosis of CS should also be noted, as ophthalmic and otologic symptoms often do not occur simultaneously, rendering diagnosis more difficult. Orsoni et al. state the need for a broad multidisciplinary approach to optimize early diagnosis, especially in systemic autoimmune diseases such as CS.31 This underlines the benefits of physicians being aware of possible skin manifestations to use as a clue in CS when the hallmark symptoms have not fully manifested yet.</td>
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Other Cases
Although CS is not characteristically described to present with dermatologic manifestations, there have been several reports. Table 1 summarizes dermatologic symptoms described among various case reports of CS.

Treatment
Medical treatment varies based on symptom severity and the extent of the disease. Steroid treatment is the common therapy no matter the degree of severity. Mild eye symptoms warrant the use of topical glucocorticoids and cycloplegics. Topical cyclosporine A has also been found to be effective in severe anterior segment inflammation. However, when there is posterior segment inflammation, systemic treatment is the preferred treatment of choice. Due to the pathophysiology of CS, which involves various organs (primarily the inner ear, the eye, and/or systemic vasculitis), immunosuppressive therapy is the goal. Systemic corticosteroids are the gold standard of care.3

As previously mentioned, early treatment is important in CS due to the progressive audi vestibular degradation that may be irreversible if left untreated for too long. The moment audi vestibular dysfunction is noted, high-dose corticosteroids should be administered (1 mg/kg to 1.5 mg/kg of prednisone daily). Signs of reversal of audi vestibular symptoms should be noticed within two to three weeks. Following improvement, the steroid dose should be slowly decreased and continued for two to six months. Infliximab in particular seems effective if started during the beginning of inner-ear damage. It has also been useful in maintenance of remission in CS patients with treatment failure. If sensorineural hearing loss progresses due to treatment failure, cochlear implant surgery is suggested.11

If corticosteroid therapy is contraindicated or the treatment regimen fails, other immunosuppressants, such as cyclophosphamide, azathioprine, methotrexate, cyclosporine and tumor necrosis factor-alpha blockers, should be used.33,40-42

Conclusion
Skin manifestations among CS patients are rare; nevertheless, it is important to report unusual cases such as this one, especially with less common findings, as they add to the pre-existing pool of literature and further the understanding and identification of varying presentations of such a rare condition. Cutaneous manifestations of CS present along a spectrum, from non-specific skin rashes and urticarial vasculitis to palpable purpura and pyoderma gangrenosum. These coexisting conditions can delay diagnosis, which can profoundly affect the patient outcome, particularly in reference to permanent sensorineural hearing loss. Irreversible loss of visual acuity can also result from delayed diagnosis and subsequent delayed treatment. Although they are the least likely of systemic manifestations, dermatologic findings are often the impetus for patients to seek healthcare, highlighting the importance of recognizing these presentations of CS.

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Syndrome de Cogan. Ann Dermatol Venereol. 1984;111:673-4


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Cutaneous Adenosquamous Carcinoma: A Case Study and Literature Review

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Abstract
Cutaneous adenosquamous cell carcinoma (ASC) is a rare variant of squamous cell carcinoma. It is an aggressive tumor with a tendency for local invasion, recurrence, and metastasis, so there is a great need for providers to recognize and understand this entity. Here we present the case of an 85-year-old Caucasian male with a rapidly growing lesion of the mandible. The pathogenesis, clinical manifestations, diagnostic evaluation, and treatments of ASC are discussed.

Introduction
Adenosquamous carcinoma (ASC) occurs primarily in the elderly population and has a slight male predominance.1-3 Fair-skinned individuals in areas of sun exposure and immunosuppressed patients are at greater risk.2-4 The lesion presents as a singular, erythematous, indurated, keratotic plaque often arising within actinic keratoses primarily on the head and neck.1,2,5 Lesions have, however, been described on the hand, foot, and thigh.3 The tumors are aggressive and can cause local ulceration, extensive destruction to the surrounding tissues, and in some instances metastasis that leads to death. In a case series by Banks and Cooper, five patients passed away from uncontrolled local recurrence, and two are alive with widespread disease and clinical evidence of lymph node involvement.2 In one patient the lesion caused fatal hemorrhage, and in another death by direct extension into the CNS. Wiedner and Foucar describe a similar case in which a recurrent lesion eroded the orbit.3

Case Report
An 85-year-old Caucasian male presented to our clinic with a reported two-week history of a smooth, dome-shaped, pink-to-erythematous, 0.6 cm x 0.6 cm nodule on the right superior mandible (Figure 1). Upon examination, the patient admitted to rapid growth of the lesion and a tendency to bleed.

Our clinical differential diagnosis included desmoplastic trichoepithelioma, basal cell carcinoma, cutaneous metastasis and keratoacanthoma. A biopsy was taken, and histopathological examination revealed an epidermis that was replaced by atypical keratinocytes with nests extending into the underlying dermis. Solar elastosis was also present. The squamous cells demonstrated acantholysis as well as multiple foci of ductal differentiation (Figures 2 and 3). A mucicarmine stain confirmed mucin within the ducts (Figure 4).

Clinical and histopathologic evidence supported a diagnosis of cutaneous adenosquamous carcinoma.

Discussion
Cutaneous adenosquamous carcinoma is a rare malignant neoplasm with mixed glandular and squamous differentiation and a propensity for local invasion, recurrence, and distant metastasis. ASC was first described in 1985 by Weidner and Foucar, who agreed with the view that ASC is best classified as a high-grade variant of cutaneous squamous cell carcinoma.1-4

Histologically, adenosquamous carcinomas often appear on a background of intense solar elastosis.4 There are features typical of classic squamous cell carcinoma, such as irregular anastomosing islands of squamous cells originating from the epidermis, keratin pearls, and intercellular bridges. The atypical squamous sheets are connected to the epidermis with intervening areas that are non-dysplastic.1 These squamous cells often exhibit a sclerosing pattern and can involve the subcutaneous tissue as well as skeletal muscle.1,4 There is true glandular differentiation with cystic spaces lined by low, columnar-to-cuboidal...
epithelial cells secreting mucin with ductular differentiation, sometimes highlighted by an eosinophilic cuticle.\textsuperscript{1,4} High-grade atypia with frequent mitotic figures is characteristic.\textsuperscript{2}

There are currently only a few cases of ASC described in the literature, though some authors refer to previously described cutaneous mucoepidermoid carcinomas (cMEC) as the same entity.\textsuperscript{6} There is controversy over whether they should be regarded as singular or distinct entities. Both lesions exhibit squamous as well as adenomatous differentiation.\textsuperscript{1,5}

Although exceedingly rare in the skin, MECs are commonly found in other organs, such as salivary glands, lungs, and the female genital tract, and are of sweat gland origin.\textsuperscript{8} MECs are low-grade, indolent neoplasms with extremely low metastatic potential.\textsuperscript{2,3} ASCs, on the other hand, are not only aggressive but exhibit high rates of both recurrence and metastasis.\textsuperscript{1-3} The reigning opinion is that ASC, due to its highly aggressive nature, should be considered separate from MEC for prognostic purposes.\textsuperscript{1-3,5,7,8} There is controversy over whether the same entity.\textsuperscript{6} There is controversy over whether they should be regarded as singular or distinct entities. Both lesions exhibit squamous as well as adenomatous differentiation.\textsuperscript{1,5}

Table 1. Differential Diagnosis of ASC with Histopathological and Immunohistochemistry Features

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Histopathology and Immunohistochemistry Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary cutaneous SCC</td>
<td>Hyperkeratosis, full-thickness atypia of epidermis, invasion of dermis by atypical keratinocytes</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>ER PR surfactant thyroglobulin CA 199</td>
</tr>
<tr>
<td>Acantholytic SCC</td>
<td>Pseudoglandular formation, PAS-negative</td>
</tr>
<tr>
<td>MEC</td>
<td>Patchy and focal p63 and cytokeratin 5/6 staining</td>
</tr>
<tr>
<td>Cutaneous adenosquamous carcinoma</td>
<td>Diffuse p63 and cytokeratin 5/6 staining, CEA+, keratin 7+</td>
</tr>
</tbody>
</table>

Table 1. Differential Diagnosis of ASC with Histopathological and Immunohistochemistry Features

In summary, adenosquamous carcinoma is best considered a locally aggressive, high-risk subtype of cutaneous squamous cell carcinoma. Due to the invasive and sclerosing pattern of these lesions, surgical resection can be difficult, but it is the treatment of choice.\textsuperscript{1} It is important to take a thorough history and perform full body scans in order to rule out an alternative primary tumor origin.\textsuperscript{13} Clinicians may also consider testing for the estrogen receptor, progesterone receptor, surfactant, thyroglobulin, and CA199 antigens in order to further rule out metastatic disease.\textsuperscript{1}

**Treatment**

Most cases report a surgical approach with Mohs microscopic surgery, in some instances followed by radiation and chemotherapy as regional recurrence is common.\textsuperscript{2,12} There are also reports on the use of cetuximab as an adjunctive therapy for the treatment of ASC. The efficacy of this recombinant human and mouse chimeric antibody against the epidermal growth factor receptor as treatment for locally advanced cutaneous ASC is still under exploration.\textsuperscript{12}

**Conclusion**

In summary, adenosquamous carcinoma is best considered a locally aggressive, high-risk subtype of cutaneous squamous cell carcinoma. Due to the invasive and sclerosing pattern of these lesions, surgical resection can be difficult, but it is the treatment of choice.\textsuperscript{1} It is important to take a thorough history and perform full body scans in order to rule out an alternative primary tumor origin.\textsuperscript{13} Clinicians may also consider testing for the estrogen receptor, progesterone receptor, surfactant, thyroglobulin, and CA199 antigens in order to further rule out metastatic disease.\textsuperscript{1}

**References**


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PATEL, NGUYEN, HOROWITZ, SHITABA
Bacterial Pseudomycoses of the Skin: A Case Report

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Abstract
Clinicians in all scopes of medicine are no strangers to misnomers. The inaccurate naming of diseases and organisms oftentimes results from their resemblance to other entities and has been known to mislead physicians regarding etiologies and histopathologies. In the field of dermatology, certain skin infections have been mislabeled to be fungal when they are actually bacterial in nature. In order to further understand the origins and development of these infectious misnomers, we present a patient diagnosed with an unusual condition involving three different pseudomycotic skin infections. We also discuss the clinical features shared between these three bacterial pseudomycoses and identify the features that differentiate them from one another histopathologically.

Introduction
Pseudomycotic infections of the skin are a subset of bacterial infections that produce lesions with clinically fungal features.1 Often, additional tests would be required to isolate the causative organism, thus delaying appropriate treatment. In order to increase the dermatologic awareness of these infections, we present an unusual case of a patient with three different bacterial pseudomycoses of the skin and discuss the clinical features, microbiology, histology, and treatment of these rare entities.

Case Presentation
A 66-year-old Hispanic male presented with a 12-year history of multiple dark nodules to his body that appeared to be getting progressively worse. Despite receiving treatment with various antibiotics, antifungals, and topical creams, his condition persisted without any signs of improvement. Physical examination revealed several non-tender, erythematous, firm nodules mixed with some largely indurated plaques diffusely wrapped around his lower abdomen and back (Figure 1).

Multiple punch biopsies obtained from these lesions displayed areas of supplicative granulomatous fibro-inflammatory response consistent with an infectious process. Gram staining performed on these lesions revealed several foci of admixed Gram-positive bacterial cocci in addition to numerous filamentous rods in the deep dermal tissues (Figures 2 and 3).

Histologic findings of these specimens were consistent with the diagnoses of botryomycosis, actinomycosis, and actinomycetoma pending the results of the tissue culture.

In order to cover for all bacterial species involved, the patient was placed on a prolonged course of amoxicillin with clavulanic acid for at least six months until complete resolution of his condition. He responded very well to treatment without any signs of recurrence to this date.

Discussion
Despite the presence of fungal nomenclature in the diagnosis of actinomycetoma, actinomycosis, and botryomycosis, all are infections of the skin caused by specific types of bacteria. These conditions are differentiated from one another depending on the appearance and size of the bacteria associated with the disease (Table 1). If histologic findings prove to be inconclusive, then additional stains and studies can be performed depending on the species of bacteria involved (Table 2).2

**Actinomycetoma**
Actinomycetoma is a chronic cutaneous infection of the skin caused by aerobic, Gram-positive Actinomycetales order of bacteria such as Nocardia brasiliensis. These organisms are phylogenetically diverse but morphologically similar, exhibiting characteristic filamentous branching into both bacillary and coccoid forms. Nocardia can be differentiated from Actinomyces by the acid-fast staining and aerobic properties of Nocardia.3

After the organism is inoculated into the skin, a pyogenic response ensues with formation of a painless nodule at the site of entry. As the nodule enlarges, a chronic inflammatory response occurs, which can remain localized or extend to involve muscle and bone.4

Diagnosis of actinomycetoma is made histologically with skin biopsy or by culturing of infected lesions. Histopathologic appearance of this condition is characterized by the appearance of delicate, filamentous Gram-positive branching. These organisms were once considered fungi because of their hyphal-like appearance, but molecular analysis of their cell wall has confirmed their classification as bacterial.1,4

Management of this condition usually

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Table 1. Appearance and size of associated bacteria

<table>
<thead>
<tr>
<th></th>
<th>Actinomycetoma</th>
<th>Actinomycosis</th>
<th>Botryomycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance</strong></td>
<td>Filamentous</td>
<td>Filamentous</td>
<td>Cocci</td>
</tr>
<tr>
<td><strong>Grain Size</strong></td>
<td>40-80 μm</td>
<td>1-3 mm</td>
<td>0.5-1 mm</td>
</tr>
<tr>
<td><strong>Organism</strong></td>
<td>Nocardia brasiliensis</td>
<td>Actinomyces israelii</td>
<td>Staphylococcus aureus</td>
</tr>
</tbody>
</table>
Staphylococcus aureus is the most common organism cultured from lesions of botryomycosis, although it is not the only organism that can cause this particular type of condition. These pathogens may include, but are not limited to, organisms such as Pseudomonas aeruginosa, Escherichia coli, Serratia, and Proteus. Cutaneous botryomycosis is the most common form of botryomycosis and usually occurs following cutaneous inoculation of bacteria due to trauma, surgery, or presence of a foreign body. Lesions typically develop very slowly and may evolve to form multiple large, subcutaneous nodules for several months to years. Diagnosis of botryomycosis can be established histopathologically with skin biopsy or by culturing the bacteria from ulcers of infected lesions. Histopathologic appearance of this condition is characterized by a central focus of necrosis surrounded by a chronic inflammatory reaction containing histiocytes, epithelioid cells, multinucleated giant cells, and fibrosis. Gram staining or silver-nitrate staining is the preferred method of identifying these causative pathogens, which may be distinguished from actinomycosis or actinomycetomas by the variable sizes and shapes of the granules. These Gram-positive cocci are oftentimes larger than 1 micron in diameter, in contrast to the branching, filamentous bacteria less than 1 micron in size for actinomycosis and actinomycetoma.

Treatment of this condition is dependent on the causative organism and severity of the infection. For Gram-positive infections such as Staphylococcus aureus, oral trimethoprim-sulfamethoxazole, clindamycin, doxycycline, or cephalaxin can be used. For Gram-negative infections such as Pseudomonas aeruginosa, intravenous ceftazidime, ciprofloxacin, aztreonam, or imipenem can be effective.

References

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Favre-Racouchot Syndrome in a Unilateral, Perioral Distribution Associated with Tobacco Use: A Case Report and Review

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Abstract

The development of Favre-Racouchot syndrome (FRS) has been well described in dermatologic literature as having a strong association with chronic sun exposure and ultraviolet damage, which result in the classic appearance of solar elastosis and dilated open comedones in a bilateral periorbital distribution. However, frequently lacking in the literature is mention of another potential risk factor: tobacco use. The authors report a unique case presentation of FRS in a unilateral perioral distribution in a 66-year-old African American female without history of chronic sun exposure, but rather associated with preferential one-sided placement of her cigarettes. It is hoped that this case report will serve to strengthen the evidence that tobacco use may be implicated in the development of FRS.

Introduction

Favre-Racouchot syndrome (FRS) has been estimated to affect up to 6% of individuals over the age of 50 and presents most commonly in Caucasian males. It has been well established by past literature that the development of the condition possesses a strong association with history of exposure to solar radiation and actinic damage. Indeed, in addition to the presence of solar elastosis, one of the hallmark characteristics of the disease, numerous periorbital open comedones, have been referred to specifically as “solar comedones.” FRS has also been described in a patient following cancer radiation treatments, thought to result from similar pathogenesis involving the interruption of keratinization of the pilosebaceous follicle. Yet, the exact pathogenesis of this disease remains poorly understood, as does the potential for other significant contributive or causative factors.

The authors attempt to demonstrate a rarely emphasized association of the development of Favre-Racouchot Syndrome with long-term tobacco use as described in a unique case presentation. So far, there have been very few but significant publications that have investigated the association of skin changes consistent with FRS and smoking. This case report is noteworthy due to the unique presentation of the patient, who had no other major risk factors for the development of FRS and who also had skin changes that were consistent with the perioral location of her tobacco habit. It is hoped that this article will emphasize that FRS, which is most often thought to result from solar/UV-induced damage, is undoubtedly a disease of multifactorial origin with a potentially strong association with tobacco use.

Case Report

A 66-year-old African American female with a history of considerable cigarette use presented with a skin eruption, which she described as “brown bumps,” under the right side of her mouth for eight months’ duration. She had previously sought treatment by her primary care physician. Although she denied any history of herpes labialis, she had been treated presumptively with a course of oral acyclovir, resulting in no improvement in appearance. The lesions were asymptomatic but aesthetically displeasing to the patient, and therefore she sought further treatment by a dermatologist.

The patient denied use of hormone replacement therapy, lithium, or epidermal growth factor receptor inhibitors. Furthermore, she denied occupational exposure to halogenated compounds. The patient admitted a 58-year history of cigarette smoking, where she preferentially and incessantly held the cigarette on the right side of her mouth. She denied alcohol consumption or any illicit drug use.

On physical exam, the patient was a well-developed, well-nourished female with Fitzpatrick skin type V. Inspection of the right lower cutaneous lip revealed small cysts and open comedones in an agminate arrangement (Figure 1). There was mild hyperpigmentation but no associated solar elastosis. The remainder of the facial skin, including the periorbicular region, was free of similar findings.

A shave biopsy was obtained and demonstrated two mildly inflamed comedonal cysts embedded in a dermis with evidence of severe nodular solar elastosis (Figures 2 and 3).

Despite the unusual location and lack of chronic actinic damage, a diagnosis of Favre-Racouchot syndrome was made on the basis of clinicopathologic findings. The patient was treated topically with tretinoin 0.04% gel and counseled on smoking cessation. At three-month follow-up, she reported mild improvement in appearance of the perioral cysts and comedones.

Figure 1. Small cysts and open comedones in an agminate arrangement post shave biopsy.

Figure 2. Photomicrograph of skin containing two mildly inflamed comedonal cysts embedded in a dermis with evidence of severe solar damage (4x).

Figure 3. Photomicrograph of the surrounding dermis demonstrating severe nodular solar elastosis indicating significant prolonged sun exposure (20x).
Discussion
The relationship of FRS with smoking has been investigated in the past, but not to a large extent. Acting on a hypothesis based on clinical experience, one dermatology clinic performed a retrospective study that revealed a statistically significant association between FRS and chronic tobacco use. Furthermore, the authors found the likelihood of developing FRS was dose-dependent when comparing heavy versus light smokers. Drawing on this study’s conclusions, a subsequent publication asserted that smoking holds a stronger association with development of FRS than ultraviolet radiation. Despite this contention, FRS continues to be regarded as a predominantly sun-damage-induced disease process, and these authors could find no further studies investigating the relationship between smoking and FRS development.

This particular case presentation is noteworthy due to the unique nature of a unilateral perioral distribution of the disease, thought to be a direct result of the habitual preference of the patient to hold her lit cigarettes in her ipsilateral mouth. In support of this assumption, changes in the elastic tissue of non-sun-exposed areas in smokers that resemble the histological findings of solar elastic tissue resulting from sun damage have been described. Past in vitro studies have indicated that tobacco-smoke extract impairs the production of collagen and increases the production of tropoelastin and matrix metalloproteinases, which in turn degrade matrix proteins and cause an abnormal production of elastosis material. Moreover, as the patient in this case report is African American, her skin possesses a higher concentration of melanin, which has been shown to be negatively associated with the development of UVR-induced solar elastosis. Complicating the picture is whether exposure to tobacco smoke is solely responsible for the development of the elastosis found in this patient or if the potential long-term exposure to heat (infrared radiation) from the lit cigarette also has impact. One study investigated this question, exposing a group of albino guinea pigs to UVA and UVB radiation with and without infrared radiation. The study found that the combination of UV and IR radiation resulted in dense, mat-like elastic fiber depositions that exceeded what was observed in either source of irradiation alone.

In addition to elastosis, other common histological findings of FRS include epidermal atrophy, basophilic degeneration of the upper dermis, and a decrease in the size of the sebaceous glands with dilated and keratin-filled pilosebaceous infundibulum. As to the unilateral distribution of the patient’s disease, albeit rare, unilateral temporal and periorbital presentations of FRS have been reported in the past linked with occupations involving chronic asymmetrical sunlight exposure. No similar reports of FRS in a unilateral, perioral distribution could be found, despite an extensive literature search. It is unclear why more individuals do not develop the skin findings this patient presented with, as tobacco use is still ubiquitous today despite widespread knowledge of many potential harms. Ultimately, sufficient research on the development of FRS is lacking, and further clinical studies should be performed to gain a better understanding of the pathogenesis and disease factors.

In reference to treatment, although benign, FRS can be aesthetically troubling to patients and has proved challenging to remedy. There have been many proposed therapeutic modalities, including direct extraction, topical or oral retinoids, chemical peels, and microdermabrasion, as well as investigations utilizing CO2 laser that have resulted in good outcomes.

Conclusion
It is hoped that the information presented in this case report will encourage providers to acknowledge that emphasizing smoking cessation in patients is also an essential adjunct treatment for the resolution of FRS and prevention of the disease process.

References

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Lymphadenopathic Form of Endemic Kaposi Sarcoma in an HIV-negative Gambian Male

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Abstract
Kaposi sarcoma (KS) is a multicentric neoplasm of vascular and lymphatic endothelial origin that can involve the skin, lymph nodes, and visceral organs. Human herpesvirus 8 has been implicated in the etiology of this disorder. Commonly seen in association with AIDS and an immunocompromised state, KS also occurs in HIV-seronegative, immunocompetent populations in parts of Africa. We report the case of a 21-year-old male from Gambia, West Africa, who presented with multiple painful nodules on the hands and feet. Histopathology confirmed a diagnosis of Kaposi sarcoma, whereas serology for HIV was negative. Positron emission tomography revealed higher-stage disease with uptake in retroperitoneal lymph nodes, also subsequently biopsy-confirmed. The patient received radiation therapy but continues to have a progressive disease course with development of new cutaneous lesions. Herein we provide a review of contemporary knowledge on the clinical features and management of this aggressive endemic subtype of Kaposi sarcoma.

Introduction
Kaposi sarcoma (KS) is a mesenchymal, angioproliferative, low-grade malignancy. Although multi-focal, KS does not become metastatic. KS is etiologically related to infection by human herpesvirus 8 (HHV-8). HHV-8 has been found in tissue biopsies of all stages and epidemiological forms of KS. Aside from causing KS, this oncogenic virus also gives rise to two other malignancies: a rare form of B-cell lymphoma called primary effusion lymphoma and a plasmablastic form of multicentric Castleman disease. HHV-8, however, is not involved in epithelial tumors. Viral infection is necessary for the occurrence of KS but not always sufficient. HHV-8 seropositivity throughout the world has been found to be greater than the prevalence of KS, with up to 80% seropositivity in some parts of sub-Saharan and equatorial Africa. Consequently, it has been speculated that there are also ethnic and genetic cofactors involved in the development of KS.

Kaposi sarcoma classically presents with the cutaneous manifestations of discrete violaceous patches, plaques, or nodules, most commonly on the lower extremities. The four most common clinical variants of the disease are classic KS, African (endemic) KS, iatrogenic/transplant-associated KS, and AIDS-associated (epidemic) KS. In 1982, Kaposi was the first to describe the disease, which he called "sarcoma idiomathicum multiple hemorrhagicum." In 1912, Sternberg labeled this condition "Kaposi sarcoma." Two years later, in 1914, the first case of African or endemic KS was described to be a more aggressive form with a higher rate of extracutaneous manifestations.

KS classically progresses through three stages representative of its morphological features: the patch, plaque, and nodular stages. These stages are common in all four of the clinical variants mentioned and correspond to certain histological features. The earliest phase of KS, the patch stage, is the most difficult to diagnostically identify, manifesting as something more akin to a mild inflammatory dermatosis. However, on histology, there may be subtle indications of newly formed ecstatic, vascular spaces with protrusion of native vascular structures into these channels creating the characteristic promontory sign. The plaque-stage lesions of KS are characterized by a more diffuse dermal vascular infiltrate and greater cellularity. Commonly, a phenomenon known as autolumination is seen, where an erythrocyte is contained in a paranuclear vacuole in a spindled endothelial cell. Nodular-stage KS is more apparent in diagnosis, characterized by dermal expansion by variable cellular proliferation of neoplastic spindled cells. The viral load in lesions correlates with the clinical progression through the patch, plaque, and nodular stages.

Staining with antibodies to HHV-8 LNA-1 and lymphatic endothelial cell marker D2-40 has proven useful in the identification of early KS development. There are myriad other histological KS variants, including those described in older literature, such as anaplastic, lymphoedematous, lymphangioma-like, lymphangiectatic, bullous, and telangiectatic KS. Anaplastic KS is rare and poorly documented. Telangiectatic KS is identified in a single case report. More contemporary variants include hyperkeratotic (verrucous), keloidal, micronodular, pyogenic granuloma-like, ecchymotic, intravascular, glomeruloid, pigmented, regressing KS (AIDS-treatment related), and KS with myoid nodules.

Case Report
A 21-year-old African male presented to our dermatology clinic with complaints of multiple painful lesions on the hands and feet. The lesions had appeared about two years earlier. Before the lesions appeared, he noticed swelling and pain in his right foot, which started seven years prior. The pain was worst upon waking in the morning and when weight bearing. Six weeks before presentation, the patient had emigrated from Gambia, West Africa. His lesions had been evaluated by physicians in Africa, and, according to the patient, they were unable to identify a diagnosis. One of the treatments tried was 100% tea tree oil, which had little effect on the lesions or his symptoms. Associated symptoms included constant sweating in the feet and ankles and knee arthralgia bilaterally. Ibuprofen did not alleviate his joint pain. The patient’s past medical history was unremarkable, and his immunizations were up to date, per the patient. At the time of initial presentation, he was not on any medications.

The patient denied any recent fever, chills, nausea, or vomiting. He had not had any excessive fatigue or weight loss. He denied noting any palpable or tender lymph nodes. He had not appreciated any gastrointestinal symptoms, including abdominal tenderness, distention, or generalized discomfort. He denied any constipation, diarrhea, or blood in the stool.

Skin examination revealed multiple hyperpigmented, firm and hyperkeratotic papules, nodules, and small tumors on the dorsal and plantar surfaces of the feet and ankles (Figure 1). On the plantar surface of the right foot, there were multiple well-circumscribed, exophytic, hyperkeratotic plaques in a cluster near the ball of the foot (Figure 2). Smaller nodules were present on the hands and fingers (Figure 3). There was mild nonpitting edema up to the mid-calf. No other cutaneous lesions were noted elsewhere.

On general physical exam, the patient was fully alert and oriented, and in good spirits. No lymphadenopathy was noted in the neck.
A complete blood count showed a white blood cell count of 6,500 per microliter, containing an elevated portion of lymphocytes (46.2%). The remainder of the values were within the normal range for hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hematocrit concentration, and platelet count. The complete metabolic panel was unremarkable other than a slightly elevated glucose level of 106 mg/dL. The patient underwent HIV testing, was found to be seronegative, and was referred to oncology.

Despite several rounds of radiation therapy, oncology noted new lesions developing on the right side of his neck and on the right hand. A PET/CT scan was performed, which showed lymphadenopathy in the retroperitoneum. The largest lymph node measured 2.7 cm in diameter. Biopsy of the lymph nodes confirmed the presence of Kaposi sarcoma there as well.

**Discussion**

Endemic KS is found most commonly in Uganda, the Congo, the Congo Republic, Burundi, and Zambia.\(^9,10\) It comprises up to 10% of malignancies in central Africa and has a male-to-female ratio of nearly 15:1 in adults. Interestingly, the ratio of KS in children is nearly 1:1 male to female. The incidence of KS varies widely with the geographic variations of the HIV/AIDS epidemic, as approximately 80% of those presenting with KS are HIV positive.\(^12,15-18\)

Consequently, the highest incidence rates of KS are seen in central and eastern Africa, where HIV infection rates are high. Across the entire continent, KS is the third most common cancer behind liver and prostate and is one of the leading causes of cancer death.\(^11-13\) In endemic areas like Uganda, for example, where the prevalence of HIV has reached up to 10%, the incidence of KS has increased tenfold compared with the pre-HIV/AIDS era.\(^2,10,14\) When regarding hospitals in and around Kenya, KS comprises 25% of all cutaneous malignancies, second only to squamous cell carcinoma (44%). Similar rates have been observed in studies in Nigeria.\(^15,19,20\)

HHV-8, a virus that can be spread via saliva and semen, is the underlying culprit to all KS. However, as mentioned earlier, HHV-8 seropositivity does not perfectly correlate with the appearance of KS. In fact, there are countries where HHV-8 seropositivity rates are high and KS is rarely reported. This includes Brazil, Thailand, Gambia, and the Ivory Coast.\(^21\) Investigators have struggled to identify additional factors that may play a role in the manifestation of KS. There are eight distinct subtypes distributed over certain geographical regions: namely A/C, J, K/M, D/E, B, Q, R, and N groups. Subtypes B, N, Q, and R are found almost exclusively among the Sub-Saharan African cases, with subtype B predominating. It is not certain whether the subtypes have different pathogenic properties.\(^4,22\)

A multitude of co-factors have been proposed in the pathogenesis of endemic KS. One of the risk factors identified for endemic KS is barefoot exposure to wet soil. The proposed mechanisms are various and include the role of high iron levels and quartzite content in African soils. In a clay emulsion, quartz particles of less than 2 um can readily enter sweat glands of the feet. Quartz can cause micro-abrasions when exposed to the skin of the feet. These quartz particles may induce lymphatic damage and fibrosis, resulting in an inflammatory response and local immune system impairment.\(^8\) This lymphedematous region is a predisposed environment for malignancy, especially vascular tumors.\(^23\)

After aluminum, iron is the most abundant mineral in African clay soils. Multiple pathways have been suggested for the role of iron. Iron may lead to immune impairment via inhibition of CD4 lymphocytes and suppression of macrophages. It can also induce production of reactive oxygen species and even directly promote
growth of spindle cells. Iron has also been found to induce anti-apoptotic signals in endothelial cells that are potential progenitors for KS cells. Lastly, iron may be conducive to KS development via increased host-cell production of viral nucleic acids.12,24-28 This theory is supported in part by the observation that endemic KS in Africa seems to be in proximity to volcanoes.29 Similarly, higher rates of KS have been seen in populations of southern Italy near Mount Vesuvius. However, further studies are warranted.30,31

Another potential co-factor is quinine and other drugs used for malaria treatment. KS and malaria show similar distribution patterns throughout sub-Saharan Africa, Italy, Greece, and Asia. In addition, quinine, chloroquine, and hydroxychloroquine may decrease immune response toward viruses. Chloroquine has been found to reduce the antibody response when given concomitantly with the rabies vaccine. These medications have been used for their immunosuppressive properties in the treatment of lupus erythematosus and rheumatoid arthritis. Quinine may act as an activating agent, converting latent HHV-8 to its lytic form.4,32,33

There are four clinical variants of endemic KS: (1) benign nodular or chronic localized, which presents as classic KS; (2) locally aggressive, invading soft tissue and bone (usually fatal in five to seven years); (3) florid disseminated, having skin and visceral involvement; (4) lymphadenopathic, rapidly disseminating to lymph nodes and visceral organs, in which there is usually an absence of cutaneous features (usually in children and usually fatal).30 KS can spread to the GI and respiratory tracts, but all visceral organs are potentially susceptible.30 Visceral involvement is often symptomless. However, gastric outlet obstruction, enteropathy, and bleeding of ulcerated KS lesions has been observed.20 Lymphadenopathy is present in about 75% of KS patients.12 The reported mortality rate in Togo for endemic KS after two years is 5%, compared to 45% for AIDS-associated KS (no HAART).15,16 Locally aggressive KS has an estimated three-year survival rate of 64%.30

Staging of KS has been difficult, and multiple classification systems have been devised. The classification system proposed by Schwartz et al. is shown in Table 1.30 Mortality rates and prognoses do not appear to be available relative to these stages. The patient presented here, given the retroperitoneal lymph node involvement and lymphedema of the leg, in addition to cutaneous features, would most likely fall into stage III of the classification system. Of the clinical variants of endemic KS mentioned, this patient may fall into the lymphadenopathic form, although cutaneous features are present in this case.

### Treatment

The treatment options for endemic KS vary widely due to its heterogeneity. There are no therapeutic guidelines. Local and topical therapies may be used in patients with minimal cutaneous disease, or reserved as palliative therapy for patients with aggressive, recurrent disease. Topical options include retinoids, imiquimod, cryotherapy, electrodessication, surgical excision, and laser therapy.5

Local chemotherapy with intralesional vincristine has been commonly used for nodular lesions. Intralesional vinblastine and bleomycin have been used, but are more painful and less effective than vincristine. Traditional low-dose radiation therapy often produces good therapeutic results by reducing pain and edema. However, one study has shown five-year survival rates of 46% for local radiotherapy due to development of KS outside the local treatment region.31 In a two-year study, treating local KS lesions smaller than 2 cm with high-dose-rate brachytherapy demonstrated a complete response in all 16 patients, with no evidence of local recurrence or tumor progression.33 The recent use of chemotherapy in combination with electroporation to enhance drug uptake into tumor cells of patients with KS not treatable with radiotherapy or vincristine demonstrated a complete response rate of 60.9%.30

In HIV-infected patients, highly active antiretroviral therapy (HAART) plays an indispensable first-line role in management, alone and in combination with other treatments. HAART exerts its therapeutic effects by inhibiting HIV replication and augmenting the immune response against HHV-8. Protease inhibitors have also been shown to have direct antiviral effects. However, the KS may initially flare in patients with very low CD4+ T-cell counts, as a result of immune reconstitution inflammatory syndrome.

Systemic chemotherapy is reserved for cases of disseminated, rapidly progressive, or life-threatening disease with visceral involvement. Intra-arterial vinblastine in combination with bleomycin is first-line therapy for advanced classic KS.30 Other chemotherapy agents include liposomal anthracyclines, paclitaxel, oral etoposide, and single-agent and combinations of doxorubicin, bleomycin, and vincristine. The response rates for combination agents range widely, from 25% to 88%, in treatment for AIDS-KS. Liposomal anthracyclines are considered first-line treatment for advanced AIDS-KS. The use of doxorubicin is supported by the fact that preclinical data shows PEGylated liposomes preferentially accumulate in KS lesions.37 Paclitaxel has shown a response rate of 59%.4

Immunological agents such as interferon-alpha and sirolimus have also been tried. In one study, sirolimus demonstrated complete regression of iatrogenic KS in 15 patients.34 Newer therapeutic approaches include anti-angiogenic agents, VEGF inhibitors, tyrosine kinase inhibitors, and matrix metalloproteinases. Irinotecan, an anticancer drug that targets DNA topoisomerase I, has been used in advanced AIDS-KS.39 Antiviral therapy with cidofovir, foscarin, or ganciclovir has demonstrated a suppression of HHV-8 replication.40 Even oral shark cartilage has been used as a treatment option.41

### Conclusion

Kaposi sarcoma is an HHV-8 associated neoplasm originating from vascular and lymphatic endothelium. Endemic KS is a more aggressive form found most commonly in HIV-seronegative Africans. The etiology of disease is multi-faceted, given that HHV-8 seropositivity does not confer the disease state. There are multiple proposed factors that potentially play a role in the development of endemic KS, including HHV-8 subtypes, soil conditions, and drug interactions, to name a few. The broad range of disease manifestations lends to the wide spectrum of treatment options, and there is currently no standard of care.

### References


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### Table 1. Classification system for Kaposi sarcoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Localized nodular KS, with ≤ 15 cutaneous lesions or involvement restricted to one bilateral anatomic site, and few, if any, gut nodules</td>
</tr>
<tr>
<td>Stage II</td>
<td>Includes both exophytic destructive KS and locally infiltrative cutaneous lesions and locally aggressive KS or nodular KS, or ≥ 15 cutaneous lesions or involvement of more than one bilateral anatomic site, and few or many gut nodules</td>
</tr>
<tr>
<td>Stage III</td>
<td>(Generalized lymphadenopathic KS) Widespread lymph node involvement, with or without cutaneous KS, but with limited, if any, visceral involvement</td>
</tr>
<tr>
<td>Stage IV</td>
<td>(Disseminated visceral KS) Widespread KS, usually progressing from stages II or III, with involvement of multiple visceral organs with or without cutaneous KS</td>
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Coexisting confluent and reticulated papillomatosis and terra firma-forme dermatosis

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Abstract
Confluent and reticulated papillomatosis (CARP) is an uncommon skin disorder that usually affects young adults. The clinical presentation most often involves the upper trunk, commonly in the intermammary area or, less frequently, the interscapular and epigastric regions.1,2 The lesions usually appear as grayish brown, hyperkeratotic, verrucous papules and patches that are confluent centrally and reticulated peripherally. While usually asymptomatic, the eruption can present with mild pruritis.3 In addition, the eruption is often fairly symmetrical across the body and trunk. We present an unusual case of CARP coexisting with terra firma-forme dermatosis in a young male, with atypical features consisting of a significant unilateral distribution with a whorled appearance.

Introduction
Confluent and reticulated papillomatosis of Gougerot and Carteaud (CARP) was first described in 1927. This condition typically has an onset during puberty, and is usually sporadic although familial cases have been reported. Young women are affected 2.5 times more frequently than young men, and blacks are affected twice as often as whites.1

There are several different theories surrounding the pathogenesis of this skin disorder. Some theorize underlying endocrine imbalance and insulin resistance, due to an association with diabetes, obesity, pituitary and thyroid disorders.1,2,3 However, others theorize a keratinization defect or an association with Malassezia furfur, due to successful treatment with retinoids and selenium sulfide, respectively.1

Terra firma-forme dermatosis is characterized by dirt-like plaques, occurring most often in children or adolescents, that cannot be washed away with soap and water but can be removed with isopropyl alcohol. Differential diagnosis often includes CARP, pityriasis versicolor, and acanthosis nigricans.4,5 Misdiagnosis of this condition often leads to unnecessary workups including skin biopsies and endocrine evaluations.

Case Report
A 15-year-old male of Middle Eastern descent initially presented to our dermatology clinic with his mother with a four-year history of an unresolving rash. He noticed gradual progression of the lesions across his neck, chest and back. He denied any associated symptoms or precipitating factors, including recent infection, fever, chills, joint aches, pain or pruritis. Past medical history and skin history were noncontributory. Cutaneous examination revealed hyperpigmented, brownish-black, warty papules and plaques, predominately unilateral, distributed across his right anterior neck, right chest, bilateral arms, epigastric skin, and back in a whorled appearance. The anterior chest revealed a vertical linear demarcation, with the right chest affected to a greater extent than the left (Figures 1, 2). At this time, the patient refused a biopsy as well as lab work. We initiated treatment with tacrolimus ointment 0.1%, which he found to provide mild improvement of dyspigmentation.

The patient then presented a year later stating that the lesions were not improving to his satisfaction and he would like to pursue more aggressive treatment. We ordered a comprehensive metabolic panel, lipid panel, antinuclear antibody, complete blood count, erythrocyte sedimentation rate, urinalysis, hemoglobin A1C and carcinoembryonic antigen, which were all within normal limits. A biopsy of the epigastric skin was also done at this time, which revealed an epidermis with slight acanthosis with papillomatosis and hyperkeratosis, and pityrosporum yeast in the cornified layer (Figure 3).

We initiated further treatment with doxycycline 100 mg...
orally once daily. At two-week follow-up, the doxycycline and topical tacrolimus had resulted in minimal improvement, and we therefore discussed other treatment options such as isotretinoin, oral minocycline, hydroquinone and antifungals. The patient refused further treatment and decided to continue with the doxycycline and topical tacrolimus. At this visit it was also discovered that some of the hyperpigmented lesions could be wiped off with gauze soaked in isopropyl alcohol, indicating a coexisting diagnosis of terra firma-forme dermatosis (Figure 4).

Figure 4. Hyperpigmented lesions could be wiped off with gauze soaked in isopropyl alcohol.

Discussion
CARP was first described in 1927. It is most common in people in their late teens and early 20s. CARP affects all racial groups but has been found to occur more frequently in blacks. The lesions begin as round, red-to-brown papules, 1 mm to 2 mm in diameter, distributed across the intermammary region and, less commonly, the interscapular and epigastric regions. As the disorder progresses, the lesions enlarge to 4 mm to 5 mm and can become hyperkeratotic and verrucous. The lesions can coalesce, and the eruption tends to spread centrifugally, becoming confluent centrally and reticulated peripherally.1,2

In our case, the lesions appeared as hyperpigmented, brownish-black papules and plaques distributed across the intermammary, epigastric and interscapular regions. The presentation of this eruption was unique due to its whorled appearance and unilateral distribution across the anterior chest. Due to these unique clinical features, our differential diagnosis was broad and included acanthosis nigricans, progressive cribriform and zosteriform hyperpigmentation, and linear and whorled nevoid hypermelanosis. Both clinically and histologically, this case resembled both acanthosis nigricans and CARP, but CARP was favored due to its whorled appearance and unilateral pattern with the coexistence of terra firma-forme dermatosis. Familiarity with terra firma-forme dermatosis can be treated successfully with cleansing with isopropyl alcohol, continued maintenance treatments may be necessary when an underlying papillomatous condition such as CARP is also present.

Conclusion
While CARP has many characteristic clinical features, there have been a variety of different manifestations reported.2 We report another manifestation of CARP, presenting primarily unilaterally with a whorled pattern and with the coexistence of terra firma-forme dermatosis. While lesions of terra firma-forme dermatosis can be treated successfully with cleansing with isopropyl alcohol, continued maintenance treatments may be necessary when an underlying papillomatous condition such as CARP is also present.

References

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A Case of Pili Annulati Following Resolution of Alopecia Areata

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Abstract

Pili annulati (PA) is a primarily inherited condition that has been reported to occur concurrently with alopecia areata (AA) and following resolution of AA. PA represents a non-fragile hair disorder that becomes more evident in adulthood, allowing it to be missed in many patients. Microscopic examination of affected hairs reveals a characteristic banded, alternating dark-and-light appearance. There is no formal treatment for PA, but proper hair care can prevent harm from external factors.

Introduction

Pili annulati (PA) is a rare, non-fragile hair disorder, often inherited in an autosomal-dominant fashion, though there are reports of sporadic cases. PA clinically presents as light spangled hair. Microscopically, it is characterized by alternating dark and light bands initiating from the hair sheath that are present in a random fashion along the length of the upper three quarters of the hair shaft.1,2 The condition may be diagnosed in the beard, scalp, pubic and axillary regions.3-5 The alternating dark and light bands appear as such due to the presence of air-filled pockets within the cortex of the hair shaft at varying locations.6 Upon microscopic examination, these pockets scatter light and appear dark due to the decreased transmission of light; however, clinically they correspond to the light strands, because under reflective light the “microscopically dark” areas actually reflect more light.6 PA has been reported concomitantly in patients with alopecia areata (AA) and following the resolution of AA.

Case Report

A 6-year-old male presented to the dermatology office with the primary complaint of “hair not growing the way it used to.” Hair loss had been occurring in a non-discrete pattern for two months’ duration. The patient reportedly had very thick hair, and changes were particularly notable after a recent haircut prior to presenting to the office. The patient had a past medical history of hay fever. Past surgical and family histories were non-contributory.

On physical examination, the patient had round patches of non-scarring alopecia with mild scaling. A fungal culture was performed for suspected tinea capitis, and the patient was prescribed 2% ketoconazole topical lotion to be applied daily, pending cultures.

Baseline laboratory examination revealed a mildly elevated white blood cell count, while the remainder of the exam was within normal limits. Fungal cultures did not reveal any growth, at which point ketoconazole therapy was discontinued and triamcinolone 0.1% cream with twice daily application was initiated for suspected alopecia areata. Further follow-up at two months revealed hair regrowth with only textural changes, and triamcinolone therapy was discontinued (Figure 1). A hair sample was sent for pathological examination to rule out a structural hair-shaft deformity. Examination of the hair shaft under polarized light revealed alternating dark and light bands with sharp-appearing edges indicative of a diagnosis of pili annulati (Figure 2).

Discussion

Hair abnormalities are subtle and therefore require extensive investigation. Pili annulati is a rare, autosomal-dominant hair shaft disorder, discovered in 1866, that has an unknown pathogenesis.7,8 Possible explanations for development of PA include a structural protein defect within the extra cellular matrix, a basement membrane zone defect, a cytokeratin abnormality and a genetic defect on the long arm of the 12th chromosome.9,9 Immunohistochemical examination for cytokeratin anomalies have not revealed any differences between PA and normal hair specimens.1 However, antibodies to aspects of the lamina densa, lamina lucida, and anchoring fibrils have been noted on immunohistochemical studies, which is supported by transmission electron microscopy of PA hair specimens that demonstrate reduplication of the lamina densa in the hair root bulb.8 Linkage analysis within families with autosomal-dominant PA has also been performed, revealing a gene locus on 12q with specific linkage between 12q24.32–24.33 regions.9,10 Although no known mutations have been isolated, having this specific locus provides an opportunity for further exploration.

The diagnosis of PA is often made by light microscopy, with increased sensitivity when a liquid medium is used to fix the hair.11 The differential diagnosis of PA includes pseudopili annulati and monilethrix. Pseudopili annulati, a twisted-hair phenotype, characteristically appears in an elliptical shape with a normal hair shaft under light microscopy, but clinically it displays banding.12 Monilethrix is an inherited, autosomal-dominant condition that has an alternating node and constricted appearance on microscopy, resembling PA, but unlike PA it is a fragile hair disorder.13,14 PA has been documented to appear in conjunction with AA and post AA, and has also been reported to disappear after resolution of AA. One European study examined the presence of PA concomitant with AA and found a statistically significant 9% prevalence of concurrent AA in the PA group.15 The study, however, suggested that the concurrence was coincidental, as the genes identified in AA do not appear to have a relationship to the gene locus identified in PA.16 However, the study size was too small to determine an actual relationship. Our patient, on
the other hand, had PA after resolution of AA. A similar case has been reported by Cruz et al., in which a 31-year-old female with severe AA in locations of the scalp as well as other hair-bearing areas had resolution of her AA after being treated with several courses of intramuscular triamcinolone. Hair shaft examination of this patient’s regrown hair revealed PA. In contrast, a case has been reported of a patient with a past history of PA who presented with hair loss, and after treatment with intramuscular triamcinolone and topical minoxidil had re-growth of normal, non-PA hair.

PA has also been identified in a patient with a complex condition of autoimmune disease comprised of IgA deficiency, thyroid disease, and AA. Although there may be no association between PA and AA, the presence of autoimmune diseases may relay some connection to antigenic changes within the hair root bulb and the polygenic nature of AA as well as the distinct locus of PA.

Although there is no treatment for PA, patients with co-existing hair loss may benefit from topical minoxidil therapy, for it is thought to allow for normal matrix production, which in turn could theoretically repair the structural defect.

**Conclusion**

Pili annulati is a rare hair phenotype that has been documented to occur with AA, after resolution of AA, and in combination with other autoimmune disorders. Due to its inheritable nature, a family history of PA may warrant examination and education of patients affected with this condition. Although no treatment exists, patients should be reassured and taught proper hair care management for this non-fragile condition.

**References**


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Two Cases of Pediatric Acral Cutaneous Calcinosis with Transepidermal Elimination Presenting as Skin-colored Papules

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Abstract

We present two pediatric cases of acral dystrophic calcinosis. Dystrophic cutaneous calcification can occur in a variety of disorders that are usually associated with prior skin damage. It represents the deposition of insoluble calcium salts in the presence of tissue damage without abnormal systemic calcium levels or defective calcium metabolic regulation.2 Deposition of insoluble calcium salts occurs in damaged tissue, and when localized, it can result in a warty papule with a clinical differential diagnosis including periungual fibroma, cyst, verruca vulgaris and fibrokeratoma, among other conditions.1 Identifying the correct lesion is important when determining the clinical management, as some lesions require treatment (e.g., verruca vulgaris), some may need further investigation (e.g., ruling out tuberous sclerosis when periungual fibromas are present), and some do not require further intervention, as with cutaneous dystrophic calcinosis. Prior needle prick trauma (i.e., neonatal) has been reported to result in cutaneous dystrophic calcification, and it is important for physicians to consider this entity within the pediatric population.1

Introduction

Many different pathological conditions can result in dystrophic cutaneous calcification; however, most commonly they are associated with prior skin damage without abnormal systemic calcium levels or defective calcium metabolic regulation.2 Deposition of insoluble calcium salts occurs in damaged tissue, and when localized, it can result in a warty papule with a clinical differential diagnosis including periungual fibroma, cyst, verruca vulgaris and fibrokeratoma, among other conditions.1 Identifying the correct lesion is important when determining the clinical management, as some lesions require treatment (e.g., verruca vulgaris), some may need further investigation (e.g., ruling out tuberous sclerosis when periungual fibromas are present), and some do not require further intervention, as with cutaneous dystrophic calcinosis. Prior needle prick trauma (i.e., neonatal) has been reported to result in cutaneous dystrophic calcification, and it is important for physicians to consider this entity within the pediatric population.1

Case Report

We present two pediatric cases of acral dystrophic calcinosis. Such lesions can clinically appear warty or as a papules. This entity is probably a more common lesion then is actually reported. A papular or warty acral lesion in the pediatric population should prompt the diagnostic possibility of a localized acral dystrophic calcinosis, especially if there is a clinical history of multiple needle sticks. The first case involves an 11-month-old male who presented with a flesh-colored papule on the right index finger since birth. The lesion began as two small white “dots” and had increased to the size of 5 mm x 4 mm. The clinical differential diagnosis of this periungual, flesh-colored papule included periungual fibroma, fibrokeratoma, pyogenic granuloma, connective tissue nevi, myxoid cyst and verruca vulgaris. Tissue sections from a biopsy revealed a distinct nodular mass of subepidermal dystrophic calcification with overlying reactive acanthosis and evidence of transepidermal elimination of calcific material (Figure 1).

The second case involves a 1-year-old female with a 4 mm, white-tan papule on the left heel. Differential diagnosis included verruca vulgaris and cyst. Skin biopsy specimen showed only stratum corneum, but revealed disrupted acral stratum corneum with intracorneal deposition of granular calcified material (Figures 2 and 3). The pathologic diagnosis on both cases was dystrophic cutaneous calcification (consistent with prior needle stick trauma).

Discussion

Dystrophic calcification represents the deposition of insoluble calcium salts in the presence of tissue damage without abnormal systemic calcium levels or defective calcium metabolic regulation.4 Calcium is important in cellular proliferation, differentiation and regulation of cell-to-cell adhesion. When tissue is damaged, cellular membrane disruption can allow calcium influx and intracellular crystallization. The acidity produced by cellular damage can also inhibit anti-calciﬁying processes.2 Dystrophic cutaneous calcification can occur in a variety of disorders that are usually associated with prior skin damage. Examples of these conditions include autoimmune connective tissue diseases, panniculitis, genetic disorders, infections and neoplasms, among many others.2 Our patients, in both cases, did not present with any biochemical, metabolic or genetic abnormalities.

The verrucous papule on the index finger (in the first case) and the papule from the heel (in the second case) both showed subepidermal dystrophic calcification secondary to traumatic needle-stick injury. A similar case of dystrophic calcification secondary to needle-prick trauma has been reported by Sakmann et al., who theorized that the needle prick introduced epidermal implantation cysts that led to dystrophic calcification of the cutaneous tissue.1 The clinical differential diagnosis of skin-colored papules includes periungual fibroma, fibrokeratoma, connective tissue nevi, myxoid cyst and verruca.

Periungual fibroma belongs to a group of lesions called cutaneous angiofibromas, which are dome-shaped lesions composed of a collagenous stroma...
with increased dermal fibroblasts and dilated, thin-walled blood vessels. Periungual fibroma is considered a major diagnostic criterion for tuberous sclerosis, seen more commonly in adults. Fibrokeratomas are uncommon, benign lesions that present in the finger of middle-aged adults. They consist of solitary, pink to skin-colored, exophytic papulonodules that may be slightly keratotic with a collarette of elevated skin. They are composed of blood vessels surrounding think collagen bundles. Connective tissue nevi, also known as collagenomas, are thin, skin-colored papules, nodules or plaques that arise during childhood or can be present at birth. They are soft nodules located in the proximal nail fold of fingernails that often drain spontaneously. Myxoid cysts are the most common nail tumors, often seen in middle-aged women. They are soft nodules located in the proximal nail fold of fingernails that often drain spontaneously.

Verruca vulgaris, also known as common warts, are exophytic, hyperkeratotic, dome-shaped papules or plaques that often present on the fingers or dorsum of the hands, but can occur anywhere in the skin surface, especially in trauma-prone sites. They can have characteristic punctate black dots as a result from thrombosed capillaries. Elongated rete ridges, marked acanthosis, and parakeratosis overlying papillomatosis are seen on histopathological examination.

Histopathologic evaluation and a good history and physical examination and review of systems are very important when trying to distinguish between these conditions.

References

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Abstract

While basal cell carcinoma (BCC) is the most common malignancy found in humans, the disease process remains localized in the great majority of cases. Recurrent, locally advanced, and metastatic disease can pose a significant management challenge. Herein, we present a case of recurrent BCC of the ear found to incidentally have perineural invasion. Identifying risk factors for recurrent and more advanced disease can aid the clinician in the early and appropriate management of patients with basal cell carcinoma.

Introduction

While basal cell carcinoma (BCC) is the most common malignancy found in humans, with over 2 million cases diagnosed each year in the United States, the disease remains localized in the great majority of cases.1 Locally advanced and metastatic disease is quite rare, with an incidence ranging from 0.18% to 3%.2 Complications of local disease include local tissue destruction, functional impairment, and cosmetic disfigurement.3 Metastatic disease causes additional complications, with the most frequently involved sites being the lymph nodes, bone, and lungs.3

The incidence of basal cell carcinoma increases with age. While it is most frequently found in light-skinned individuals, all skin types are affected. The most common risk factor for BCC development is chronic UV exposure through sunlight, tanning booths, or UV light therapy.3 The relationship between the timing and amount of ultraviolet radiation exposure has not been clearly established.3 Additional risk factors include history of exposure to ionizing radiation, arsenic exposure, and immunosuppression.3 Basal cell carcinoma may also develop in chronic scars, ulcers, or burns.

Several genodermatoses are associated with an increased risk of basal cell carcinoma. These include ocular cutaneous albinism, xeroderma pigmentosum, epidermodysplasia verruciformis, and basal cell nevus syndrome (BCNS).3,4 Rombo, Bazex-Dupré-Christol, Brooke-Spiegler, Schopf-Schulz-Passarge, and Muir-Torre are other rare syndromes associated with BCC.3,4

There are many risk factors contributing to the development of recurrent, locally advanced, or metastatic basal cell carcinoma. Anatomical locations with higher risk of recurrence include the face, eyelid, nose, lip, ear, hands and feet.3 Increased recurrence rates are further observed when poorly defined borders are present, in tumors larger than 2 cm in diameter, in perineural involvement, and in prior history of recurrent BCC.3 Patients who have had multiple lesions have a higher recurrence rate than those with single lesions.5 Tumors around the medial canthus, nose, and ear are more likely to become invasive compared to BCC of other sites.3 The most likely lesions to metastasize include large tumors or those with more aggressive histological phenotypes (morphemic, infiltrating, basosquamous).1

Several host factors are associated with an increased risk for recurrent disease. Patients who are diagnosed with BCC before the age of 40, are immunosuppressed, have a genetic syndrome and/or have a history of aggressively behaving tumors are at higher risk.1 With regard to immunosuppression, this includes patients with a history of transplant, those with leukemia/lymphoma, and those on immunosuppressants for conditions such as rheumatoid arthritis.1,5 As previously mentioned, radiation therapy, chronic scars, burns, or ulceration can make that particular area of the body more susceptible to recurrence of BCC.1

Perineural invasion has an increased occurrence in male patients and has been linked to increased incidence of regional lymph node involvement.6 Most metastatic and locally aggressive BCCs originate from the head and neck, with a mean interval of initial presentation to discovery of metastasis of approximately nine years.7 Recurrent skin cancers with prior resection and/or radiation therapy are more commonly associated with perineural invasion than the primary untreated skin cancer.8

Case Report

A 65-year-old Caucasian male presented to the dermatology clinic for evaluation of a recurrent lesion involving the mid-helix of his right ear. He first noticed this growth approximately one month prior to presentation. He reported a history of basal cell carcinoma of this site around 2008, which was treated by excision with subsequent graft placement. In 2012, he developed recurrent superficial spreading BCC. This was managed with Mohs micrographic surgery. The surgical defect was repaired by plastic surgery, and the patient applied imiquimod 5% to the area after healing from the procedure. There was no past medical history of immunosuppression, radiation exposure, or arsenic exposure. He did admit to chronic sunlight exposure as a child and as an adult (working outdoors on heavy machinery). He denied a history of any other skin cancers.

On physical examination, the right mid-helix demonstrated a 6 mm papule with central hyperkeratotic crust and rolled borders (Figure 1). This was located along the edge of a smooth, round cicatrix from prior graft. A shave biopsy of the lesion was performed and demonstrated basal cell carcinoma extending to the deep margin of the biopsy. The patient was then referred back for Mohs surgery. After performing two stages of Mohs, the margins were still found to be positive. The patient was very concerned about losing a significant portion of his ear and was unwilling to continue with further excision. At that point, a wedge resection was performed to remove a little more tissue, as well as allow for closure of the surgical defect. This tissue was sent for permanent processing. Hematoxylin and eosin stain (H&E)
Perineural invasion is characterized by growth of tumor cells within any of the three layers of the nerve sheath. This is believed to be a result of reciprocal interactions between cancer cells and nerve elements. Perineural spread may be facilitated by neural secretion of glial-derived neurotrophic factor (GDNF), which phosphorylates the RET tyrosine kinase receptor, triggering downstream signaling pathways that promote cancer-cell migration and invasion. High RET receptor expression has also been found in patients with pancreatic and prostate carcinomas, which are found to express perineural characteristics.

Perineural invasion may be categorized as either incidental invasion, which is asymptomatic, or clinical perineural invasion, which presents with cranial-nerve deficits such as paresthesia, pain, and numbness. Perineural spread from the head and neck tends to involve the trigeminal nerve, resulting in paresthesia. Facial nerve involvement results in palsy, as these nerves have a rich network of cutaneous endings.

Identifying risk factors for recurrent and advanced disease can aid the clinician in the appropriate management of patients with basal cell carcinoma. The location of this patient’s basal cell carcinoma, the ear, is a site known to be associated with more aggressive tumors. Studies suggest that there is a preference for tumor cells to grow in this area due to a larger degree of angiogenesis, making this an ideal environment for tumorigenesis and uncontrolled growth. This shows that there is a correlation between angiogenesis and increased aggressiveness, requiring more Mohs stages to achieve tumor-free margins.

Following the identification of perineural spread of basal cell carcinoma, the patient should undergo additional studies to further delineate the extent of disease. A complete skin examination should be performed, as patients often have additional cancer at other sites. Any suspicious lesion requires a biopsy for definitive diagnosis. A thorough history regarding paresthesias or palsy should be elicited, as the new onset or progression of paresthesias may be the only presenting sign of perineural spread. Gadolinium-enhanced MRI or MR neurography are the best imaging studies for the detection of perineural spread and are used to assess the extent of disease spread along the cranial nerves. Other signs of perineural invasion include enhancement with or without enlargement of the nerve, mass in the cavernous sinus or Meckel cave. Denervation of a group of muscles innervated by the affected cranial nerve is an indirect sign of perineural spread. Plain radiographs and CT scan are used to visualize expansion of neural foramina and canals such as the inferior alveolar canal, infraorbital foramen, foramen rotundum or facial (Fallopian) canal. PET scan can also be used to visualize possible extension through the bone and foramina. In cases where the tumor has spread to regional lymph nodes, visualization can be seen on MRI.

There is no universally accepted protocol for the treatment of basal cell carcinoma with perineural invasion. Treatment is mostly individualized, depending on the patient’s co-morbidities, anatomical location of the lesion, previous treatment history, patient preference, and other factors. Adequate surgical removal based on histologic findings is the primary treatment used with adjunctive radiotherapy. Surgical treatment methods include Mohs surgery, standard surgical excision, curettage alone, and curettage and electrodesiccation. Non-surgical methods include topical chemotherapy, radiation therapy, and photodynamic therapy. The five-year recurrence rates for recurrent basal cell carcinoma are significantly higher than with primary BCC. They are estimated as follows: 5.6% with Mohs surgery, 17.4% with surgical excision of the tumor, 40% with curettage and electrodesiccation, and 13% with radiation therapy.

Hedgehog pathway inhibitors, including vismodegib, may have a potential role in the treatment of advanced or metastatic cases of basal cell carcinoma when surgery is contraindicated or deferred by the patient. A recent study of 499 patients with advanced or metastatic disease who were ineligible for surgical treatment found that 302 of 453 patients with locally advanced basal cell carcinoma had an overall response to daily treatment with vismodegib. Of the 302 patients, 153 had a complete response, and 149 had a partial response. In addition, 11 of 29 patients with metastatic basal cell carcinoma had an overall response (two complete responses, nine partial responses). The long-term efficacy and tolerability of hedgehog pathway inhibitors is still being investigated.

In non-melanoma skin carcinomas, radiation can be used as primary treatment or as adjuvant therapy. Radiation works by inducing death of cancer cells present along the invading nerve and can interrupt paracrine interactions between cancer cells and nerves, in particular the GDNF-RET axis. There are three different radiation methods used: orthovoltage superficial X-rays, megavoltage electron-beam therapy, and Brachytherapy. Radiotherapy can be low-energy, which treats superficial lesions, or high-energy, which can spare the skin and penetrate to deep-seated lesions.

Patients with focal, incidental perineural invasion with negative margins, such as BCC that is not adjacent to a major cranial nerve, are likely to...
be cured with surgery alone. However, those with multifocal perineural spread should be considered for postoperative radiotherapy, especially patients with recurrent cancers, those who are immunocompromised due to solid organ transplant and/or chronic lymphocytic leukemia, and those with tumors in locations close to cranial nerves V and VII. Since patients with extensive microscopic BCC with perineural invasion have a high risk for recurrence, they should be considered for radiotherapy as well. Radiotherapy can be effective in treating microscopic deposits of cancer cells that remain after surgical removal of the tumor mass. It may also be used for tumor destruction in places that are difficult to reach by surgical excision.

Not all patients with tumors characterized by perineural invasion are able to receive adjuvant radiotherapy. Some patients are unable to tolerate the side effects, such as redness and irritation of the area treated. Recurrent lesions that are close to a site previously treated by irradiation cannot be treated with radiotherapy due to risk of necrosis. Radiotherapy can cause orbital and central nervous system damage as well as bone exposure, fistula formation, and wound infection. Patients with connective tissue diseases and those with genetic conditions that predispose them to skin cancer, such as xeroderma pigmentosum, are more susceptible to radiation and therefore should not receive radiation treatment.

**Conclusion**

Perineural invasion of basal cell carcinoma is a poor prognostic indicator, associated with higher rates of morbidity and mortality. Management of advanced disease such as this can be challenging. This case study demonstrates a rare circumstance in which a basal cell carcinoma located on a high-risk site recurred twice in a patient with no known personal risk factors.

**References**


A few months later, the patient developed more peripheral T-cell lymphoma. Biopsy with flow cytometry demonstrated a sign of malignancy. Left axillary lymph-node mild acute and chronic inflammation, with no signs of mastitis. The patient did not respond to two lymphadenopathy, which raised a concern for warmth, peau d’orange appearance, and axillary radiation. The patient also had breast tenderness, pruritus and hyperpigmented lesions and did not meet the criteria for Sézary syndrome. The neoplastic T-cells did not express CD56 or CD26. The clonal T-cell receptor gamma gene rearrangement was detected, and the CD4:CD8 ratio was approximately 15:1 (Figure 6, p. 50).

The patient was diagnosed with an atypical case of Sézary syndrome associated with a prominent CD4+/CD7+, “mycosis fungoides-like” cutaneous histology. The presence of epidermotropism, atypical T-cell morphology and clonal T-cell rearrangement helped distinguish this case from reactive benign dermatoses.

The patient was staged IVA1. She was started on bexarotene, prednisone, photophoresis and topical pimecrolimus.
In the case presented here, the patient’s initial cutaneous patches and the histological evaluation showing epidermotropism of atypical lymphocytes lead to a possible diagnosis of mycosis fungoides. However, the patient’s rapid progression of skin involvement along with persistent CD7 expression on the lymphocytes and presence of circulating atypical (CD4+/CD7+/CD26-) lymphocytes in the blood supported the diagnosis of Sézary syndrome. Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, accounting for approximately 50% of the cases. It has three primary, distinct clinical stages: patch, plaque, and tumor. All stages are characterized by epidermotropic infiltrates of small- to medium-sized neoplastic T cells. MF has a median age of presentation of 57 years, affecting men more often than women with a 2:1 ratio. It is commonly seen in photoprotected areas, especially the buttocks, groin, upper thighs, breasts, and axilla. The patch stage is characterized by 5 cm to 10 cm, round, erythematous patches with a wrinkled appearance and a fine overlying scale. The plaque stage is very similar but with elevation and induration present, typically presenting in continuity with the patches. Tumors develop within the patches or plaques, but not all patients progress to this stage. Histologically, neoplastic T-cell infiltrates appear within the superficial dermis accompanied by sparse epidermotropism and no spongiosis in the early stages of the disease. As the lesions progress, intraepidermal collections of lymphocytes (Pautrier microabscesses) and well-developed, band-like lichenoid lymphocytic infiltrates are seen. Early MF tends to have neoplastic lymphocytes with an immunohistochemical profile positive for CD3, CD4 and CD45, and negative for CD7 and CD8. Even though the immunohistochemical profile of our patient was CD7+, there have been reports of CD7+ MF reported in the literature. T-cell clones are identified in anywhere from 57% to 70% of cases. Loss of pan-T-cell antigens (CD2, CD5, and CD7) has also been reported in early patch stages of MF, which can be useful to distinguish it from psoriasis and spongiosis dermatitis. Detection of the same clones from two different anatomical locations, as occurred in our case, has been shown to increase sensitivity and specificity when diagnosing MF. Early MF can be very difficult to diagnose, often requiring years and many different biopsies. The differential diagnosis includes spongiotic dermatitis, psoriasis, dermatomyositis, contact dermatitis, and lymphomatoid drug reactions. Pagetoid reticulosis, primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), and types B and D lymphomatoid papulosis (LyP) are lymphomas that may be nearly identical to MF histopathologically. Clinical presentation is most helpful in differentiating these cases, highlighting the importance of good communication between the dermatologist and dermatopathologist in this case.

A recent study demonstrated that only 9% of the lesional lymphocytes are atypical and that reactive lymphocytes are also present in addition to the neoplastic cells, making architectural abnormalities more important than cytological differences when diagnosing MF. Prognosis varies according to the stage of the disease and the surface area involved. The risk of progression and visceral involvement tends to increase with increasing surface area, presence of tumors and erythroderma. Subtypes of MF with no difference in prognosis include dyshidrotic MF, hypopigmented MF, and acanthosis-nigricans-like MF. Sézary syndrome (SS) is a rare, leukemic variant of cutaneous T-cell lymphoma. It is characterized by cerebriform cells (Sézary cells), erythroderma, pruritus and circulating mature neoplastic T-cells. Palmpoplantar keratoderma, subungual hyperkeratosis, yellow discoloration, nail thickening, onychomadesis, alopecia, and ectropion are also distinguishing features of SS. Symptoms often develop insidiously, making the diagnosis very difficult, often taking an average of 20.5 months from symptom onset to diagnosis. Epidermotropism is often absent or minimal in SS, therefore, only approximately 60% of skin biopsies are diagnostic for SS. An atypical lymphocyte infiltrate at the dermoepidermal junction, eosinophilia, parakeratosis, acanthosis, and spongiosis are the most common histopathological features of SS. However, those findings are also commonly seen in many benign inflammatory conditions.

Sézary syndrome typically is diagnosed based on evidence of molecular clonality of T-cell gene rearrangement, absolute Sézary cell count greater than or equal to 1,000 cells/mm², a CD4:CD8 ratio greater than or equal to 10 by flow cytometry, ≥40% loss of CD7, ≥36% loss of CD26, and presence of CD25.

The differential diagnosis for Sézary syndrome includes (but is not limited to) generalized atopic dermatitis, pityriasis rubra pilaris, erythodermic hypersensitivity reactions, parapsoriasis, DRESS syndrome, dermatomyositis, graft-versus-host-disease, generalized anaphylaxis, erythodermic MF, acute or chronic leukemias, CTCL spectrum disease. Prognosis is generally poor, with a median survival of four years from time of diagnosis. Sézary syndrome has historically been considered to arise from pre-existing MF, as an advanced systemic presentation. However, recent lymphocyte studies suggest that SS and MF are two distinct entities arising from two different subsets of atypical T-cells. CD26 is a dipeptidyl peptidase IV normally expressed in the majority of T lymphocytes in the peripheral blood. It is a surface proteolytic enzyme related to cellular activation, and its absence or decreased expression is highly characteristic of mycosis fungoides and Sézary syndrome. Jones et al. reported CD26 positivity ranging from 56% to 86% of CD4+ T-cells of healthy control subjects. They also reported loss of CD26 expressivity in 59 of 66 cases of MF or SS, with the remaining seven cases having only a dim expression of CD26. They concluded that absence of CD26 is a very useful marker when diagnosing MF or SS. CD7 is a glycoprotein belonging to the immunoglobulin gene superfamily and is thought to be involved in signal transduction. It is expressed in almost all CD8+ T-cells and in approximately 90% of CD4+ T-cells. CD7 expression in healthy subjects has been reported to be positive in 73% to 97% of non-neoplastic lymphocytes. The percentage of CD4+/CD7- T-cells may correlate with Sézary-cell counts in SS, but it is unknown whether this is a result of neoplastic expansion of CD4+/CD7- cells or aberrant loss of CD7 expressivity in malignant T-cells. Loss of CD7 expressivity has been reported to be the most commonly used method for detection of cutaneous T-cell lymphomas. It is also believed that the size of the CD7- T-cells correlates with disease progression in MF and SS. However, CD7 expressivity has been reported to be highly variable; Studies have found up to 50% of MF or SS patients with a positive CD7 marker in their neoplastic T-cells. Jones et al. speculated that CD7 expression may be vulnerable to reactive T-cell populations, concurrent illness, and effects of treatments.
Studies have also found that some patients who were CD4+/CD7+ in early studies demonstrated loss of CD7 expressivity over time.3,5 This could explain the highly variable CD7 expression in MF and SS and makes it a less reliable marker to separate normal from neoplastic cell populations.

It is possible that our patient presented with a very early stage of Sézary syndrome in which there has not been enough CD7 loss, but the fact that the patient did not express CD26 is a confirmatory marker for the presence of Sézary syndrome. Failure to meet the required criterion of 1000 Sézary cells/μL can also be attributed to early stages of the disease.

Some sources define a Sézary cell count of >500 cells/μL as diagnostic “substantial peripheral blood involvement” when erythroderma is also present.4

Conclusion

The overlapping features of mycosis fungoides and Sézary syndrome seen in this patient posed a diagnostic dilemma. The patient had severe pruritus and was initially diagnosed with a T-cell lymphoma by axillary-node biopsy. Subsequent skin biopsies showed significant atypical lymphocytic epidermotropism and histologically appeared as mycosis fungoides, with a CD4:CD8 ratio of approximately 15:1 and T-cell clonal rearrangement. There was retention of T-cell CD7 expression on the atypical lymphocytes, and the patient proceeded to develop erythroderma with evidence of circulating (CD4+/CD7+/CD26-) Sézary cells but did not fulfill the diagnostic criterion of a 1,000 cells/μL Sézary cell count.

This case was classified as “atypical” because the patient had clinical features of Sézary syndrome with evidence of circulating (CD4+/CD7+/CD26-) Sézary cells but also had significant epidermotropism, which is not typically seen with Sézary syndrome. Thus, a diagnosis of an atypical Sézary syndrome was favored, instead of erythrodermic MF, due to the advanced stage of disease at clinical presentation and rapid progression of skin involvement. This case is anticipated to undergo genotypic profiling to better understand the complexity of the circulating T cell (CD4+/CD7+/CD26-) subset seen in this patient with atypical Sézary syndrome.

References


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Introduction
Lupus erythematosus (LE) is a disorder with varied manifestations ranging from cutaneous findings to severe organ system involvement such as in SLE. Cutaneous lupus erythematous (CLE), such as discoid lupus erythematous (DLE), lupus panniculitis, hypertrophic LE, and TLE, can be divided into acute, subacute, and chronic cutaneous LE. Patients with TLE rarely present with other systemic or cutaneous disease signs and symptoms. It is a diagnostic challenge to correctly identify TLE and accurately exclude other cutaneous diseases, which it mimics frequently.

Case Presentation
A 35-year-old male with a history of SLE and end-stage renal disease (ESRD) secondary to lupus nephritis on dialysis presented to the emergency department with fever and shortness of breath. He reported dyspnea, coughing, wheezing, and malaise, which began four days prior to presentation. He was a boat mechanic and had been spending an extensive amount of time in the sun for the past couple of days. He had a similar episode of worsening shortness of breath and hemoptysis a few months prior, for which he was admitted to the hospital.

In the emergency department, he was tachycardic at 112 beats per minute, tachypneic at 24 breaths per minute, hypertensive at 159/94 mm Hg and febrile at 103 degrees Fahrenheit, with an oxygen saturation of 97% on 4 L/min nasal cannula. On physical exam, he demonstrated wheezing and crackles bilaterally throughout. Cardiac exam revealed tachycardia, without murmurs, rubs or clicks. A left forearm fistula was present with an appreciable bruit, without erythema, tenderness or discharge.

Skin examination revealed multiple erythematous and violaceous papules and plaques on his bilateral upper extremities (Figure 1), upper back, and thighs. Purpura was evident on his bilateral shins (Figure 2). An erythematous malar rash extending onto his nasal bridge as well as perioral erythema was evident on his face. Neurological, abdominal, musculoskeletal, and genitourinary exams were unremarkable. Further workup with a CT scan of the chest revealed multiple, subcentimeter opacities throughout both lung fields. Differential diagnoses included septic emboli, vasculitis, and atypical infections causing multifocal pneumonia. A cardiac echocardiogram revealed no verrucous (Libman-Sacks) or septic vegetations. Blood and urine cultures were negative. A sputum culture was positive for rare Candida albicans, considered a contaminant. Toxicology screen was negative.

Dermatology was consulted, and skin biopsy of upper arm and thigh lesions revealed perivascular lymphocytic infiltration with lack of interface changes at the dermal-epidermal junction (Figure 3) as well as abundant mucin in the dermis (Figure 4), consistent with tumid lupus erythematosus.

Abstract
Tumid lupus erythematous (TLE) is an uncommon autoimmune condition that has infrequently been described in the literature and is difficult to distinguish from other cutaneous diseases. It is a subtype of discoid lupus erythematous (DLE). TLE usually follows a favorable course and responds well to antimalarias, local corticosteroids and, more recently, photodynamic therapy and topical tacrolimus. Very rarely, TLE is associated with systemic lupus erythematous (SLE). In the following case presentation, we describe an individual with a history of SLE and subsequent lupus nephritis presenting with worsening respiratory complaints. Further workup and CT imaging revealed lupus vasculitis with concomitant TLE. Even though these two conditions rarely coexist, it is important to raise awareness of this possible occurrence so that clinicians may reach the proper diagnosis and management.
Antibiotics were initiated and then stopped, as blood cultures were negative. At the time of discharge, the patient was diagnosed with concurrent SLE, lupus vasculitis and TLE. He improved with a tapering course of corticosteroids and bronchodilators and was advised to follow up with the dermatologist as an outpatient.

Discussion

Tumid LE, first described in 1909 by Eric Hoffman, is a rare autoimmune condition characterized by smooth, nonscarring, pink or erythematous papules, nodules or plaques usually in a symmetric distribution. The lesions usually present on sun-exposed areas such as the face, neck, arms and upper back and typically spare the lower extremities.

TLE may resemble many other cutaneous dermatidities such as eczema, psoriasis, erythema multifforme, urticarial lichen planus, lymphocytic infiltration of the skin, pseudolymphoma, graft-versus-host disease, other lesions of cutaneous LE, or polymorphous light eruption. Due to its rare occurrence, its varied clinical manifestations, and scarcity of cutaneous findings, TLE is often difficult to diagnose, and its precise definition remains elusive. Multiple case reports of TLE have been described over time, and some studies do offer criteria for definition and differential diagnosis, delineated in Table 1.

The histopathological characteristics of TLE are dermal mucin deposition, usually with an interstitial distribution, and perivascular lymphocytic infiltration. Tumid LE typically lacks interface changes, although there are some reports of focal interface changes at the dermal-lacks interface changes, although there are some lymphocytic infiltration. Tumid LE differs from SLE and other chronic cutaneous LE in that the cutaneous lesions of TLE are fixed and of long duration. The serologic profile is similar to other forms of chronic cutaneous LE, with approximately half of patients having low antinuclear antibody (ANA) titers (1:160) and a negative remaining autoantibody panel. The association with systemic disease is low. The female-to-male ratio in tumid LE, 8:7, is similar to that seen in the chronic cutaneous forms of LE and is in contrast to the female predominance observed in systemic LE, with a ratio of 8:1 to 10:1. Although the literature contains conflicting reports regarding the coexistence of TLE with SLE or other variants of cutaneous lupus, there have been a number of case reports documenting this combination.

In the case presented here, the recent UV exposure was likely the trigger for the patient’s new cutaneous eruption and the worsening of his systemic symptoms. The literature demonstrates that lupus photosensitivity may be caused by an aberrant response of keratinocytes to UV injury, defective clearance of apoptotic cells or an enhanced inflammatory response to these cells. Therefore, a thorough education of the patient regarding UV exposure as a disease trigger is paramount.

Conclusion

Although TLE is rarely associated with SLE, the astute clinician should maintain a high index of suspicion when examining patients presenting with signs and symptoms of either condition. An established diagnosis of SLE should not preclude additional cutaneous lupus findings. As in the case presented, a patient may concomitantly manifest SLE nephritis, tumid lupus and lupus vasculitis. Given the rarity of TLE’s reported association with systemic lupus erythematosus, it is important that patients with a diagnosis of TLE be followed closely for any signs or symptoms of systemic involvement.

Table 1. Proposed criteria for TLE diagnosis

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Papules, plaques, and/or nodules</th>
<th>Pink-to-violaceous color</th>
<th>Absence of surface changes</th>
<th>Non-scarring</th>
<th>Photodistribution</th>
<th>Chronic (&gt; 5 months)</th>
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</thead>
<tbody>
<tr>
<td>Histopathologic Findings</td>
<td>Moderate to dense, superficial and deep, perivascular, lymphocytic infiltrate</td>
<td>Absent to focal dermo-epidermal junctional involvement</td>
<td>Mucin deposition in papillary and reticular dermis</td>
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<tr>
<td>Immunohistochemical Findings</td>
<td>Predominantly T cells (CD3+)</td>
<td>CD4 predominant (&gt; 68% of infiltrate)</td>
<td>CD8 minority (&lt; 50% of infiltrate)</td>
<td>CD4:CD8 ratio &gt; 2:1</td>
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References

A Vesiculobullous Eruption Following Solid Organ Transplantation

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Abstract

Viruses are the most frequent cause of cutaneous infections in organ transplant recipients, and herpes simplex virus (HSV) is one of the most commonly implicated, especially in the first few months post-transplant. Given a nonspecific presentation in these patients, it is essential to confirm the diagnosis with further laboratory testing. Notably, cutaneous cytomegalovirus (CMV) infection may mimic HSV or may co-infect affected skin lesions. Cutaneous CMV is present in approximately 20% of systemic CMV infections, and if left untreated it has a high mortality rate due to increased risk of graft rejection and other secondary infections. We describe a case of a chronic vesiculobullous eruption in a 75-year-old liver transplant recipient whose diagnosis of HSV was determined during her initial office visit using the reliable Tzanck smear, therefore allowing for rapid initiation of antiviral treatment. Confirmatory viral cultures were also performed to verify the causative agent and to rule out the possibility of co-infections.

Introduction

Herpes simplex virus infection is usually a relatively straightforward diagnosis to make. However, organ transplant recipients or immunosuppressed patients may present with clinically atypical lesions, necessitating the need for accurate diagnosis and prompt treatment to prevent dissemination to visceral organs. Moreover, other viral infections, such as cytomegalovirus, must be excluded from the diagnosis as they often significantly increase morbidity and mortality in organ transplant recipients.

Case Report

A 75-year-old Hispanic female presented to our outpatient dermatology clinic complaining of a three-week history of a burning, painful eruption on her buttocks. She admitted that this had been occurring intermittently for years. Her past medical history was significant for hypertension and a liver transplant in 1998 secondary to autoimmune hepatitis. At the time of her presentation, the patient was on several immunosuppressive agents including mycophenolate mofetil, cyclosporine, and prednisone. Other medications included valsartan, bisoprolol, and folic acid. A review of systems was negative for any fever, malaise, vision change, shortness of breath, chest pain, and gastrointestinal disturbances.

On physical examination, there were multiple shallow ulcers and grouped vesicles on the buttock region (Figures 1 and 2). The patient had no mucous membrane or other cutaneous involvement. There was no inguinal lymphadenopathy. Our initial differential diagnosis included a viral skin infection such as HSV types 1 and 2, varicella-zoster virus (VZV), and cytomegalovirus (CMV). Other diagnostic considerations were dermatitis herpetiformis and bullous allergic contact dermatitis.

A Tzanck smear was performed and showed characteristic multinucleated giant cells (Figure 3). Therefore, a presumed diagnosis of herpes simplex infection was made, later confirmed by viral culture. A skin biopsy was not performed. The patient was treated with valacyclovir 1 gram twice a day for one week and silver sulfadiazine cream twice daily to eroded areas. At one-month follow-up, the patient had dramatic improvement in the lesions, and a prophylactic twice daily dose of valacyclovir 500 mg was initiated.

Discussion

Organ transplant recipients are prone to developing a variety of skin diseases secondary to the potent immunosuppressive agents used to guarantee long-term graft survival and prevent organ rejection.1 Cutaneous infections occur in up to 80% of organ transplant recipients, and viral infections are the most common of these.2 The herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family and are distinguished by their ability to remain latent within a host and spontaneously reactivate with trauma, UV exposure, fever, or immunosuppression. The latent virus travels from the nerve root to innervated skin regions. Transplant patients can be infected with HSV-1, HSV-2, or both types, with prevalence similar to the distribution by age in the general population.1 Typically, reactivated, localized HSV infections occur within the first few weeks of transplantation, and mucocutaneous lesions of the oropharynx or genital regions are the most common presentation in organ transplant recipients.1,4 Compared to the general population, manifestation of HSV reactivation in immunosuppressed patients results in chronic, larger, slower-healing ulcers with greater potential for dissemination to visceral organs.1,2 Systemic involvement may manifest as fever, leukopenia, esophagitis, hepatitis,
pneumonitis or myocarditis.\textsuperscript{2,3} Widespread cutaneous dissemination is rare, but when it occurs it is associated with high mortality rates.\textsuperscript{4}

Diagnosis of HSV can be approached in several ways. A positive culture of the vesicles or ulcers indicates active infection. Furthermore, HSV-1 and HSV-2 can be distinguished by monoclonal antibody staining. Skin biopsy for histopathology may be performed, and common findings include keratinocytes with uniform steel-gray nuclei and margination of chromatin, ballooning degeneration with secondary acantholysis, multinucleated giant cells and an underlying mixed inflammatory cell infiltrate. The Tzanck smear, although underutilized in the clinical setting, is a rapid, simple, noninvasive method for the diagnosis of infections, autoimmune disorders, and less commonly for the diagnosis of various neoplasms and granulomatous diseases.\textsuperscript{5} A study by Eryilmaz et al. found that the Tzanck smear was a reliable diagnostic test for erosive vesiculobullous disease. A positive Tzanck smear shows multinucleated keratinocytes and acantholysis. However, the Tzanck smear and tissue histopathology without immunohistochemistry stains do not distinguish between HSV-1, HSV-2 or VZV.

According to Wilck et al., in the absence of antiviral prophylaxis, HSV-seropositive organ transplant recipients are at risk for clinical reactivation, even if they had not had prior clinical HSV disease. The incidence of clinically apparent HSV disease in seropositive patients not receiving prophylaxis, Wilck et al. state, ranges from 35% to 68%.\textsuperscript{6} HSV prophylaxis using acyclovir, valacyclovir, or famciclovir should be considered for all HSV-1 and HSV-2 seropositive organ recipients for the first month after transplantation.\textsuperscript{8} Following the first post-transplant period, treatment should be initiated promptly based on clinical diagnosis for improved clinical outcome. Of interest, a recent study by Mues et al. investigated dynasore, a small-molecule inhibitor of dynamin. Dynasore was found to have multiple deleterious effects on HSV-1 and HSV-2 infection by impeding crucial steps in the viral life cycle. This is a new and promising approach to HSV treatment and prevention that is on the horizon.\textsuperscript{9}

Acyclovir-resistant HSV should be suspected if there are very frequent recurrences while on suppressant therapy, which will require treatment with either ganciclovir or valganciclovir.\textsuperscript{1} Furthermore, if an ulcer fails to respond to therapy, HSV infection with concomitant CMV infection must also be considered. Schoenfeld et al. describe two cases of HIV patients who presented with genital ulcers in which both HSV and CMV were proven to be the causative agents. They stress that it is crucial to at least consider CMV as a causative agent when an immunocompromised patient presents with genital lesions, especially in those not responding to the usual treatment, as CMV may be a marker of impending systemic infection.\textsuperscript{10} Cutaneous infection by CMV is diagnosed by immunohistochemical staining or viral culture, while systemic disease or acute viremia is diagnosed by a CMV antigenemia assay or polymerase chain reaction.\textsuperscript{11}

In organ transplant patients, CMV is a major cause of disease and mortality, with a symptomatic infection occurring in 20% to 60% of all transplant recipients.\textsuperscript{4} Infection can occur as a result of reactivation of an existing latent infection in the recipient, from a donor strain of CMV, or as a primary infection in a previously CMV-naïve individual. Cutaneous CMV is present in 10% to 20% of patients with systemic infection, and its presentation is often nonspecific and varied. Clinical manifestations include ulcers, morbilliform rash, petechiae, purpuric eruptions, necrotic papules, and vesiculobullous eruptions.\textsuperscript{1} Systemic manifestations include fever, leukopenia, malaise and arthralgias.\textsuperscript{11} Chronic CMV infections are associated with risk of acute and chronic graft rejection and an increased risk of subsequent bacterial and fungal infections. Wilck et al. state that when ganciclovir, acyclovir, valacyclovir and valganciclovir are given in standard doses for CMV prevention, they will also prevent most HSV reactivation. Ganciclovir, valganciclovir, foscarnet, and cidofovir have all been approved for the treatment of CMV, with foscarnet and cidofovir reserved for strains exhibiting ganciclovir resistance.\textsuperscript{10,11}

**Conclusion**

We describe a severe but typical presentation of HSV-1 occurring on the bilateral buttocks in an immunosuppressed organ transplant patient. The diagnosis was quickly confirmed at the patient’s initial presentation using the underutilized but reliable Tzanck smear, enabling prompt treatment with valacyclovir 1 gm twice daily. Practitioners should be mindful to send viral cultures in immunosuppressed patients presenting with vesiculobullous lesions to rule out primary or concomitant CMV infection.

**References**


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A rare case of verrucous psoriasis in young female: A case report and review of clinicohistologic presentation and variable therapeutic response

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Introduction
Psoriasis is a common, chronic, immune-mediated disorder that results in epidermal hyperproliferation. In addition to the most typical presentation of erythematous plaques surmounted by micaceous scale with a predilection for the scalp, lower back, and extensor surfaces of the limbs, several distinct clinical variants include erythrodermic, guttate, and pustular psoriasis. One particularly rare clinicohistologic variant is verrucous psoriasis (VP), which has engendered far less documentation in the medical literature. A PubMed search of VP yielded only 12 relevant articles.

VP most commonly presents clinically as a wart-like lesion.1 Histopathologic assessments reveal a combination of verruca and psoriasis, including localized hyperkeratosis with parakeratosis, hypogranulosis, Munro’s microabscesses, papillomatosis, dilated capillaries in dermal papillae, and perivascular lymphocytes.2 While the case we present describes a usual clinicopathologic representation of this rare form of psoriasis, it is unique because it’s the first documented case of VP in a child. After discussing the case, we will review previous case reports of VP focusing on suggested etiologies, clinical presentations, and treatments.

Case report
A 14-year-old Hispanic female presented to the office with the chief complaint of a large, pruritic lesion on her right medial forehead that had been present and enlarging for more than a month. Her primary care physician had prescribed a six-week course of griseofulvin for presumed tinea capitis. No biopsy or culture was performed, and no improvement ensued. The patient reported no previous dermatologic disease. Review of systems and medical and social histories were unremarkable. On presentation to our office, she was taking no medications.

Cutaneous exam revealed a hypertrophic plaque with verrucous scale located on the right medial forehead (Figure 1). A 2-cm verruca vulgaris was also noted on the right thumb. A shave biopsy of the forehead lesion revealed hyperkeratosis with neutrophils within mounds of parakeratosis, digitated and psoriasiform epidermal hyperplasia, mild spongiosis, dilated blood vessels at the tips of dermal papillae, and superficial perivascular mixed inflammatory-cell infiltrate (Figures 2, 3). Clinical and histopathological observations were consistent with verrucous psoriasis.

The patient was prescribed clobetasol propionate 0.05% foam twice daily for five days and fluocinolone acetonide 0.01% topical solution thereafter until her return appointment. She was also advised to use 3% salicylic acid shampoo.

The patient returned to the office 10 days later with significant improvement (Figure 4). She had applied clobetasol propionate 0.05% foam twice daily for two days and then fluocinolone acetonide topical solution for seven days. She had used the shampoo three times the first week and two days during the week she came back to the office.

Discussion
Verrucous psoriasis is an infrequent phenomenon in dermatology. There are a limited number of case reports, and this variant of psoriasis does not appear in the majority of currently published general dermatologic textbooks. While the exact
etiology of VP is presently unknown, there are a handful of theories as to the cause. Khalil et al. suggested that repeated trauma in an individual with preexisting psoriasis may result in lesions of VP. This case report also proposed pulmonary dysfunction and phlebitis as predisposing conditions to VP due to the anoxic conditions in the peripheral tissues and circulation. Based on comorbidities present in their patients, other authors have postulated diabetes mellitus, autoimmune hepatitis, and chronic hepatitis C treated with interferon as conditions contributing to the pathogenesis of VP. Since our patient had a verruca vulgaris on the right thumb, we considered the possibility of super-infection of the psoriatic plaque with human papillomavirus (HPV) as the cause of our patient's VP. We subsequently performed immunohistochemical staining for HPV in our patient's forehead tissue, and the results were negative.

Most reported cases of VP presented as clinical and histological hybrids of psoriasis and verruca vulgaris. However, there have been several reports of histologically confirmed VP with unusual clinical presentations. For example, one case of histologic VP presented clinically as widespread hypertrophic verrucous plaques on a broad, inflamed erythematous background. Prior to biopsy, the differential diagnosis included T-cell lymphoma, Darier's disease, verrucous carcinoma, and pityriasis rubra pilaris. We compiled a list of all known published case reports of VP and their documented clinical presentations and treatments (Table 1). Interestingly, this investigation revealed that all patients previously diagnosed with VP were adults. This makes our

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**Table 1. VP clinical presentations and treatments**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>Lesion localization</th>
<th>Lesion type</th>
<th>Successful treatments</th>
<th>Failed treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura, et al.³</td>
<td>M</td>
<td>60</td>
<td>Trunk, extremities, fingers</td>
<td>Erythematous papules, plaques</td>
<td>Topical corticosteroids, 2% coal tar ointment, PUVA (ineffective on papules but effective on plaques), cryosurgery (resolved papules)</td>
<td>None</td>
</tr>
<tr>
<td>Kawtar, et al.⁴</td>
<td>F</td>
<td>43</td>
<td>Thigh, fingers, perianal area</td>
<td>Verrucous plaques</td>
<td>No treatment reported</td>
<td>No treatment reported</td>
</tr>
<tr>
<td>Scavo, et al.⁵</td>
<td>M</td>
<td>44</td>
<td>Trunk, glans penis, external auditory canals, scalp, toes, fingernails</td>
<td>Erythematous-desquamative plaques</td>
<td>Lesion regression 2 weeks after stopping interferon treatment for HCV, plus emollients and systemic antihistamines</td>
<td>None</td>
</tr>
<tr>
<td>Curtis, et al.⁶</td>
<td>M</td>
<td>46</td>
<td>Trunk, extremities, face, scalp, genital area</td>
<td>Verrucous plaques manifesting as erythroderma</td>
<td>Moderate improvement with ustekinumab</td>
<td>Topical keratolytics, high-potency topical steroids, acitretin (3 mos), methotrexate (6 mos), etanercept (4 mos), adalimumab (3 mos), infliximab (2 mos)</td>
</tr>
<tr>
<td>Emel, et al.⁷</td>
<td>F</td>
<td>22</td>
<td>Upper and lower back</td>
<td>Symmetric, annular, erythematous plaques with verrucous, papular, yellow-gray scaling</td>
<td>Healing of lesions after 15 days of 5% crude coal tar, moderate-potency topical steroid ointment</td>
<td>None</td>
</tr>
<tr>
<td>Monroe, et al.⁸</td>
<td>F</td>
<td>84</td>
<td>Posterior arm, lumbosacral back, thigh, distal leg, chest, abdomen</td>
<td>Verrucous papules, plaques</td>
<td>Initial resolution of extremity and chest lesions with topical fluocinonide and keratolytic agents, urea and salicylic acid, but flares ultimately continued on extremities and trunk even with topical steroid treatment</td>
<td>None</td>
</tr>
<tr>
<td>Munoz, et al.⁹</td>
<td>M</td>
<td>60</td>
<td>Extremities, trunk</td>
<td>Erythematous lesions covered by thick, adherent scales</td>
<td>Resolution of lesions after two months of oral etretinate</td>
<td>Topical steroids and topical vitamin D3 with PUVA</td>
</tr>
<tr>
<td>Hall, et al.¹⁰</td>
<td>M</td>
<td>44</td>
<td>Frontal scalp, trunk, extremities</td>
<td>Verrucous papule</td>
<td>No successful treatment reported</td>
<td>Topical salicylic acid</td>
</tr>
<tr>
<td>Katayama, et al.¹¹</td>
<td>M</td>
<td>55</td>
<td>Trunk, extremities</td>
<td>Verrucous scale on erythematous plaque</td>
<td>Marked improvement with adalimumab</td>
<td>Numerous topical psoriasis agents</td>
</tr>
<tr>
<td>Current case</td>
<td>F</td>
<td>14</td>
<td>Right medial forehead</td>
<td>Hypertrophic verrucous plaque with scale</td>
<td>Clobetasol propionate 0.05%, fluocinolone acetonide 0.01%, 3% salicylic acid shampoo</td>
<td>None</td>
</tr>
</tbody>
</table>
finding in a 14-year-old the first known case of VP reported in a child.

Treatment of VP has proved challenging in the majority of previously reported cases. Attempted therapies have included both topical and systemic agents used in other variants of psoriasis. After review, we found that most patients’ VP improved with either topical or intralesional steroids, which holds true for our patient. Combination topical therapies have been successful in some patients. One patient with annular VP responded to a combination of 5% crude coal tar and moderately potent steroid ointment. Another report showed healing of VP plaques on the chest and extremities with a combination of topical fluorocinonide, urea, and salicylic acid. Systemic agents, specifically biologics, have variable success in the treatment of VP. The erythrodermic variant of VP discussed earlier was calciferol resistant to varying combinations of acitretin (50 mg daily), high-potency topical steroids, methotrexate (15 mg weekly), and multiple biologics (etanercept, adalimumab, and infliximab). The patient finally showed signs of moderate improvement on 45 mg ustekinumab every 12 weeks after nine months of treatment. Another case showed remarkable improvement of a VP plaque after treatment with adalimumab. Similar to the biologics, results with methotrexate have not been consistent. In one case report, the addition of methotrexate to topical and intralesional steroids caused significant regression of VP lesions. The only retinoid that produced good treatment results with VP was oral etretinate, reported in the case of a male from Japan. However, this drug is banned in the United States. Other oral retinoids, specifically acitretin, did not produce results in cases we reviewed; however, a report of a case that was diagnosed as verrucous carcinoma and treated successfully with acitretin was argued by others to have been a case of VP. This suggests that acitretin could be a viable treatment for VP in some cases. Any therapeutic results reported in VP need to be interpreted with caution given the small sample size and varying clinical scenarios.

Conclusion
VP is a rare and distinctive variant of psoriasis that presents with overlapping clinical and histological features. The literature on VP is lacking, and while further research is desirable to delineate the specific etiology, the likelihood of such research is remote given the rarity of the condition. The limited numbers of published case reports have suggested some potential treatments for VP. Our patient, representing a typical clinicopathologic presentation of localized VP in a child, showed excellent response to treatment with topical steroids and 3% salicylic acid shampoo. At this point, it is difficult to know whether cases of VP represent unique pathophysiologic circumstances resulting in common clinical presentations or whether this rare histopathologic variant of psoriasis has unifying etiologic factors among patients in whom it presents. Further case series may help to uncover the answers to this question.

References

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**BIPHASIC CREAM** for sustained relief.1,2
**PLASTIBASE® OINTMENT** for enhanced spreadability and appeal.3

**INDICATIONS AND USAGE:** HALOG (Halcinonide, USP) 0.1% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

For topical use only. For Important Safety Information, please see Brief Summary on reverse. For full Prescribing Information see Product Package Insert at HalogRx.com

**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.
HALOG®
(halcinonide, USP) Cream and Ointment 0.1%
BRIEF SUMMARY

Brief Summary (For full Prescribing Information and Patient Information, refer to package insert.)

INDICATIONS AND USAGE
HALOG® CREAM or HALOG® OINTMENT is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

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

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- Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients.
- Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.
- Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
- Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.
- This medication is to be used as directed by the physician. It is for dermatologic use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
- Patients should report any signs of local adverse reactions especially under occlusive dressing.
- Pregnancy Category C: Topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
- Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

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