Common Phototherapy Mistakes & How to Avoid Them

Also in this issue:
- Nodular Kaposi's in an Immunocompetent Female
- Beyond Argyria? The Growing Problem of Silver Exposure
- Perspective: The Forgotten Tool for Rhytides
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TABLE OF CONTENTS

ORIGINAL ARTICLES AND CASE REPORTS

A Novel Case of Scrotal Angiolymphoid Hyperplasia
Renee N. Lucero, BS, Derrick H. Adams, DO, FAOCD ........................................... 23

Verrucous Intertriginous Plaques in a Young Female
Joseph Dyer, DO, Kathleen P. Soo, DO, FAOCD, George Gibbons, MD .......................... 24

Lupus Pernio: A Case Presentation and Review of Treatment Options
Teresa Ishak, DO, Mayha Patel, DO, David Horowitz, DO, FAOCD .............................. 26

Cutaneous Rosai-Dorfman Disease: A Case Report and Review
Khasha Touloei, DO, Adam Wiener, DO, Angela Macri, DO, Bradley P. Glick, DO, MPH, FAOCD .............................. 28

A Case of Punctate Porokeratotic Keratoderma: Manifestation of Uncontrolled Hyperlipidemia or Delayed Paraneoplastic Syndrome?
Charisse McCall, DO, Sanyosh Singh, DO, Michael Berry, MD .................................. 30

Multiple Eruptive Dermatofibromas Following Immunosuppressive Therapy in a Patient with Systemic Lupus Erythematosus
Maria Tempera, BS, Peter Saitta, DO, FAOCD, Cherise Khani, DO, Cindy Hoffman, DO, FAOCD, Ronald Brancaccio, MD, FAAD ........................................................... 32

Darier's Disease: A Case Study and Review of the Literature
Jeffrey Kushner, BA, David A. Kasper, DO, FAOCD, MBA ........................................... 34

Erythrodermic Psoriasis: A Case Report and Literature Review
Jacqueline Fisher, DO, Nanda Channaiah, DO, FAOCD ............................................... 36

Iatrogenic Kaposi's Sarcoma Arising After Renal Transplant Immunosuppression
Katherine Johnson, DO, Jessica Garelik, DO, Howard D. Lipkin, DO ......................... 41

Pagetoid Reticulosis (Woringer-Kolopp Disease) in a 43-Year-Old Woman
Helia Eragi, DO, Matthew Koehler, DO, Paul Shitabata, MD, David Horowitz, DO, FAOCD .................................................. 43

Blue Vein at the Nasal Root: A Case Presentation and Discussion A Case Report and Review of the Literature
Adam Sorenson, DO, Harper Price, MD, Stephen Kessler, DO, Rebecca E. Fisher, PhD .................................................. 47

Combination of Photodynamic Therapy with Blue Light for Treating Pyoderma Faciale in a Post-partum, Breast-feeding Patient: A Case Report and Literature Review
Dorene Nio, BS, Patrick Keehan, DO ................................................................. 48

A Case of Pseudoxanthoma Elasticum (PXE) in a 14-year-old Female: A Case Report and Review of the Literature
D. Ryan Skinner, DO, Samuel Ecker, BS, Daniel Hurd, DO, FAOCD ......................... 50

Vibrio Vulnificus Septicemia Presenting as Fevers, Bullae, and Compartment Syndrome: A Case Presentation and Review of the Literature
Alissa T. Lamoureux, DO, Brad P. Glick, DO, MPH ......................................................... 52
Dear Colleagues,

I am just getting back from our Dallas Midyear Meeting and couldn't be happier. Thank you for the positive feedback. Our attendance was among the highest it has ever been for a Midyear Meeting. In addition, we had more exhibitors than we have ever had at any meeting, which translates to our ability to host a great event in a great venue.

All of the wonderful talks from the meeting are available online. To access them, just log into the members area of the AOCD website (www.aocd.org). Apart from the invaluable updates on conditions like melanoma, lymphoma, and psoriasis, and treatment modalities like Mohs, we also learned about avoiding medical errors, creating cosmetic workflows, dealing with potential legal dilemmas, complying with OCC requirements, adopting the ICD-10, embracing future changes to the practice of medicine, and how to maintain personal and practice finances. (And perhaps most important, we learned from Dr. Brown to “never take a sleeping pill and a laxative in the same night.”) All of this knowledge is geared toward helping us achieve our greatest long-term goal: delivering the best care we can to our patients and being happy while doing it.

Finally, we have some potentially exciting news for those reading this right now: The process for CME reading credit approval for the JAOCDD is in its final stages. Our journal is currently being reviewed by the AOA CCME, and I anticipate that at some point this year, the JAOCDD will be able to start providing credits to make it just a little bit easier to get to those 120 hours.

Fraternally,
Karthik Krishnamurthy, DO
Editor-in-Chief, Journal of the American Osteopathic College of Dermatology
2nd Vice President, American Osteopathic College of Dermatology
Greetings, everyone!

Our Dallas Midyear Meeting was a huge success! Dr. Karthik Krishnamurthy put together a fabulous program for the attendees.

Our next Annual Meeting, taking place in Seattle, is being chaired by Dr. Rick Lin, and we can surely expect another great event. Look for meeting information on our web site, www.AOCD.org. We will also update everyone through the regular Thursday Bulletin.

**Save the Dates!**

Our 2014 Fall Meeting will take place October 25th through 28th. Please note the first day of lectures will be Sunday, October 26th. This is a new meeting cycle the AOA is implementing. Monitor the AOCD and AOBD web sites (www.aobd-derm.org) for updates concerning the conference schedule and testing dates and locations.

Our 2015 Midyear Meeting will take place from April 23rd through 26th at the Ritz Carlton in Charlotte, North Carolina. The Program Chair is Dr. Daniel Ladd.

**Staying In-the-Know**

We have several avenues for our members to remain updated on all things AOCD. In addition to the JAOC, the Dermline publication provides valuable information. As of 2014, we are switching to an online-only Dermline. We will be monitoring member feedback to decide whether this change is permanent or we go back to a printed newsletter, so please make your opinion known.

The AOCD Insights is a weekly newsletter full of recent articles related to dermatology.

The Thursday Bulletin is intended to keep members updated regarding AOCD news and events. Please let me know if you have information you think would be helpful to our membership, and we can include it in an upcoming Thursday Bulletin.

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

Sincerely,

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

I write my letter to you now during a period of great transition. What lies in store for the AOCD will be determined by you, our membership. As of publication time, the ACGME and AOA have entered into an agreement for a unified accreditation system. This, in short summary, will allow all graduating DO students to go into allopathic or osteopathic residency programs. The same is true for all graduating MD students.

This has come about for several reasons, including a government push for one system and the fact that there will be insufficient residency slots for DO graduates by the year 2022.

With this comes many changes, and change is not easy for many. I believe the AOCD will prevail in this new system. The AOA web site (www.osteopathic.org) has all the current facts about the merger, but there is still much to be worked out. We know the transition will take place over the next five years, during which all AOA programs will apply for ACGME accreditation. By the year 2020, there will no longer be standalone DO residencies, although there will be osteopathic-focused residencies. All DO program directors will be working with their MD counterparts.

So, where does this leave us?

I believe in osteopathic medicine and in the AOCD. We have a transition committee in place already. A document for comparison of residencies will be available soon and can be used by programs to help meet ACGME standards. Some of our own standards will be included in the overall process, as well.

We will need to redefine ourselves and our mission in this new system. Our new strategic plan will reflect our future goals. Ultimately, though, we are who we are and we are proud of it, and we will capitalize on our uniqueness to establish ourselves amongst our colleagues. Our approach to the patient will not change. Our membership must persevere. We are committed to CME and to all of you.

We are DO dermatologists, and we stand strong!

I am truly proud to be one of us and your president.

Sincerely,
Suzanne Sirota-Rozenberg, DO, FAOCD
President, American Osteopathic College of Dermatology
The Dermatology Foundation’s Board of Trustees is pleased to announce and recognize Charles and Daneen Stiefel for their recent gift of $1 million, the largest single contribution ever received by the DF.

“We have enormous respect for the work of the Dermatology Foundation, and we wanted to do something special to support its mission,” Mr. Stiefel explains. At the Stiefels’ request, these funds will be dedicated to advancing research in autoimmune and/or connective tissue diseases through a new research award intended for early to mid-career investigators. They hope their gift will lead to better treatments for these diseases and to an improved understanding of their causes and their association with cancer. “My primary philanthropic focus has been—and continues to be—cancer research,” Mr. Stiefel notes. This holds deep personal significance for him, because many members of his family have battled cancer. He himself has suffered from two different types of cancer.

Mr. Stiefel’s unwavering support of the DF has long been part of both his private and public lives. He is a member of the Annenberg Circle and Fitzpatrick Legacy Fund, and is the former Chair and CEO of Stiefel Laboratories, a Corporate Honor Society member and supporter of the DF.

Mr. Stiefel’s dedication to the Foundation reflects his belief that building the scientific base of dermatology is critically important. “Throughout its 50-year history, the Foundation has played a prominent role in advancing the science and the practice of dermatology,” he says—“and I strongly believe it will continue to do so.”

The DF Trustees extend their deep gratitude to Charles and Daneen Stiefel for their exceptional generosity, and their decision to support the future of the specialty.

"The Dermatology Foundation was established in 1964 and is the leading private funding source for skin disease research. It provides funding that helps develop and retain tomorrow’s teachers and researchers in dermatology, enabling advancements in patient care."
Finacea® (azelaic acid) Gel, 15% is a topical prescription medication used to treat inflammatory papules and pustules of mild to moderate rosacea.

Rosacea is with him wherever he goes. So is Finacea®.

It's true. Rosacea is complex and it's with them for life. Finacea® treats the papules and pustules with associated erythema of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated. You have made Finacea®, the #1 Dermatologist-prescribed topical rosacea brand.¹

INDICATION & USAGE
Finacea® (azelaic acid) Gel, 15% is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

IMPORTANT SAFETY INFORMATION
Skin irritation (e.g., pruritus, burning or stinging) may occur during use with Finacea®, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and persists during use with Finacea®, discontinue use and institute appropriate therapy. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, monitor these patients for early signs of hypopigmentation.

Avoid contact with the eyes, mouth, and other mucous membranes. In case of eye exposure, wash eyes with large amounts of water. Wash hands immediately following application of Finacea®.

Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents. Avoid the use of occlusive dressings or wrappings.

In clinical trials with Finacea®, the most common treatment-related adverse events (AE's) were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). Contact dermatitis, edema and acne were observed at frequencies of 1% or less.

Finacea® is for topical use only. It is not for ophthalmic, oral or intravaginal use. Patients should be reassessed if no improvement is observed upon completing 12 weeks of therapy.

Please see Brief Summary of full Prescribing Information on adjacent page.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

¹ According to IMS NPA™ (National Prescription Audit) July 2010-October 2013
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study. Some improvement in irritation was demonstrated over the course of the clinical trials, but this
of asthma, vitiligo, depigmentation, small depigmented spots, hypertrichosis, reddening (signs of
reported in human dermal safety studies.

Avoid contact with the eyes, mouth and other mucous membranes. If FINACEA Gel does come in
contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye
irritation persists [see Adverse Reactions (6.2)].

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed
in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug
and may not reflect the rates observed in practice.
In two vehicle-controlled and one active-controlled U.S. clinical trials, treatment safety was monitored
in 788 subjects who used twice-daily FINACEA Gel for 12 weeks (N=333) or 15 weeks (N=124), or
the gel vehicle (N=331) for 12 weeks. In all three trials, the most common treatment-related adverse
events were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). In the active-controlled trial, overall adverse reactions (including burning,
stinging/tingling, dryness/lightness/scaling, itching, and erythema/irritation/redness) were 19.4%
(24/124) for FINACEA Gel compared to 7.1% (9/127) for the active comparator gel at 15 weeks.

Table 1: Adverse Events Occurring in >1% of Subjects in the Rosacea Trials by Treatment Group and
Maximum Intensity*  

FINACEA Gel, 15%  
N=457 (100%)  
Vehicle  
N=331 (100%)  

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Burning/stinging/tingling</td>
<td>71 (16%)</td>
<td>42 (9%)</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29 (6%)</td>
<td>18 (4%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Scaling/dry skin/xerosis</td>
<td>21 (5%)</td>
<td>10 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Erythema/irritation</td>
<td>6 (1%)</td>
<td>7 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
</tr>
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FINACEA Gel N=461 (102%)  
<table>
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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning/stinging/tingling</td>
<td>42 (9%)</td>
<td>17 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Scaling/dry skin/xerosis</td>
<td>31 (9%)</td>
<td>14 (4%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Erythema/irritation</td>
<td>8 (2%)</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Acne</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

FINACEA Gel N=464 (102%)  
<table>
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<td>7 (2%)</td>
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<td>Erythema/irritation</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred
terms may exceed the number of subjects with at least 1 cutaneous adverse event.

6.2 Post-Marketing Experience
The following adverse reactions have been identified post approval of FINACEA Gel. Because these
reactions are reported voluntarily from a population of uncertain size, it is not always possible to
reliably estimate the frequency or establish a causal relationship to drug exposure:
Eyes: iridocyclitis upon accidental exposure of the eyes to FINACEA Gel

7 DRUG INTERACTIONS
There have been no formal studies of the interaction of FINACEA Gel with other drugs.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. Therefore, FINACEA Gel should
be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid,
15% gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits,
and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all
three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of
azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500
mg/kg/day [162 times the maximum recommended human dose (MRHD) based on body surface
area (BSA)], rabbits given 150 or 500 mg/kg/day [19 or 65 times the MRHD based on BSA] and
cynomolgus monkeys given 500 mg/kg/day [65 times the MRHD based on BSA]. Azelaic acid. No
teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats,
rabbits and cynomolgus monkeys.
An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered
from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Em-
byrotoxicity was observed in rats at an oral dose of 2500 mg/kg/day [162 times the MRHD based
on BSA] that generated some maternal toxicity. In addition, slight disturbances in the post-natal
development of fetuses was noted in rats at oral doses that generated some maternal toxicity
(500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual
maturity of the fetuses were noted in this study.

8.3 Nursing Mothers
It is not known whether azelaic acid is excreted in human milk; however, in vitro studies using equilibrium
dialysis were conducted to assess the potential for human milk partitioning. The studies demonstrated
that, at an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7
and the milk/buffer distribution was 1.0. These data indicate that passage of drug into maternal milk
is not expected to cause a significant change from baseline azelaic acid levels in the milk. Nevertheless, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of FINACEA Gel in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of FINACEA Gel did not include sufficient numbers of subjects aged 65 and over to
determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION
Inform patients using FINACEA Gel of the following information and instructions:
Use only as directed by your physician.
• For external use only.
• Before applying FINACEA Gel, cleanse affected area(s) with a very mild soap or a soapless cleansing
lotion and pat dry with a soft towel.
• Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
• Avoid contact with the eyes, mouth and other mucous membranes. If FINACEA Gel does come in
contact with the eyes, wash the eyes with large amounts of water and consult your physician if eye
irritation persists.
• Wash hands immediately following application of FINACEA Gel.
• Cosmetics may be applied after the application of FINACEA Gel has dried.
• Avoid the use of occlusive dressings or wrappings.
• Skin irritation (e.g., pruritus, burning or stinging) may occur during use of FINACEA Gel, usually during
the first few weeks of treatment. If irritation is excessive or persists, discontinue use and
consult your physician.
• Report abnormal changes in skin color to your physician.
• To help manage rosacea, avoid any triggers that may provoke erythema, flushing, and blushing.
These triggers can include spicy and thermally hot food and drinks such as hot coffee, tea, or alcoholic
beverages.
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Manufactured for:
Bayer HealthCare Pharmaceuticals
Wayne, NJ 07470
Manufactured in Italy
67068C8S
HALOG® Cream and Ointment are designed for a difference your patients can truly feel.

**BI-PHASIC CREAM** for sustained relief.¹²

**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.

PRECAUTIONS
- Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients.
- Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.
- 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.
Abstract

Phototherapy is one of the oldest therapeutic modalities to treat psoriasis. Even after decades of use, phototherapy continues to maintain its long track record for safety and efficacy. Optimization of phototherapy, however, requires both time and effort in order to define the ideal therapeutic dose for each individual patient. Therein lies the art of the process: achieving the right balance between dosage requirement and tolerance. It is not uncommon for missteps to occur before the appropriate dosimetry for a patient is determined. If not recognized and addressed, missteps may precipitate adverse effects or premature termination of therapy. We outline some of the more common missteps, as identified at the University of California Psoriasis and Skin Treatment Center under Director John Koo, MD, and discuss how they can be avoided. We also provide an overall phototherapy treatment algorithm.

Failure to adequately determine optimal dosimetry

Though skin type and ethnic background are suggestive as to the optimal dosimetry, each individual can differ significantly from the expected light tolerance. Moreover, the threshold for improvement (and phototoxic reaction) is different not only between individuals but also within the same individual. The extremities (especially the legs) typically need many times the dosimetry of the trunk. In fact, difficult-to-treat areas like the elbows and shins can have a minimal erythema dose that is two to three times greater than that of the trunk.

At the University of California Psoriasis and Skin Treatment Center, we typically divide phototherapy into three sequential exposures to ensure that an adequate dosimetry is provided for each body part. First, the whole body is treated (including the face if involved with disease). Second, the face is covered from forehead to chin, and the remaining area is treated. Third, the face and trunk are covered, and only the extremities are treated. By assessing the skin’s reaction to each treatment and taking into account differences in regional dose requirements, the practitioner can determine whether the patient has reached his or her ideal therapeutic light dose. Further, it may be helpful to counsel patients before their first treatment that it is common to experience a mild phototoxic reaction during the course of phototherapy. In fact, these reactions are helpful, because they ensure that an appropriate dosimetry is being used.
Failure to recognize initiation burn

Some patients may experience a burn or other sensitivity to light very early in the course of phototherapy with low dosimetry. This is experienced most frequently in patients with atopic dermatitis. When a patient cannot tolerate very low fluences of light early on in treatment, this may not indicate a failure of the therapy; rather, this may indicate “initiation burn.”

It is frequently possible to get around this “initiation burn” by reducing the dosimetry and then, after multiple exposures to a tolerable dosimetry, re-challenging the patient by increasing the dose incrementally. When the clinician finally “breaks through” the barrier of the initiation burn, the dosimetry can often be increased to a level far higher than that which caused the initiation burn. Eventually, the real limit of the patient’s tolerance -- the minimal erythema dose, or MED -- is reached. By using this strategy, we can avoid the pitfall of erroneously labeling the patient as a “phototherapy failure.”

Failure to distinguish between pruritus from disease and pruritus from treatment

Patients with pruritic skin disorders often respond well to phototherapy; however, pruritus is also one of the most common side effects experienced by patients exposed to narrowband UVB. One of the most challenging nuances to grasp as a phototherapy provider, then, is the distinction between the primary disease process and the side effects of treatment. Since pruritus from the primary disease process is often highly unpredictable both in anatomical distribution and chronology, it can be easily misinterpreted as a side effect of treatment with narrowband UVB.

The timing of onset provides valuable information, as pruritus from treatment with narrowband UVB usually begins four to eight hours after treatment. Outside of this time period, pruritus is likely a manifestation of active disease. If the origin of pruritic symptoms is ambiguous, one distinction strategy is to slightly increase the dosimetry and monitor the response to the light. If the pruritus is secondary to a phototoxic reaction, then an incremental increase in dosimetry may cause erythema. Although it may be intimidating to increase dosimetry in fear that it will lead to a phototoxic reaction, it may be better to cause a mild burn and successfully define the maximal tolerable dose than to chronically undertreat the patient.

Failure to educate
(Once burned, twice shy)

Phototherapy often requires carefully pushing the dosimetry close to the MED in order to define the optimal dosimetry to meet a patient’s therapeutic need while avoiding a phototoxic reaction. During this process, patients may experience a phototoxic reaction, such as an initiation burn. If this happens and the patient has not been counseled about the possibility of irritation and discomfort from a phototoxic reaction, the patient may become noncompliant or discontinue phototherapy altogether.

Proactively educating the patient can help. A patient who knows from the outset that a mild burn helps to define the level of optimal dosimetry and thus is actually helpful in improving the skin condition is less likely to become excessively fearful of phototherapy when a phototoxic reaction does occur. Another effective strategy is reassurance of control: reminding phototherapy patients that the dosimetry is always under the direct control of the clinician. If the patient experiences a phototoxic reaction to the current dose of light, the dose can always be lowered, and future phototoxic reactions will be avoided. This knowledge is reassuring to the patient and helps prevent premature discontinuation of phototherapy.

Failure to address anatomical peculiarity in terms of light tolerance

There is an extremely rare subset of patients that may experience burning from phototherapy in a highly unusual anatomical distribution. For example, a patient may experience a phototoxic reaction only in one horizontal dermatome on the trunk. Failure to recognize this possibility and adjust for the anomalous reaction can ultimately lead to phototherapy failure.

With knowledge that these rare reactions do occur, once recognized, the sensitive region of the body can be selectively covered after a limited light exposure, allowing the clinician to continue to steadily increase the dosimetry for the rest of the body. Eventually, the sensitive area may become more tolerant of higher dosimetry. It may even “catch up” to the rest of the body.

Conclusion

Phototherapy offers the advantage of a safe, whole-body treatment for generalized psoriasis, even during a prolonged maintenance phase of management. Although the majority of patients respond to phototherapy, this response often relies on the patience and skill of the practitioner. The successful delivery of phototherapy is an art, and by developing an awareness of some common pitfalls and strategies to avoid them, clinicians may be able to help a subset of patients who might otherwise miss out on the benefits of the treatment.
An Unusual Case of Nodular Kaposi’s Sarcoma on the Dorsal Hand in a Non-HIV Latina Female

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Abstract
Kaposi’s sarcoma (KS) is a multicentric neoplasia of microvascular origin with four main subtypes: classic KS, endemic African KS, immunosuppression (iatrogenic) KS, and AIDS-KS. KS is commonly found in HIV-infected, elderly, Eastern European and Mediterranean males. We present the unusual case of a biopsy-proven Kaposi’s sarcoma of the left dorsal hand in an immunocompetent, HIV-negative woman. Although there have been several reports in the literature discussing atypical cases of KS, there are very few reports of nodular Kaposi’s in HIV-negative women. Knowledge of atypical presentations of KS is important for proper assessment, biopsy, diagnosis and treatment of this condition.

Introduction
Kaposi’s sarcoma (KS) is a multifocal neoplasm of the reticuloendothelial system that is seen most commonly in elderly Eastern European and Mediterranean males. Since 1979, KS has been found to occur with greater frequency in immunosuppressed individuals, such as organ transplant recipients and patients infected with the human immunodeficiency virus (HIV). In 1872, Moritz Kaposi, a Hungarian dermatologist, first talked about findings of an aggressive “sarcoma idiopathic multiplex hemorrhagicum” and published case reports of five elderly men with skin lesions. The clinical course of this classic KS is protracted and usually benign. Since then, three more variants have been identified. The endemic African variant often affects HIV-negative adults and children, and in its aggressive form affects the lymph nodes. The immunosuppressive (iatrogenic) form of KS occurs in patients status post solid organ transplantation on immunosuppressive therapy. In 1981, AIDS-associated KS was first described, with visceral and mucosal involvement occurring in 10 percent of these patients in the fifth and sixth decades of life. KS is commonly found in HIV-infected males and seldom seen in HIV-negative or immunocompetent women. We report the unusual case of an immunocompetent, HIV-negative woman with biopsy-proven Kaposi’s sarcoma of the left dorsal hand, focusing on the rarity of this finding.

Case Report
A 56-year-old Latina woman presented to her PCP with a three-month history of a rapidly enlarging, painful red nodule on the left dorsal hand (Figure 1). Incision and drainage (I&O) and a bacterial culture were performed for a suspected infected abscess. The culture yielded heavy growth of Staphylococcus aureus, and the patient was treated with a course of oral clindamycin and topical mupirocin. The patient was referred to our dermatology office two weeks later when this treatment failed. The patient denied shortness of breath, cough, oral lesions, pain, swollen lymph nodes, hematuria or any other skin lesions. She had a past medical history of hypercholesterolemia and osteoporosis but denied any history of immunodeficiency. An ANA screen, ASO titer, rheumatoid factor, chlamydia, gonorrhea, RPR and HIV test were all negative.

The patient was referred to oncology with the diagnosis of a classic, nodular, low-risk Kaposi’s sarcoma. As of this paper’s submission, she has undergone 23 days of external beam radiation to the dorsal hand with complete resolution of the tumor.

Discussion
Kaposi’s sarcoma (KS) is a mesenchymal tumor involving blood and lymphatic vessels. The pathogenesis of KS involves viral oncogenesis and cytokine-induced growth, together with some state of immunocompromise. In 1994, a previously unknown virus was discovered and termed human herpes virus 8 (HHV8), also known as Kaposi’s sarcoma-associated herpes virus. The modes of transmission of HHV8 are yet to be fully described. In the United States, sexual transmission may be an important route; however, throughout sub-Saharan Africa, KS has been seen in children since before the era of AIDS, suggesting other possible routes of transmission, including mother-to-child or child-to-child via saliva.
In immunocompetent children, HHV8 occurs with a febrile maculopapular skin rash. In adults, it is associated with bone marrow failure, splenomegaly and fever in organ transplant patients.

It appears that HHV8 initiates and promotes the development of KS lesions through the viral interleukin-6 (IL–6) and the vascular endothelial growth factor (VEGF) it produces. There is an important difference in the pathogenesis of KS in HIV-negative versus HIV-positive individuals. KS in immunocompetent persons runs a more indolent course than in patients infected with HIV. In HIV-infected patients, the HHV8 virus interacts synergistically with the Tat protein produced by the HIV, promoting the migration and proliferation of cytokine-activated T-cell lymphocytes and stimulating KS cell growth. Similarly, a latency-associated nuclear antigen from the HHV8 virus activates long terminal repeats of HIV through the Tat protein. HIV-negative persons do not possess this protein.

This difference in pathogenesis shows that the evolution and progression of KS relies on different cofactors and mechanisms in HIV-positive versus HIV-negative patients.

The four most common forms of KS are: classic KS, endemic African KS, immunosuppression (iatrogenic) KS, and AIDS-KS. Other less common forms of KS include: telangiectatic KS, presenting with translucent nodules and telangiectasia; ecchymotic KS, appearing as periorbital ecchymoses with a large number of extravasated red blood cells; keloidal KS, demonstrating brown-violaceous nodules with a keloidal component; cavernous KS, a rare type of locally aggressive KS that histologically resembles cavernous hemangiomas; and lymphangioma-like KS, presenting with bullous-like, compressible eruptions in vascular spaces on the lower legs.

Classic KS is seen in elderly men of Mediterranean, eastern European, or Jewish descent with a peak incidence occurring after the sixth decade of life. It originally appears as erythematous, violaceous macules that progress to multiple, firm, purple-reddish-brown plaques and nodules on the lower extremities, occasionally associated with lymphedema and hyperkeratosis.

Within this variant there are three subtypes: cutaneous, which runs a prolonged course with a mean survival of eight to 13 years; nodular, with aggressive, fungating, exophytic, ulcerating growths that infiltrate through large areas of the skin and subcutaneous tissue; and disseminated, presenting with widespread cutaneous lesions with lymph node and visceral involvement in Europeans.

Endemic KS is a more aggressive variant mostly found in those of African descent, presenting with a high frequency of extracutaneous manifestation. There are four clinically distinct ways to describe endemic KS: benign nodular cutaneous disease, which looks like classic KS and is predominantly seen in young adults around 35 years of age; aggressive localized cutaneous disease, which targets soft tissue and bone and is fatal within five to seven years; florid mucocutaneous and visceral disease; and fulminant lymphadenopathic disease, occurring in children around 3 years of age and spreading rapidly to lymph nodes and visceral organs with no signs of cutaneous manifestation.

Immunosuppressive KS occurs 500 times more often in recipients of organ transplants currently on immunosuppressive therapy. The clinical appearance of KS in patients status post organ transplant is limited to the skin.

AIDS-KS presents quickly, in a few days, beginning as macules and evolving to papules and tumors. Before the HAART treatment protocol became the standard of care for AIDS patients, oral KS lesions were the first clinical sign in 25 percent of patients. KS involving ocular adnexal structures has been reported in up to 20 percent of patients with AIDS-KS. AIDS-KS lesions often disappear spontaneously, with new lesions appearing at neighboring sites. AIDS-KS causes significant morbidity and mortality, with lymphatic obstruction and rapidly progressive pulmonary failure.

The clinical characteristics and treatments of each variant are summarized in Table 1.

A study of 438 patients by Hiatt et al. compared classic KS in HIV-negative patients to AIDS-KS over a two-decade time period and found 354 cases of AIDS-KS. Of those 354 patients, there was a male predominance characterized by more aggressive behavior and higher rates of visceral and disseminated disease. This further illustrates the rarity of KS in HIV-negative women.

**Histology**

The histology of KS can be broken into three stages: patch, plaque and nodular. Some studies have reported slight histopathologic differences between HIV-associated KS and non-HIV-associated KS biopsies. In HIV-negative patients, mitoses and cellular anaplasia are more common, whereas AIDS-KS lesions tend to display more extensive dissecting vessels.

The patch-stage clinically appears as a macule and arises in the reticular dermis. A proliferation of small, irregular endothelium-lined spaces surrounding normal dermal vessels and adnexal structures infiltrated by inflammatory lymphocytes is characteristic.

The second stage is the plaque-stage, clinically appearing as small, palpable lesions that histologically represent the expansion of a spindle-cell vascular process throughout the dermis and often into the subcutaneous fat. Spindle cells are found throughout the dermal collagen bundles forming irregular, cleft-like, angulated vascular channels with erythrocytes. Hemosiderin deposits and eosinophilic hyaline globules with a perivascular inflammatory infiltrate are seen. Histocytes with the phenotype of either factor XIIIa or S-100 dermal dendritic cells are present, as are T-cells and B-cells, including plasma cells.

The third stage is the nodular stage, composed of sheets and fascicles of spindle cells with moderate atypia, single-cell necrosis, and trapped erythrocytes within an extensive network of slit-like vascular spaces. The spindle cells present in all KS lesions are thought to represent the neoplastic component, and most express endothelial markers CD31 and CD34, along with smooth muscle cell markers.

It was recently reported that all KS spindle cells express vascular endothelial growth factor (VEGFR-3), which is usually only expressed by lymphatic endothelium and neovasculogenic vessels, showing that KS spindle cells probably belong to the endothelial lineage that can differentiate into lymphatic cells.

They also overexpress matrix metalloproteinases (MMP), which are enzymes that facilitate the destruction of extracellular matrix proteins.

In summary, the main histologic features of all forms of KS include irregularly shaped, slit-like vascular spaces lined by spindle cells with well-defined borders, extravasated erythrocytes, a lymphoplasmacytic infiltrate, hemosiderin-laden macrophages, and intracellular and extracellular eosinophilic hyaline globules representing erythrocyte breakdown products.

In addition, immunohistochemistry and in situ hybridization studies have shown oxtocin-receptor expression in the cells of classic and AIDS-KS. Oxytocin can stimulate KS cell proliferation and may be a pathogenic growth factor involved in the development of Kaposi’s sarcoma.

The histological differential diagnosis of cutaneous KS includes fibrous histiocytoma, targetoid haemosiderotic haemangioma, acroangiokeratomatosis (pseudo-Kaposi’s), angiokeratoma of Mibelli, cutaneous angiosarcoma, spindle-cell hemangiendothelioma, benign lymphangiendothelioma, angiolipoma, and bacillary angiomatosis.

**Treatment**

Treatment for KS depends on the variant of disease. Patients with classic KS typically respond well to local therapy such as excision, laser, cryotherapy and intraläsional injections, although the disease tends to recur. Watchful observation is generally acceptable for immunocompetent, asymptomatic patients. If cryotherapy is used, treatment should be given at three-week intervals with a mean of three treatments for the best response. Endemic African KS excluding lymphadenopathic disease responds favorably to systemic therapies, while iatrogenic, immunosuppressive KS generally...
regresses after immunosuppressive therapy is stopped. For AIDS-KS, no curative therapy exists. Neither local nor systemic treatments for AIDS-KS have been shown to prolong survival. Radiation therapy is a well-tolerated treatment for large, localized lesions and has been used for many years as they are highly radiosensitive. Adverse effects of this therapy include residual hypopigmentation, radiodermatitis, and ulceration of the skin. Recent studies have also experimented and shown some success with hormonal and immunomodulating therapies such as interleukin-2, chorionic gonadotropin and interferon. A study by Hong et al. demonstrated an antiproliferative effect of toremifene on KS cells first detectable at 24 hours after use. Toremifene, a selective estrogen-receptor modulator that opposes estrogen activity, was found to be causing the upregulation of growth-inhibitory factor TGF-ß1 at the transcriptional level. TGF-ß1 is known to be a down-regulator of estrogen and a potent inhibitor of KS cell growth. Toremifene's direct mechanism of action in this case is not through its anti-estrogen-receptor activity (there are no estrogen receptors on KS cells), as seen in breast cancer, but instead is through TGF-ß1. However, the indirect effect of TGF-ß1 on the down-regulation of estrogen suggests there may be an agonistic relationship between estrogen and KS that should be further investigated, particularly in women. This study also showed that topical toremifene administration can be a beneficial mode of localized treatment without the risk of side effects.

Table 1 - Kaposi’s Sarcoma Variants

<table>
<thead>
<tr>
<th>Variant</th>
<th>Epidemiology</th>
<th>Variant</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic KS</td>
<td>- Elderly males</td>
<td>- Erythematous, violaceous macules</td>
<td>Local therapy</td>
</tr>
<tr>
<td></td>
<td>- Mediterranean or East European</td>
<td>- Progresses to purple-red-brown plaques/nodules</td>
<td>- Induce a mild inflammatory response</td>
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<tr>
<td></td>
<td>- Jewish ancestry</td>
<td>- Lower extremities</td>
<td>- Lead to tumor flattening, disappearance</td>
</tr>
<tr>
<td></td>
<td>- Sixth decade of life</td>
<td>- Lymphedema/hyperkeratosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Rarely metastasizes</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Subtypes:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Cutaneous: long course; avg. survival 8-13 yrs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Nodular: fungating, exophytic, ulcerating growths; diffuse, infiltrative; subcutaneous tissue</td>
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<tr>
<td></td>
<td></td>
<td>3. Disseminated: widespread cutaneous lesions; lymph node and visceral involvement</td>
<td></td>
</tr>
<tr>
<td>Endemic KS</td>
<td>- African descent</td>
<td>Subtypes:</td>
<td>Systemic therapies</td>
</tr>
<tr>
<td></td>
<td>- Children, adolescents, adults</td>
<td>1. Benign nodular cutaneous: young adults</td>
<td></td>
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<tr>
<td></td>
<td>- More aggressive course</td>
<td>2. Aggressive localized cutaneous: soft tissue, bone; avg. survival 5-7 yrs.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3. Florid mucocutaneous, visceral</td>
<td></td>
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<td></td>
<td></td>
<td>4. Fulminant lymphadenopathic: young children; lymph nodes, visceral organs; no cutaneous lesions</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic KS</td>
<td>Organ transplant recipients on immunosuppressive therapy</td>
<td>Limited to skin involvement</td>
<td>Regresses after reduction/cessation of immunosuppressive therapy</td>
</tr>
<tr>
<td>AIDS-KS</td>
<td>HIV-positive patients</td>
<td>- Multifocal and symmetric</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Macules evolve to papules/tumors</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Ocular adnexal structure involvement in up to 20%</td>
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<tr>
<td></td>
<td></td>
<td>- Lymphatic obstruction or rapidly progressive pulmonary failure</td>
<td></td>
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<tr>
<td>Telangiectatic KS</td>
<td>Translucent nodules w/ prominent telangiectasia</td>
<td></td>
<td></td>
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<tr>
<td>Ecchymotic KS</td>
<td>- Periorbital ecchymoses</td>
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<tr>
<td></td>
<td>- Extravasated red blood cells</td>
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<tr>
<td>Keloidal KS</td>
<td>- Brown-violaceous nodules</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Keloidal component</td>
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</tbody>
</table>
Conclusion

Although there have been several reports in the literature discussing atypical cases of KS, there are very few reports of nodular Kaposi’s in non-HIV infected women. Since classic KS is typically found in elderly, immunocompromised, Eastern European and Mediterranean males, it is important to note the rare case of an isolated, nodular Kaposi’s sarcoma on the upper extremity in an HIV-negative, immunocompetent Latina woman. Knowledge of atypical presentations of KS is important for proper assessment, biopsy, diagnosis and treatment of this condition.

References


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Asymptomatic Hyperpigmentation in an Elderly Male

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Abstract

Silver dermatoses (argyria) have increased in incidence throughout the United States since the 1990s, when fears of antibiotic shortages became increasingly common. With a proven history of antiseptic properties, the ingestion of colloidal-silver solutions is a common treatment modality in many cultures that practice alternative medicine. We report a case of an 85-year-old male who presented to our clinic with an asymptomatic, slate-gray-blue hyperpigmentation distributed in sun-exposed areas.

Case Report

An 85-year-old male presented to our office as a new patient for a full-body skin exam. The patient’s past medical history was significant for hypertension and atrial fibrillation, while his dermatological history included actinic keratoses. Medications consisted of warfarin and lisinopril. Upon entering the room, it was immediately noted that the patient appeared cyanotic but was not in distress. A prompt vital-sign check yielded an oxygen saturation of 98% on room air and a blood pressure of 128/78 with a regular pulse of 80.

On physical exam, the patient was noted to have a strikingly slate-gray-blue hyperpigmentation that was most prominent in sun-exposed areas including the head, neck, and upper extremities (Figure 1). Non-sun-exposed areas, including the chest, back, and lower half of the body, were uninvolved. Examination of the fingernails and toenails revealed a dark-gray hyperpigmentation of the lunula on every digit (Figure 2). Both oral and nasal mucous membranes displayed a diffusely scattered hyperpigmentation, while the sclerae were normal.

After several minutes of questioning, the patient admitted to drinking a homemade silver solution on a daily basis. Preparing this concoction involved purchasing 99-percent pure silver from a local jewelry store in sticks that measure 6 inches long by 2 inches wide. The patient would then connect the two silver sticks in series with a 14-gauge stainless steel wire and three 9-volt batteries and submerge it in a bath of distilled water and sea salt. The 9-volt batteries were activated by an electrical charge, and the solution cooked until the water became “foggy” and a vapor of steam was emitted from the bath.

The patient had been making “silver water” for more than 10 years for antiseptic purposes. For example, the patient admitted to drinking a cup of silver water when he started to feel an impending sore throat or food poisoning, and he sprayed the solution into his nose for sinus clearance and upper respiratory infections. Moreover, the patient would put a dose of silver water into a gallon of milk to extend the shelf life and prevent curdling.

Our working differential diagnosis included argyria, warfarin-induced hyperpigmentation, amiodarone-induced hyperpigmentation, porphyria, hemochromatosis, chrysiasis, and dermal melanocytosis. Lab studies such as a serum iron level were considered, but the patient refused. A 4-0 punch biopsy was performed on a hyperpigmented area from the neck, which portrayed numerous fine, black granules surrounding the eccrine glands (Figure 3). The results were consistent with argyria both clinically and histologically. The patient was advised against using his homemade tonic, and sunscreen use was recommended to prevent further hyperpigmentation.

Discussion

Argyria is a rare cutaneous dyschromia caused by chronic exposure to products containing silver. A slate-colored pigmentation develops from silver-granule deposition in the skin that is most noticeable in sun-exposed parts of the body. However, hyperpigmentation can also develop in nails, mucous membranes, conjunctiva, and sclera.

Hyperpigmentation occurs through several different mechanisms that yield a combined effect of reduction of the silver compound as well as an increase in melanin production. Through a process that is similar to the development of a photo, sunlight acts as a catalyst in reducing colorless silver compound to elemental silver. Metallic silver is then oxidized by the tissue and becomes bound as silver sulfide. Black silver sulfide is what makes up the granule deposition around eccrine glands. Finally, silver further increases dyschromia by stimulating melanocyte tyrosinase activity with a resulting expansion of melanin synthesis. Argyria can present as localized hyperpigmentation or as diffuse, blue-gray hyperpigmentation in sun-exposed areas. Cases of localized argyria involve direct silver deposition into the skin, while generalized argyria involves ingesting silver solution. The consumption of colloidal silver has gained popularity worldwide secondary to evidence of its antiseptic properties.
In alternative medicine, colloidal silver is widely marketed as a dietary supplement with untested claims of beneficial effects in diabetes mellitus, AIDS, arthritis, cancer and many other diseases.\(^7\) Colloidal silver products are marketed in a variety of forms as well as generators are easily available through the Internet.

Localized argyria can present up to 30 years after the permanent deposition of insoluble silver compound. The condition has been illustrated in previous case reports secondary to embedded acupuncture needles or topical application of silver nitrate.\(^8\) Most of the former cases occurred in Japan, where the injection of acupuncture needles was once a popular traditional Japanese therapy to control refractory back pain, arthralgias, neuralgias, and migraines.\(^4\)

Although embedding acupuncture needles is no longer a common treatment modality, accidental breakage of acupuncture needles can still be an etiology of localized argyria. Other reported cases of localized argyria involve the volar aspects of jewelers’ forearms, the mouths of patients with amalgam fillings, and mirror shards embedded during motor vehicle accidents.\(^3,6\)

As aforementioned, the pathogenesis of argyria is secondary to the deposition of insoluble silver granules into the basal lamina of eccrine glands and blood vessels. The histological features can create a concerning clinical appearance of melanocyte proliferation with a differential diagnosis that includes metastatic melanoma, blue nevus, or traumatic tattoo. Moreover, melanodacryorrhea has been reported in a patient with bilateral argyrosis of the conjunctiva.\(^1\) In this clinical portrait of black tears, it is imperative to question the history of topical medical use or silver ingestion, because it has also recently been reported in a patient with necrotic ureal melanoma.\(^7\)

Other cutaneous differential diagnoses of diffuse blue-gray hyperpigmentation in sun-exposed areas include drug-induced hyperpigmentation (DIH), Addison’s disease, hemochromatosis, Wilson’s disease, porphyria, melanoma, exogenous ochronosis, and lichen planus pigmentosus (LPP). A thorough history and physical examination can help to elucidate each differential diagnosis and possibly avoid the need for a punch biopsy. The definitive diagnosis of argyria is confirmed by a punch biopsy showing black granules surrounding the eccrine glands. Adjunctive tests include a serum iron level, which should remain elevated months after discontinuation of silver intake. Other techniques such as scanning electron microscopy with energy dispersive spectroscopy can aid in the diagnosis of chemical elements within skin biopsies.

Although the Agency for Toxic Substances and Disease Registry (ATSDR) considers silver deposits in tissues to be relatively harmless and without serious health effects, a small number of case reports have stated otherwise, particularly regarding the brain and kidney.\(^5,9\) In previous literature, silver deposits were described in the basement membrane of the glomerulus, peritubular capillaries, and the elastic lamellae of arteries of the kidney on autopsies.\(^10\) However, new research has concluded that silver is non-toxic to the kidneys after animal studies failed to reveal structural damage to the kidneys at massive exposure to silver nitrate in rats.\(^11\)

Regarding the brain, Mirsattari et al. reported a 71-year-old man who developed myoclonic status epilepticus and coma after daily ingestion of colloidal silver for four months.\(^12\) The patient remained in a persistent vegetative state until his death five months later. This case leads to the hypothesis that silver products can cause irreversible neurologic toxicity associated with a poor outcome.\(^12\)

Treatment for argyria is limited. The first recommendation is to eliminate exposure to silver immediately. Beyond that, a standard of care does not currently exist, although laser therapy with the quality-switched 1,064-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser has been effective in a small number of case series.\(^13\) The 1,064-nm Nd:YAG laser penetrates into the deep reticular dermis, targeting dermal melanophages as well as silver granules that surround the eccrine glands. Saager et al. reported the removal of pigment in a 3 mm to 6 mm treatment area with a Q-switched 1,064 Nd:YAG laser at 0.8-2 J/cm\(^2\) per area.\(^14\) In this study, there was an absence of discoloration recurrence at one-year follow-up when the face, neck, upper chest and arms were treated over multiple sessions under general anesthesia.\(^14\) In addition to laser treatment, it is of utmost importance to educate patients about eliminating silver exposure and utilizing sunscreen due to its numerous potential systemic complications as well as permanent discoloration of the skin.

With a fear of antibiotic shortage and a broadening spectrum of alternative medical practices, a public health initiative should be undertaken to heighten awareness of the permanent sequelae related to silver. From cutaneous manifestations to internal involvement, it is best to counsel patients on the possible harmful outcomes and encourage the termination of any silver exposure. Public awareness of the potential toxicity of silver exposure is important to prevent the chronic morbidity and incipient mortality seen in patients with argyria.

References

Manual Dermabrasion: The Forgotten Tool for Perioral Rhytides

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Abstract

Manual dermabrasion is a cost-effective, safe, and efficient method of facial resurfacing that has been largely ignored in recent literature. We report a case of a highly successful manual dermabrasion of the perioral region. Manual dermabrasion has fared well in comparison to more expensive and high-tech methods of resurfacing. We would like to remind our profession of this simple and viable technique for perioral rhytide resurfacing.

Case

A 65-year-old, healthy female with Fitzpatrick skin type II presented to the clinic seeking perioral rhytide treatment. She was a current smoker and had only recently started wearing protective sunscreen. She had previously undergone fractional ablation CO2 laser treatment and hyaluronic acid filler at another clinic about a year prior with mild improvement.

Upon examination, she was noted to have advanced-to-severe (Glogau type III-IV), static vertical rhytides periorally (Figure 1). Drywall sandpaper at 150-grit was obtained from a local hardware store and then autoclaved per clinic protocol. Regional dental blocks using bupivacaine achieved acceptable anesthesia to the treatment area. Her face was cleaned with chlorhexidine, and she was prophylaxed with acyclovir and cephalexin before the procedure. Using firm pressure, the sandpaper was worked in a circular motion across the perioral region, and in straight lines perpendicular to the vermilion border rhytides, until papillary dermal bleeding was achieved. The patient tolerated the procedure well, and there were no complications. Postoperative instructions included twice-daily diluted vinegar soaks (1:4) with application of petroleum jelly, as well as strict sun avoidance. She returned to the clinic 36 days post-operatively, with pleasing results (Figures 2 and 3). Residual erythema was noted but was of no concern to the patient.

Discussion

There are several effective and successful treatment options available for perioral rhytides. Depending on the underlying skin tone, medical history, and severity of rhytides, patients can seek rejuvenation through methods such as dermabrasion, CO2 lasers, permanent or absorbable fillers, and chemical peels. Selected patients with advanced-to-severe rhytides are encouraged to pursue ablative techniques for more dramatic results.3,4 Although a variety of ablative techniques have proved successful, recent studies show comparable results between manual dermabrasion and other ablative resurfacing modalities, each having specific advantages and disadvantages.5,6 With similar cosmetic outcomes and at a fraction of the cost, manual dermabrasion should be considered an effective and resourceful treatment option for ablative rhytide rejuvenation.

Ablative resurfacing involves the removal of the epidermis to the depth of the dermis.2,5 Following ablation, support cells within the dermis facilitate the growth of supplemental collagen parallel to the epidermis and deep to the dermal-epidermal junction.2 Collagen formation continues postoperatively and is responsible for the desired cosmetic outcomes and rejuvenation.2 Generally, patients with fairer complexities (Fitzpatrick skin types I-III) and more severe photaging and rhytides (Glogau type III-IV) are considered ideal candidates for ablative resurfacing.2,6 Patients with darker skin types have greater risk for hypopigmentation complications and are therefore encouraged to pursue non-ablative procedures.2,6

For an experienced physician, complications associated with ablative resurfacing are rare.2,6 Intraoperative risks are typically associated with the modality used and an error in technique.2,6 On the contrary, postoperative complications such as scarring, infection, hyperpigmentation and hypopigmentation, erythema, dyschromia, milia and acne flares can occur in any ablation technique but can be largely avoided through respective preoperative precautions.2,6 Activation of the herpes simplex virus is one of the more common and feared complications, and to avoid this and other infections, prophylactic antiviral and antibacterial medications are administered preoperatively.2,6 The formations of scars are generally attributed to ablation that occurs at the subcutaneous level, and if identified early postoperatively, scars can be treated with serial intralesional triamcinolone injections.2,6 Although most complications are considered universal, the rates of occurrence between ablative modalities can vary, each having respective advantages and disadvantages.2,6

This case exemplifies the seemingly forgotten potential that manual dermabrasion has for resurfacing perioral rhytides. Since ancient Egypt, physicians have been using sandpaper to successfully resurface scars and rhytides.2 Despite its proven efficacy, newer resurfacing techniques, such as CO2 lasers and powered dermabraders, have stolen the spotlight from manual dermabrasion.4
Perhaps a major influence in this transition has been the industry promotions behind more modern instruments. As sandpaper is the main apparatus for manual dermabrasion, there are no apparent marketing incentives associated with advertising its use. On the contrary, newer modalities have been advocated throughout the medical community, which may contribute to their widespread use.

Today, the majority of dermabrasion cases are performed using powered, hand-held dermbraders with wire brushes, diamond fraise, and serrated wheel end pieces.3 These interchangeable end pieces come in a variety of shapes and designs that allow the physician to quickly adjust to variations in tissue contour.3,4 With rotation speeds as high as 15,000 RPM to 30,000 RPM, however, these instruments pose risks for damaging loose tissue and exposing medical staff to potentially infectious bloodborne pathogens and skin fragments.3,8 These infectious agents have also been noted to produce a bloody field which may impair the surgeon's ability to make an accurate assessment of the depth of ablation.3,9 Additionally, powered dermabrasion typically requires use of a cryogenic spray, particularly when using the wire brush end pieces.3,8 which can increase the risk of hypopigmentation and hypertrophic scarring when used incorrectly.4,8,9 Alternatively, manual dermabrasion is a safer, more affordable, and less technically difficult method for perioral rhytide resurfacing.3,4 Perhaps the most obvious advantage of manual dermabrasion in comparison to other ablative resurfacing techniques is the cost of purchasing and maintaining equipment. There are also a wide range of sandpaper coarseness options that can be utilized for more conservative or aggressive approaches and adjusted depending on the physician's experience.4 Manual use of sandpaper also minimizes the airborne pathogens and tissue fragments, and thus provides the surgeon with a clear field for a more thorough intraoperative assessment.3,4 Additionally, firm pressure applied on the sandpaper can provide sufficient skin turgor, so cryogenic instruments are not required.3,4 Despite these advantages, the clinical use of manual dermabrasion has been overshadowed by newer techniques, most notably CO2 laser resurfacing instruments.

CO2 laser resurfacing techniques are based on selective photothermolysis, where a 10,600 nm wavelength of light targets water as the chromophore.5-14 When this light energy interacts with intracellular water, it immediately vaporizes and thermally ablates superficial tissue layers.10 As thermal energy is the method for ablation, CO2 lasers also coagulate, via the photocoagulative effect, which results in a virtually bloodless procedure.10,11 Residual thermal energy, however, can damage surrounding tissue, in particular the older continuous-wave models, and therefore is considered a primary limitation that is not encountered in dermabrasion.4,9 However, newer modalities, such as pulsed, fractional, or computer-scanned continuous wave CO2 lasers, can deliver fluences in less than 1 ms with tissue vaporization range of 20-50 µM per pass and 30-150 µM of residual thermal damage.3,11 This improvement in residual thermal damage and associated decreased risk of scarring have increased the popularity of CO2 lasers for perioral resurfacing.3,4,14

To those who promote fractional, pulsed, and computer-scanned CO2 lasers, these methods are considered to be more reproducible, precise, and operatively faster in comparison to manual dermabrasion.3,5,10,14 When compared to powered dermbraders, both manual dermabrasion and CO2 lasers reduce the risk of airborne infectious agents in the operating room, but it should be noted that viral pathogens have still been discovered in the laser plume.3,4 Additionally, laser equipment can result in ocular injury when used incorrectly.4 However, the primary disadvantage of CO2 lasars is the high cost of purchasing and maintaining these instruments, especially when compared to the costs associated with manual dermabrasion. Although CO2 lasers are known to be faster operatively, when treating a smaller cosmetic area, such as the perioral region, the difference should be considered insignificant.3,4 According to recent studies, dermabrasion and CO2 lasers have shown comparable results clinically.3,4 Holmkvist et al. conducted a study comparing the clinical outcomes and adverse effects of manual sandpaper dermabrasion and super-pulsed CO2 laser treatment on the perioral region.4 It was found that both methods significantly improved the rhytide scores, with no statistically significant difference between them.4 Similarly, Gin et al. compared the clinical results of manual dermabrasion to a computer scanned 950 µsec dwell time CO2 laser for upper lip rhytides.3 This study also showed comparable cosmetic results, along with similar respective disadvantages for each method.3 The associated disadvantages of the CO2 treatment included more extensive postoperative crusting, more pronounced erythema, and slower re-epithelialization.3,4 Disadvantages for manual dermabrasion were noted to include decreased acute hemostasis, longer operating time, and variability in the depth of tissue ablation.3,4 There was no reported difference between the two when it came to common complications such as postoperative herpes infections, scarring, hypopigmentation, hypopigmentation, milia formation, and acne flares.3,4

Conclusion

Of the various treatment options available for ablative facial resurfacing, manual dermabrasion is a safe, resourceful, and comparably effective method. Alternative treatment modalities, such as powered dermbraders and CO2 lasers, show similar cosmetic results to manual dermabrasion but are more expensive to maintain and are associated with method-specific complications.3,4 Although these techniques are faster operatively in comparison to manual dermabrasion, this difference is insignificant when treating a small cosmetic unit such as the perioral and upper-lip region.3,4 Manual dermabrasion, therefore, should regain its clinical recognition as a viable method of perioral resurfacing, despite its current lack of industry support and prevalence in clinical literature.

References


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A Novel Case of Scrotal Angiolymphoid Hyperplasia

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Abstract

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare, cutaneous vascular proliferation classically observed on the head and neck areas. We are reporting only the second known case of ALHE appearing on the scrotum.

Case Report

A 17-year-old male with a history of refractory verrucous vulgaris presented for asymptomatic nodules on the scrotum, increasing in size and number over the last three years (Figure 1). The patient denied any sexual history, pain, discharge, or trauma to the area. A biopsy was taken to rule out scrotal syringomas or steatocystoma multiplex. Dense collections of lymphocytes with scattered histiocytes and eosinophils were appreciated against a background of increased vasculature (Figure 2). Microbial stains to rule out an infectious trigger were negative. Angiolymphoid hyperplasia with eosinophilia was diagnosed. Treatment options were discussed with the patient, but he has yet to decide upon a course of action. Molecular clonality was not investigated due to cost constraints.

Discussion

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon vascular proliferation. The wide histologic variations in presentation have spawned an equally wide variety of nomenclature for the condition. Epithelioid hemangioma, pseudopericytic granuloma, inflammatory angiomatous nodule, popular angioplasia, subcutaneous angiolastic lymphoid hyperplasia with eosinophilia and lymphoid folliculosis, intravenous atypical vascular proliferation, and histiocytoid hemangioma have all been utilized with eosinophilia have been inconsistent and incorrect diagnosed as Kimura’s disease (KD).2 While ALHE and KD have similar characteristics, they are now characterized as different disorders.1,7,10 Histologically, the main characteristic of ALHE is vascular proliferation sometimes demonstrating cobblestoning with an eosinophil infiltrate. KD is generally deeper, with lymphoid follicles, dense fibrosis, and an eosinophil infiltrate.2,7 ALHE is a benign, primary vascular proliferation, while KD is due to chronic inflammation and is either an allergic or autoimmune disorder.7

Many treatment modalities have been used in attempts to clear ALHE lesions, but it is notoriously refractory to treatment. Surgical excision is often used after other non-invasive options have failed. Other commonly used treatments include intralesional corticosteroids and laser therapy. Lesions after surgical excision have a 33 percent to 50 percent recurrence rate. Mohs micrographic surgery has also been used for treatment, with results showing promise of completely resolving lesions with no recurrence and minimal destruction of healthy tissue.3 The high cost and exclusion criteria, however, preclude most patients from considering this option. Other treatment modalities have included topical tacrolimus, electrocoagulation, corticosteroids, sclerotherapy, indomethacin, retinoids, cryotherapy, pentoxifylline, intravenous vinblastine sulfate, radiotherapy, interferon α-2b therapy, intralesional bleomycin, and radiofrequency excision.1,5,10

Conclusion

We have reported only the second known case of scrotal angiolymphoid hyperplasia with eosinophilia. It is a rare but benign vascular
proliferation that typically presents on the head or neck area. Due to the high rates of recurrence, many treatment modalities have been used in attempts to clear lesions.

References

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Abstract
We report on a woman who presents with chronic fungating plaques in intertriginous areas and discuss salient features of her history, physical examination, and histopathology. After a diagnosis of keratitis-ichthyosis-deafness syndrome is made, we provide commentary on the condition and elaborate on its history, pathophysiology, and prognosis.

Case Report
A 25-year-old black female presented with history of malodorous intertriginous plaques for one year. The patient was unable to hear and communicated through sign language with the help of her husband. The patient was visually impaired. Limited finances precluded previous treatment.

Physical exam revealed verrucous plaques and erythematous nodules in the pubic, inguinal, and inframammary areas (Figure 1). Conjunctival injection was observed in both eyes, and the patient appeared to be squinting due to ocular discomfort (Figure 2). Rugated skin surrounded her mouth. Thickened palmar skin showed hyperlinear creases and a stippled appearance. Her fingernails and toenails were dystrophic and yellowed. Eyelashes and eyebrows were scant. Routine hematological parameters were unremarkable.

A biopsy was obtained from the left groin. Hematoxylin and eosin (H&E) stains showed digitated acanthosis and hyperkeratosis with numerous melanophages, lymphocytes, and plasma cells in the dermis (Figure 3). Periodic acid-Schiff stain demonstrated the presence of numerous septate fungal hyphae in the thickened cornified layer (Figure 4), and subsequent cultures grew Trichophyton rubrum.

A diagnosis of dermatophytosis in the setting of keratitis-ichthyosis-deafness (KID) syndrome was made. The patient had a daughter, age 6, and a son, age 2, who displayed similar ocular, dermatologic, and audiologic stigmata. Notably, the daughter was prone to abscess and kerion formation and had been hospitalized for surgical debridement of pyoderma of the scalp. Subsequent to the birth of her son, our patient underwent a bilateral tubal ligation.

In this case, management was multifaceted. The patient was started on terbinafine 250 mg daily for three months, monitoring periodically for liver transaminitis and neutropenia. In
addition, she was directed to soak in therapeutic baths, alternating between 1 cup of vinegar per bath and 1 cup of bleach per bath, to prevent superinfections. Ammonium lactate emollients were recommended for liberal application to thickened, dry skin, and tretinoin 0.05% cream was prescribed for facial hyperkeratosis. Finally, the patient was referred to an ophthalmologist and audiologist for further evaluation.

Discussion

Keratitis-ichthyosis-deafness syndrome is a rare ectodermal dysplasia with about 100 cases in English literature. Most are reported to occur sporadically, although a minority show documented transmission from one generation to the next. The name KID syndrome emphasizes the three principle features of the condition: keratitis, ichthyosis, and deafness. Some authors contend that the cutaneous findings do not represent true ichthyosis, but rather erythrokeratoderma and hyperkeratosis. However they are categorized, typical skin manifestations include symmetric, coalescent plaques of the face and occasionally the knees, elbows, and buttocks, along with palmoplantar keratoderma. The skin may become diffusely thickened, leathery, and xerotic. Ophthalmologic problems develop over time, beginning in childhood with photophobia and blepharitis. Eventually, a vascularizing keratitis with subsequent scarring may obstruct vision. In contrast, hearing deficits are non-progressive and present from birth. Auditory disability is generally profound, affecting both ears. Other distinguishing symptoms include ungual dysplasia, varying degrees of alopecia, and a characteristic facies with perioral furrows that make the patient appear older than the stated age.

Beyond the acronymic triad, patients with KID syndrome are prone to repeated bacterial and fungal infections. No clear immune deficit has been identified in KID syndrome, but defects in chemotaxis and absence of lymphocyte stimulation have been noted. The phenotype of KID syndrome stems from an autosomal-dominant mutation in connexin 26 or connexin 30 genes. These genes code for gap junction proteins that allow for intercellular communication and transportation of small molecules. To date, six heterozygous missense mutations have been identified: p.Asp50Asn, p.Ser17Phe, p.Asp50Tyr, p.Gly45Glu, p.Gly12Arg, and p.Ala88Val. The majority of patients harbor the p.Asp50Asn mutation. Although limited by rarity and scant clinical descriptions in some reports, genotype may relate to prognosis. There is some evidence that the p.Ser17Phe mutation is associated with more severe skin involvement and a fatal squamous-cell carcinoma of the tongue. The p.Gly45Glu and p.Ala88Val mutations may portend poor prognosis, as the patients in whom these were identified died in infancy. Although most cases of KID syndrome arise de novo, approximately 10 percent to 36 percent show a familial inheritance.

Conclusion

KID syndrome is a rare genodermatosis with a devastating constellation of manifestations. Our case affirms that an exuberant fungal infection may be the presenting feature of KID syndrome. Further, it is noted that specific genotyping may render important prognostic information in this case and should be advised as financial resources dictate.

References


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Lupus Pernio: A Case Presentation and Review of Treatment Options

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Abstract

Sarcoidosis is a systemic disease characterized by the formation of non-caseating granulomas in various tissues. Lupus pernio is the most characteristic cutaneous involvement, occurring in 25 percent to 35 percent of patients, and most often is the initial manifestation of the disease. It is a disfiguring sarcoidosis that is difficult to treat, often causing psychosocial effects that may adversely affect the patient’s quality of life. We present the case of a 57-year-old female with biopsy-proven lupus pernio and the various treatment options available.

Introduction

Lupus pernio is the most characteristic cutaneous manifestation of chronic sarcoidosis. It is most commonly seen in black women and is a distinctive feature of chronic fibrotic disease. It presents as an indolent, red-purple or violaceous, indurated skin lesion that most commonly occurs on the nose, cheeks, ears, lips, and forehead. A granulomatous infiltration of the nasal mucosa and bone with ulceration and septal perforation can occur with involvement of the nose in lupus pernio. In addition, lupus pernio is often associated with concomitant involvement of the upper respiratory tract in sarcoidosis. Typically, it is associated with pulmonary fibrosis, chronic uveitis, and bone cysts. Treatment options include the use of steroids, THF-alpha inhibitors, and laser treatments. We present the case of a 57-year-old African American female with lupus pernio, and we discuss several treatment options.

Case Report

A 57-year-old African American female presented to the clinic with several flesh-colored, pedunculated papules and nodules of the bilateral nasal ala (Figure 1). Lesions had been present for four years prior to the initial visit to our office. Biopsy showed naked granuloma, confirming the diagnosis of sarcoidosis (Figure 2). The patient had tried mycophenolate mofetil with a previous physician, which failed to improve her cutaneous symptoms. Methotrexate was also attempted but quickly discontinued, as the patient did not tolerate the side effects. She also had evidence of sinus involvement of sarcoidosis. When she presented she was on prednisone 10 mg daily. In our office, the patient was placed on prednisone 20 mg orally every other day and started on hydroxychloroquine 200 mg twice daily. This combination in conjunction with monthly intralesional triamcinolone injections at 10 mg/cc over 10 months produced favorable results (Figure 3).

Discussion

Sarcoidosis is a multi-organ, granulomatous disease most commonly involving the lungs, lymph nodes, and skin. Cutaneous involvement is present in more than 25% of sarcoidosis cases and is the initial disease manifestation in approximately one-third of patients. The incidence of sarcoidosis varies among different ethnicities, with high prevalence in Sweden and the United States. There is a racial distinction in sarcoidosis incidence in the United States, with Caucasians accounting for 10 to 14 per 100,000 cases and African Americans accounting for 35.5 to 64 per 100,000.1

Lupus pernio (LP) is characterized by chronic, indolent, violaceous and indurated, small papules to large plaques predominantly affecting the nose and cheeks. The lesions can enlarge and become confluent to form nodular plaques on the face.1 LP is the most characteristic skin feature of chronic sarcoidosis and is found in patients with chronic progressive systemic sarcoidosis with both severe pulmonary and extrathoracic involvement.2 LP was named in 1889 by Besnier, who reported an association between reddish-blue lesions of the face and nose and swellings of the fingers.4 It is these fibrotic lesions that typically scar and distort facial structures. In addition, the lesions can involve the upper respiratory tract and cause nasal ulceration and obstruction and perforation of the nasal septum. Some patients have developed plaques on the arms, thighs, and buttocks.1 Lupus pernio plaques can also affect the bones of the fingers and present with cystic bone lesions on radiographic examination.5 The ear lobes can also become infiltrated. In a series of 35 lupus pernio cases by Mana et al. in 1997, intrathoracic involvement was present in 74 percent of patients, sarcoidosis of the upper respiratory tract in 54 percent, bone cysts in 43 percent, and ocular involvement in 37 percent.6

The histological findings of sarcoidosis are the classic non-caseating granulomas with collections of macrophages and epithelioid cells centrally, encircled by lymphocytes. These granulomas are formed by the stimulation of an uncontrolled type 1 helper T-cell immune response triggered by foreign antigens.7 The extrinsic antigen or antigens causing this reaction are thought to originate...
from a persistent infectious organism or agent associated with environmental or occupational exposure.1 Mycobacteria have long been implicated in the etiology of sarcoidosis. Other infectious agents with speculated associations are propionibacterium acne, Epstein Barr virus, and herpes virus.6 Genetic involvement is evident through familial case reports, increased incidence in monozygotic twins, and human leukocyte antigen association.7-10 Granuloma resolution within two years to five years, sans sequelae, is evident in 60 percent of cases.1,11

Cutaneous sarcoidosis is classified into two categories: specific and nonspecific. Specific eruptions indicate the presence of non-caseating granulomas on biopsy, and nonspecific eruptions indicate the development of lesions through a reactive process and not through granuloma formation.11 Specific lesions are more often associated with a chronic disease course, whereas nonspecific lesions are more common with the acute presentation of sarcoidosis.12 Specific lesions include lupus pernio, infiltrated plaques, maculopapular eruptions, subcutaneous nodules, and infiltration of old scars. An example of the most common non-specific skin lesion is erythema nodosum (EN).13 It has been reported that specific lesions develop in 3% to 15% of all sarcoidosis patients. In a case series by Haimovic et al. in 2012, of the 330 patients diagnosed with sarcoidosis, 37 patients (11%) showed the typical sarcoid granulomas on biopsy. Another study by Yanardag et al. in 2003 found that out of 516 sarcoidosis patients diagnosed within a 36-year period, 14 (2.7%) had skin lesions that were pathologically and clinically diagnosed as LP, and of those, nine patients (63.4%) were identified as having pulmonary involvement.14

**Treatment**

Treatment for cutaneous sarcoidosis is often guided by the extent of disfiguration and symptomatic disease, and is limited by comorbidities that increase the risk of drug toxicity. LP is often recalcitrant to most therapeutic modalities and may be an indicator of current or impending systemic involvement.15 Topical or intralesional corticosteroids are the first-line therapy for localized and mild disease limited to the skin.

Oral corticosteroids are the drug of choice for rapidly progressive or unresponsive lesions.16 Corticosteroid-sparing agents are often added to the oral corticosteroid taper, as it is believed they accelerate the taper without recurrence of disease. It is generally accepted that these agents are indicated in patients requiring 10 mg of prednisone daily.17 The treatment options include: methotrexate, hydroxychloroquine, chloroquine, tetracyclines, and TNF alpha inhibitors such as infliximab and adalimumab.18 Methotrexate has been used successfully in the treatment of sarcoidosis, showing a response rate of greater than 80 percent.19 One clinical trial of 15 patients showed clinical resolution in 12 patients at a dose of 25 mg of methotrexate weekly.16 Hydroxychloroquine or chloroquine has been used successfully in the treatment of sarcoidosis as monotherapy. In one literature review, 57 of 78 patients showed improvement of skin lesions with hydroxychloroquine or chloroquine alone.17

Tumor necrosis factor-alpha inhibitors such as infliximab and adalimumab have been shown to be beneficial in recalcitrant, disfiguring lupus pernio.1 A retrospective study by Suga et al. in 2009 showed improvement in 54 patients treated in a sarcoidosis clinic for lupus pernio and found that drug regimens containing infliximab were superior to corticosteroids plus non-corticosteroids, corticosteroids alone, and non-corticosteroids in achieving resolution of disease.18 The results also showed that systemic corticosteroids are effective in improving, but rarely resolving, lupus pernio lesions. More than 70 percent of the patients on infliximab had improvement of their lupus pernio, and 25 percent had resolution or near-resolution. This is compared to a 29-percent improvement seen in patients on the corticosteroids plus non-corticosteroid regimen.18 Treatment with an anti-TNF-a antibody such as infliximab was recommended as second-line therapy for corticosteroid-unresponsive lupus pernio. In cases of an allergy to infliximab, adalimumab can be used. In one case report by Judson in 2011 involving a 37-year-old African American woman with a history of lupus pernio, an infusion of 5 mg/kg infliximab caused a severe allergic reaction. The patient was subsequently treated with subcutaneous adalimumab at 40 mg per week. The cutaneous lesions improved noticeably after one month of therapy, and after nine months they had resolved with post-inflammatory hyperpigmentation remaining.20

Thalidomide has also been tried as a treatment for lupus pernio. It was administered in an open-label trial to 15 patients with lupus pernio and systemic sarcoidosis in doses ranging from 50 mg to 200 mg daily. Fourteen patients showed improvement of their cutaneous lesions. In another case series, the biopsy specimens of eight patients treated with thalidomide revealed a reduction in the size of granulomas and in epidermal thickness. However, because of its teratogenicity and high risk of peripheral neuropathy, this study recommended that other agents be evaluated as first-line treatment.1 Mycophenolate mofetil was reported to improve cutaneous symptoms in five patients with systemic and cutaneous sarcoidosis whose conditions were recalcitrant to other treatment modalities.20

Laser therapy has also been used in a handful of patients with moderate success. The first type of laser used to treat lupus pernio was the flashlamp pulsed dye laser in 1992, which produced good results although relapses occurred after six to 10 months.19 The VersaPulse system (532 nm) was used for the first time in 2005 with significant clearance of erythema and a three-year remission seen in patients.21 A carbon dioxide laser was also used on three patients by O’Donoghue and Barlow, but relapse occurred at nine and 14 months.22

**Conclusion**

Lupus pernio is the most characteristic skin feature of chronic sarcoidosis and a more frequent skin lesion in middle-aged females, advanced-stage patients, and patients with extrapulmonary involvement. In most patients, LP will be the initial presenting sign of sarcoidosis. Corticosteroids remain the mainstay of therapy, although many other treatments have been found effective. Given the lack of level 1 evidence, therapy remains at the discretion of the dermatologist based on clinical experience. Infliximab appears superior to systemic corticosteroids with or without additional agents for the treatment of lupus pernio. In cases of an allergic reaction to infliximab, adalimumab can be used.

**References**


Cutaneous Rosai-Dorfman Disease: A Case Report and Review

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Abstract
Rosai-Dorfman disease (RDD) is a rare, benign, proliferative disorder of histiocytes in the lymph nodes that may have extranodal involvement. RDD limited to the skin without nodal involvement, known as cutaneous Rosai-Dorfman disease, is even rarer. We describe a 29-year-old male with RDD of the skin over the abdomen. Histopathology showed many large histiocytes (Rosai-Dorfman cells) exhibiting emperipolesis, among many plasma cells, lymphocytes and neutrophils throughout the dermis and subcutaneous tissue. The histiocytes were immunohistochemically positive for S-100 protein but negative for CD1a. Physical examination showed no lymphadenopathy or any extra-cutaneous lesions. The diagnosis of cutaneous RDD may be difficult in the absence of associated lymphadenopathy. Hence, not only is histopathological examination required for definitive diagnosis, but a high index of suspicion is essential to help diagnose this very rare disease.

Introduction
Sinus histiocytosis with massive lymphadenopathy (SHML) was first described by Destombes in 1965.1 However, it was introduced by Rosai and Dorfman in 1969 as a well-defined clinicopathologic entity that is now widely known as Rosai-Dorfman disease (RDD).2 RDD is a rare, non-malignant, histiocytic proliferative disorder that typically presents in male children and young adults.3 Classic presentation includes painless, bilateral lymphadenopathy, fever, leukocytosis, elevated sedimentation rate, and polyclonal hyper-gammaglobulinemia.1 Forty percent of patients have extranodal involvement, most commonly presenting on the skin.1 RDD without lymph-node involvement that is limited to the skin is called cutaneous Rosai Dorfman disease (C-RDD). The etiology of RDD is uncertain but may be immune-mediated.4 Associations with HHV6 and parvovirus B19 have been found.5,6 The disease typically runs a self-limiting course, and only a small number of patients will have extensive systemic disease that leads to death.4

Case Report
A 29-year-old Caucasian male presented to the clinic with a persistent rash. He had several lesions on his trunk, present for months, without any associated symptoms. The lesions were erythematous, oval papules, 3 mm to 4 mm in diameter, scattered on the trunk (Figure 1). Multiple biopsies revealed a perivascular and interstitial infiltrate throughout the dermis, composed of plump cells with ample, somewhat foamy cytoplasm (Figures 2a, 2b). Significant

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Figure 1. Erythematous, scattered annular papules.

Figure 2a. Monomorphic proliferation of large histiocytes exhibiting inflammatory cells within their cytoplasm.

Figure 2b. 400x magnification
Discussion

The first report of C-RDD was in 1978 by Thawerani et al. The gross presentation of the skin lesions in C-RDD and RDD are the same. C-RDD is not associated with any other symptoms or abnormal lab values and is more commonly seen in adults and females. Skin lesions may be solitary or multiple and range from papulonodular (79.5%), indurated plaque (12.8%), and tumor (7.7%), with the extremities most frequently involved. The characteristic histiocyte, the “Rosai-Dorfman cell” (RD cell), is the diagnostic hallmark for RDD. It is histologically recognized by abundant amorphous cytoplasm, indistinct borders, and a large, vesicular nucleus with prominent nucleoli. Phenotypically, RD cells uniquely express monocyte/macrophage markers such as lysozyme, Mac-387 and CD68, as well as the dendritic/Langerhans cell marker CD1a, which confirms the diagnosis.

C-RDD has a good prognosis and tends to resolve over months to years. Cutaneous lesions do not require treatment, but surgical excision may be indicated for cosmetic reasons or symptomatic relief. Cutaneous lesions have also responded to radiotherapy and thalidomide. Other treatment methods that have been used include radiotherapy, cryotherapy, chemotherapy, isotretinoin, hydroxychloroquine, and dapsone.

**References**


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Abstract

Punctate porokeratotic keratoderma is a rare dermatologic condition characterized by numerous pinpoint projections on the palms and soles. Although the cause is unknown, sporadic cases have been associated with dyslipidemia, renal cysts, chronic renal failure, myelofibrosis, spondylolisthesis and asthma. Of most concern, this condition has been reported in association with malignancy, not necessarily running parallel courses. We report a case of punctate porokeratotic keratoderma in a patient with uncontrolled hyperlipidemia and a history of endometrial cancer. Our case presentation promotes awareness of a rare dermatologic condition and supports the need to perform age-related cancer screenings upon diagnosis. Multiple treatment modalities have been reported in the past, such as topical urea, salicylic acid, retinoids and 5-fluorouracil, with variable efficacy. We report successful treatment with imiquimod cream and propose it as a new treatment modality.

Introduction

Punctate porokeratotic keratoderma is an uncommon disorder. It presents as numerous pinpoint projections resembling the spines of an old-fashioned music box cylinder, appearing on the palms and soles.1-3 In 1971, Brown reported the first case of a keratoderma marked by numerous tiny spicules on the palmoplantar surfaces.4 The condition has since been described in the literature under the names filiform hyperkeratosis, minute digitate hyperkeratosis, punctate keratoderma, porokeratosis punctata palmaris et plantaris, and spiny keratoderma.5-7 The disorder has been reported in all races, with the age of onset ranging from 12 to 50 years.8 Woods light examination may be a helpful diagnostic tool, revealing a white fluorescence likened to stars under the moonlight.9 Although most cases are sporadic, inherited forms have been described. The exact etiology is unknown, but there have been cases associated with systemic disease. Of most concern, this condition has been linked to malignancy. We report a case of punctate porokeratotic keratoderma in a patient with uncontrolled hyperlipidemia and a history of endometrial cancer.

Case Presentation

A 48-year-old white female presented to the office complaining of rough palms with asymptomatic, tiny bumps for about four months duration. She had never been treated by a physician for this condition but admitted to using nail files and pumice stones to file the bumps down, only for them to return in a matter of days. She reported a past medical history of endometrial cancer treated by hysterectomy and bilateral salpingo-oophorectomy 16 months prior. She also had a course of radiation, which was completed one year prior. In addition, the patient reported a history of hyperlipidemia, which worsened just before the onset of the lesions and caused her primary care doctor to increase her simvastatin dose.

Physical exam revealed multiple 1 mm, flesh-colored, spine-like hyperkeratotic papules on the palms and soles (Figures 1 and 2). Shave biopsy revealed cornoid lamellae, consistent with a diagnosis of punctate porokeratotic keratoderma (Figure 3). She was treated with imiquimod 5% cream nightly, and her condition was nearly resolved at two-week follow-up, considered to be 90% better by both patient and physician. The patient had a few scattered spiny papules remaining, so we added a salicylic acid plus urea compounded cream in the morning. The combination of this compound once daily and the imiquimod cream once daily maintained patient satisfaction without adverse effects at three-month follow-up.

Discussion

Differential Diagnosis

There are several skin conditions that clinically resemble punctate porokeratotic keratoderma. Many keratodermas are associated with systemic syndromes and can be differentiated by the presence of other classic physical findings. If the etiology is still uncertain, a skin biopsy is indicated. The lesions of multiple filiform verrucae are similar in appearance to punctate porokeratotic keratoderma but are usually seen on the face around the lips, nares or eyelids. Acrokeratoelastoidosis lichenoides are 1 mm to 4 mm, round-to-oval, sometimes umbilicated papules on the borders of hands, feet and wrists, and they can become confluent. These lesions may be associated with Cowden’s disease or Darier’s disease. Palmar keratoses may also be seen in Cowden’s syndrome. Neviod basal cell carcinoma is associated with palmar pits but not spiny lesions. Arsenical keratoses are round, verrucous or acuminate. It is important to inquire about history of arsenic exposure via drinking water or occupation. Clinicians should be aware of the risk of these lesions progressing to SCC. Punctate keratoses of the palmar creases are 1 mm to 5 mm depressions confined to flexural creases and are commonly seen in patients of Afro-Caribbean descent. These lesions are benign but can sometimes cause discomfort.5

Associated Conditions

Punctate porokeratotic keratoderma has been
reported in association with various neoplasms such as bronchial carcinoma, renal cancer, rectal carcinoma, esophageal carcinoma, chronic lymphocytic leukemia, breast cancer, melanoma and ovarian carcinoma.1,10-11 Most studies report that spiny keratodermat arises just before the internal malignancy is diagnosed. However, one researcher reported a 30-year discrepancy between the onset of spiny keratodermad and diagnosis of a lymphoproliferative disorder. This shows that the dermatosis and the underlying malignancy do not necessarily run parallel courses and leads us to wonder whether the lesions can manifest after the eradication of a cancer. Our patient was treated for endometrial cancer with surgery and radiation, which completed one year prior to the onset of the palm and sole lesions. She has maintained close follow-up with her oncologist, who reports no recurrence. She is also up to date on all of her age-appropriate cancer screenings, including colonoscopy and mammography.

Punctate porokeratotic keratoderma has also been linked with several other systemic diseases, including hyperlipidemia, and our patient reported a spike in her cholesterol levels that prompted her primary medical doctor to increase the dose of her statin medication. The lesions appeared two weeks after this increased dose, so the patient had initially viewed the lesions as a type of medication reaction. From what we have learned in previous studies, it is more likely that the worsening hyperlipidemia contributed to the onset of the keratoderma. Data to explain the pathophysiology behind an underlying neoplasm or systemic disease leading to the development of PPK is currently lacking. Further studies are warranted to help make this connection and classify the timing of the two events. Multiple treatment modalities have been reported to improve cosmesis. However, it is most important to emphasize age-related cancer screenings upon diagnosis. In the past, topical urea, salicylic acid, retinoids and 5-fluorouracil have shown variable efficacy. To our knowledge, we are the first to report imiquimod 5% cream as a successful treatment modality.

Conclusion
We have described an interesting case of punctate porokeratotic keratoderma of the palms and soles. The etiology of these lesions in our patient may be idiopathic or related to one of her underlying medical problems. The association between punctate porokeratotic keratoderma and internal malignancy has been well documented in the literature. Most studies describe the onset of the spiny lesions just before the diagnosis of internal malignancy; however, one case described a patient with punctate porokeratotic keratoderma for 30 years prior to diagnosis of a lymphoproliferative disorder. This shows that the dermatosis and the underlying malignancy do not necessarily run parallel courses and leads us to wonder whether the lesions can manifest after the eradication of a cancer. Our patient was treated for endometrial cancer with surgery and radiation, which completed one year prior to the onset of the palm and sole lesions. She has maintained close follow-up with her oncologist, who reports no recurrence. She is also up to date on all of her age-appropriate cancer screenings, including colonoscopy and mammography.

Histopathology
Histopathology typically reveals lack of granular layer and enhanced epidermal proliferation of the basal layer under columnar parakeratoses.1,2 The spines seen on clinical presentation correspond to parakeratotic columns, located over the eccrine ducts, follicles, or interadnexal epidermis.1 The lesions have been shown to stain with AE13, an immunohistochemical stain for a hair-type keratin, suggesting ectopic hair formation.5

Treatment
Spiny keratoderma is difficult to manage, with available treatment options showing minimal success. The spines tend to be a nuisance, and patients often seek treatment for cosmetic reasons. Reported management involves various modalities such as paring, dermabrasion and mechanical debridement. Topical therapies such as urea, salicylic acid and retinoids have also been reported as successful treatment options. Recently, 5-fluorouracil has been reported to alleviate symptoms. Besides aesthetic treatments, of more importance is the awareness of a possible underlying malignancy. A thorough history and physical and age-appropriate cancer screenings are essential to early detection of associated disease.6

References

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Multiple Eruptive Dermatofibromas Following Immunosuppressive Therapy in a Patient with Systemic Lupus Erythematosus

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Abstract

Dermatofibromas (DF) are common, benign dermal tumors typically occurring as single lesions located on the lower extremities of young women.1 In contrast, multiple eruptive dermatofibromas (MEDF) are rare and commonly associated with autoimmune diseases and immunosuppressive therapy.2 We present a case of a patient with systemic lupus erythematosus (SLE) and MEDF of her lower extremities. Our patient demonstrated a significant increase in dermatofibromas with corticosteroid treatment, supporting the association between MEDF and immunosuppressive therapy.

Report of a Case

A 53-year-old woman initially presented to our clinic with a history of numerous, pruritic lesions covering her body, the majority of which involved her lower extremities. The patient was first diagnosed with SLE in 1977. At that time, she was started on oral corticosteroids, and has received continuous corticosteroid therapy ever since. In 1994, she experienced an initial episode of MEDF, with an eruption of approximately 30 lesions. Fifteen years later, she developed end-stage renal disease, requiring a kidney transplantation. Her subsequent immunosuppressive regimen consisted of a significantly increased prednisone dose, as well as initiation of tacrolimus 0.5 mg twice daily. In 2010, following organ transplantation and an alteration of daily medications, the patient experienced a second episode of MEDF, this time with roughly 90 lesions. Family history was significant for scleroderma, but not MEDF. No significant social history was reported, and her only drug allergy was to penicillin. Her medicines included long-term use of systemic corticosteroids. Physical examination revealed 90 non-tender, brown papules ranging from 3 mm to 8 mm (Figures 1 and 2). The lesions demonstrated the characteristic dermatofibroma “dimple sign.”

Punch biopsy of two upper-extremity lesions revealed epidermal hyperplasia and basal-cell-layer hyperpigmentation overlying a spindle-cell arrangement of fibroblasts and histiocytes, with associated thickened collagen bundles (Figures 3 [40x] and 4 [100x]).

The results of the pathologic and clinical examinations supported a diagnosis of MEDF.

Discussion

Solitary dermatofibromas (or superficial, benign, fibrous histiocytomas) are common skin tumors that usually develop on the lower extremities and are frequently asymptomatic, although there have been reports of pruritus as a symptom.3 Dermatofibromas affect females more commonly than males, at a ratio of 4:1.4 The mean age of onset is typically in young adulthood. Classically, dermatofibromas are solitary, flesh-colored-to-brown, 0.5 cm to 1 cm, firm nodules.5 A useful clinical sign for diagnosis is the tethering of the overlying epidermis to the underlying lesion with lateral compression, known as the “dimple sign.”6 Some dermatofibromas arise as a reactive process after insult to the skin, such as trauma or arthropod assault, while others appear spontaneously.6

In contrast to the classic, solitary dermatofibroma, multiple dermatofibromas (MDF) are rare. This infrequency was first described by Baraf and Shapiro in 1970 when they noted patients with three or more dermatofibromas as occasionally observed but those with more than 15 dermatofibromas (MDF) as rarely observed.7 The definition of multiple eruptive dermatofibromas (MEDF) is subjective but has been acknowledged as the presence of five to eight dermatofibromas developing in a period of less than four months.8 The literature has shown that the onset of MEDF is usually in conjunction with an underlying immunosuppressive disease and/
or immunosuppressive therapy. MEDF can be associated with SLE, human immunodeficiency virus, myasthenia gravis and Hashimoto’s thyroiditis, implicating the condition as a manifestation of immune-mediated disease.9

The pathogenesis of MEDF is not fully understood. The serum of SLE patients expresses a greater-than-normal growth-stimulatory activity on both normal and derived fibroblasts. The serum from SLE patients with MDF has been found to contain basic fibroblast growth factor (bFGF) as well as antiplatelet-derived growth factor (PDGF), which stimulates fibroblast proliferation.10 One postulation is that the growth effects are inhibited by antibodies to antiplatelet-derived growth factor and basic fibroblast growth factor.11

Some patients with immune-mediated diseases developed MEDF after intake of immunosuppressive drugs or after an increase in the dose of immunosuppressive medication. Our patient’s number of DF increased from 30 to 40 lesions to 90 lesions after taking an increased dose of corticosteroids. It is proposed that immunosuppressants impede the function of down-regulatory T-cells, causing an immunologic upregulation.12

Treatment of DF is not obligatory, as they are solely treated for cosmetics. The lesions may be shaved with a surgical blade or completely excised. Cryosurgery may instead be employed to eliminate unwanted dyspigmentation.12

Conclusion

Solitary dermatofibromas represent a benign reactive process due to various insults to the skin. They are commonly encountered in the clinical setting and do not require treatment. Multiple eruptive dermatofibromas, however, are rare occurrences that are strongly associated with both autoimmune disease and immunosuppressive therapy. Our patient demonstrated both of these associations, as she had systemic lupus erythematosus and developed MEDF after starting oral corticosteroid therapy.

References


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Abstract
Darier’s disease is an autosomal-dominant disorder caused by a mutation on the ATP2A2 gene, which encodes a calcium pump. We present a case of an 81-year-old Caucasian female who presented to the clinic complaining of a blistering rash that was described as both itchy and painful. The pathogenesis, histology and clinical manifestations of Darier’s disease are reviewed. We also discuss some of the treatment modalities available and the challenge of managing a genetic disease.

Introduction
Darier’s disease, also known as Darier-White disease or keratosis follicularis, was independently identified in 1889 by both Jean Darier of Hospital Saint-Louis in Paris and James White of Harvard University.1 It is an autosomal-dominant disorder altering the ATP2A2 gene, which encodes for a calcium pump. Patients often present with greasy, yellow-brown, hyperkeratotic lesions in the seborrheic areas with accompanying nail changes. Due to the chronicity of the disease, diagnosis and treatment can sometimes be challenging. We present a case of an 81-year-old Caucasian female with an extensive history of an unremitting rash that was still symptomatic despite prior treatment. A punch-biopsy revealed Darier’s disease, and the patient was subsequently treated with clobetasol 0.05% cream, amlactin 12% cream, and amoxicillin.

Case Report
An 81-year-old Caucasian female presented to our office with a rash located on her trunk that had been present since childhood and had waxed and waned for several years. At presentation, she described her rash as blistering, burning, itchy and painful. The patient was currently being treated with topical econazole, hydrocortisone and triamcinolone creams. The patient mentioned that her two sons also have the same rash. Her past medical and surgical history included hypertension, hypercholesterolemia, and hysterectomy secondary to uterine cancer.

Physical exam revealed palmar hyperkeratotic pits and yellowish-to-brown, greasy papules that coalesced into erythematous plaques along the abdomen, trunk and inframammary creases (Figures 1 and 2). Additionally, some of her plaques were impetiginized. Her nails were dystrophic with V-nicking and longitudinal red bands (Figures 3 and 4).

Two 3 mm punch biopsies were performed from the abdomen and sent for routine H&E and direct immunofluorescence. The differential diagnoses included pemphigus, Darier’s disease and Grover’s disease. Final histological diagnosis demonstrated acantholysis in the lower epidermis as well as the presence of corps ronds and grains (Figure 5). No specific immunoreactants (IgM, IgG, IgA, C3, fibrin and albumin) were detected. Based on the history, clinical appearance and histologic findings, a diagnosis of Darier’s disease was made.

The patient was first instructed to discontinue the current antifungal and low-mid potency corticosteroid creams since she had minimal response to this treatment. After a thorough discussion with our patient regarding treatment options, she refused to take any oral medication such as acitretin or isotretinoin given their side-effect profiles. To better control her symptoms while simultaneously avoiding systemic agents, she was switched to clobetasol 0.05% cream twice daily with lactic-acid 12% cream applied nightly to the affected areas. Additionally, the patient was given amoxicillin 500 mg tablets twice daily for 15 days for secondary infection.

On follow-up at two weeks, our patient tolerated the amoxicillin, clobetasol 0.05% and lactic-acid 12% creams very well and became asymptomatic. Her impetiginized lesions cleared, and post-inflammatory erythema was noted (Figure 6). She was instructed to continue the lactic-acid 12% cream daily but to stop the clobetasol 0.05% cream to minimize adverse side effects. She was then advised to use triamcinolone 0.1% cream when her lesions flared up again. At the three-month follow-up visit, the patient continued to be asymptomatic, and her erythema was clearing.

Discussion
Darier’s disease, an autosomal-dominant genetic condition, is linked to a mutation in the ATP2A2 gene on 12q23-24 encoding for the sarco/endoplasmic reticulum Ca2+ ATPase (SERCA2), which normally acts as a pump to maintain a low calcium level in the cytoplasm.2 The mutation causes distortions in the proteins responsible for normal cell-to-cell-adhesion, resulting in desmosome breakdown. This ultimately causes acantholysis while also promoting caspase-driven apoptosis and dyskeratosis.3 Darier’s disease has complete inheritance with variable expressivity, and thus rarely skips generations. Affecting
infection, sunshine or friction. Patients often required for oral involvement. Often asymptomatic, treatment is usually not as fine, granular-to-coarse, “pebbly” textured. Prevalence of oral involvement ranges from 15 percent to 50 percent, and the palate may appear V-shaped notches are pathognomonic, the disease. Red and white longitudinal banding white nail changes are often evident upon masses. Palmoplantar papules with red and occasionally appear as malodorous fungating macules are also common, while intertriginous (scalp, face, trunk, and neck). Hypomelanotic keratotic papules involving the seborrheic areas. Onset usually begins during puberty, most males and females equally, this condition has a prevalence of 1 in 100,000 in Scandinavia, 1 in 55,000 in central England, and 1 in 36,000 in northeast England. The histopathological hallmark of Darier’s disease is suprabasal acantholytic dyskeratosis with an overlying hyperkeratosis. Dyskeratosis is apparent in two types of cells, “corps rods” and “grains.” Corps rods are abnormal keratinocytes found in the stratum spinosum and stratum granulosum with a pale halo surrounding the eosinophilic nucleus. Grains are flat, basophilic cells found in the stratum corneum with cigar-shaped nuclei.

Onset usually begins during puberty, most frequently appearing as greasy, yellow-brown, keratotic papules involving the seborrheic areas (scalp, face, trunk, and neck). Hypomelanotic macules are also common, while intertriginous lesions (groin, axillae and submammary fold) occasionally appear as malodorous fungating masses. Palmoplantar papules with red and white nail changes are often evident upon inspection. Nail involvement is characteristic of the disease. Red and white longitudinal banding and V-shaped notches are pathognomonic, while subungual hyperkeratosis is also evident. Prevalence of oral involvement ranges from 15 percent to 50 percent, and the palate may appear as fine, granular-to-coarse, “pebbly” textured. Often asymptomatic, treatment is usually not required for oral involvement.

Darier’s disease is a chronic condition with frequent exacerbations precipitated by heat, sweat, infection, sunshine or friction. Patients often complain of moderate itching, malodorous skin, and concerns over their appearance. Secondary infection with bacteria, yeast or dermatophytes is a possible complication to the primary lesions. Staphylococcus aureus and herpes simplex are particularly common in patients with Darier’s disease. Other less frequent complications include salivary gland obstruction, parotid swelling secondary to hyperplasia, mental retardation, epilepsy, schizo-affective disease, depression leading to suicide, and cutaneous squamous cell carcinoma. Additionally, there are several clinical variants of Darier’s disease including vesiculobullous, cornifying, comedonal, acral, hemorrhagic and linear.

Diagnosis is made by a combination of clinical suspicion and histological examination of a skin biopsy. A differential diagnosis includes acrokeratosis verruciformis of Hopf, Hailey-Hailey disease, seborrheic dermatitis, and Grover disease. Acrokeratosis verruciformis of Hopf is an autosomal-dominant disease presenting at birth with clinically indistinguishable involvement of the hands and feet compared to Darier’s disease. Some clinicians even consider this to be an extension of Darier’s disease rather than a separate entity. Differentiating the two diseases is the lack of acantholytic and dyskeratotic keratinocytes seen with acrokeratosis verruciformis. Hailey-Hailey disease also affects the intertriginous areas but frequently lacks the nail changes. Seborrheic dermatitis and Grover disease both lack the palmoplantar and mucosal changes seen in Darier’s disease, and also appear different histologically.

Since Darier’s disease is a genetic condition, there is no cure. The overall goals are to improve quality of life through symptomatic management and minimize secondary infections. Treatment guidelines include minimizing sun exposure and sweating with appropriate sunscreen and cotton clothing. Patients on lithium should consider altering medications, as the drug is known to exacerbate Darier’s disease. Keratolytic moisturizers are recommended to reduce scaling and improve appearance, while antiseptic washes decrease malodorous skin bacteria. Topical options include corticosteroids (class four to six) to decrease inflammation as well as retinoids such as tretinoin 0.1%, adapalene 0.1%, and tazarotene 0.05% to reduce hyperkeratosis. Alternating these topical treatments is common to help alleviate irritation. Second-line topical therapies include 5-fluorouracil, tacrolimus, and pimecrolimus. Oral retinoids such as isotretinoin and acitretin are the treatment of choice for generalized disease and instances refractory to topical therapy. However, oral retinoids typically do not result in prolonged remission, so long-term treatment with these agents is often required to prevent relapse. Therapy should be continued for at least three months to achieve reduction in malodor, decrease hyperkeratosis, and smooth papules. However, significant adverse side effects are possible and can include mucosal dryness, photosensitivity, hair loss, hyperlipidemia, elevated liver transaminases, and depression. As a result, baseline lipid and enzyme levels should be taken and periodically monitored throughout treatment. The decision whether to use isotretinoin vs. acitretin depends upon multiple factors such as length of treatment, age of patient, and gender. For instance, both acitretin and isotretinoin are teratogenic, pregnancy category X. For women of childbearing age with Darier’s disease, isotretinoin may be a more attractive option since iPledge helps regulate the medication, and patients only need to avoid pregnancy for one month after discontinuation as opposed to three years with acitretin.

Additionally, Kontochristopoulos et al. report that botulinum toxin type A is a possible adjuvant treatment to acitretin for challenging patients who remain symptomatic despite therapy. Their patient was treated with a single injection of botulinum toxin to the left inframammary area and showed significant improvement for four months, at which point injections were done bilaterally. Cyclosporine has also been used to treat rebound or flared disease states. Skin improvement is evident in 90% of cases, most noticeably with reduced hyperkeratosis and flattening of papules. Patients should be aware of the adverse effects of oral retinoids, which include: teratogenic effects if taken during pregnancy, cheilitis, mucosal and skin xerosis, elevated transaminases, hypercholesterolemia, and photosensitivity. In the case of recalcitrant lesions in flexural areas, surgical excision, debridement, or laser removal are treatment considerations. Topical antibiotics, antifungals, and chlorhexidine washes are used concomitantly to manage secondary infections. Patients with Darier’s disease can expect a normal life expectancy. However, due to the chronic nature of this disease, relapses occur frequently when treatment is discontinued. Lifelong treatment is usually necessary to prevent these relapses.

Conclusion
Darier’s disease is an intriguing dermatologic condition due to its genetic basis and characteristic findings on exam. The disorder can be diagnosed based upon its unique clinical presentation and classic histological findings. The chronicity of the disorder can present challenges in long-term treatment. After confirmation of the diagnosis, our patient was being treated effectively and reported significant improvement of her symptoms.
References

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Abstract
Erythrodermic psoriasis is a rare clinical phenotype of psoriasis. The condition is characterized by generalized erythema and scaling covering the majority of the body surface. The diagnosis of erythrodermic psoriasis is primarily through clinical presentation while excluding other etiologies of erythroderma. Treatment is often difficult due to the combination of cutaneous and systemic symptoms that contribute to an increased risk for morbidity and mortality. Current treatment requires the use of systemic agents, but the specific regimen is based on the patient’s level of clinical severity and comorbidities. We present the case of a 31-year-old male diagnosed with erythrodermic psoriasis and review the current literature on the disease. The clinical findings, differential diagnosis, and treatment options will be discussed.

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Introduction
Erythrodermic psoriasis is the most severe variant of psoriasis, and it is often challenging to treat. Of the 2 percent of the world population affected by psoriasis, the erythrodermic subtype is estimated to affect only 1 percent to 2.25 percent.1,2 It most commonly arises in a patient experiencing an extensive exacerbation of plaque psoriasis but can occur during periods of psoriatic inactivity. Other etiologies of erythroderma should be considered and excluded when diagnosing a patient with erythrodermic psoriasis. Currently, first-line treatment requires systemic therapies, including the conventional medications methotrexate, cyclosporine, and acitretin, or biological therapies targeting specific pathogenic mechanisms of psoriasis. Identification and prompt treatment of erythrodermic psoriasis is necessary due to the risk of severe complications. We report the case of a 31-year-old male with a history of plaque psoriasis presenting with diffuse erythroderma after abrupt discontinuation of acitretin.

Case Report
A 31-year-old Caucasian male presented with generalized scaling erythema covering greater than 90 percent of his body following abrupt discontinuation of acitretin. The patient’s past medical history included plaque psoriasis. Two months prior, he was treated for an acute exacerbation of severe plaque psoriasis triggered by tanning-bed use. At that time, he was treated with a medium-potency topical steroid for his face and groin psoriasis and a high-potency topical steroid for the remaining body psoriasis. For increased efficacy, he was advised to wrap affected areas in wet towels for ten minutes per day for one week. At the patient’s four-day follow-up visit, acitretin 10 mg was started due to persistence of generalized erythema, mild chills, and palmoplantar desquamation. One month

Figure 1. (A and B) Thin, confluent, scaling erythematous plaques covering >95% of patient’s body.
follow-up showed the patient doing remarkably well on a combination of acitretin and topical steroids. Considerable improvement of his systemic symptoms and extent of scaling was noted on exam. An attempt was made to increase the patient’s acitretin dosage, but the patient was non-compliant with laboratory requests and then lost to follow-up for several weeks.

The patient returned one month later with acute erythroderma after abruptly discontinuing acitretin early in his treatment course. Review of systems was positive for severe generalized pruritus, mild tenderness to palpation, and stiff, painful joints. On physical examination, the patient's skin was malodorous, diffusely bright red, and warm, with scaling inflammatory patches and plaques covering at least 95 percent of his total body surface area (Figures 1 and 2). Only his cheeks, forehead, lower lip, and genitalia were spared. Significant onychodystrophy and onycholysis to all digits were noted (Figure 3). Lymphadenopathy and joint effusions were absent. The patient was instructed to resume his topical steroid regimen with 10 mg of oral acitretin. In addition, he was placed on an oral antibiotic and an antibacterial wash due to malodorous skin and concern for a secondary bacterial infection. He was then lost to follow-up again. Given the patient's personal history of plaque psoriasis along with classic and significant psoriatic nail and cutaneous findings, erythrodermic psoriasis was diagnosed over other etiologies of erythroderma.

**Discussion**

Erythrodermic psoriasis is a rare and severe morphologic variant of psoriasis, and onset may be acute or gradual. It is characterized by erythema with confluent scaling plaques covering at least 90 percent of a person's total body surface.\(^1,3,4\) Associated signs and symptoms include edema, nail dystrophy, alopecia, pruritus, and/or pain.\(^1\) Systemic manifestations can include fever, chills, fatigue, myalgias, arthralgias, high-output cardiac failure, and increased risk for sepsis from bacterial colonization by cutaneous pathogens.\(^1\)

Erythrodermic psoriasis may develop gradually or acutely during the course of chronic plaque psoriasis, but it may also be the first manifestation of psoriasis, even in children.

**Pathogenesis**

The specific pathogenesis of erythrodermic psoriasis has yet to be determined, although it's likely similar to the underlying pathogenesis of psoriasis. The mechanism for psoriatic keratinocyte proliferation was once thought to be regulated by the keratinocyte itself. However, the current focus in psoriasis pathogenesis has shifted to helper-T (Th) cell subsets and secreted cytokines that are well documented to reside within the epidermis and dermis of lesional skin.\(^5,6\) Th17 cells produce interleukin-22 (IL-22), and its receptor is expressed on epidermal keratinocytes. IL-22 is the strongest cytokine in keratinocyte-proliferative ability and correlates with disease severity.\(^5,6\) Th1 cells release tumor necrosis factor-α (TNF-α) and interferon gamma (IFN-γ), which amplify the inflammatory cascade, acting on keratinocytes. IL-23 is released by TNF-α and is required to maintain Th17 cells. Some of the phenotypic variations of psoriasis, such as vasodilation-induced by inducible nitric-oxide synthase (iNOS) and accumulation of T cells in the epidermis, are thought to be explained by the IFN-γ pathway.\(^5,6\) Erythrodermic psoriasis may occur from the interactions between these immunologic modulators, causing an increase of the epidermal turnover rate while decreasing the time required for cells to mature and travel through the epidermis.\(^6\) This may manifest as increased loss of epidermis, giving the characteristic superficial scaling and exfoliation seen in erythrodermic psoriasis.\(^6\)

**Diagnosis**

The diagnosis of erythrodermic psoriasis is based largely on a thorough history and physical examination at the time of clinical presentation. There is currently no laboratory test to specifically diagnose the disease.\(^6\) Erythrodermic psoriasis classically presents with generalized erythema and confluent scaling plaques and patches encompassing greater than 90 percent of the total body surface area.\(^6,9\) The scaling in erythrodermic psoriasis is thinner, flakier, and more desquamative compared to the thick, silvery, rough scales of chronic plaque psoriasis.\(^9\) Pruritus of varying intensity often accompanies these cutaneous findings.\(^9\) In one clinical study, 78 percent of patients with erythrodermic psoriasis had nail abnormalities ranging from mild pitting to complete dystrophy.\(^9\) Patients who present with nail involvement have a higher propensity for scalp psoriasis and psoriatic arthritis.\(^6,9\)

Erythrodermic psoriasis has been associated with a variety of systemic complications.\(^3,4,12\) Lymphadenopathy and feelings of fatigue are fairly common accompanying symptoms.\(^3,4,9\) Hyperthermia can result from an increased basal metabolic rate and generalized cutaneous vasodilation causing increased blood perfusion and transepithelial water loss.\(^3,9\) Hypothermia can also occur because of excessive heat loss due to the generalized vasodilation, causing patients to experience chills to increase their core body temperature.\(^13\) The vasodilation contributes to loss of fluid, electrolytes, and protein out of capillaries and into the interstitial space. This phenomenon has the potential for development of peripheral edema, hypoalbuminemia, electrolyte imbalance, and high-output cardiac failure due to shunting of blood through inflamed skin.\(^3,4,9\) One study reported the mortality rate directly related to erythrodermic psoriasis to be as high as 15%.\(^1\) Laboratory abnormalities can include elevated erythrocyte sedimentation rate (ESR) or leukocytosis due to the body's increased inflammatory response.\(^3,4,12\) Occasionally, elevated liver transaminases can result from erythroderma.\(^4,12\)

Contrary to typical psoriasis patients, those
with erythrodermic psoriasis appear to be at an increased risk for bacterial colonization and overgrowth, especially by *Staphylococcus aureus*. Typically, patients diagnosed with plaque psoriasis are believed to be at decreased risk for cutaneous infections due to the increased antimicrobial peptides released by Th1/Th17 subclasses. Erythroderma, however, regardless of its underlying etiology, seems to correlate with increased likelihood of *S. aureus* colonization. One case-control study found 100 percent of erythrodermic patients were colonized by *S. aureus* compared to only 60 percent of patients with psoriasis and 88% of patients with atopic dermatitis. This study also suggests the more severe the disease process of psoriasis, the more likely the patient is to be colonized by *S. aureus*. The exact etiology of this difference is unknown. Colonization with *S. aureus* might play a role in the development of erythroderma or propagation of disease possibly from staphylococcal antigens, such as toxic shock syndrome toxin-1 (TSST-1). Erythrodermic patients seem to be at an increased risk for *Staphylococcus aureus* septicemia, possibly as a result of the compromised cutaneous barrier being perpetuated by exotoxins acting as superantigens, allowing *S. aureus* to gain access to systemic circulation through excoriations and fissures. A series of case studies looked at five patients presenting with fever, chills, and erythrodermic psoriasis and found all five also had staphylococcal septicemia.

Even though an astute physician can diagnose erythrodermic psoriasis based on history and physical examination, a skin biopsy can help support the diagnosis. Erythrodermic psoriasis histopathology includes confluent parakeratosis where the keratinocytes of the stratum corneum retain their nuclei, which is seen in scaling of psoriasis. Collection of neutrophils, known as Munro microabscesses, would also be expected within the stratum corneum due to the body’s underlying inflammatory response.

Other etiologies of erythroderma that could present clinically similar to erythrodermic psoriasis include generalized atopic dermatitis, pityriasis rubra pilaris, cutaneous T-cell lymphoma, drug reactions, and a rare presentation of cutaneous mastocytosis (Table 1). Generalized atopic dermatitis can present with lesions of erythema, excoriations, and scaling with associated pruritus. In atopic dermatitis, however, unlike in erythrodermic psoriasis, it is the patient’s habitual scratching of dry, pruritic skin that creates the rash of red scales, papules, and/or lichenification. Pityriasis rubra pilaris generally begins as a small, red-orange, scaling plaque on the face or upper body that expands and progresses into erythroderma with areas of uninvolved skin or “skip spots.” The face, palms and soles are usually covered in thick, tight red scales. Pruritus is not usually associated with pityriasis rubra pilaris, although onycholysis is often present. Cutaneous T-cell lymphoma and the leukemic form, Sézary syndrome, have been associated with a clinical presentation of erythroderma, although lymphomas may not respond to corticosteroid therapy as erythrodermic psoriasis would. Lymphadenopathy is usually present in cutaneous T-cell lymphoma but may or may not be present in erythrodermic psoriasis. A skin biopsy showing atypical lymphocytes would suggest a diagnosis more consistent with a cutaneous T-cell lymphoma. A Sézary-cell/immature-neutrophil count from a blood sample can rule out Sézary syndrome.

Numerous topical and systemic medications have been known to cause erythroderma/exfoliative dermatitis. These include, but are not limited to, antiepileptic medications, antihypertensive...
medications, antibiotics, and calcium-channel blockers.8,21 “Drug-induced rash” should always be considered on a differential diagnosis list if a new medication was started within two weeks of an appearance of a dermatologic condition.21 The most frequent patterns of cutaneous drug-induced rashes are morbilliform, urticarial, and/or generalized pruritus possibly progressing to generalized, exfoliative dermatitis.8,21 A rare variant of cutaneous mastocytosis, erythrodermic diffuse cutaneous mastocytosis should be considered as a cause of generalized erythroderma, especially if seen in a pediatric patient. In contrast to erythrodermic psoriasis, the cutaneous manifestations of erythrodermic mastocytosis have been described as having a doughy consistency and a leathery appearance.22

Another important distinguishing feature of erythrodermic mastocytosis is the tendency to develop pruritic and raised wheals after light stroking to the skin.22 This urticarial reaction is due to the large release of histamine from cutaneous mast-cell invasion, which is believed to be the underlying cause of the diffuse erythroderma seen in erythrodermic mastocytosis.22

Erythrodermic psoriasis usually arises in a patient who is currently experiencing an active exacerbation of extensive plaque psoriasis, although it is possible for it to occur during a period of psoriasis inactivity.2,23 Even plaque psoriasis that is fairly controlled can evolve into erythrodermic psoriasis if treatment is abruptly stopped.2 Other precipitating factors that can trigger erythrodermic psoriasis include abrupt withdrawal of topical ultrapotent or systemic steroids; excessive use of topical steroids; discontinuation of methotrexate; sunburn; systemic illness; emotional stress; or colonization of psoriatic plaques with Staphylococcus aureus.4,23 Traumatic injury to the dermis of a psoriasis patient, such as that produced by a sunburn, can cause plaque psoriasis lesions to develop at the site of injury and even lead to erythroderma.1,4,12

**Treatment**

Erythrodermic psoriasis is a potentially severe disease that requires prompt initiation of treatment upon clinical presentation. The first step in management is to discontinue the use of any potentially offending agents or provocative factors.3 Systemic treatment that focuses on short-term efficacy with a quick onset of action and the significant improvements seen in patients over a short time period.5,21 Ultimately, further research with prospective clinical trials is needed to determine the place of biologics in the treatment of erythrodermic psoriasis.

Regardless of what first-line systemic therapy is chosen, it is generally recommended to initiate adjuvant treatments such as medium-potency topical steroids, calcipotriene/betamethasone, moisturizers, wet dressings, oatmeal baths, and continued supportive care.5 Combination treatments may provide greater efficacy than the use of monotherapy and reduce the incidences of adverse effects as lower doses of each individual agent are used.28 Once the acute erythrodermic episode is well controlled, therapy can focus on medications with long-term efficacy for improving the underlying psoriasis and preventing future episodes of erythrodermic psoriasis.21

**References**


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Iatrogenic Kaposi’s Sarcoma Arising After Renal Transplant Immunosuppression

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Abstract

Kaposi’s sarcoma (KS) is a spindle-shaped, vascular-cell tumor associated with human herpes virus 8 (HHV-8). It most commonly presents as multiple, bilateral, violaceous-to-brown papules, plaques or patches distributed on the lower extremities. Of the four clinically defined types of KS, iatrogenic KS most often occurs in organ transplant recipients who are immunosuppressed after receiving post-transplant chemotherapeutic agents to prevent allograft rejection. We present a case of a 67-year-old, post-renal-transplant Caucasian male with a chief complaint of pruritic, purple plaques on his legs and axillae.

Case Report

History

A 67-year-old Caucasian male presented to the clinic with a chief complaint of lower extremity swelling, pruritus, pain and discoloration of one-month duration. He also complained of dark patches on his right arm and axillae. He had recently visited his podiatrist, an emergency room, and an urgent care over the concern that one of his feet was “turning black.” Laboratory studies, radiographs, and an EKG were all found to be normal. The patient’s past medical history included a renal transplantation in October 2010, and he was maintained on mycophenolate mofetil 1 g PO BID, tacrolimus 3 mg PO BID, and prednisone 10 mg PO daily. Pertinent family medical history included a brother who was deceased due to malignant melanoma found in the axillae.

Examination

Physical examination revealed violaceous papules and plaques over the extensor surfaces of the right upper and lower extremities. In addition, there were violaceous plaques on the bilateral plantar surfaces and 2 mm to 4 mm erythematous macules on the bilateral dorsal feet and anterior lower legs (Figures 1–3). The right lower extremity had pitting edema and pain upon palpation.

Laboratory

An HIV screen was negative.

Histopathology

Punch biopsies of the right upper extremity and right plantar foot were performed, which demonstrated a proliferation of endothelial cells forming bizarre-shaped, thin-walled vessels that followed pre-existing vascular plexuses (Figures 4 and 5). A CD31 stain was performed, highlighting the vascular proliferative changes, and an HHV-8 stain decorated many spindle cells that were associated with the vessels (Figure 6).

Course and Therapy

In light of the histopathology results and with approval of his renal transplant team, mycophenolate mofetil was discontinued, and tacrolimus was maintained at the same dose. The patient began showing regression of his lesions shortly after discontinuing the mycophenolate mofetil. He was also scheduled to initiate treatment with sirolimus.

Discussion

Kaposi’s sarcoma (KS) is an angioproliferative disorder, characterized by a spindle-shaped vascular-cell tumor. It can occur in the skin and visceral tissues and is associated with human herpes virus 8 (HHV-8) infection. There are four clinically defined types of KS, which include the classic form, endemic (African) form, HIV-associated form, and iatrogenic form. Iatrogenic Kaposi’s sarcoma most commonly occurs in organ transplant recipients secondary to post-transplant treatment with chemotherapeutic agents, which are used to suppress the immune system and thus prevent allograft rejection.

The incidence of Kaposi’s sarcoma among solid organ transplant recipients has been found to be 500-fold higher than the general population, and renal transplant patients are 10
to four-fold. The incidence of skin cancer in transplant recipients: Squamous cell cancer has compared to the incidence of other skin cancers study of 820 kidney transplant patients, 13 people after transplantation. This is significant when 20 times more likely to suffer a malignancy to IL-2 production and lymphocytic activation. While mTOR plays a key role in controlling cell growth and division, hyperactivation of its signaling pathway has been implicated in many human cancers, like Kaposi’s sarcoma.

The approach to treating iatrogenic KS involves a complex set of targets including IL-2 production and mTOR inhibition, while maintaining adequate immunosuppression to avoid graft rejection. When this balance can be accomplished, it often leads to spontaneous regression of the KS. Conversely, an increase of immunosuppression can cause recurrence of KS. Immunosuppressive regimens can include a variety of medication combinations. Commonly used medications in renal transplant patients include prednisone, cyclosporine, mycophenolate mofetil, tacrolimus and sirolimus.

Cyclosporine is a calcineurin inhibitor commonly used post-organ transplant to prevent allograft rejection. Cyclosporine binds to cyclophilin to induce inhibition of calcineurin. Similarly, tacrolimus inhibits calcineurin, but by binding to FK-506 binding protein. The complex then exerts its inhibition on calcineurin. Both medications act as immunosuppressants by blocking production of IL-2 via calcineurin inhibition, thus reducing lymphocyte activation and decreasing T-cell-mediated rejection of the transplanted organ. However, the immunosuppressive actions of these drugs pose risks of development of KS in transplant patients by allowing HHV-8 replication, especially in genetically predisposed individuals.

Studies have shown that sirolimus, a rapamycin inhibitor, which acts by inhibiting mTOR, prevents acute graft rejection and blocks cytokine signal transductions. This provides both anti-neoplastic and immunosuppressive effects. It may also restore functional balance of cell growth and reduce HHV-8 activity, leading to both regression of KS in kidney transplant recipients and a decreased risk of malignancy. The immunosuppressant effects of sirolimus are also useful in maintaining an anti-rejection environment on organ allografts. Monotherapy with sirolimus in the treatment of KS may not be adequate when high dosage of immunosuppression is required, in which case other topical or systemic therapies may need to be added.

Many studies compare both individual medications and combination therapies. A 2012 study evaluating sirolimus/tacrolimus vs. mycophenolate mofetil/tacrolimus found the combination of sirolimus/tacrolimus to be better tolerated and overall more effective in renal and pancreatic transplants, resulting in fewer rejections within the first year after transplantation.

Other studies have shown that when compared to cyclosporine, tacrolimus has a significantly lower incidence of acute rejection without an increase in adverse side effects associated with long-term immunosuppression. It has also been shown that tacrolimus results in patients needing less medication to control hyperlipidemia and hypertension, comorbidities which worsen the long-term prognosis of transplant patients. Despite cyclosporine and tacrolimus having similar mechanisms of action, data indicates that they are not equally efficacious and do not have similar adverse-effect profiles in renal transplant patients.

Treatment modalities involving the use of sirolimus in transplant recipients, combination therapies of sirolimus/tacrolimus, as well as potentially effective anti-herpes virus therapies have added new opportunities for preventing Kaposi’s sarcoma in transplant recipients.

**Conclusion**

Iatrogenic Kaposi’s sarcoma most commonly occurs in solid-organ transplant recipients due to post-transplant immunosuppressive treatment with chemotherapeutic agents. HHV-8 is involved in its pathogenesis; the immunosuppressive agents that are used to prevent organ rejection can enhance the virus’s replication. Treatment is aimed at decreasing immunosuppressive medications when possible. In addition, sirolimus may be useful due to its antineoplastic and immunosuppressive properties, reducing HHV-8 activity, which frequently results in improvement
of KS. These broadened treatment modalities have allowed for better treatment of Kaposi’s sarcoma in post-transplant individuals.

References


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Pagetoid Reticulosis (Woringer-Kolopp Disease) in a 43-Year-Old Woman

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Abstract

Pagetoid reticulosis (PR), or Woringer-Kolopp disease (WKD), is a rare variant of mycosis fungoides with a generally benign and indolent course. Woringer-Kolopp disease classically presents as a slowly growing, solitary hyperkeratotic plaque on a distal extremity. Histology shows marked acanthosis and epidermotropic neoplastic cells. The immunophenotypes CD4–/CD8+, CD4+/CD8+, and CD4–/CD8+ have been reported, and all phenotypes carry an excellent prognosis. While mortality has never been reported in Woringer-Kolopp disease, morbidity and disease progression in spite of treatment can occur. Accurate diagnosis requires careful analysis of both clinical and histopathological features. Treatment of choice is radiation therapy, but skin-directed therapies, systemic therapies and surgical excision are also effective options. We present a case of pagetoid reticulosis expressing CD8+ cells in a 43-year-old female, and we review diagnostic features of and current treatment options for this uncommon disease.

Case Report

A 43-year-old woman presented with a lesion on her left heel that she first noticed a few months prior. The lesion was asymptomatic and had slowly grown to its current size and thickness. She denied any other similar lesions present at that time or in the past. No treatments had been attempted prior to presentation. Dermatologic history was significant for malignant melanoma on her right forearm that was successfully removed 25 years earlier. Physical exam showed a 1 cm, sharply demarcated, hyperkeratotic plaque with irregular pigmentation adjacent to the left lateral heel (Figures 1 and 2). Clinical differential diagnosis was broad and included verruca vulgaris, dysplastic nevus, inflammatory dermatosis, pagetoid reticulosis expressing CD8+ cells in a 43-year-old female, and we review diagnostic features of and current treatment options for this uncommon disease.

The histopathological sections revealed acral skin showing an extensive atypical lymphoid infiltrate with extensive epidermotropism by the lymphocytes (Figures 3 and 4). The intraepidermal lymphocytes showed enlarged and hyperchromatic nuclei with extensive intercalation with the basal keratinocytes, focially forming Pautrier-like microabscesses in the stratum malpighii. Immunohistochemical analyses revealed primarily CD8+ T cells, with a background of CD4–highlighted, small, reactive T-lymphocytes (Figures 5 and 6). CD30 was negative. Based on the clinical and histopathologic examination, the diagnosis of pagetoid reticulosis, or Woringer-Kolopp disease, was established. The patient was referred to radiation oncology for treatment. As of this article’s writing, the patient has not returned for follow-up.
Discussion

Pagetoid reticulosis is a rare form of cutaneous T-cell lymphoma (CTCL) defined as a variant of mycosis fungoides characterized by the presence of localized patches or plaques with an intraepidermal proliferation of neoplastic T cells. Classic presentation is of a solitary hyperkeratotic or psoriasiform plaque or plaques on the extremities with a slowly progressing course. Lesions generally start as patches and progress to plaques, but papules, tumors and ulcerating lesions have been reported. Lesions are most commonly on distal extremities but may occur more centrally or even on the perioral region and tongue. Because of its rarity and indolent nature, diagnosis is often delayed for years or decades. Middle-aged men are most commonly affected, but the disease has been reported in patients of all ages, including children only a few months old.

Histopathologic features universally demonstrate a hyperplastic epidermis with an epidermotropic infiltrate of atypical pagetoid cells, singly or in aggregates. As lesions mature, marked hyperkeratosis and acanthosis may occur. Dermal infiltrates contain mostly histiocytes and reactive lymphocytes, but not neoplastic T cells. Atypical cells contain abundant cytoplasm and may have hyperchromatic and cerebriform nuclei. Clonality is frequently seen in WKD, but it may be absent and is not a requisite for the diagnosis.

Differentiating pagetoid reticulosis from other similar diseases requires a combination of careful clinical and microscopic examination to make an accurate diagnosis. Clinically, early mycosis fungoides (MF) and pagetoid reticulosis can be indistinguishable; MF, however, has a propensity for the buttocks, trunk and proximal extremities, while pagetoid reticulosis prefers distal extremities. Immunohistochemistry does not usually aid in an absolute distinction since the majority of cases of pagetoid reticulosis exhibit a preponderance of CD4+ intraepidermal lymphocytes with loss of CD7 and CD62L, which is also the most common immunohistochemical staining pattern with mycosis fungoides and one basis for categorizing pagetoid reticulosis as a histopathological variant of mycosis fungoides. In both diseases, there may be heterogeneity with the immunophenotype, with CD8 variants and co-expression of CD4 and CD8. Epidermotropism is found in both early MF and pagetoid reticulosis. In pagetoid reticulosis, though, as lesions mature, epidermotropism remains, with progression of hyperkeratosis and acanthosis; but as MF lesions mature, they may lose their epidermotropism and diffusely infiltrate the dermis, particularly in the tumor stage. Mycosis fungoides can progress to extracutaneous dissemination, and possibly death, which has never been reported in WKD.

Considering the location of this lesion -- adjacent to the heel -- the differential could also include mycosis fungoides palmaris et plantaris (MFPP), a rare form of MF presenting as slowly growing, thin, acral plaques confined to the palms and soles. MFPP has an indolent course and is often confused with recalcitrant hand dermatitis. Tumor progression and spread of MFPP is usually limited to palms and soles, and maturing lesions do not have the progressive thickening and hyperkeratosis that pagetoid reticulosis lesions can demonstrate. Atypical cells in MFPP also show CD4+ staining, but there have been reports of MFPP lesions expressing primarily CD8+ epidermotropic lymphocytes.

Histologically, MFPP resembles mycosis fungoides. Our case, containing strongly positive CD8+ tumor cells in a verrucous and hyperkeratotic plaque, leads to a diagnosis of PR rather than MFPP.

Ketron-Goodman Disease (KGD) has similar histopathologic findings to pagetoid reticulosis but a markedly different clinical presentation. KGD has widespread, disseminated cutaneous involvement, can have extracutaneous involvement, is more likely to present with ulcerative and eroded lesions, and has a more aggressive clinical course with a guarded prognosis. Because the histopathology and immunophenotypes of Woringer-Kolopp disease and KGD are indistinguishable, they were previously described as localized and disseminated pagetoid reticulosis, respectively. However, because of their drastically different clinical courses, the term "pagetoid reticulosis" should be used exclusively for Woringer-Kolopp disease. One reason for their clinical differences could be related to the complete loss of CD45 in WKD compared to a partial loss in KGD. As CD45 is an important component in lymphocyte growth and transformation, this could explain the relatively benign nature of WKD. There is some controversy regarding the classification of KGD, with some papers suggesting it is a variant of cytotoxic CD8 lymphomas and others a variant of mycosis fungoides. Since nearly all cases of KGD have a more aggressive clinical course compared to WKD, it may be prudent to consider KGD as an epidermotropic variant of mycosis fungoides, distinct from Woringer-Kolopp.

Our patient's stable and benign clinical course is consistent with the diagnosis of WKD, not KGD.

The dermoscopic findings of pagetoid reticulosis, described by Suzuki et al. as a “homogenous pinkish area in the central area of the lesion and a whitish network in the marginal area with dotted and glomerular vessels,” are similar to the pattern found in Bowen’s disease. However, those authors state that pagetoid reticulosis can be differentiated from Bowen’s by the less-prominent glomerular vessels, corresponding to an absence of glomerular vessels in the dermal papillae and papillary dermis.

Initial workup of pagetoid reticulosis should include a complete physical exam including lymph node assessment, complete blood count, a comprehensive metabolic panel, chest X-ray, and flow cytometry to screen for Sezary cells. The clinical differential diagnosis is broad and can include contact dermatitis, psoriasis, atrophic porokeratosis, Bowen’s disease, bacterial infection, fungal infection, verruca vulgaris, and other forms of CTCL. See Table 1 for a more thorough differential diagnosis.

Treatment of choice for PR, especially extensive or refractory cases, is localized radiation therapy. Localized electron beam therapy (EBT) is useful, as radiation is localized to the dermis and epidermis. Studies with MF patients show a near 100 percent response rate to EBT, with full response rates ranging from 40 percent to 98 percent depending on extent of skin involvement. Maintenance PUVA or other localized treatments may be used after EBT as maintenance therapy, but formal recommendations are lacking.

Due to the localized nature of PR, topical strategies are an attractive alternative to radiation therapy, offering patients the convenience of at-home use. Topical hexarenone targets retinoid
Table 1 - Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
<th>Histopathology</th>
</tr>
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<tbody>
<tr>
<td>Dermatitis – Contact/Allergic</td>
<td>Acute vesicular reaction common. Pruritic plaques may become chronic with continued irritation. Inflamed skin thickens, and skin markings become accentuated.</td>
<td>Acute lesions show marked spongiosis and progress to acanthosis in chronic lesions. Perivascular lymphocytes in dermis and epidermis.</td>
</tr>
<tr>
<td>Fungal Infection</td>
<td>Nummular or annular lesion with hyperkeratotic scaling border. Lesions classically have expanding mobile borders. May occur anywhere on the body in any age group.</td>
<td>Fungi noted in stratum corneum with staining. Orthokeratosis is observed with parakeratosis. Spongiosis and perivascular inflammation often present</td>
</tr>
<tr>
<td>Verruca Vulgaris</td>
<td>HPV infection of keratinocytes that produces cylindrical projections and evolve into dome-shaped hyperkeratotic growths. Hands and feet are most common, but may occur anywhere.</td>
<td>Immunoperoxidase staining can confirm HPV capsid antigen. Hyperkeratosis, parakeratosis, and acanthosis present. Vacuolized basophilic and irregular nuclei.</td>
</tr>
<tr>
<td>Porokeratosis (Mibelli)</td>
<td>Autosomal–dominant clonal disorder of keratinization with malignant potential. Annular atrophic and hypopigmented plaque surrounded by hyperkeratotic border known as cornoid lamella.</td>
<td>Hyperkeratosis, acanthosis and parakeratosis present in epidermis. Cornoid lamella lacks a granular cell layer, and central portion displays atrophy.</td>
</tr>
<tr>
<td>Bowen's Disease (squamous cell carcinoma in situ)</td>
<td>Slow-growing, asymptomatic, solitary, erythematous scaly plaque with distinct borders. Lesion may become hyperkeratotic, crusted or ulcerated, and foci of pigmentation may be present. Common in sun-exposed areas and with arsenic exposure.</td>
<td>Atypical keratinocytes and full-thickness anaplasia of epidermis. Acanthosis and hyperkeratosis present. Dermis shows chronic inflammation. Bowen's disease is positive for CK 5/6 and 7.</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
<td>Slow-growing, progressive cutaneous T-cell lymphoma. Lesions typically centrally located patches or plaques. Older adults most commonly affected. Widespread involvement and death possible.</td>
<td>T-cell subtype always CD3+, CD4+, CD7+, and CD8+. CD30 neg. or weakly pos. Proliferation rate (Ki-67) neg. or weakly pos. Epidermotropism may be present in early MF; tumor cells present in dermis and epidermis as disease progresses. Microabscesses with lymphocytes (Pautrier's microabscesses).</td>
</tr>
<tr>
<td>Mycosis Fungoides Palmaris et Plantaris</td>
<td>Rare variant of MF. Presents as palmar or solar plaques, often confused with recalcitrant hand or foot dermatitis. Plaques remain thin but may spread to other acral sites.</td>
<td>Identical to MF. Acanthosis and hyperkeratosis less prominent than in WKD.</td>
</tr>
<tr>
<td>Woringer-Kolopp Disease</td>
<td>Solitary hyperkeratotic or psoriasiform plaque or plaques on the extremities with a slowly progressing course. Plaques may thicken, but advancement is localized. Widespread involvement or death not reported.</td>
<td>T-cell subtypes are variable. CD30 is variable and often exceeds 50%. Proliferation rate (Ki-67) usually more than 30%. Tumor cells restricted to epidermis.</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Chronic inflammatory disease with recurrent, round plaques with distinct borders and thick silvery scale. Lesions may remain for months or years.</td>
<td>Epidermal hyperplasia with test-tube–shaped rete ridges. Prominent dermal papillae with thin overlying skin. Tortuous capillary loops. Microabscesses may be present containing polymorphonuclear leukocytes (microabscesses of Munro).</td>
</tr>
</tbody>
</table>

X-receptors and is approved for use in early- and late-stage cutaneous T-cell lymphomas in patients who have failed or do not tolerate other therapies. Specifically, bexarotene has been used with good results in pagetoid reticulosis. The most common adverse effects are local irritation, pain and pruritus, which can be controlled with the addition of topical steroids. The nitrogen mustard mechlorethamine is an alkylating agent that has also proven beneficial in the treatment of localized CTCLs. Because 10% of patients will develop an allergy to mechlorethamine, it is usually compounded as an ointment to reduce sensitization, even though this may diminish effectiveness. It is applied daily until remission and then continued for months to years afterward depending on treating institution. Concentrations may be titrated until response is achieved. Topical Carmustine (BCNU) is another alkylating agent that is used on patch- and plaque-stage cutaneous lymphomas. Efficacy is excellent in localized CTCL, but side effects and systemic absorption limit its use to lesions <3% of total body surface area. Bone marrow suppression is possible, and routine blood work is required. Telengectasias, hyperpigmentation, atrophy and burning are reported, but these effects are usually self-limited and short-lasting. Topical steroids can be used as the sole agent, and often with excellent results, but are frequently used in combination with other therapies to mitigate irritation and enhance overall efficacy of treatment.
have shown success and are considered an acceptable alternative treatment for pagetoid reticulosis. Further, additional topical therapies can be added to PUVA to enhance response. Case reports have shown photodynamic therapy and eximer lasers to be useful in curing or inducing remission, as well.24-26 Surgical excision is usually unnecessary, since non-surgical options are so efficacious. Systemic therapies using interferons, retinoids and chemotherapeutics can be considered with extensive disease burden or failure of localized therapies, but this is rare with pagetoid reticulosis.

With no known fatalities from PR, prognosis is excellent. However, significant morbidity in the form of aesthetically distressing lesions, superinfection, loss of function and pain can occur. Reports of recalcitrant cases of pagetoid reticulosis with many bouts of recurrence, growth in spite of treatment and dissemination have caused some to question the benign nature of PR.3,27-30 Because of this, it is prudent to deliver focused treatment with careful and regular follow-up for all patients. Most cases appear to be quite manageable, however, with many effective treatment options available. Radiation therapy is the recommended initial treatment, but clinician experience, regional access to therapies and patient preference should be considered when making individual treatment recommendations. More studies are needed to guide future treatment recommendations.

Conclusion

Pagetoid reticulosis, or Woringer-Kolopp disease, is a rare and indolent variant of mycosis fungoides with an excellent prognosis. Practitioners should consider pagetoid reticulosis when presented with a solitary, slow-growing, unremitting hyperkeratotic lesion on the distal extremities. A combination of clinical characteristics in conjunction with microscopic findings will lead the diligent practitioner to the correct diagnosis, ensuring the best outcome for patients.

References


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Blue Vein at the Nasal Root: A Case Presentation and Discussion A Case Report and Review of the Literature

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Abstract

A blue vein at the root of the nose in lighter-skinned children is a not-uncommon finding, but it may nonetheless concern parents. It usually represents the nasal arch, a communicating vein between the right and left frontal veins that can be transiently visible in early childhood. Its appearance may be due to a mild translucency of developing skin with a relative lack of subcutaneous fat in this location. Correct identification is important, as the vein is often mistaken for a hemangioma, vascular malformation, or tumor, and it has a variety of interpretations in Folk and Chinese medicine. The prognosis is completely benign, and the vein is usually no longer visible by 1 to 2 years of age. We present here several cases of a visible nasal arch, a brief discussion of the differential diagnosis, and several non-medical interpretations of this finding that a practitioner may encounter.

Introduction

The nasal arch is a transverse vein usually spanning the root of the nose. It receives venous return from the two frontal veins and then joins the supraorbital veins at either angle of the orbit, forming the angular veins.1 This normally inconspicuous vessel can cause concern to parents and practitioners when it becomes visible in a young child or infant. In our experience, the typical presentation is that of a healthy infant or toddler brought to dermatologic attention for concerns of a hemangioma, vascular malformation, or tumor.

Case Report

An 8-month-old female was referred to the Phoenix Children’s Hospital dermatology clinic with a history of an asymptomatic, blue macule on the bridge of her nose (Figure 1); there were no local symptoms. The macule appeared shortly after birth but had not grown in size since its initial appearance and did not swell with crying or straining. On physical exam, there was a somewhat linear, deep blue, non-tender, smooth, blanchable macule on the bridge of the patient’s nose that was compressible and soft. The patient’s family was reassured that this was a normal variant found in many infants and young children and that no intervention was warranted.

Discussion

The significance of a visible nasal arch in children has been considered in Western and Chinese medicine for at least a century, with several colorful interpretations. An article in the British Medical Journal from August 1887 discusses an association with what might be chronic rhinitis affecting the more “feeble offspring of the poorer classes.” It describes a “black distended vein at the root of the nose” and predicts: “On investigation, these children will be found to have a neglected or intractable chronic catarrh (inflammation) of the nose and pharynx, often with swollen middle turbinated bodies and rhinorrhea, and are generally in a low state of health; and on further examination chronic congestion or hypertrophy of post-nasal mucosa, or post-nasal veins will be found.” Proposed treatment of the condition involves local blood-letting, applications of astringents, and removal of nasal “vegetations.”2

Chinese medicine offers an alternative interpretation, stating that when examining a child’s facial complexion one should specifically “look at the vein at the root of the bridge of the nose between the two eyes.” This area is known as shan gen in Chinese, or “the root of the mountain.” A visible blue vein in this location is seen as a “very reliable diagnostic sign” that the baby’s spleen (i.e., digestion) is weak.3 In Japanese pediatric acupuncture, the visible blue vein has been referred to as a “sugar bug” associated with a syndrome of “Kanmushi,” which according to varying explanations may involve hyperactivity, poor sleep, a proclivity for sweets, and/or food sensitivity. Of note, Kanmushi is also one of many mythical illness-causing parasites in Japanese traditional medicine.4

Differential Diagnosis

The important differential diagnostic considerations for a visible nasal arch include a deep hemangioma and a venous malformation. Hemangiomas are benign vascular tumors of infancy. Since they usually begin with a precursor lesion that may be blue or bruise-like, confusion with the nasal arch is possible. Unlike a hemangioma, however, the nasal arch does not grow or evolve over time and should not deform the skin contours or have any nodular component. Venous malformations tend to have a soft and compressible quality and often swell with Valsalva, exercise, or crying; also, unlike with a visible nasal arch, pain is fairly common.5

Conclusion

Despite the variety of interpretations of a visible nasal arch, there is likely little significance to the finding. In our experience, it seems to disappear around age 2 or 3, without sequelae. The appearance of the vein may be due to the relative thinness of the skin in young children in an area with relatively low levels of both subcutaneous fat and pigmentation, which results in some translucency; however, this phenomenon might also be due to a simple anatomical variant, and a definite etiology is not clear.

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Abstract

Pyoderma faciale is a rare skin disease that can present suddenly in young women in their 20s. It is characterized by coalescent nodules and draining sinuses with severe facial erythema. The condition is often localized to the face. The standard treatment is either the retinoid drug isotretinoin in combination with systemic corticosteroids or else high-dose oral tetracycline antibiotics alone. Due to the negative consequences of isotretinoin during pregnancy, alternatives are needed for pregnant patients who present with pyoderma faciale. This case report describes the efficacy and safety of photodynamic therapy (PDT) with blue light in treating a 29-year-old, post-partum, breast-feeding woman. To the best of our knowledge, this is the first reported case of pyoderma faciale treated with PDT with aminolevulinic acid (ALA). The results were considered excellent by both investigators and the patient.

Introduction

In 1940, O’Leary and Kierland of the Mayo Clinic reported an unusually severe disease that presented unlike the commonly encountered acne vulgaris. Thirteen cases out of 1,600 were characterized as a “sudden, fulminating onset of pyoderma in young women.” In 1992, Plewig et al. reported an additional 20 cases concluded to be an extreme form of rosacea and not of acne, establishing the term “rosacea fulminans.”

The onset of the disease is sudden, without prodromes. Lesions consist of often-painful pustules, papules, nodules, cysts and draining sinuses over a surface of erythematous skin. Current treatments function to counteract the inflammation present with nodular acne and provide rapid control to prevent scarring. However, issues with long-term risks of retinoid and antibiotic use in pregnant patients has generated interest in alternative therapies. This report describes the use of PDT with blue light to treat pyoderma faciale in a post-partum, breast-feeding, 29-year-old woman.

Case Report

A 29-year-old, post-partum woman presented with erythematous papules, pustules, and severe scarring localized to her face (Figures 1 & 2). A trial of oral and topical clindamycin prescribed by her primary care provider offered minimal relief. Upon further questioning, the patient described a similar episode that occurred after a miscarriage more than one year prior. The patient reported little improvement with triamcinolone injections administered at that time.
cleansed and sunblock applied. The patient was advised to avoid the sun for 48 hours following PDT treatment. After one month, the patient returned with improvement, and no new lesions were noted (Figure 3).

The patient continued with PDT therapy for a total of seven treatments, with applications one month apart. Figure 4 reveals the patient’s condition after the fifth treatment. Over the course of treatment, the patient experienced post-inflammatory hyperpigmentation and one episode of reappearance of new lesions over her forehead and cheeks.

Discussion

Traditional systemic medications for nodular inflammatory acne include isotretinoin, systemic corticosteroids, and high-dose oral tetracycline. When treating patients who present in pregnancy, isotretinoin and tetracyclines are contraindicated due to the risks of congenital anomalies and impaired bone growth.

Alternatives have been attempted, including a trial of oral erythromycin and prednisolone in a pregnant female during her first trimester. Rapid improvement occurred, and the patient was placed on a maintenance treatment of prednisolone. At 30 weeks, fetal arrhythmia occurred, and elective admission for steroids was planned. However, severe oligohydramnios soon followed. The patient subsequently presented with an intrauterine death.

Alternative effective treatments are needed for pregnant patients presenting with such severe conditions. Several light and laser therapies have been cleared by the FDA for acne vulgaris, including intense pulsed light therapy (IPL) and blue-light therapy. However, the combination of photosensitizer and light, as photodynamic therapy, has not yet been approved. This new treatment involves PDT, in which a topical application of ALA is followed by light therapy. ALA is absorbed by the sebaceous gland and then metabolized to protoporphyrins, primarily protoporphyrin IX (PpIX). These protoporphyrins absorb light, with maximum absorption at 410 nm. Following application of ALA, blue light is administered to the skin, resulting in photodestruction of Propionibacterium acnes (P. acnes) with shrinkage of sebaceous glands.

PDT using ALA induces transient antimicrobial and anti-inflammatory effects. Studies have shown narrowband blue light may have anti-inflammatory effects, enhancing the therapeutic benefits. When exposed to blue light, keratinocytes decrease cytokine-induced production of IL-1a and intracellular adhesion molecule-1 (ICAM-1). High-intensity blue light provided a 59 percent to 67 percent reduction of inflammatory acne lesions in patients for up to eight weeks after treatment.

Blue light also may function to decrease sebum production. Light sources with long wavelengths are required to reach facial sebaceous glands, as they are located deep beneath the cutaneous surface. In studies evaluating the quantity of P. acnes after PDT, a decrease in sebum production was observed. It has been proposed that toll-like receptor 2 (TLR-2) is involved in inflammatory responses in sebocytes. PDT is thought to moderate the increased expression of TLR-2 that is observed in acne.

ALA-PDT with blue-light therapy has been shown to achieve successful results. In patients with moderate to severe acne, Goldman and Boyce found a 32 percent improvement with ALA-PDT followed by blue-light therapy. A 68 percent reduction in papule counts also occurred. The concern for high risk of fetal defects in pregnant patients was tested by use of photodynamic therapy for condyloma acuminata. The study treated five pregnant patients with three to four treatments of ALA-PDT. Follow-up occurred for six months to 23 months after treatment. All pregnancies resulted in healthy live births without delivery complications, and treatment was reported as well-tolerated by the patients. Further studies are needed to continue testing the safety and efficacy of photodynamic therapy use in pregnant patients with various conditions.

Conclusion

Despite the current off-label indication of PDT for acne in the United States, success has been shown in patients who are unable to receive currently approved treatments like isotretinoin. Use of ALA followed by blue light appears to be an effective alternative modality to treat pyoderma faciale. Further study is necessary to determine if such treatment provides positive long-term results without pregnancy complications. To the best of our knowledge, this is the first report describing PDT-ALA as a successful treatment for pyoderma faciale.

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A Case of Pseudoxanthoma Elasticum (PXE) in a 14-year-old Female: A Case Report and Review of the Literature

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Abstract

Pseudoxanthoma elasticum (PXE) is an inherited disorder characterized by calcified elastic fibers found in the skin, eyes, and cardiovascular system. Although the pathomechanics of PXE are poorly understood, the discovery of an inactivating gene mutation encoding a hepatic efflux pump suggests PXE is a metabolic disorder with secondary tissue mineralization due to decreased circulation of hepatic enzymes. As more is understood about this process, effective therapeutic options can be developed to restore mineral homeostasis within affected tissues. We present a case of PXE in a 14-year-old female who presented with a four-year history of asymptomatic white papules on her neck. We also discuss recent advances that have been made in understanding the pathogenesis of this currently untreatable disorder.

Case Report

A 14-year-old female presented to the dermatology clinic with asymptomatic white papules on her neck that appeared four years prior. The patient denied any family history of similar symptoms. On physical exam, multiple yellow-to-flesh-colored papules were present on the lateral aspects of her neck (Figure 1). Her oral mucosa and gingiva appeared uninvolved. The affected total body surface area was less than 5 percent, and there was no palpable lymphadenopathy.

A cutaneous biopsy of the lateral neck was performed (Figure 2), which demonstrated abnormal, thickened basophilic elastic fibers in the reticular dermis (Figure 3). Orcein elastic stain revealed numerous black fragmented and irregularly shaped fibers (Figure 4). Her complete blood count with differential and lipid profile were within normal limits.

The clinical and laboratory findings were consistent with a diagnosis of pseudoxanthoma elasticum (PXE). The patient was counseled regarding the cardiovascular and ophthalmologic manifestations seen in this disorder. She was referred to a cardiologist and ophthalmologist for further cardiac and fundoscopic evaluation.

Discussion

PXE, also known as Grönblad-Strandberg syndrome, is an inherited disorder characterized by calcification of elastic fibers affecting the skin, eyes and vasculature. PXE demonstrates autosomal-recessive inheritance with extreme variability in phenotypic expression. The incidence rate is estimated to be in the range of 1:50,000 to 1:70,000. It occurs in all races and appears to have a slight female preponderance. The average age at diagnosis is 8 to 12 years; however, diagnosis may be delayed until the third or fourth decade after gastrointestinal or ocular complications develop.² The pathogenesis of PXE is not completely understood. A loss-of-function mutation in the ABCC6 gene on the short arm of chromosome 16 is identified in the majority of patients with PXE. This gene encodes multidrug-resistance protein 6 (MRP6), which is primarily expressed in the liver and kidneys but rarely found in tissues affected by PXE.³ MRP6 is thought to function as an efflux pump in the liver that facilitates transport of molecules from hepatocytes to the general circulation.⁵ Consequently, many experts believe PXE is the result of a metabolic disease in which decreased levels of circulating hepatic enzymes leads to increased calcium and phosphate mineralization in the skin, eyes and systemic vasculature in the setting of normal serum calcium and phosphate levels.⁶ Matrix gla protein, which prevents tissue mineralization when fully carboxylated, may also play a role in the pathogenesis of PXE.⁷,⁸

Cutaneous features of PXE are characterized by yellow papules coalescing into plaques with an appearance that is commonly described as “plucked chicken skin.” Redundant and lax skin folds may also be present. Affected areas include the neck, axillae, antecubital fossae, umbilicus, groin, and thighs as well as oral, rectal and vaginal mucosa.⁹

The hallmark retinal finding seen in PXE is angioid streaks, which represent breaks in the calcified elastic lamina of Bruch’s membrane. They appear as lightly colored gray, brown or red streaks extending from the optic disc. The majority of patients with PXE will have angioid streaks on fundoscopic exam; after age 30, nearly 100% of patients have this finding.⁹ These lesions may result in progressive loss of visual acuity, but rarely lead to legal blindness.¹⁰

The major life-threatening complications of
PXE are myocardial infarction, gastrointestinal hemorrhage and stroke, which result from calcification of the elastic media and intima of mid-sized arteries. Additional cardiovascular sequelae include angina pectoris, mitral valve prolapse, renovascular hypertension and claudication.

Histologically, PXE demonstrates fragmented basophilic elastic fibers in the mid and deep reticular dermis. Verhoeff-Van Gieson and Orcein elastic stains may help identify these fibers in early-stage disease. Calcified tissue also stains black with von Kossa stain.

The differential diagnosis of PXE includes solar elastosis, elastoderma, PXE-like papillary dermal elastolysis, white fibrous papulosis of the neck, and PXE-like phenotype seen in β-thalassemia and sickle-cell anemia. Most of these disorders lack retinal or vascular involvement. Patients with β-thalassemia or sickle-cell anemia may demonstrate similar cutaneous findings, angiod streaks and vascular changes, but do not have an associated ABCC6 mutation. Elastoderma occurs in more localized areas of the neck, trunk and arms and shows elastic fibers extending into the subcutis on histologic examination. PXE-like papillary dermal elastolysis and white fibrous papulosis of the neck demonstrate decreased elastic fibers in the papillary dermis.

There is no definitive treatment for PXE, and management is based on routine follow-up with a multidisciplinary team of physicians. Patients should be evaluated by an ophthalmologist for routine fundoscopic examination at least once every two years and are advised to avoid activities associated with retinal injury such as contact sports and heavy lifting. Following a healthy diet, regular exercise and smoking cessation can help reduce cardiac risk. A Doppler ankle-brachial index study or echocardiography may be considered in patients with claudication or heart murmur.

Symptom-specific therapeutic options include surgery to remove redundant skin folds and low-dose acetylsalicylic acid or clopidogrel for intermittent claudication. Some authors recommend limiting patients’ dietary calcium and phosphorus based on the belief that high calcium intake during childhood or adolescence leads to a more severe phenotype. This recommendation is controversial, and many experts do not recommend reducing calcium intake. Recent studies have shown clinical improvement in patients treated with aluminum hydroxide, an oral phosphate binder. Studies in mice also suggest increased dietary magnesium may prevent tissue mineralization. Laser photocoagulation and intravitreal injection of bevacizumab, a VEGF inhibitor, have been used to treat choroidal neovascularization. Gastrointestinal bleeding can usually be managed conservatively and rarely requires surgical intervention.

Information about patient support groups can be found online through the National Association for Pseudoxanthoma Elasticum (www.napxe.org) and PXE International (www.pxe.org).

**Conclusion**

PXE is a rare, autosomal-recessive disorder affecting elastic fibers in the skin, eyes and vasculature. Phenotypic expression is highly variable, suggesting multiple genetic and environmental etiologic factors. Patients require multidisciplinary long-term monitoring to screen for ocular and cardiovascular complications and are encouraged to reduce known risk factors. Future studies are needed in order to investigate therapeutic options to counteract low levels of circulating anti-mineralization hepatic factors and restore mineral homeostasis in affected tissue.

**References**


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**Vibrio Vulnificus Septicemia Presenting as Fevers, Bullae, and Compartment Syndrome: A Case Presentation and Review of the Literature**

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Abstract

*Vibrio vulnificus* is an oxidase-positive, halophilic (requiring salt,) gram-negative bacillus. *V. vulnificus*, a noncholera variant of the Vibrio species, is often associated with food-borne and flesh-borne illness, including necrotizing fasciitis, gastroenteritis, and septicemia. In the United States, it is the most common cause of death resulting from the consumption of contaminated seafood. Effects of the bacteria are worsened if the host has underlying liver dysfunction or an immunocompromising condition.

Introduction

*V. vulnificus* is an aquatic bacterium that naturally inhabits warm coastal waters throughout the world, in particular the United States and Taiwan. In the U.S., the bacterium is found in the ocean waters of the Northern Pacific, Gulf of Mexico, Mid-Atlantic and New England. In these waters, circulating *V. vulnificus* is eaten by shellfish and then transferred to humans when raw shellfish, in particular oysters, are consumed and introduced into the gastrointestinal tract. However, appropriate preparation with conventional cooking methods renders these bacteria inactive. Recent literature notes that “low-temperature pasteurization, high-pressure processing, and irradiation” eradicate the bacterium to undetectable levels.

An immunocompetent host who ingests the bacterium may suffer from upset stomach, diarrhea or vomiting, whereas the immunocompromised host may experience more severe and life-threatening effects such as severe skin infections, multi-organ failure, sepsis, and death. In addition to immunosuppressed states, alcohol-induced liver disease, dialysis-dependent renal disease, diabetes, HIV, hemochromatosis, thalassemia, hemolytic anemia, and conditions in which free-iron levels are increased confer susceptibility to infection.

According to the U.S. Centers for Disease Control (CDC), there are approximately 50 culture-confirmed cases of *V. vulnificus* infection annually, including 45 hospitalizations and 16 deaths, from the U.S. Gulf Coast region alone. The total cases reported nationwide in 2011 numbered 154, and among those, the most common subtypes were *V. parahaemolyticus* (75 [49%]), *V. alginolyticus* (26 [17%]), and *V. vulnificus* (13[8%]).

The CDC reported a 24% decrease in incidence in the most common food-transmitted bacteria in 2011 as compared with the period of 1996 to 1998. The key food-borne pathogens, listed from most to least, include Shigella, Yersinia, STEC O157, Listeria, Campylobacter and Vibrio. Of these, Vibrio was the only pathogen to increase in incidence, at a rate of 76 percent, from 1996 to 2011. Of recent note by the CDC, infection due to all Vibrio species in 2012 increased 43 percent from the period of 2006 to 2008. However, the incidence of *V. vulnificus*, the most pathogenic strain, did not increase.

Case Presentation and Hospital Course

A 36-year-old Hispanic male presented to the emergency room (ER) in South Florida with complaints of fever, chills and severe upper-extremity pain. He admitted to being in good health until one day prior, when symptoms developed while he worked to repair air conditioners. At home, his temperature rose to a maximum of 103 degrees Fahrenheit (39°C). In the ER, he admitted to pain in his forearms, with the right being worse than the left, while denying any history of trauma, injury or similar symptomatology in the past. However, four days prior to the onset of symptoms, he ate raw oysters.

Medical history was largely negative other than a fracture to the right arm and persistent chronic contractures in his right hand. Social history was positive for alcohol consumption, stated as “heavy at times” but without diagnosis of liver disease. Intravenous drug use was denied.

Initial physical exam revealed an alert and oriented 36-year-old male of stated age, thin and in obvious discomfort. His vitals were significant for fever, sinus tachycardia and hypotension. Mucous membranes were moist and without lesions. Abdominal exam was positive for right lower quadrant pain without rigidity, rebound or guarding. Bilateral upper extremities demonstrated swelling, with the right being worse than the left. There was significant pain on palpation of bilateral forearm volar compartments accompanied by pain in the digits with active range of motion. Pulses at the bilateral wrists were not palpable; however, they were faintly heard on Doppler ultrasound. Capillary refill was sluggish, but there was no altered range of motion of the upper extremities. Initial examination of the legs revealed tenderness without skin lesions. Subsequently, a patch of purple ecchymosis developed in the location where a blood pressure cuff had been placed. Within a few hours, the ecchymotic area on the leg erupted into a tense bullous lesion (Figure 1).

The patient was admitted to the medical ICU with sepsis of unknown etiology. Disseminated intravascular coagulation (DIC) panel was pending. Pain and swelling worsened in the extremities and prompted the ER staff to consult Orthopedic Surgery to rule out compartment syndrome and possible necrotizing fasciitis in the arms and legs. In addition, due a multitude of laboratory abnormalities, Infectious Diseases, Nephrology, and Hematology were consulted.

Emergent evaluation by Orthopedics resulted in an immediate transfer of the patient to the operating room for urgent decompression of early compartment syndrome by bilateral upper-extremity volar and dorsal fasciotomies. Intraoperative findings were negative for necrotizing tissue or muscle. Post-operatively, both arms were provisionally closed with sterile vessel loops secondary to the inability to approximate due to significant swelling (Figure 2). In the ICU, the patient remained intubated, sedated, and on multiple pressors, and broad-spectrum antibiotics were started, including vancomycin and cefazidine. However, the Infectious Diseases specialist promptly initiated treatment with doxycycline and imipenem for suspected *V. vulnificus* septicemia. The first two
sets of blood cultures revealed gram-negative rods identified as V. vulnificus.

Within the first few days, the bullae on the patient’s legs multiplied to cover more than 50 percent of his lower extremities, for which Wound Care was consulted (Figure 3). The bullae became tense and burst, yielding sanguinous fluid. Shortly thereafter, Plastic Surgery evaluated the patient for grafting of the forearms and wound care. The legs were dressed in double antibiotic ointment, silver sulfadiazine, and bismuth tribromophenate-petrolatum, while the upper extremities were dressed and elevated daily in foam wafers (Figure 4). Intraoperative cultures of the forearm tissue were positive for V. vulnificus.

The patient’s critical illness resulted in a three-week stay in the ICU and was complicated by multiple-system organ failure. Acute respiratory distress syndrome (ARDS) developed shortly after the fasciotomies and led to prolonged intubation and difficulty weaning the patient from ventilatory support. Hematology continued to monitor his anemia and thrombocytopenia, suspected to be secondary to underlying liver failure. Secondary to his critical illness, antibiotic therapy began. In spite of platelet transfusion, coagulopathy persisted, as did thrombocytopenia. Heparin-induced thrombocytopenia (HIT) was suspected, and blood analysis yielded positive antibodies. Bilateral volar forearm compartment swelling decreased, and delayed primary closure was being considered. Bilateral lower extremities showed healthy granulation tissue (Figure 5). Repeat negative blood cultures and patient improvement indicated clearing of V. vulnificus infection.

In spite of multiple alterations to fluids and medications by Nephrology to address persistent renal dysfunction, electrolyte abnormalities, acidosis and azotemia, blood-urea nitrogen slowly started to rise. Orders were placed to decrease protein in tube feeds, which had previously been added to augment albumin to aid in wound healing. Secondary to liver failure and intra-abdominal hypertension, the patient’s abdomen became tense with fluid. On hospital day 20, the patient underwent paracentesis, yielding a transudate as calculated by Light’s criteria.

Three days later, hemodialysis was reinitiated. That evening, a “code blue” was called secondary to bradycardia that progressed to asystole. The patient was coded and re-intubated, and a viable rhythm was restored. On the following day, Gastroenterology reevaluated the patient for upper and lower gastrointestinal bleeding. At that time, the patient was unresponsive, with pupils that were fixed and dilated. In his critically ill state, investigational procedures to determine the source of bleeding were not engaged. Mid-morning on hospital day 24, the patient again coded, and he expired.

**Discussion**

Vibrio vulnificus was first recognized as an agent of disease in 1976, with the first documented case reported in 1979. Most cases result in gastrointestinal (GI) upset, including nausea, vomiting and diarrhea. Studies suggest that progression to septicemia yields a 50-percent mortality rate. In 70 percent of cases, skin lesions are present. Epidemiologic data across multiple studies suggest a male predominance for the disease.

The virulence of V. vulnificus is attributed to several features, including a chitinase, “a digestive enzyme that breaks down glycosidic bonds in chitin, which allows Vibrio to embed themselves in the exoskeleton of most arthropods, particularly crustaceans.” The species also possesses a protein called hemolysin, which is thought to be responsible for the gastroenteritis symptomatology as well as the wound infection characterized by necrotizing fascitis or hemorrhagic bullae. The septicemia caused by V. vulnificus is attributed to protease mechanisms that induce increased vascular permeability.

Characteristics of aquatic environments where V. vulnificus live include warmer temperatures, typically above 18°C (64°F), and a low-to-moderate salt concentrations. As temperatures climb in the summer months, bacteria concentrations rise. Infection by this bacterium is conferred to the host by either trauma or ingestion. In the setting of trauma, the host may step on a contaminated shell at the beach or may self-inoculate during harvesting or preparation of the shellfish. In these cases, the infection may manifest as a bulla, edema or pain in an extremity.

On histologic examination of involved tissue, epidermal necrosis in a focal distribution and a mild perivascular lymphohistiocytic inflammatory cell infiltrate can be appreciated (Figure 6a). Additional features may include extensive necrosis of the secretory cells of sweat glands and eosinophilic homogenization of the cytoplasm (Figure 6b). When contaminated shellfish are ingested, the host may develop a spectrum of systemic disorders ranging from gastrointestinal upset to fulminant septic shock. As in our patient, many require management in the ICU secondary to sepsis or limb-threatening fasciitis.
One study concluded that V. vulnificus-infected patients with “hemorrhagic bullous skin lesions, necrotizing fasciitis, skin or soft tissue infections involving two or more limbs, or higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores...have a high risk of death,” though the prognosis improves if surgical treatment occurs within 24 hours of hospital admission. 11 Jien-Wei Liu et al. postulated that within 48 hours of admission of cases of V. vulnificus that involve hypotension and necrotic skin lesions, mortality rates can be as high as 50%. 7

U.S. research in 2007 concluded that of the Vibrio species, V. vulnificus “are the most serious threat to raw oyster consumers, as they account for nearly all fatalities associated with seafood consumption in the U.S.” That study found the majority of virulent oysters to be harvested from the Gulf Coast and the Mid-Atlantic region in the summer season. Of note, oysters from the Pacific Northwest have never been implicated in V. vulnificus infection. 13 V. vulnificus is reportable to the CDC. Prevention strategies include warnings on menus alerting consumers of the dangers of eating raw oysters. California legislation bans the importation of oysters from the Gulf of Mexico during April through October unless they’ve been pretreated to eradicate the bacterium. 14 The U.S. Food and Drug Administration (FDA) recommends that people at high risk of contracting V. vulnificus only eat oysters that are thoroughly cooked. Despite these measures, the mortality rate from infection has not declined. 1

Treatment
Prompt recognition is essential in treating patients with V. vulnificus infection. Tetracycline antibiotics that cover this gram-negative bacterium, such as doxycycline, are first-line. In an eight-year retrospective analysis, three antibiotics were studied for their effectiveness in treating V. vulnificus infection with necrotizing fasciitis in conjunction with surgical intervention. The study concluded that fluoroquinolones or a third-generation cephalosporin in combination with minocycline, a member of the tetracycline group, is critical. Common treatment guidelines suggest using a tetracycline such as doxycycline (oral or intravenous) in combination with a third-generation cephalosporin such as cefazidime (intravenous). Various other combination regimens, including fluoroquinolones and aminoglycosides, have also been recommended.

Conclusions
The Vibrio genus of bacteria is responsible for a variety of infections. Vibrio vulnificus, a noncholera variant, is the most pathogenic species in the genus, yielding the highest mortality rate from shellfish contamination in the United States. Immunocompromised states predispose the host to greater risk of septicemia and death. Early recognition of the illness, prompt surgical debridement, immediate initiation of antibiotic therapy, fluid and electrolyte replacement and close monitoring in the ICU aid in decreasing mortality. In spite of prompt treatment, mortality rates, in particular in septic patients, remain high.

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