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Journal of the American Osteopathic College of Dermatology
Help the JAOCDD to grow...

Hello, members and residents,

The JAOCDD is now well into the application process to become indexed with PubMed. We are making sure that we are compliant with the International Committee of Medical Journal Editors’ Uniform Requirements. Julia Layton, our dedicated and efficient copy editor, and I have been working closely to get the JAOCDD indexed in a timely manner. One of the requirements is that we publish our journal quarterly. We are now able to meet that requirement with the number of manuscripts being accepted for publication. We also have 53 Associate Editors who are a part of the peer review process. Being indexed will make it more desirable to authors to submit their manuscripts for consideration for publication.

We continue to have five dedicated sponsors that support our efforts. Our journal could not exist without the continued support of Global Pathology, Medicis, Galderma, Ranbaxy, and Intendis. We appreciate our dedicated and loyal AOCD sponsors.

Our members and resident members need to continue to support the JAOCDD by submitting manuscripts for publication. As we mention in almost every issue, we must continue to have the program directors review, correct and approve each resident’s manuscript before it is submitted for consideration for publication.

All in all, the JAOCDD is doing quite well, growing, and thriving, and will continue to do so with the increased support of our membership. At the end of 2012, I will be stepping down as Editor of the JAOCDD. I founded the journal in 2002 when I completed my residency program with Dr. Skopit, and I have held that position for a decade. I am actively looking for a qualified member of our college to step up and take over as editor. I will stay on until the end of the year to assist the new editor in this position. I will be leaving the JAOCDD in a very strong position. It is now well supported, and financially sound, and it will hopefully be indexed by the end of the year.

Sincerely,

Jay Gottlieb, DO, FAOCD
Editor-in-Chief
Founding Editor
Hello, everyone,

In January, Dr. Glick and I attended the CME Sponsors Conference in Ft. Lauderdale. This conference is required by the AOA for all accredited CME sponsors, and we learned about a new requirement for the 2013-2015 CME cycle dealing with Outcome Measurements. One program MUST be outcomes-based starting in 2013. To prepare everyone to meet this requirement, the AOA has asked that each sponsor conduct a trial run in 2012. Our annual meeting in San Diego will be our trial run. Our CME committee will be preparing Pre-tests/Post-tests/Post-post Tests. The AOA will require us to submit proof of this documentation to them. Your responses and feedback are vital! Members are encouraged to fill out all evaluation forms from our meetings.

We are now in the third year of the three-year CME cycle. The Continuing Medical Education Guide for Physicians, 2010-2012, can be found on the AOA’s website: www.osteopathic.org. You should continually monitor your CME activity with the AOA.

**Important CME Changes**

Beginning with the current CME cycle ending Dec. 31, 2012, AOA members will have five months to fulfill their CME requirements. Previously, members were allowed 17 months following the close of a cycle to fulfill the CME requirement and maintain their AOA membership and AOA board certification. If you have questions about the change, contact the CME Service Center at cme@osteopathic.org.

The AOA is continuing to monitor the situation with Medicare physician payments. Please continue to use your 2011 Medicare fee schedules until further notice. Additional information can be found at the links below:

www.osteopathic.org/sgr
www.capwiz.com/aoa-aoa

Another topic that will impact our residency programs is that of the ACGME’s proposed new Common Program Requirements. Information can be found at the following links:

http://www.osteopathic.org/inside-aoa/Pages/stop-ACGME-training-limits-for-DOs.aspx
http://www.osteopathic.org/inside-aoa/Pages/acgme-policy-timeline.aspx

Finally, we hope to see you in Branson for our 2012 Midyear Meeting taking place April 19-22. We have many great speakers lined up and will be having a session on OCC. The schedule can be found on our website.

The AOCD is your organization! Please let the National Office know what we can do to improve communications with you. I welcome your comments and suggestions.

Sincerely,

Marsha A. Wise
Executive Director, AOCD
Dear Fellow and Resident members of the AOCD,

Happy New Year to you all, and greetings from South Florida!

Let me begin by saying how privileged I am to serve as your AOCD President. Much has happened since commencing my term in office. I started off the presidency working closely with our Board of Trustees to counter an allegation by a website claiming a copyright issue related to a topic in our AOCD website database. The allegation was of course proven false. The positive outcome in this matter reflects how our Board works in a collaborative manner toward the continued well-being of our College.

In December 2011, with the assistance of Marsha Wise, Executive Director of the AOCD, I produced the first AOCD e-Wire, a monthly report to our members providing an update of the goings on of our College, including a brief summary of the activities of some of the Committees that work so diligently for our membership. I encourage ALL members to get involved and actively participate in these Committees. You will soon receive an email regarding AOCD Committees which will list all Chairs and provide a link to receive more information on the College’s committees. I hope all of you will “get closer” to the College and join a Committee of your choice.

From January 12-14, 2011, John Minni, DO, Dwayne Montie, DO, Marsha Wise and I attended the Annual AOA CME Meeting in Ft. Lauderdale. This was one of the most enlightening meetings I have ever attended in that it provided the most current information for the proper form, structure and function of our Annual and Mid-Year meetings. This meeting also enabled us to establish potentially collaborative relationships with Executive Directors and CME Committee members from other organizations and Colleges within the AOA.

I would also like to report that David Grice, DO, AOCD 1st Vice President, has compiled a tremendous group of speakers for our Mid-Year meeting in Branson, Missouri in April. Don’t forget to block out your schedules for this meeting. In October, the Annual AOCD meeting/OMED 2012 will be held at the San Diego Convention Center, and James Towry, DO, AOCD President Elect and Program Chair, is already working diligently to develop one of the most memorable AOCD conferences on record.

I am enjoying my work as President of the AOCD and remind all of you that I am always available to discuss any matters related to our College. All the best to you and your families throughout 2012 and always. See you in Branson!

Fraternally,
Brad

Brad P Glick, DO, MPH, FAOCD
President, American Osteopathic College of Dermatology - AOCD
DERMATOLOGY OFFICE PLANNING: RADIO FREQUENCY FROM DESICCATORS TURNING ON AUTOMATIC FAUCETS AND TOWEL DISPENSERS

*Atlantic Dermatology Associates, P.A., Wilmington, NC
**University of North Carolina at Wilmington, Wilmington, NC
***Lee Cowper Construction, Wilmington, NC
****New Hanover Regional Medical Center, Wilmington, NC

ABSTRACT

In opening our brand-new, 20,000 square-foot dermatology facility, we were excited to have the latest technology. We opted for hands-free faucets and hands-free towel dispensers so as to minimize disease spread. At first we were very excited about the new technology, until we discovered that electrosurgical machines could trigger the water faucets and towel dispensers. This in turn wasted paper and soaked both employees and other equipment. It became so frustrating that we ended up replacing over 20 faucets throughout the office, moving back to the old, hand-operated technology. We don’t want others to make this same mistake.

Introduction

We used hands-free faucets provided by Delta manufacturer, and the hands-free paper-towel dispensers were Tork Intuition Hand Towel Dispensers. Both the faucets and the towel dispensers work by detecting infrared radiation instead of responding to touch. The infrared detectors in the faucets are powered via the wall outlet; the dispensers are powered with three D batteries.¹² We soon found that both of these technologies would also be turned on when we used our AARON 900 desiccators, provided by Bovie Medical. These desiccators use “disposable dermal tips,” which serve the function of limiting the spread of disease, much like the sensors do.³ The radio frequency emitted by this machine is 550 kHz (5.5x10⁵ Hz).

Discussion

Radio covers a broad frequency range, from approximately 5x10⁴ Hz to 5x10⁸ Hz. The upper end of this range is three orders of magnitude from the range of infrared frequencies, which range from 5x10¹¹ Hz to around 5x10¹³ Hz. Because the frequencies of radio waves and infrared radiation are separated by only 1000 Hz, there is some room for interference.¹ Though the AARON 900 desiccator has a listed output frequency of 550 kHz or 5.5x10⁵ Hz, some of the frequencies emitted may possibly be higher than is listed.³ Also, the infrared detection systems used by the Delta faucets and the Tork Intuition Hand Towel Roll Dispensers for H1 towels may be able to detect frequencies that are lower than infrared, allowing for the possibility of interference at the lower end of the sensors’ sensitivity range.¹²

Conclusion

When designing a medical office where electrosurgical machines may interfere with infrared-activated appliances.

References

1. Delta Faucet: www.deltafaucet.com/
2. Tork: www.torkusa.com/product/309606/

Sink prior to electro-desiccator use.
Sink during electro-desiccator use.
**SCROTAL SYRINGOCYSTADENOMA PAPILLIFERUM: A CASE REPORT AND DISCUSSION**

Mounir Wassef, D.O.,* Layne Nisenbaum, D.O., FAOCD**
*Second-year Dermatology Resident, Columbia Hospital, West Palm Beach, FL
**Program Director, Palm Beach Center for Graduate Medical Education (PBCGME) - Columbia Hospital Dermatology Residency, West Palm Beach, FL

**ABSTRACT**

Syringocystadenoma papilliferum (SCAP) is a benign, rare, adnexal neoplasm occurring at any stage of life. Three clinical types have been described: plaque type (presenting mostly as an area of the scalp devoid of hair); linear type (most commonly seen on the neck or face); and solitary nodular type (mostly seen on the trunk – shoulders, axillae, and genital area). In general, SCAP usually presents as a papular lesion or a plaque on the head and neck, or less commonly on the extremities. Characteristically, SCAP is described as being a solitary, gray or brown, papillary or verrucous, exophytic lesion with a moist appearance that emerges from a flat and smooth, skin-colored to brown plaque that increases in size at puberty. A third of the time, SCAP arises within a nevus sebaceous (a circumscribed hamartomatous lesion predominantly composed of sebaceous glands), while the majority of the time it arises de novo. Those lesions arising within a nevus sebaceous are at increased risk for malignant potential. Basal cell carcinoma is associated with such lesions in up to 10% of cases. Less commonly, SCAP associated with a nevus sebaceous may progress to squamous cell, verrucous, or ductal carcinoma. The diagnosis of SCAP involves a certain degree of clinical suspicion along with histologic confirmation. Due to the aforementioned association with malignant potential, complete surgical excision along with thorough histological examination is the treatment modality of choice.1–3

**Case Report**

A 55-year-old male with no significant previous medical history reported changes in a skin lesion on the scrotum. The skin lesion had been present for over 25 years and had been gradually increasing in size over the past two years. The lesion was a gray-white cystic structure filled with soft, yellow-grey material. It was located on the inferior pole of the right hemiscrotum, 4 mm x 4 mm in size, with a well-defined margin. The patient denied any bleeding or discharge from the lesion. On microscopic examination, the epidermis showed varying degrees of papillomatosis. One or several cystic invaginations extended downward from the epidermis. The upper portion of the invaginations and, in some instances, large segments of the cystic invaginations were lined by squamous, keratinizing cells similar to those of the surface epidermis (Fig. 1). The papillary projections and the lower portion of the invaginations were lined by glandular epithelium often consisting of two rows of cells. The luminal row of cells consisted of high columnar cells with oval nuclei and faintly eosinophilic cytoplasm (Fig. 2).

**Discussion**

Syringocystadenoma papilliferum occurs most commonly on the scalp or the face; however, in about one fourth of the cases, it is seen elsewhere. It is usually first noted at birth or in early childhood and presents as a papule or several papules in a linear arrangement or as a plaque. The lesion increases in size at puberty, becoming papillomatous and often crusted. On the scalp, syringocystadenoma papilliferum frequently arises around puberty within a nevus sebaceous that has been present since birth. SCAP arising on the scrotum is exceedingly rare.

**References**

Aplasia cutis congenita (ACC) is a rare congenital disorder characterized by the localized absence of epidermis, dermis, and at times subcutaneous tissues. Scalp is involved in 80-90% of cases and most commonly manifests as a solitary defect. However, it may present as multiple lesions involving the face, trunk, and extremities. Commonly manifests as a solitary defect. Most cases of ACC belong to the first group: solitary lesion on the scalp without multiple abnormalities. The “hair collar sign,” a ring of hypertrophic dark and/or coarser hair surrounding the scalp defect, can usually be appreciated.

Although most ACC presents as a solitary lesion on the scalp, more complex presentations may warrant further examination, as evident in our case. Based on Frieden’s classification, our patient belongs to the fifth group: ACC with fetus papyraceous (vanishing twin syndrome) or placental insufficiency. Fetus papyraceous is found at the time of delivery (if not sooner by ultrasound) and results from the death of a twin fetus early in the second trimester. It is hypothesized that the death of one twin in utero allows for the passage of thrombogenic material to the living twin via vascular anastomoses. Activation of the coagulation cascade in the living twin occurs, resulting in disseminated intravascular coagulation, which may cause ischemia in the developing skin. Consequently, the surviving child is affected with ACC and usually is otherwise normal.

Imaging studies are seldom required for small circular or oval ACC of the scalp with no apparent associated anomalies, as in our case. Atypical or very large scalp defects should be imaged for possible underlying bone or soft-tissue defects. These studies should be performed based on clinical suspicion of an underlying abnormality or syndrome, since the majority of ACC cases are uncomplicated.

Management

Outcome and management of ACC is dependent on the extent of the lesion. Small lesions usually heal spontaneously and require no treatment other than simple cleaning. Recovery is uneventful, with gradual epithelialization and formation of a hairless, atrophic scar over several weeks. Small, underlying bony defects usually close spontaneously during the first year of life.

Conservative treatment with antibacterial prophylaxis using silver sulfadiazine ointment and appropriate dressings may be used to allow spontaneous wound epithelialization. However, several risks may be incurred with conservative treatment including infection with Staphylococcus, Pseudomonas, and B-hemolytic Streptococcus. Although surgical treatment is not recommended initially, it may be necessary for large or multiple scalp lesions to prevent potential complications of hemorrhage, secondary local infection, meningitis, or sagittal sinus thrombosis. Larger lesions associated with underlying bony defects may result in death secondary to central nervous system infection or hemorrhage from the sagittal sinus. Surgical repair of large or multiple scalp defects with excision and primary closure, if feasible, or with the use of tissue expanders and rotation of a flap may be considered. Truncal and limb defects, despite their large size, usually epithelialize and form atrophic scars spontaneously, which can later be revised if necessary.

Conclusion

We present a case of a 10-month-old boy with ACC of the scalp associated with fetus papyraceous for its rarity and clinical interest. Although most cases of ACC present as an isolated lesion on the scalp, more complex presentations warrant further investigation, as in this case. Management is based on the extent of the lesion and associated complications. Our patient had no bony abnormalities or other congenital defects present; thus, no treatment was needed at the time except for wound-care discussion for any future trauma to the area.

References


Aplasia cutis congenita associated with fetus papyraceous: a case report and review

Donna D. Tran, MSIII,* Patrick Keehan, D.O.**
*3rd-year Medical Student, University of North Texas Health Science Center, Fort Worth, TX
**Board-certified Dermatologist, Premier Dermatology, Fort Worth, TX

Clinical synopsis

A 10-month-old boy of non-consanguineous parents presented with an asymptomatic patch on the crown of the scalp that had been present since birth. The mother denied any developmental delays in the child. Examination revealed a 20 x 10 mm, atrophic scar with alopecia and coarser hair present at the periphery. The scalp defect with atrophic, membranous, bullous, or parchment-like scars with alopecia. The etiology of aplasia cutis congenita remains unclear, and it is likely that more than one mechanism is involved. Genetic factors, teratogens (especially methimazole), compromised vasculature to the skin, and trauma have all been implicated. We report a case of a 10-month-old boy with ACC associated with fetus papyraceous.

Management

Outcome and management of ACC is dependent on the extent of the lesion. Small lesions usually heal spontaneously and require no treatment other than simple cleaning. Recovery is uneventful, with gradual epithelialization and formation of a hairless, atrophic scar over several weeks. Small, underlying bony defects usually close spontaneously during the first year of life.

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References


10 APLASIA CUTIS CONGENITA ASSOCIATED WITH FETUS PAPYRACEUS- A CASE REPORT AND REVIEW
Table 1. Nine subtypes of aplasia cutis congenita (7)

<table>
<thead>
<tr>
<th>Group</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Scalp ACC without multiple abnormalities</td>
</tr>
<tr>
<td>2</td>
<td>Scalp ACC with limb abnormalities: hypoplastic or absent distal phalanges, syndactyly, club foot, others</td>
</tr>
<tr>
<td>3</td>
<td>Scalp ACC with epidermal and organoid nevi</td>
</tr>
<tr>
<td>4</td>
<td>ACC overlying embryologic malformations such as gastroschisis, omphalocele, meningomyelocele, and others</td>
</tr>
<tr>
<td>5</td>
<td>ACC with fetus papyraceus or placental infarct</td>
</tr>
<tr>
<td>6</td>
<td>ACC associated with epidermolysis bullosa</td>
</tr>
<tr>
<td>7</td>
<td>ACC limited to extremities without epidermolysis bullosa</td>
</tr>
<tr>
<td>8</td>
<td>ACC due to teratogens such as HSV, VZV, or medications (methimazole)</td>
</tr>
<tr>
<td>9</td>
<td>ACC as part of malformation syndrome such as Goltz syndrome, trisomy 13, ectodermal dysplasia, and others</td>
</tr>
</tbody>
</table>

Position Available

Long Island, New York

Dermatologist in solo practice seeks to add a FT/PT BC/BE DO to an established general Dermatology practice located 35 miles from midtown Manhattan.

High volume general dermatology practice with Xtrac laser and UVA/UVB booth.

Candidate will be involved in the continued growth of a busy clinical practice encompassing medical, surgical and cosmetic dermatology.

Compensation commensurate with production. Tremendous opportunity to succeed.

Please email CV to skindeepdo@aol.com
Case Presentation

A 56-year-old female presented with a 10-year history of scleroderma, three-month history of pulmonary hypertension, and gastroesophageal reflux disease (GERD). The patient history also included swelling of the ankles and hands for the past 10 years, with recent exacerbation of both.

On examination, non-pitting edema and cutaneous induration were observed on the hands and digits bilaterally along with 1+ pitting edema of both ankles. With the use of a dermatoscope, telangiectasias and dilated loops were seen in the proximal nail folds. Palmar erythema was also noted on both hands (Fig. 1). Furthermore, matted telangiectasias and erythema on the sun-exposed areas of the face, back and chest were noted (Fig. 2,3,4). Subcutaneous palpable masses were present in the left axillary region (Fig. 5).

A 4mm punch biopsy obtained from the left axilla confirmed the numerous fragments as non-specific heterotrophic calcification, a condition usually associated with chronically inflamed lesions. X-ray (AP and Y-axis view) confirmed the presence of calcification in the left axilla (Fig. 6).

The diagnosis of systemic sclerosis was made based on the presence of cutaneous scleroderma of the hands, sclerodactyly, and pitting scars on the digits. The inclusion of CREST syndrome is due to prior diagnosis of GERD, axillary calcinosis, telangiectasias, sclerodactyly, and Raynaud's phenomenon. The patient was prescribed amlodipine 5 mg daily for pulmonary hypertension and sildenafil 50 mg daily for prevention of digital ulceration associated with Raynaud's phenomenon. The patient was given a referral for surgical evaluation to remove axillary calcifications.

Discussion

Systemic sclerosis, synonymous with scleroderma, is an autoimmune connective-tissue disease of unknown etiology. The incidence of systemic sclerosis within the United States is 20:1,000,000 cases, and women are affected three to four times as often as men. Even though there is worldwide and cross-racial distribution of the disease, black patients have a lower mean age of onset and higher occurrence of diffuse disease [1].

The diagnosis of systemic sclerosis (SSc) is based on clinical findings of one major and a minimum of two minor criteria set forth by the American College of Rheumatology. Scleroderma proximal to the metacarpo/metatarsal phalangeal joints represents the major criterion, while the minor criteria include sclerodactyly, digital ulcerations, and bibasilar pulmonary fibrosis. The two subtypes of SSc are diffuse and limited, distinguished by the degree of dermal sclerosis. Both subtypes can involve multi-organ changes, but limited SSc implies skin changes in only the hands, fingers, and face, while diffuse SSc also involves the truncal and proximal extremities [1].

Many features overlap within diffuse SSc and limited SSc, but CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia) syndrome is commonly associated with the latter (Table 2) [3].

Typically, the earliest features of systemic sclerosis involve vascular and skin changes. Excess collagen production leads to the cutaneous fibrosis seen with SSc. Dysfunction of various dilatory or constrictive factors is thought to play a role in resultant hypoxia, which leads to altered collagen

ABSTRACT

Systemic sclerosis (scleroderma) is an idiopathic autoimmune connective-tissue disease with two sub-types: limited and diffuse. The disease primarily involves the skin, viscera, and blood vessels. The diagnosis of scleroderma is based on guidelines from the American College of Rheumatology, requiring the presence of one major and two minor criteria. The location of skin changes determines the subtype distinction between limited and diffuse scleroderma. The authors present a case of a 56-year-old female with scleroderma and multi-organ involvement.
Table 1. Systemic manifestations of diffuse scleroderma

<table>
<thead>
<tr>
<th>Organ</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>90-95</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>60-90</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>90</td>
</tr>
<tr>
<td>Lungs</td>
<td>40-60</td>
</tr>
<tr>
<td>Heart</td>
<td>59-90</td>
</tr>
<tr>
<td>Kidneys</td>
<td>35-70</td>
</tr>
</tbody>
</table>


Table 2. Comparison of diffuse and limited SSc clinical and laboratory features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Diffuse (%)</th>
<th>Systemic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud’s phenomenon</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>Finger swelling</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Tendon friction rubs</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>Proximal weakness</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Mat telangiectasia[*]</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>Esophageal dysmotility</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>Small-bowel involvement</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5</td>
<td>25</td>
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<tr>
<td>Cardiomyopathy</td>
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<td>10</td>
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<td>Renal crisis</td>
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<td>10</td>
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<tr>
<td>Sicca syndrome</td>
<td>15</td>
<td>10</td>
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<tr>
<td>Antinuclear antibodies</td>
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<td>90</td>
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<tr>
<td>Anticentromere antibody</td>
<td>5–30</td>
<td>50–90</td>
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<tr>
<td>Anti-Scl-70 antibody</td>
<td>20–60</td>
<td>10–15</td>
</tr>
<tr>
<td>Cumulative survival (5 years)</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>Cumulative survival (10 years)</td>
<td>50</td>
<td>70</td>
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</table>


<table>
<thead>
<tr>
<th>Systemic Sclerosis</th>
<th>Morphea (localized scleroderma)</th>
<th>Eosinophilic Fasciitis</th>
<th>Scleroderma</th>
<th>Sclero-myxedema</th>
<th>Nephrogenic Systemic Fibrosis</th>
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</thead>
<tbody>
<tr>
<td>Raynaud’s phenomenon</td>
<td>almost always</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Symmetric induration</td>
<td>almost always</td>
<td>rare</td>
<td>almost always</td>
<td>almost always</td>
<td>almost always</td>
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<tr>
<td>Sclerodactyly</td>
<td>almost always</td>
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<td>rare</td>
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<td>Facial involvement</td>
<td>common</td>
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<td>rare</td>
<td>sometimes types I and II-type III</td>
<td>common</td>
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<td>common</td>
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<td>almost always</td>
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<tr>
<td>Antinuclear antibodies</td>
<td>almost always</td>
<td>sometimes found in generalized and linear-plaque type</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Anticentromere antibodies</td>
<td>common (limited type)</td>
<td>rare</td>
<td>rare</td>
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</tr>
<tr>
<td>Anti-topoisomerase I (anti-Scl-70) antibodies</td>
<td>common (diffuse type)</td>
<td>rare</td>
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<td>rare</td>
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<tr>
<td>Monoclonal gamopathies</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
<td>common type II</td>
<td>almost always</td>
</tr>
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production and fibroblast activation [7]. Other common features that arise due to endothelial insult include edema, which leads to sclerodactyly and pulmonary fibrosis.

Patients often present with various degrees of diffuse hyperpigmentation along with a distinct pattern of leuokoderma known as “salt and pepper” sign. Leukoderma can be described as a localized area of depigmentation with sparing of perifollicular skin, most often found on the upper trunk and central face [1]. Telangiectasias are commonly found in varying diameters on the face, lips, and upper trunk (dorsal and ventral) and are more commonly associated with limited SSc. Distinctly, telangiectasias in SSc present as either squared-off or matted, while hereditary telangiectasias are raised lesions. SSc telangiectasias typically present around the mouth along with skin tightness, lip thinning and radial furrowing [3]. Calcinosis has no specific pattern in patients with diffuse or limited forms but occurs frequently on the digits and less frequently around the knees, elbows and hips, which contributes to loss of motion.

A multi-disciplinary approach is crucial to the management of a patient with SSc due to the extra-cutaneous organ involvement. The lungs, gastrointestinal tract, heart and kidneys are the most commonly affected organs, leading to significant complications and mortality. The most common gastrointestinal problem occurring in scleroderma patients is esophageal reflux and dysmotility [1]. Fibrosis is a common change that occurs within the lungs and heart and can be detected by chest radiography and electrocardiographic changes, respectively. The kidneys undergo nephrosclerosis, and renal failure eventually ensues. ANA autoantibodies are found in most cases of systemic scleroderma and can be used as a diagnostic tool and prognostic indicator for complications. Laboratory tests useful in the diagnosis of SSc include anticientromere antibody, highly specific for CREST syndrome (associated with limited subtype), and anti-Scl-70, specific for diffuse systemic sclerosis.

Comparison of major clinical and laboratory features are helpful in the differential diagnoses, which include disseminated morphea, sclerodermatomyositis, mixed connective-tissue disease, eosinophilia-myalgia syndrome, diffuse fasciitis with eosinophilia, and scleroderma of Buschke. SSc can be clinically diagnosed and distinguished using specific findings such symmetric skin induration of distal extremities, nail-fold capillary findings, CREST syndrome, and the presence of autoantibodies (Table 3) [1].

Generally, diffuse systemic sclerosis has a worse prognosis, but other factors influence the mortality rate such as age, sex, race, and organ involvement. Black male patients with an early age of diagnosis and multi-organ involvement typically have a poorer prognosis. Of the major complications of systemic sclerosis, pulmonary fibrosis leads to the highest mortality rate [4]. Patients with 60% or greater reduction in pulmonary diffusing capacity have a five-year survival rate of 10% [9]. The presence of telangiectasias or calcinosis is insignificant for patient prognosis.

The disease state cannot be reversed, and treatment is non-specific, primarily involving symptomatic management. Since the progression of SSc is inevitable, a multidisciplinary team approach must be used to manage the visceral complications of the disease. Prevention of digital ulceration is crucial; the patient is advised to avoid cold atmospheres, trauma, and smoking to manage Raynaud’s phenomenon [6]. Anti-hypertensives such as minoxidil and captopril are prescribed to manage symptomatic cardiac and pulmonary complications [5]. Reducing blood pressure using vasoactive drugs is crucial to maintain renal function. For the management of inflammation, cyclophosphamide, azathioprine, methotrexate and low-dose corticosteroids are preferred. For facial skin, 0.025-0.05% tretinoin can be used to decrease perioral tightening [10]. Phototherapy and vasoactive agents (calcium-channel blockers, endothelin-receptor antagonists, prostacyclins) are used to control fibrosis and vascular disease, respectively. Often, the course of the disease is unpredictable and can lead to resolution in some patients and rapid, diffuse progression in others.

References
2. Braun-Falco O. Braun-Falco’s Dermatology 2009: 704-709
Indication for VANOS® Cream

VANOS Cream is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in patients 12 years of age or older. Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 60 g/week because the safety of VANOS Cream for longer than 2 weeks has not been established and because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Therapy should be discontinued when control of the disease is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary. No more than half the 120 g tube should be used per week.

Important Safety Information for VANOS Cream

- Reversible HPA-axis suppression may occur with potential glucocorticosteroid insufficiency after withdrawal of treatment. HPA-axis suppression was demonstrated in two out of 18 adult patients with psoriasis treated twice daily for two weeks and one out of 31 adult patients with atopic dermatitis treated once daily for two weeks. HPA-axis suppression has not been evaluated in psoriasis patients who are less than 18 years of age. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a higher risk than adults of HPA-axis suppression and Cushing’s syndrome when they are treated with topical corticosteroids.

- If irritation develops, VANOS Cream should be discontinued and appropriate therapy instituted.

- VANOS Cream should not be used on the face, groin, or axillae; or for treatment of rosacea or perioral dermatitis.

- The safety and efficacy in patients younger than 12 years of age have not been established.

- The most commonly reported adverse events were headache, burning at the application site, nasopharyngitis, and nasal congestion.

BRIEF SUMMARY (see package insert for full prescribing information)

VANOS® (flunisolide) cream, 0.1% For topical use

INDICATIONS AND USAGE
Indication
VANOS (Flunisolide) Cream, 0.1%, is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older [see Use In Specific Populations].

Limitation of Use
Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 60 g per week for children younger than 12 years of age and 120 g per week for adults [see Overdosage].

None.

WARNINGs AND PRECAUTIONs
Effect on Endocrine System
Systemic absorption of topical corticosteroids, including Vanos Cream, can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid. In addition, the use of VANOS Cream for longer than 2 weeks may suppress the immune system [see Nonclinical Toxicology].

HPA axis suppression has been observed in patients receiving Vanos Cream, 0.1% applied once or twice daily in 2 out of 18 adult patients with plaque-type psoriasis, 1 out of 31 adult patients with atopic dermatitis and 4 out of 123 pediatric patients with atopic dermatitis [see Use In Specific Population and Clinical Pharmacology].

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

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

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

Studies conducted in pediatric patients demonstrated reversible HPA axis suppression after use of VANOS Cream. Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of VANOS Cream due to their larger skin surface-to-body mass ratios [See Use In Specific Populations].

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

Concomitant Skin Infections
If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of VANOS Cream should be discontinued until the infection has been adequately controlled.

Allergic Contact Dermatitis
If irritation develops, VANOS Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with symptoms similar to those of asthma may develop by inhalation of removed topical corticosteroids. Manifestations of systemic contact dermatitis may include generalized urticaria, fever, dyspnea, laryngeal edema, anaphylaxis, and cardiovascular collapse.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects:
Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Therefore, VANOS Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tissue Disorders:
Skin and Subcutaneous Disorders:
acne, dry skin, rash, exfoliation and skin tightness.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

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Skin and Subcutaneous Disorders:
acne, dry skin, rash, exfoliation and skin tightness.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

OVERDOSAGE
Vanos cream can be absorbed in sufficient amounts to produce systemic effects [see Warnings and Precautions].

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of VANOS Cream because of severe immunosuppression induced in a 28-week dermal rat study. The effects of fluonisolide on fertility have not been evaluated.

Fluonisolide revealed no evidence of mutagenic or clastogenic potential based on the results of two in vivo genotoxicity tests (Ames test and chromosomal aberration assay using human lymphocytes). However, fluonisolide was positive for clastogenic potential when tested in an in vitro micronucleus assay.

Topical (ermal) application of 0.003%-0.03% fluonisolide cream to rats once daily for 13 weeks resulted in a toxicity profile generally associated with long-term exposure to corticosteroids including decreased skin thickness, adrenal atrophy, and severe immunosuppression. A NOAEL could not be determined in this study.

In addition, topical application of 0.1% fluonisolide cream plus UV exposure to hairless mice for 13 weeks and 150-900 mg/kg/day of 0.1% fluonisolide cream to mice to mimics a model more closely approximates human skin) for 13 weeks produced glucocorticoid-related suppression of the HPA axis, with some signs of immunosuppression noted in the dermal minipig study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk for carcinogenesis.

HOW SUPPLIED/STORAGE AND HANDLING
Vanos Cream is white to off-white in color and is supplied in tubes as follows:
30 g (NDC 99207-525-33)
60 g (NDC 99207-525-63)
120 g (NDC 99207-525-10)

Store at controlled room temperature: 15° to 30° C (59° to 86°F).

Manufactured by:
Medicis, The Dermatology Company
Scottsdale, AZ 85256

Manufactured by:
Medicis Pharmaceutical Corporation
Medicis, The Dermatology Company
Scottsdale, AZ 85256

Made in Canada

U.S. Patents 6,765,001; 7,217,422; 7,220,424 and Patents Pending

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When the flares of dermatitis strike…

On target relief

KENALOG® SPRAY
Triamcinolone Acetonide Topical Aerosol USP

Precision application when treating hard to reach areas

- Indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
- 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. (See the Precautions section in Full Prescribing Information)
- Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio.

For topical use only
Please see Brief Summary on reverse side.
In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only; avoid contact with the eyes and inhalation of the spray.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped to be as occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions to the physician.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

Pregnancy: Teratogenic Effects

Category C. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Drops of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

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

Pediatric Use

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

IAPA axis suppression, Cushing’s syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

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

ADVERSE REACTIONS

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

DOSAGE AND ADMINISTRATION

Directions for use of the spray can are provided on the label. The preparation may be applied to any area of the body, but when it is sprayed about the face, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided.

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

Oclusive Dressing Technique

Oclusive dressings may be used for management of psoriasis or other recalcitrant conditions. Spray a small amount of preparation onto the lesion, cover with a pliable nonporous film, and seal the edges. If needed, additional moisture may be provided by covering the lesion with a dampened cotton cloth before the plastic film is applied. Oclusive dressings should be held in place by a bandage or elastic bandage. Areas covered by these dressings should be cleansed with water immediately prior to applying the medication. The frequency of changing dressings is best determined on an individual basis. It may be convenient to apply the spray under an oclusive dressing in the evening and to remove the dressing in the morning (i.e., 12-hour occlusion). When utilizing the 12-hour occlusion regimen, additional spray should be applied, without occlusion, during the day. Reapplication is essential at each dressing change.

If an infection develops, the use of oclusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

Store at room temperature; avoid excessive heat.

Manufactured for Ranbaxy Laboratories Inc. 22225/22277 USA 2007 November 5

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Case Report
A 19-year-old Caucasian female presented to the office for a follow-up visit to recheck moles that were now itchy. The patient runs 3.5 miles outside daily. She denied ever using a tanning bed or having any family history of skin cancer.

Physical exam revealed a 0.6 x 0.5 cm pigmented papule with color variation and scale on the left lateral shoulder. There also was a 0.6 x 0.5 cm pigmented papule with color variation and irritation on the left lateral neck and a 1.2 cm tender nodule on the left occipital scalp. The rest of the physical exam was negative for suspicious skin lesions.

Written informed consent was obtained to do a biopsy on the three lesions spoken of above. Shave biopsies were performed, and the specimens were sent to pathology. The pathology report stated that the lesions on the neck and scalp came back as intradermal nevi. The lesion on the left shoulder came back as superficial spreading malignant melanoma, Clark level III. The Breslow thickness was at least 0.46 mm, as the tumor was present at the deep margin. It showed both junctional (Figure 1) and dermal (Figure 2) mitoses with pagetoid spread (Figure 3).

The patient was scheduled to have the melanoma excision 11 days later. The area was locally anesthetized, an elliptical incision was made encompassing the lesion with 1 cm margins, and the lesion was excised. The defect was 2.5 cm x 5.6 cm, and closure was 6.6 cm. The lesion was sent to pathology. Pathology report showed no residual melanoma.

The patient was advised to wear sunscreen (SPF 30 or greater) on exposed skin daily, to wear a brimmed hat while outside and to avoid mid-day sun when possible. Monthly self-exams were recommended, and she was to call if there were any new or changing lesions.

Introduction
Malignant melanoma is a devastating and life-threatening disease. There are several subtypes of melanoma. Some of the most common types of melanoma are superficial spreading, nodular, lentigo maligna melanoma, and acral lentiginous melanoma.

In this case, the patient was diagnosed with superficial spreading melanoma, which represents 70 percent of all melanomas. The most common places for it to occur are on the legs in women and on the back in men. As we see with this case, it is important not to overlook other locations on the body, as this patient’s appeared on the shoulder. This form typically comes from preexisting nevi and exhibits irregular borders, pigment variation, and asymmetry.

Melanoma is increasing in incidence at a higher rate than any other type of cancer in the United States. It is the sixth most common cancer in women and the second most common cancer in women ages 20 to 29. Epidemiological studies have shown a dramatic increase in the incidence of melanoma. The lifetime risk of developing melanoma in 1935 was 1 in 1,500. It more than doubled by 1960 at 1 in 600. In 1996, it was 1 in 87, and in 2002 it increased to 1 in 68. Between 1950 and 2001, the incidence of melanoma has gone up by 610 percent.

In the late 1980s and early ‘90s, several studies were published that stated that the incidence in the younger population, aged 15-30, was finally leveling off. Unfortunately, recent data released from the Surveillance, Epidemiology and End Results (SEER) program have indicated that the incidence of melanoma has continued to increase in young white females between 1997 and 2004.

In the ‘70s, the incidence in young males increased by 7% each year and in young females by 9% each year. In the 1980s, the incidence leveled off for the males of that age group, while it has continued
to rise in young women. In fact, in the United States, the incidence of cutaneous melanoma has increased among Caucasian females between the ages of 15 to 30 by another 50 percent between 1980 and 2004. This brings us to an important question: What are the causes of this devastating trend?

**Discussion**

It is a well-known fact that sun tanning and tanning salons are associated with an increased risk of developing melanoma and other forms of skin cancer. The new tanning beds with high-pressure tanning bulbs have been reported to have 12 to 15 times the strength of the sun. Those that have used tanning beds more than once have a 55% increased chance of developing melanoma. This is one of the possible reasons for the increased incidence of melanoma in young females. It has been determined that 71% of those using tanning beds are women ages 16 to 19.

Recent studies have indicated that 36.8% of white female adolescents report using a tanning booth at least once in their lives, as compared to 11.2% of their male counterparts. The number of females who have used tanning beds three or more times is 11.2% in 13- to 14-year-olds, while it is 47.0% in 18- to 19-year-olds. The same study reports that dieters, regardless of BMI, and those using two to three substances (including tobacco, alcohol, and/or marijuana) were more likely to use indoor tanning beds. Incidentally, the use of tanning beds was decreased among those with higher cognitive ability, individuals with college-educated mothers, and those who regularly exercise.

It has been determined that there is a correlation between melanoma incidence and socio-economic status. A study was done in California with 3,800 non-Hispanic white females ages 15 to 39. The study showed surprising results, as melanoma was more closely linked with socio-economic status than with those living in a high-UVR neighborhood. In fact, there was almost a six-fold increase in melanoma in those in the affluent neighborhoods versus those in the poorest neighborhoods. The authors of that study stated that it is not likely that this difference is due to the higher accessibility of health care for the wealthier girls. People who are financially stable have more luxury time, and this time is being spent exercising outside, gardening, swimming in the pool, and sun tanning on the beach. Mid-winter trips to Hawaii or Mexico also require the appropriate finances and could be another explanation for this phenomenon.

Often, one sees the incidence of a disease increase when screening methods become more sensitive and it is picked up sooner in the screening process. Our more effective screening abilities for finding melanoma may have contributed to the increasing incidence of the disease over the last century. This could explain why although we are seeing an increase in morbidity, at the same time we are experiencing a much lower increase in mortality. Yet in the recent past, it is not likely that the cause of the increased incidence is only a more aggressive screening process. This wouldn’t explain why incidence continues to increase in females while it stays much more stagnant in males of the same age group.

Another possible reason for this trend could be changes in the ozone layer. Again, this would only seem to explain the rise in incidence among all races, ages, and genders. This would not explain the split we see among genders.

There have been many advances in the treatment of melanoma, and survival percentages are increasing. The survival percentages are tightly linked to the stage of the lesion. According to the American Cancer Society, the five-year survival rate is 97% if the cancer is stage 1A, less that 1 mm thick. If the cancer is stage 4, having metastasized distally, the five-year survival rate is much more dismal at 15 to 20%. Thus, early detection is vital to improve the prognosis.

Even with our increase in survival percentages, we are still seeing an increase in mortality. Another way of looking at this is that we are continuing to see more deaths from this disease because the rise in incidences has outweighed our increasing ability to cure.

**Conclusion**

With this in mind, until we find a better cure, our focus should be on risk reduction. Educating our young women about sun protection, the risk factors of skin cancer and skin self-examination should be our goal. One of our biggest adversaries is the image society portrays about tanning. The media depicts tanning as looking healthy, sexy, and wealthy. A recent study looked at a variety of teen magazines to analyze how they portrayed sun tanning. The magazines talked about the benefits of tanning beds twice as much as they did the consequences. Thirty-one percent of the articles that talked about tanning also mentioned self-examination, and only 16% covered how to do one. It is of the author’s opinion that we must find more effective methods to educate young women about the dangers of tanning to protect them from the hazardous influences of the media. Then we will all see a lower incidence of melanoma in this demographic.

**References**


20 INCREASED INCIDENCE OF MALIGNANT MELANOMA IN YOUNG CAUCASIAN FEMALES
GIANT CONGENITAL MELANOCYTIC NEVI (CMN): A LITERATURE REVIEW AND CURRENT TREATMENT UPDATE

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ABSTRACT

Giant congenital melanocytic nevi (CMN) are rare occurrences that present significant challenges to dermatological care. Giant CMN are defined as being greater than 20 cm in diameter and can increase in size through development. The clinical appearance varies depending on pigmentation, with or without the presence of hair and nodules. NRAS mutations have been suggested as a possible pathogenesis for giant CMN; no specific genetic inheritance pattern has been identified to date. Overall, patients with giant CMN have a greater risk of developing malignant melanoma and neurocutaneous melanosis. Such risks emphasize the importance of routine dermatological examinations to detect subtle changes in the nevi in addition to an initial screening MRI in infancy. Prophylactic surgical excision is often the first-line recommendation for treatment of giant CMN, whereas more conservative therapies such as dermabrasion, curettage, and laser therapy can be used as alternatives in cases refractory to surgery.

Classification & Clinical Features

Giant congenital melanocytic nevi (CMN) are a challenging dermatological condition for physicians and patients alike. Overall, the occurrence of giant CMN in the population is rare, with an incidence of 1 in 20,000 newborns, and the even larger, “bathing trunk” nevi occur at a rate of 1 in 500,000 newborns. Giant CMN are primarily classified based on diameter. For the purpose of this review, a nevus that exceeds 20 cm in diameter is defined as a giant CMN. Small and medium congenital CMN are less than 1.5 cm and between 1.5 and 19.9 cm, respectively. Additional classification systems involve the percentage of total body surface area involved or the anatomical location. For instance, a lesion covering greater than 1% of body surface area in the face and greater than 2% elsewhere on the body is defined as a giant CMN. Giant CMN also expand in proportion to one’s growth. One study estimates the rate of growth enlargement to be 1.7 on the face, 3.3 on the lower extremity, and 2.8 on the upper extremity. The appearance of giant CMN is similar to that of common acquired nevi. Giant CMN may be oval to round in shape and have well-defined borders. Satellite nevi may also be present at birth. The nevi may change in appearance as the child ages. Often at birth, the giant CMN may appear light and hairless, without areas of elevation; through time, the nevi may increase in pigmentation from tan to black and present with coarse hairs. Additional features include: variable surface texture (verrucous, pebbly, or cerebriform), irregular borders, pigmentation variations, and the presence of nodular or ulcerative proliferations. The presence of ulcerations can be concerning for an underlying melanoma. Leech et al. discussed two case studies in which newborns had proliferating nodules in a giant CMN at birth. The first newborn had a large (>1 cm) nodule with a benign proliferation of monomorphous nevus cells. The second newborn had a large ulcerative nodule that showed a pattern of hypercellularity and pleomorphic cells in various stages of division which blended into the surrounding nevus without necrosis; it was later determined to be benign. In spite of the alarming pattern of the second case, neither child has shown any signs of malignancy to date.

A giant CMN may regress over time if is located on the scalp. Strauss et al. reported nearly complete resolution of medium to giant size CMN on the scalp at a mean age of 30 months in seven children. The presence of a halo around a giant CMN may also signal potential resolution. This occurrence is likely to result in flattening and lightening of the nevus secondary to a potential immune response directed against specific antigens in the nevus. However, most giant CMN persist and will require a multi-disciplinary health team to address management.

Histological Characteristics

The histological features of giant CMN are relatively similar to that of small CMN. The nevomelanocytes are often found in the lower two thirds of the dermis interspersed among collagen bundles in single file and other structures such as hair follicles, sebaceous glands, vascular units, arrector pili and nerves. Such an arrangement of nevomelanocytes may result in inflammation and erythema in the dermis. Multiple histological patterns have been recognized in a giant CMN that are similar to those found in a wide spectrum of clinical nevi, including neural nevi. These nevomelanocytes undergo a process called neutroitization whereby the clinical development of soft nodules and plaques similar to a neurofibroma occurs on the back and buttocks. Interestingly, both neurotized CMN and neurofibromas stain S-100 positive, but CMN often lack the molecular hallmarks of a neurofibroma such as glial fibrillary acidic protein and myelin basic protein. Perhaps the presence of neural differentiation in a giant CMN may confer an increased risk of a comorbid neurological disorder.

Histologically, these nevi manifest as wavy, spindle cells with tapered ends embedded within a delicate fibrous stroma; nevic corpuscles may also be observed. Although giant CMN can present with a variety of histological features, it is atypical for nevomelanocytes to reside in the epidermis, exhibit a pagetoid pattern, or have coexisting dermal nodules, most of which are benign. Such atypical variations may result from excision or represent variants of giant CMN called “dysplastic” congenital nevi.

Embryology & Molecular Postulations of Giant CMN

The neural crest gives rise to melanoblasts which migrate and differentiate into nevomelanocytes in the epidermis and dermis. This differentiation is regulated by an interplay of genes including the microphthalmia-associated transcription factor gene, c-kit proto-oncogene, and the c-met/hepatocyte growth factor scatter factor. Mutations among these genes may lead to aberrant differentiation and deposition of melanocytes in the leptomeninges and placenta. Furthermore, the variant of a rare type of CMN such as a divided nevus can provide insight into the embryological origins of CMN. This nevus is seen on both sides of one’s face along the upper and...
lower eyelids and appears as a single lesion when the eyelids are closed; this suggests that CMN develop between the 9th and 20th week of gestation, when the eyelids and other structures (such as the glans of the penis) fuse.1,3

Although mutations disrupting embryological processes may lead to the development of a giant CMN, other mutations play a role in the pathogenesis. A mutation known as NRAS was common in giant CMN, occurring in 18 of 24 cases, and therefore could exert a significant influence in the growth of a giant CMN.3,11 Another mutation which could be a potential player in the development of a giant CMN is BRAF. The BRAF mutation often occurs in malignant melanoma secondary to UV exposure.11,12 However, Bauer et al. showed no BRAF mutations in 32 melanocytic nevi present at birth; rather, 26 of 32 cases tested positive for NRAS mutations.12 What is interesting is that when a subset of melanocytic nevi not detected at birth was analyzed, a majority was found to contain the somatic BRAFV600E mutation.12 Overall, the absence of the BRAF mutation in congenital melanocytic nevi suggests that UV-light-induced mutations do not play a role in the development of giant CMN and may confer a decreased risk of malignant melanoma given the difference in mutational patterns. Finally, upon analysis of a giant CMN lesion, chromosomal rearrangements including 1p, 12q, and 19p were reported in a culture of melanocytes.13 To date there is no specific inheritance pattern of giant CMN. Wijn et al. presented two cases of familial giant CMN where one patient with giant CMN also had an affected sibling and another patient had a cousin affected with giant CMN.9 The authors also reviewed the literature for familial occurrence of giant CMN and hypothesized that the sporadic nature of giant CMN in families, in addition to the discordance in monozygotic twins, may suggest a type of “paradominant inheritance” where the disease manifests itself due to a postzygotic mutation that results in loss of heterozygosity.7

**Giant CMN & Risk of Melanoma**

There is ongoing debate whether having a giant CMN increases a patient’s risk for malignant-melanoma development during childhood. Several longitudinal studies have gathered data regarding the potential for CMN to contribute to melanoma risk. Marghoob et al. published an update of malignant-melanoma development from the New York University School of Medicine Large Congenital Melanocytic Nevi (NYU-LCMN) Registry, at which time 92 patients with giant CMN were entered into the database with an average follow-up of 5.4 years (median age, 3 years).3,12 Malignant melanoma developed in three patients at extracutaneous sites (two in the CNS and one in the retroperitoneum), and the five-year cumulative life-table risk for malignant-melanoma development was estimated to be 4.5%.3 Bittencourt et al. provided a follow-up study of the NYU-LCMN with 160 patients who were followed for an average of 5.5 years (median age, 14 months).14 No additional melanomas had developed since the previous study, reducing the five-year cumulative life-table risk to 2.3%.14 Patients were excluded in both studies if they had previous melanoma development prior to entry into the database.

However, there remain discrepancies in the literature regarding the precise melanoma risk with a comorbid giant CMN. In a systematic review of 14 articles, Krenkel et al. reported that the frequency of melanoma occurrence in CMN ranged from 0.05% to 10.7%, with a greater proportion occurring in smaller studies, possibly due to selection bias.15 Nine of the studies focused on large or giant CMN, and out of 1,539 patients, 39 or 2.5% developed melanoma in the presence of a large or giant CMN; hence the proportion of melanomas occurring in a large or giant CMN was greater than the total melanoma occurrence (0.07%) in CMN among the 14 studies.15 Additionally, the majority of melanomas were found to arise within the CMN, in 33 of 49 cases or 67%, in contrast to the 22% that arose in extracutaneous or unknown primary sites.15

Overall, the occurrence of a giant CMN increases a patient’s chance for developing melanomas.2,5,14-17 Certain risk factors also increase the likelihood of developing malignant melanoma with a giant CMN. Melanomas are more likely to occur if the giant CMN has a diameter that exceeds 49 cm.14,16 Localization of a giant CMN on the trunk (compared to the scalp or extremities) is another risk factor for melanoma development.2 Increased numbers of satellite nevi are associated with greater melanoma occurrence rates, and in the Bittencourt et al. study released in 2000, 145 of the total 160 included participants had satellite nevi.14

**Neurocutaneous Melanosis**

Neurocutaneous melanosis (NCM) is a rare but serious complication of giant CMN. This condition refers to the proliferation of melanocytes in the central nervous system along the leptomeninges, resulting in increased intracranial pressure and symptoms such as headache, focal neurologic deficits, and, in severe cases, seizures.2,17 DeDavid et al. reviewed the records of 117 patients from the NYU-LCMN registry and 172 cases of LCMN worldwide and found that of the 289 total patients with large CMN, manifest CNS involvement was present in 33 patients.18 All of these patients had nevi in a posterior axial location in addition to the presence of satellite nevi in 31 of the 33 patients with manifest NCM.18 Furthermore, this systematic review reported that at the time of the study, six of the 33 patients with symptomatic disease were alive, while half of those who had died had passed away before age five.18 Among the 33 patients with NCM, 21 or 64% had comorbid CNS melanomas.18 A later follow-up study of the NYU-LCMN including 160 patients showed that only four patients had manifest NCM, resulting in a five-year life-table risk of 2.5% for developing NCM; interestingly, two of the four patients had CNS melanomas, and all four of the patients were deceased at the time of publication.14 Similar to melanoma development, certain risk factors, such as posterior axial location and satellite nevi, increase a patient’s risk for NCM.14,16 Marghoob et al. showed that giant-CMN patients having greater than or equal to 20 satellites had a 5.1-fold increased risk for NCM compared to those patients with fewer than 20 satellite lesions.2,17 Given its poor prognosis, the potential for patients with a giant CMN to develop NCM is a serious complication that must be addressed in patient management.

**Treatment Overview**

The presence of a giant CMN often presents a psychosocial burden for both the patient and family members. Children with giant CMN are more likely to suffer from anxiety, depression, and other behavioral problems.2,13 Hence, treatment must be multifaceted to address the dermatological, psychological, and other health concerns of a giant CMN. Current treatment options include: dermabrasion, curettage, chemical peels, laser therapy, and surgical excision. Dermabrasion removes the epidermis and the upper dermis (where nevomelanocytes often concentrate in infancy), lightening the nevus and enabling easier detection of melanomas in deeper tissues; however,
the resulting skin texture becomes more sensitive, with reduced hair density. Curettage is another treatment that takes advantage of a cleavage plane present in early infancy to separate the superficial and deeper layers of the dermis and remove nevomelanocytes. Laser therapy using lasers such as the Q-switched ruby, alexandrite, and Nd:YAG are commonly used to treat CMN, with the Q-switched ruby laser being the best studied for giant CMN. The laser emits certain wavelengths that absorb the melanin pigment and uses thermal energy to destroy the melanocytes, resulting in decreased pigmentation and scar tissue compared to dermabrasion and curettage. Waldorf et al. used the Q-switched ruby laser in the treatment of 18 patients with small CMN and attained an average clearance of 76% after eight sessions; in only five patients was the clearance of pigment greater than 90%. Furthermore, histological studies showed clearing of nevus cells in the upper reticular dermis only, with no reduction in the lower reticular dermis. In spite of improvements in cosmetic appearance in each of the above treatment modalities, repigmentation and the persistence of dermal nevomelanocytes that can mask a potential melanoma secondary to scar tissue remain current disadvantages. Yet, when surgical intervention is not possible, these therapies do provide alternative treatment options for patients with giant CMN.

Surgical excision is often sought to further improve cosmetic appearance of CMN. The primary indication for surgery is the occurrence of melanoma and/or other malignancy. Given that the likelihood of developing melanoma is higher in childhood, surgical intervention should be performed as early as six months. In addition, infants and younger children may be better able to tolerate multiple surgical excisions and stages with greater healing rates and less chance for scarring than older children. The limitations of surgery, however, include infection, discomfort, anesthesia risks, immobility secondary to scar formation, and psychosocial factors. Kishi et al. treated five patients with giant CMN on the trunk with an enzymatically separated epidermal sheet graft at two months. The procedure was tolerated well in all five patients, and the grafted areas became soft, lighter and lacked hair growth over a few months; in addition, one-year follow-up histological studies of the grafts showed no nevus cells. In another study, Schiestl et al. tested an artificial skin graft known as Integra Artificial Skin (Integra) to treat giant CMN in 12 patients. The Integra implant involved two stages, with the insertion of Integra in the first stage and removal of the silicone layer in the second stage; the take rates of Integra ranged from 95 to 100% in the first stage, and the second skin graft resulted in take rates ranging from 95 to 100% as well. Integra was successful in eight of the 12 patients and failed in the other four secondary to infection complications; overall, the Integra patients reported a functional and cosmetic benefit of Excellent in 58% of cases, Good in 25%, and Fair in 15%, within a follow-up period of six months to four years. In yet another study, Fahmy et al. performed a staged excision and used tissue expanders (TE) from distant skin to treat 12 patients with giant CMN using 37 different sizes of TEs for a total of 86 operative procedures. Complications arose in seven or 19% of the 37 TEs due to complications such as exposure of the expander, infection, expander failure and/or port failure. However, patient satisfaction was based on 10 items (including body image), and 58% of the patients reported a good satisfaction rate while 8% reported mild satisfaction due to the experience of complications. Certainly, surgical advances have improved the functional and cosmetic outcomes of giant CMN and will continue to advance as new biotechnologies such as autografts and biological growth factors become available.

Current Recommendations & Conclusion

Giant CMN remain a clinical challenge, and care must be taken to educate patients and families on the risks, treatment course, and preventative measures involved with giant CMN. Giant CMN are often associated with developmental disorders including but not limited to spina bifida, tethered cord syndrome, scoliosis, clubfoot, rhabdomyosarcoma, liposarcoma, subcutaneous atrophy, choroid plexus papilloma, and cranial bone hypertrophy. The increased risk of developing melanoma is higher in older children. The limitations of surgery, however, include infection, discomfort, anaesthesia risks, immobility secondary to scar formation, and psychosocial factors. Kishi et al. treated five patients with giant CMN on the trunk with an enzymatically separated epidermal sheet graft at two months. The procedure was tolerated well in all five patients, and the grafted areas became soft, lighter and lacked hair growth over a few months; in addition, one-year follow-up histological studies of the grafts showed no nevus cells. In another study, Schiestl et al. tested an artificial skin graft known as Integra Artificial Skin (Integra) to treat giant CMN in 12 patients. The Integra implant involved two stages, with the insertion of Integra in the first stage and removal of the silicone layer in the second stage; the take rates of Integra ranged from 95 to 100% in the first stage, and the second skin graft resulted in take rates ranging from 95 to 100% as well. Integra was successful in eight of the 12 patients and failed in the other four secondary to infection complications; overall, the Integra patients reported a functional and cosmetic benefit of Excellent in 58% of cases, Good in 25%, and Fair in 15%, within a follow-up period of six months to four years. In yet another study, Fahmy et al. performed a staged excision and used tissue expanders (TE) from distant skin to treat 12 patients with giant CMN using 37 different sizes of TEs for a total of 86 operative procedures. Complications arose in seven or 19% of the 37 TEs due to complications such as exposure of the expander, infection, expander failure and/or port failure. However, patient satisfaction was based on 10 items (including body image), and 58% of the patients reported a good satisfaction rate while 8% reported mild satisfaction due to the experience of complications. Certainly, surgical advances have improved the functional and cosmetic outcomes of giant CMN and will continue to advance as new biotechnologies such as autografts and biological growth factors become available.

References

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Case Report:
A 52-year-old African-American female presented with complaints of having “stiff skin” that progressively impaired her movement over the past five years. The skin “tightness” had started on the body, and then progressed to include her hands, trunk, legs and finally face. She complained of constant pain, with restrictions of movement requiring use of a walker. She experienced worsening of the pain in her hands, accompanied by color changes and tingling in cold weather. She had seen a doctor years prior, who told her she had an untreatable condition. At that time, the patient was offered no therapy. Her review of systems was positive for difficulty swallowing, acid reflux, dyspnea on exertion, nonproductive cough, diffuse arthralgias and myalgias, subjective decreased range of motion, and chronic fatigue. Her past medical history was significant for hypertension and gastroesophageal reflux disease. Her past medical history was significant for hypertension and gastroesophageal reflux disease. Her past medical history was significant for hypertension and gastroesophageal reflux disease. The patient was taking Lisinopril and Percocet, and denied alcohol and drug use. Her family history was negative for any significant dermatologic diseases or autoimmune disorders.

Physical exam revealed taught, shiny skin with a salt and pepper pigmentation throughout the abdomen, back, and extremities. There was complete hair loss of both upper and lower extremities. Hyperpigmented, thickened plaques spanned the trunk, thighs and upper extremities bilaterally. There were patchy areas of sparing in affected locations, including complete sparing of both antecubital fossas (Figures 1-3). The hands and feet revealed sclerodactyly, a localized thickening and tightness of the skin of the fingers and toes, often accompanied by atrophy of underlying soft tissue. There were ulcerations on the dorsal aspect of the skin overlying the proximal interphalangeal (PIP) joints of the right second and third digits (Figures 4). The nail plate and bed were unable to be assessed, as patient was wearing acrylic nails.

Laboratory analysis showed a high positive ANA screen, with an ANA titer of 1:320 nucleolar pattern. Antibodies to ribonuclear protein (RNP), centromere, and Scl70 were all found to be negative. Rheumatoid factor (RF) was also negative. Urinalysis and complete metabolic panel were normal, and glomerular filtration rate was decreased to 51.98. Complete blood count revealed a hemoglobin of 11.0, hematocrit of 33.9, and mean corpuscular volume of 76.2.

A 3mm punch biopsy of the left upper arm was taken, which revealed extensive fibrosis. The pan-dermal fibrosing reaction was evident by numerous collagen bundles extending to the subcutis (Figures 5 and 6). The histologic specimen revealed a reduced number of adnexal structures, with minimal inflammatory cell infiltrate (Figure 7). This is characteristic of systemic sclerosis, and distinct from localized scleroderma (morphia), in which there is a prominent inflammatory cell infiltrate.

The clinical presentation of this patient led to the diagnosis of diffuse cutaneous systemic sclerosis. Her diagnosis was confirmed by histological evaluation of a skin biopsy. The patient’s bloodwork supported the diagnosis, as a nucleolar pattern ANA titer is more specific for systemic sclerosis than other patterns, despite being less common. Although she did not have anti-Scl70 or anti-centromere antibodies, these are found in less than 30% of patients with the diffuse form of disease. The patient was transferred to another facility for further workup and management. Treatment was initiated with colchicine, topical clobetasol/ vitamin D therapy, Lipitor, lisinopril and nifedipine. The patient was also referred to rheumatology, gastroenterology and pulmonology. After missing several appointments, her treatment with methotrexate and prednisone had to be deferred. Unfortunately, the patient was lost to follow-up.

Discussion:
Systemic sclerosis (SSc), also known as scleroderma, is a complex disorder characterized by vascular alterations, autoantibodies against various cellular antigens, and extensive fibrosis. Although...
at present there is no single unifying hypothesis to explain all aspects of the disease, evidence has shown the primary insult to be directed against blood vessels, causing endothelial cell injury. Chronic inflammatory cell infiltration and subsequent cytokine production, combined with oxidative damage and cell injury, results in the development of tissue fibrosis. The disease is divided into two conventionally used subsets, despite microarrays revealing more subsets than previously appreciated. Autoantibodies are used to help classify subtypes and convey both diagnostic and prognostic information. The most prevalent autoantibodies associated with SSc are antitopoisomerase antibodies, anti-topoisomerase I (or anti-Scl70) antibodies and anti-RNA polymerase III antibodies. They are all mutually exclusive, and tend not to overlap with autoantibodies from other autoimmune diseases.

The two main subsets of SSc are limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc). The limited cutaneous form is characterized by an initial onset of Raynaud’s phenomenon in the early stages of disease. Raynaud’s phenomenon is a reversible spasm of the small arteries and arterioles in the fingers and toes. Several years after the appearance of Raynaud’s, the cutaneous fibrosis component manifests, but only as thickening of the skin of fingers and hands. CREST syndrome represents a subset of lcSSc, defined by calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias. Seventy percent of lcSSc patients have antitopomerase antibodies, which confer an increased risk of pulmonary artery hypertension (PAH). The antitopomerase antibodies associated with lcSSc are typically more common in Caucasians. Diffuse cutaneous systemic sclerosis presents initially with symmetric finger and hand swelling. It later generalizes to the forearms, arms, face, trunk, and lower extremities. In general, the onset of edema in dcSSc occurs shortly after the first episode of Raynaud’s. The edema becomes a firm, bound-down induration, with fibrosis leading to deformities of the digits such as fixed flexion contractures of the proximal interphalangeal joints. Twenty percent of dcSSc patients have anti-topoisomerase I antibodies, which confer a worse prognosis with increased pulmonary disease and increased mortality. The presence of anti-topoisomerase I antibodies is found to be more common in African Americans. Another twenty percent of dcSSc patients have anti-RNA polymerase III antibodies, which confer an increased risk of scleroderma renal crisis (SRC).

Environment and Genetics

The extremely complex pathogenesis of SSc generally involves abnormalities of both the vascular and immune systems, which ultimately lead to fibrosis of end organs. Several etiologies are suspected to be linked to the pathogenesis of SSc. Environmental factors such as occupational and industrial exposure to vinyl chloride, silica dust, and organic solvents, as well as drugs such as bleomycin, pentazocine, and cocaine have all been implicated as potential causes of disease. Gadolinium-based MRI contrast has been reportedly linked to nephrogenic systemic fibrosis, a condition of renal dysfunction with thickening and hardening of the skin. Nephrogenic systemic fibrosis has recently been demonstrated to have increased expression of transforming growth factor beta (TGFβ), which is one of the most well-described growth factors involved in the pathogenesis of SSc.

Infectious agents have also been shown to play a role in the immunopathogenesis of SSc. Viruses such as cytomegalovirus (CMV) and parvovirus B19 have been linked to SSc development. It is thought that molecular mimicry occurs, whereby antibodies that recognize viral antigens cross-react with endothelial cells to induce apoptosis. More recent studies have expanded the link between infectious agents and SSc to include Epstein-Barr virus (EBV), hepatitis B virus (HBV) and Toxoplasma gondii, shown by demonstrating high titers of antibodies against these infectious antigens in patients with scleroderma.

There is conflicting evidence to support the contribution of genetics to SSc pathogenesis. The largest twin study to date showed a low concordance rate of SSc among identical twins, suggesting a low heritability component in the development of disease. However, despite this seemingly low rate, it is still approximately 300 times higher than the frequency expected by chance alone. The Choctaw Indians of Oklahoma reportedly had the highest worldwide prevalence rates of SSc, and a unique human leukocyte antigen (HLA) haplotype that may confer a genetic risk. Furthermore, studies of a Korean cohort and two Caucasian cohorts showed susceptibility at two HLA loci. Several genetic polymorphisms have been identified to confer susceptibility to SSc; however, they have failed to be confirmed in follow-up studies. Overall, a specific genetic mode of inheritance of SSc remains to be elucidated. Despite the lack of a clear genetic inheritance, gene expression in scleroderma skin is distinct from that of healthy controls, with over 2,000 genes differentially expressed. This was demonstrated in studies showing both lesional and nonlesional biopsies of SSc patients to exhibit nearly identical patterns of gene expression, ones which are distinct from healthy controls. Based on the currently available data, it is likely that genetic factors provide a susceptible environment that predisposes individuals to the development and progression of SSc.

A highly controversial theory behind development of SSc is the concept of microchimerism. It has been hypothesized that allogenic fetal and maternal cells which cross the placenta during gestation may contribute to disease pathogenesis. HLA compatibility allows for fetal or maternal cells to cross the placenta and persist in the bloodstream. The theory states that these engrafted fetal cells become activated by some external trigger and mount a graft-versus-host response on the mother or future offspring, thus resulting in SSc disease manifestation. Another concept linked to the development of SSc is alterations in collagen transcription genes. In SSc, fibroblasts have an increased expression of genes involved in the production and deposition of type I collagen. Type I collagen is the most prevalent protein found in patients with SSc and is thought to be responsible for the most severe clinical symptoms. The disease state of SSc can be distinguished from normal wound healing by the autonomous and persistent upregulation of collagen gene expression.

Immunologic alterations

Immune dysregulation and increased circulating levels of cytokines also play a role in the development of SSc. The humoral immune system has gained recent attention, as one of the most common manifestations of SSc is the presence of specific autoantibodies. Some of them have been described as exclusively associated with SSc, while others are associated with various clinical manifestations of the disease such as pulmonary or other organ involvement. Despite the well-described presence of autoantibodies, the jury remains out on whether or not they are directly involved in actual disease development and progression. Although microarray analyses of skin biopsies have shown conflicting
results, a role of B-cell autoantibodies in the pathogenesis of SSc is implicated. Lung-tissue histology from SSc patients has demonstrated lymphoid aggregates of B cells, suggesting their involvement in lung disease. Investigators have also shown an overexpression of activation markers for memory B cells in SSc patients compared to controls.3

The cellular immune system, and activity of T helper (Th) cells, is tightly linked to SSc. Studies have shown a predominance of Th2 peripheral blood cells in SSc patients, as compared to Th1 cells. Of note, these immune cells are most pronounced in those with interstitial lung disease, corresponding to a decreased forced vital capacity. Furthermore, increased IL-13 correlates with a greater degree of fibrosis, particularly in those with diffuse-type SSc. It is suspected that IL-13 contributes to fibrosis through TGFβ induction by macrophages.3 Th2 cytokines such as IL-4, IL-5, IL-13 and IL-21 can also act independently of the TGFβ signaling pathway in stimulating fibroblast proliferation and collagen deposition.10 Several reports have implicated the role of Th1 cells in SSc, specifically from observations of increased interferon (IFN) gene-expression signatures. There was found to be increased IFN-α mRNA in vascular and perivascular cells. This data suggests a local activation of leukocytes within the vasculature. It has also been shown that anti-topoisomerase I antibodies induce significantly elevated IFN-α levels, while anticientromere antibodies appear to have a negative regulatory impact on IFN-α. Lung biopsies have linked increased induction of IFN-α with greater tissue injury. This provides partial evidence for the diverse phenotypes seen in limited compared to diffuse SSc subsets, by demonstrating increased degrees of IFN response leading to a more severe lung fibrosis.3 Numerous chemokines have been implicated in the development of SSc, but chemokine CCL2 has received the most attention. Both the skin and serum of SSc patients have shown elevated levels of CCL2, in some cases corresponding to major organ involvement such as pulmonary fibrosis. It has been suggested that an autocrine loop of CCL2 and its receptor, CCR2, may be contributing to the early stages of fibrosis.3

Fibrosis

Fibrosis results from chronic inflammation, defined as an immune response that persists for several months, in which tissue remodeling and repair processes occur simultaneously. This is in contrast to acute inflammation, characterized by rapidly resolving vascular changes, edema, and a neutrophilic response. Chronic fibrosis usually results from a common persistent irritant that sustains production of growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines. The irritants leading to tissue damage include infections, autoimmune reactions, toxins, radiation and mechanical injury. These irritating stimuli result in the deposition of connective-tissue components that progressively remodel and destroy normal tissue architecture.10 In SSc, the previously described etiologic factors, as well as endothelial cell damage and vascular alterations which will be detailed later, represent the irritating stimuli that result in fibrosis.

The process of tissue repair typically involves a regenerative phase and a fibrosis phase. The regenerative phase has no lasting evidence of damage, as injured cells become replaced by cells of the same type. In the fibrosis phase, or fibroplasia, normal parenchymal tissue is replaced by permanent fibrotic scar tissue.10 Under normal conditions, fibroblasts produce little extracellular matrix (ECM) components.3 However, the generally beneficial repair process becomes pathogenic when normal tissue is replaced by permanent fibrotic scar tissue from substantial deposition of ECM.10 The myofibroblast is a modified fibroblast, which exhibits features of smooth-muscle cells that are critical for tissue contraction and remodeling during the wound-healing process.3 Fibrosis occurs when the synthesis of new collagen by myofibroblasts exceeds the rate of degradation, leading to an overall increase in collagen.10 This unregulated wound healing due to activation and differentiation of fibroblasts into collagen and ECM-producing myofibroblasts is a highly complex process. It is partially attributable to local tissue injury causing the release of cytokines and growth factors.3 In SSc, this remodeling and fibrosis ultimately leads to organ failure and death.

Fibroblasts obtained from lesional skin or fibrotic lungs in SSc patients were shown to have constitutively activated myofibroblast-like phenotypes, characterized by enhanced ECM synthesis with secretion of cytokines and chemokines and increased expression of cell surface receptors.10 Various mechanisms are thought to be responsible for regulating myofibroblast activity. The exact origin of myofibroblasts in SSc has yet to be definitively established; however, a few potential sources have been described. They are thought to be derived from local fibroblasts; transdifferentiation of epithelial and endothelial cells known as epithelial- or endothelial-mesenchymal transition; bone-marrow stem-cell derived fibrocytes; or smooth-muscle-like pericytes found in vascular walls.3 It is thought that the SSc fibroblast phenotype is maintained by an autocrine TGFβ signal, since these fibroblast characteristics are reproducible in normal human fibroblasts following TGFβ stimulation. The cytokine TGFβ is the most extensively studied regulator of the ECM and is tightly linked to the development of fibrosis in disease.10 TGFβ induces fibrosis via stimulation of ECM synthesis by fibroblasts and myofibroblasts.3 It also acts by decreasing the synthesis of collagen-degrading metalloproteinases and stimulating production of metalloproteinase inhibitors.3 TGFβ is secreted by numerous cell types including fibroblasts, myofibroblasts, T cells, monocytes, macrophages and platelets, though circulating monocytes and macrophages are the primary source of TGFβ. Regulation occurs at the level of TGFβ secretion and activation, as opposed to transcriptional expression. TGFβ is stored in its latent form and activated by various proteases.10 TGFβ signal transduction is highly intricate, involving multiple receptors and signaling intermediates. It appears that TGFβ sensitizes fibroblasts and maintains them in a persistently activated state via an autocrine mechanism loop, leading to further TGFβ production.3

Critical to pathogenesis of SSc is the
signaling cascade involving the SMAD family of proteins. Activated TGFβ signals phosphorylation of SMAD protein intermediates via transmembrane receptors to modulate the transcription of collagen. Once activated, TGFβ binds to its receptor, which then becomes phosphorylated. The phosphorylated receptor subsequently signals phosphorylation of SMAD2 and SMAD3, thereby activating them. Activated SMAD2 and SMAD3 then form a complex with SMAD4, which allows for translocation of the entire complex into the nucleus. Once within the nucleus, intranuclear proteins aid the complex in binding directly to promoter regions of genes responsible for collagen production. Dysregulation of the SMAD and non-SMAD downstream pathways of TGFβ activation contributes to the abnormal fibrogenic response seen in SSc. Of note, SMAD7 is an inhibitory SMAD which can bind to the TGFβ receptor complex early in the cascade and prevent phosphorylation of SMAD2 and SMAD3. Recent studies have described substantially decreased SMAD7 levels in fibroblasts and skin of SSc patients.

Evidence exists to support the role of connective-tissue growth factor (CTGF) and endothelin-1 (ET-1) in persistent fibroblast activation due to the autocrine TGFβ loop, as these factors are induced by TGFβ. CTGF is involved in angiogenesis and structural organization of connective tissue. It also exerts a profibrotic effect via upregulation of collagen, fibronectin and integrin and stimulation of fibroblast proliferation. Although the exact pathogenesis of CTGF is not fully understood, it is postulated to represent a downstream mediator of TGFβ. ET-1 is a potent vasoconstrictor, with additional pro-fibrotic properties.

**Vascular and endothelial aberrations**

Chronic fibrosis in SSc is tightly linked to vascular disruption, which precedes the fibrotic changes. Vascular disease results from damage to the endothelial-cell layer of the microvasculature. This injury leads to over-expression of adhesion molecules, leukocyte and pericyte proliferation, platelet adhesion and activation, and influx of perivascular infiltrate. Myofibroblasts in the endothelium create a vasculopathy of intimal thickening, fibrosis, and marked luminal narrowing, with fairly normal media and smooth-muscle hypertrophy. This results in compromised regional blood flow, with tissue ischemia and fibrosis that ultimately lead to organ dysfunction.

Electron microscopy of skin biopsies from SSc patients show signs of endothelial injury, apoptosis, and perivascular edema. In SSc there exists endothelial-cell injury and capillary destruction, accompanied by a perivascular reaction involving immune cells and fibroblasts. Increased vascular permeability allows mononuclear cell transmigration into the perivascular space, resulting in edema. This vascular-cellular interaction precedes the later tissue fibrosis, occurring as vessels loose elasticity to become fibrotic and occluded.

When vascular endothelium is disrupted, there is a downstream alteration of "biomarkers," which are certain molecules having increased production or impaired release. This imbalance of regulatory factors alters local blood flow and contributes to the vascular instability of SSc. Disrupted endothelial cells result in increased coagulation, platelet activation, and release of adhesion molecules and proangiogenic factors. The highly upregulated proangiogenic factors such as platelet-derived growth factor (PDGF), TGFβ, ET-1 and chemokine CCL2 are activators of smooth-muscle cells and stromal fibroblasts, thus contributing to proliferative vasculopathy and fibrosis. The platelet products PDGF and TGFβ also increase production and deposition of ECM. Skin biopsies have demonstrated increased circulating levels of the biomarker von Willebrand factor, shown to leak into the perivascular space of scleroderma patients. There is a further increase in the potent vasoconstrictor ET-1, which acts on vascular smooth-muscle cells to potentially induce myofibroblast expression along with exhibiting pro-fibrotic properties via activation of TGFβ, as previously mentioned.

Despite an increase in the aforementioned proangiogenic factors, in vitro studies paradoxically show defective angiogenesis in SSc patients, evidenced by decreased capillary density and low expression of molecules which facilitate the action of vascular endothelial growth factor (VEGF). Some studies have led to the implication of a soluble inhibitor of angiogenesis. During the early, acute phase of SSc, proangiogenic factors like VEGF are released; however, antiangiogenic proteolytic enzymes also become activated. More severe disease is noted to have elevated levels of endostatin, an angiogenesis inhibitor derived from collagen. Stabilization of proangiogenic factors becomes blocked by the concurrent up-regulation of these angiogenesis inhibitors. This imbalance of proangiogenic and antiangiogenic factors favors decreased ability for new vessel formation.

Systemic sclerosis is also characterized by impaired vasculogenesis, or vascular repair. Endothelial progenitor cells (EPCs) are mononuclear cells produced in the bone marrow, which travel to sites of vascular injury and ischemia to mediate vasculogenesis. Advanced stages of SSc have shown patients with significantly fewer and functionally impaired EPCs. When bone-marrow mesenchymal cells are defective, SSc patients are unable to repair or replace endothelial cells after injury. Studies have shown that administration of statins (HMG-CoA reductase inhibitors), which increase progenitor cells necessary for vasculogenesis, result in increased circulating endothelial cells. Further research is needed to confirm this finding.

Nitric oxide (NO) is a potent vasodilator, which also inhibits platelet aggregation and reduces endothelial cell activation by cytokines. Angiotensin II (ANG II) is a vasoconstrictor which regulates cell growth, inflammation, and vascular fibrosis by increasing activation of TGFβ and CTGF. In SSc patients, dysfunctional vascular tone is attributed to both an intrinsic defect in NO production in endothelial cells and an increased level of ANG II. Raynaud’s phenomenon, characterized by vasospasm of digital arteries and cutaneous vessels, is partly influenced by impaired vasodilation from a deficiency of the vasodilatory neuropeptides substance P and calcitonin gene-related peptide (CGRP).

The exact pathogenesis leading to endothelial cell injury in SSc is not entirely elucidated, but several possible causes have been proposed. Data has suggested that activated cytolytic T cells cause endothelial cell injury via release of granzyme proteolytic enzymes. The role of anti-endothelial cell antibodies (AECAs) has also been proposed, and it is suggested that the presence of AECAs may correlate with EPC death by apoptosis. Systemic sclerosis patients possess IgG antibodies that react with endothelial cells. It remains unclear whether these antibodies serve as a primary mechanism of endothelial damage or represent a secondary consequence of such injury. Nonetheless, the presence of these antibodies correlates with more severe clinical vascular disease including digital ischemia, abnormal nailfold capillaries, PAH and microvascular disease in pulmonary fibrosis. As previously described, viral and bacterial infection might play a role in endothelial
apoptosis, as there are increased anti-CMV antibodies found in SSc patients. Furthermore, activation of the cellular and humoral immune system is thought to lead to endothelial injury. Studies have shown defective complement due to loss of protective molecules, representing either a sign of vascular injury itself or a contributing factor to the damage via complement activation. Pericytes are cells that support endothelial-cell functions in arterioles, capillaries and venules. In scleroderma, pericytes are hyperplastic, and when activated they express PDGF and interact with fibroblasts in the early stages of the disease. It is possible that these pericyte-fibroblast interactions contribute to the vascular disruption seen in SSc.

Several studies have shown decreased serum antioxidant levels and increased markers of oxidative damage in scleroderma patients. One cohort of SSc patients was shown to have deficiencies of ascorbic acid and selenium, while another showed reduced concentrations of alpha-tocopherol (vitamin E) and carotene. Signs of lipid peroxidation were demonstrated using the clinical marker F2 isoprostanes. These F2 isoprostanes represent a family of compounds generated from arachidonic acid via a free-radical-catalyzed mechanism. Elevated levels of urinary concentrations of F2 isoprostanes have been shown in SSc when compared to healthy control subjects. Despite clear evidence of oxidative damage, the primary insult leading to reactive oxygen species (ROS) generation remains to be elucidated. It is known that vasoconstriction leading to decreased tissue perfusion and hypoxia causes cell injury and alterations in function. Tissue hypoxia induces ECM genes, which mediate fibrosis. Ischemia leads to the release of free radicals into the vascular cells from macrophages, endothelial cells, and vascular smooth-muscle cells. Lipoproteins represent an additional contributor to oxidative damage. Studies show that SSc patients have increased levels of oxidized lipoproteins such as LDL, which has innate properties of enhancing smooth-muscle-cell proliferation and activating endothelial cells. The oxidative stress caused by these reactive oxygen species mediates fibrosis via direct activation of fibroblasts and endothelial cells, and by releasing the pro-fibrotic cytokines TGFβ and PDGF. Perivascular cells in SSc are also shown to have increased PDGF receptors. Continuous oxidative stress from repeated ischemia-reperfusion injury might lead to expression of neoantigens that perpetuate an autoimmune response. The question remains, however, whether ROS initiate the vascular damage and instability leading to Raynaud’s phenomenon, or if the ischemia-reperfusion injury from vasospasm leads to ROS generation.

The role of antiphospholipid antibodies in SSc is unclear, although they are suggested to be involved in macrovascular disease, as their presence has been shown to be associated with digital ischemia. Alterations in coagulation are thought to be attributable to endothelial-cell injury as well. The endothelium is responsible for maintaining an antithrombotic lining, with tight regulation of the coagulation process. In patients with SSc, elevated fibrinogen levels and defective tissue plasminogen activator (tPA) release alters the balance of intravascular coagulation and fibrinolysis to favor coagulation. A deficiency of tPA alters the fibrinolytic pathway, thus predisposing SSc patients to fibrin deposition and vascular obstruction due to thrombosis.

Clinical manifestations

Within the skin of SSc patients, there is increased collagen, abnormal vasculature, and an inflammatory infiltrate. The collagen consists of a homogenous, hyalinized pattern extending from the papillary dermis to the subcutis. This increased collagen ultimately replaces subcutaneous fat and eccrine sweat glands, which have atrophied. Direct immunofluorescence studies are usually negative for immunoglobulin deposition at the dermoepidermal junction and within the microvasculature, distinguishing SSc from other autoimmune connective-tissue disorders such as systemic lupus erythematosus (SLE). Although SSc has long been considered a disease of tissue fibrosis, the associated endothelial-cell injury and vascular disruption play a fundamental role in tissue damage. The clinical consequences of vascular disease are not limited to cutaneous vessels but also involve vasculature of the extremities and multiple organs. The widespread effects of vascular disease and tissue fibrosis can lead to internal organ dysfunction, a significant cause of morbidity and mortality among SSc patients.

Raynaud’s phenomenon is caused by disease of the thermoregulatory vessels in the skin and small to medium vessels of the peripheral arterial system of limbs. The normal vasospastic response to environmental decreases in temperature is exaggerated, resulting in color changes of the skin (pallor, cyanosis, or hyperemia). The attacks are typically symmetrical and resolve 15-20 minutes after re-warming. Systemic sclerosis patients experience frequent ischemic events that can result in digital ulcers or amputation. The nailfold capillaries are also impacted by microvascular disease in SSc. The damage is characterized by cutaneous capillary structural alterations and decreased density and blood flow. Nailfold capillaries demonstrate enlarged capillary loops surrounded by avascular areas. Telangiectasias of the face, hands, fingers and mucous membranes are common among scleroderma patients as well. While more likely to occur with limited SSc subtypes, they are present in later stages of all subtypes. Telangiectasia lesions consist of vasodilated postcapillary venules, without inflammation or neovascularization. They are thought to arise from a failed or aberrant effort of angiogenesis.

As clinical disease is not limited to the skin, there are widespread systemic effects occurring in SSc patients, often entailing a macrovascular disease of arteries. Intestinal pulmonary disease represents the most common cause of death in SSc patients. This life-threatening pulmonary pathology can result from either a nonspecific interstitial pneumonia leading to pulmonary fibrosis or a pulmonary-artery hypertension (PAH) due to an obliterator vasculopathy. Pulmonary fibrosis begins as patchy inflammatory infiltrates of lymphocytes, eosinophils and macrophages within alveolar walls, which then progresses to fibrosis as the alveolar septa thicken. Pulmonary-artery hypertension occurs by large-artery intimal thickening and proliferation. Scleroderma renal crisis (SRC) is characterized by accelerated hypertension and acute renal failure. It is caused by reversible vasospasm of arcuate and interlobular renal arteries, as well as duplication of the elastic lamina and intimal proliferation with luminal occlusion. Cardiac dysfunction results from both occlusive vascular disease and intermittent vasospasm known as “intramyocardial Raynaud’s phenomenon.” This leads to ischemic events and contraction-band necrosis from reperfusion injury. Fibrosis of the cardiac conduction system can also lead to arrhythmias. Loss of bowel smooth muscle and tissue fibrosis from mouth to anus leads to gastrointestinal manifestations of neurogenic dysfunction and bowel dysmotility, as well as malabsorption.
Treatment and therapeutic strategies

Important treatment advances for SSc would entail the development of therapeutic strategies that limit the progression of fibrosis without adversely affecting the overall repair process. To date, there are no entirely effective antifibrotic therapies available for patients with SSc. Penicillamine, methotrexate, photopheresis, relaxin, interferons, and cyclosporine have each been studied in clinical trials with variable response rates. In recent studies targeting the role of B cell autoantibodies, recent studies have evaluated treatment with rituximab, an autoantibody directed against the CD20 protein found on the surface of mature B-cells. One study showed that treatment with rituximab may improve lung function in SSc patients, evident by improved forced vital capacity. They also demonstrated improved skin scores in patients treated with rituximab. Various trials have shown conflicting results regarding skin disease and pulmonary-function improvement with rituximab, and larger trials are necessary. Imatinib, a tyrosine kinase inhibitor, has recently been considered a potential target for SSc therapy, with case reports showing positive outcomes. The rationale for clinical improvement is that imatinib can block the PDGF and TGFβ signaling pathway. Imatinib exhibits dual antifibrotic effects by inhibition of c-Abl, which is important for activation of TGFβ-induced factors, and of the PDGF receptor, which is itself a tyrosine kinase receptor. However, this data is limited by the uncontrolled study designs, and true insight into the efficacy of imatinib treatment relies on placebo-controlled, large-scale studies.

Targeting growth factors involved in the TGFβ autocrine loop represents another possible treatment option. CTGF is a potential target of interest, as is ET-1. An oral prostacyclin, iloprost, has been shown to have in vivo antifibrotic activity via down-regulation of CTGF expression. Bosentan, an endothelin-receptor antagonist which blocks the binding of ET-1, has been shown to have success in treating PAH associated with SSc. One recent study in the literature mentions urotenin II as elevated in SSc patients when compared to controls, and correlated to ET-1 levels. Urotensin II is a vasoactive peptide with profibrotic features that is thought to play a role in the pathogenesis of SSc. Further research is required in order to establish efficacy of this peptide; however, it might represent another target for treatment options.

There are currently no guidelines in place for the treatment of SSc-related vascular disease. Therapy relies on options to alleviate symptoms by addressing the vasospasm, vasculopathy with luminal occlusion, and thrombosis occurring with SSc vascular disease. Despite the evidence of platelet activation and release of prothrombotic growth factors in SSc, antiplatelet therapy has not shown conclusiveness in controlled trials. On the other hand, calcium-channel blockers are being used in treatment of Raynaud’s phenomenon and digital ischemia. The dihydropyridine calcium-channel blockers are potent vasodilators, with additional antioxidant, antithrombotic, and antiapoptotic effects. Clinical trials have shown some benefit in managing Raynaud’s phenomenon with a serotonin-2 receptor antagonist, ketanserin, as the neurotransmitter serotonin is a selective vasoconstrictor. Prostaglandins, which are potent vasodilators, have shown efficacy as well, seen particularly in pulmonary vascular disease and PAH. Prostacyclin, another vasodilator, has protective effects on the endothelium due to its antiproliferative effect on smooth-muscle cells and inhibition of platelet aggregation.

Phosphodiesterases inactivate the second messengers cAMP and cGMP, for prostacyclin and nitric oxide, respectively. Phosphodiesterase inhibitors thus prolong and enhance the effects of both the abovementioned vasodilators. Phosphodiesterase-5 inhibitors sildenafil and tadalafil have been shown to be associated with reduced plasma ET-1 levels, as well as improved capillary flow velocity in patients with Raynaud’s phenomenon. Nitrates represent another possible therapeutic option but are not free of limitations. One laboratory study showed that intra-arterial infusion of nitroprusside or L-arginine (the substrate for NO) decreased cold-induced vasospasm in SSc patients with Raynaud’s phenomenon. However, excessive levels of NO pose the issue of furthering tissue damage by adding to oxidative stress. Few studies have addressed the role of antioxidants in SSc; however, since lipoproteins such as LDL have been shown to contribute to oxidative stress, treatment with cholesterol-lowering medications might provide benefit for scleroderma patients via reduction of oxidative damage.

Severe cases of Raynaud’s phenomenon that are refractory to medical management have shown some improvement with selective digital sympathectomy. The procedure is done under general anesthesia, where vascular innervations visualized under a microscope are physically separated from the blood vessels. Botulinum-toxin injections have a role in nonsurgical sympathectomy, by targeting neurovascular bundles supplying involved digits. Significant pain reduction and improved healing of digital ulcers have been reportedly observed in SSc patients. Reversal of some of the vasculogenic and angiogenic defects seen in SSc, particularly in cases with severe digital ischemia, has been reported with autologous stem-cell transplantation. Hematopoietic stem-cell transplantation provides new sources of mesenchymal stem cells and progenitor cells and alters the cytokine milieu, leading to an overall recovery of the vascular network, restoration of blood flow, and decreased skin necrosis.

A treatment strategy which has not yet been reported in the literature involves targeting the SMAD family of proteins, specifically by increasing SMAD7 in scleroderma patients. It has been documented that SSc patients have decreased SMAD7, and it is well-known that SMAD7 is an inhibitor of SMAD3. Investigators have reported plasmid gene transfer of SMAD7 among knockout mice, demonstrating a correlation between degree of SMAD7 expression and both fibroblast proliferation and collagen accumulation resulting from cellular responsiveness to TGFβ. A therapeutic strategy involving plasmid transfection and increased expression of SMAD7 represents a newly proposed target pathway for the treatment of SSc. Despite the crucial involvement of TGFβ in regulating fibrosis, inhibition of its autocrine loop may consequently lead to numerous unwanted effects given its role in additional immune functions. A study involving knockout mice with TGFβ null mutants showed death within 3-4 weeks from a rapid wasting syndrome with a widespread inflammatory reaction. Thus, potential therapeutic options aiming to inhibit TGFβ must be approached with caution and should avoid complete abolition of its function. Nevertheless, a dual-acting therapeutic regimen that increases SMAD7 expression as well as blocks SMAD3 (potentially via receptor antagonism) could hinder the TGFβ signaling pathway, theoretically counteracting the intrinsic defect in SSc tissue fibroblasts.

In conclusion, systemic sclerosis is a multifaceted autoimmune disorder, of which the etiology remains to be fully understood. Several concepts and theories have been studied to explain the pathogenesis of disease, and it is found to be attributed to a pronounced vasculopathy and endothelial cell damage, leading to microvascular and macrovascular...
alterations. There is accompanying vast autoimmune dysregulation, which furthers vascular disruption. Both immunological and vascular aberrancies contribute to the severe, progressive cutaneous and visceral fibrosis characteristic of SSC. Cutaneous fibrosis and internal organ dysfunction represent a major cause of morbidity and mortality among scleroderma patients. Curative treatment options for this disease do not yet exist; however, increasing understanding of the pathogenesis of SSC will allow for further elucidation of potential therapeutic targets and the possibility for future treatment success.

References


**Case Study**

A 38-year-old, healthy, South American male presented with a 10-year history of unchanging, tender, brown-pink, 0.5 cm to 1.0 cm papules and nodules on his chest, shoulders, and face (Figures 1-3). He denied any preceding illnesses, medication use, and prior treatments. His medical history and current medication use was otherwise negative. He denied any family history of immunological disorders or skin, renal, or internal cancers, except multiple leiomyomas in his mother and brother. Physical exam revealed a Fitzpatrick type IV skin type and skin findings previously noted. Excisional biopsy of one of his lesions revealed findings consistent with piloleiomyoma by the characteristic features of bundles of smooth muscle interlaced around follicular structures in the dermis (Figures 5-8). Our patient underwent genetic testing showing positive mutation results: heterozygous for the IVS2+(1_10)del10 mutation in the fumarate hydratase (FH) gene. Subsequently, he underwent CT scan of the abdomen and pelvis with contrast. Results were unremarkable, showing kidneys, ureters, and bladder of normal size and position, without masses, calculi, or hydronephrosis. The patient was treated with two courses of intralesional 5-fluorouracil (5-FU) six weeks apart.

**Introduction**

Clinically, piloleiomyomas appear as firm dermal papules with a skin-colored, pink or reddish-brown surface and are commonly located on the extremities. Multiple lesions occur much more frequently than solitary lesions. When multiple, lesions are commonly widespread and distributed in a clustered, linear, or zosteriform pattern, or along Blaschko’s lines.1 Most tumors measure from a few millimeters to 2 cm, and the most common sites of involvement are the extremities and trunk, especially the shoulders.

Multiple leiomyomas occur equally between the genders. Most patients are adults with a wide age distribution; however, most often lesions appear in the 2nd or 3rd decade of life.2 Rare cases of congenital piloleiomyomas have been reported. A study by Akay et al. presents a case of a rare congenital piloleiomyoma found in a two-month-old male, present since birth.3 Despite common recurrence after excision, piloleiomyomas are considered benign smooth-muscle tumors with no metastatic potential. The rare, malignant counterparts, leiomyosarcomas, arise from the dermis or subcutaneous tissues. Although dermal lesions have a 40% recurrence rate, they almost never metastasize in comparison with subcutaneous lesions, which metastasize in half of cases and are associated with 30% mortality. Some authors argue that dermal lesions should not be considered within the framework of leiomyosarcomas at all, as they behave in a more benign fashion.4 The subtypes of leiomyomas associated with pain are often described as burning, pinching, or stabbing. The mechanism of the pain is unclear. The pain may be spontaneous or induced by cold pressure.5 Contraction of smooth muscle, compression of nearby nerves, or an increased number of nerve bundles have been proposed as possible etiologies. The differential diagnosis of cutaneous painful tumors includes blue rubber bleb nevus, leiomyoma, eccrine spiradenoma, neurofibroma, dermatofibroma, angiolipoma, neurilemroma, endometrioma, glomus tumor, and granular cell tumor.

**Genetic Associations**

Multiple cutaneous leiomyomas are associated with a germline mutation of the fumarate hydratase (FH) gene, which maps to chromosome 1q42.3-4. Mitochondrial FH functions as an enzyme in the tricarboxylic acid (TCA) cycle, where it
of the papillary type. The association of renal-cell carcinoma mainly with cutaneous piloleiomyomas, symptomatic of piloleiomyoma and uterine myoma is classified as Reed's syndrome.

Hereditary leiomyomatosis and renal-cell cancer (HLRCC) is the tumor susceptibility syndrome characterized by multiple cutaneous piloleiomyomas, symptoms of intermingled collagen (Figure 7). The common feature of HLRCC is leiomyomatosis of the skin, with a reported penetrance of 76%. Toro et al. reported that 98% of women with cutaneous leiomyomatosis also had uterine leiomyomatosis.

HLRCC is less common in HLRCC, affecting 1%-14%, but it represents the most serious clinical manifestation of the syndrome and is often metastatic at time of diagnosis. As RL is a rare disease, specific screening guidelines do not exist and are often individual and treatment-center dependent. The main focus of management in HLRCC is prevention of disease and death due to renal cancer. Relevant issues are the lifetime risk of renal cancer in FH mutation carriers, age at onset, biological behavior of the disease and options for early diagnosis and treatment.

Pathophysiology
Leiomyomas were first described by Virchow in 1854. In the skin, they are nonencapsulated, mid-dermal masses composed of smooth-muscle cells, originating in the arrector pili musculi. They are benign dermal tumors and may arise from the arrector pili muscles, the dartoi, vulvar or mammary smooth muscles, or the muscles enveloping dermal blood vessels. Accordingly, they are subclassified into pilar leiomyomas, solitary genital leiomyomas and angioleiomyomas, respectively. Leiomyomas can present as solitary or multiple dermal nodules. Cutaneous leiomyosarcoma is the malignant counterpart of cutaneous leiomyomas and is classically divided in two groups, those arising from the dermis and those that involve the subcutis. These various types of smooth-muscle tumors are differentiated through histopathologic evaluation.

Leiomyomas of the skin are divided into three distinct groups based on the smooth muscle of origin. Piloleiomyomas, or pilar leiomyomas, originate from the arrector pili muscle. Genital leiomyomas arise from the smooth muscle of the scrotum, labia majora, or nipple. Angioleiomyomas stem from the tunica media of blood vessels.

Histopathologic Diagnosis
Cutaneous smooth-muscle tumors are rare, and differences are subtle among the various types. Criteria among leiomyomas, leiomyosarcomas, angioleiomyomas, pilar leiomyomas, and genital leiomyomas have been studied with a review of the literature. Histopathologic characteristics are favored as the primary diagnostic tool. Histologically, piloleiomyomas and genital leiomyomas are poorly circumscribed lesions consisting of interlacing smooth-muscle-fiber bundles with varying degrees of intermingled collagen (Figure 7). The neoplasms are located within the dermis and may encroach upon the subcutaneous tissue. The overlying epidermis may be effaced, hyperplastic, or normal. The smooth-muscle fibers are composed of eosinophilic cytoplasm with elongated, blunt-ended nuclei with little to no waviness. Slight cytoplasmic vacuolization and a perinuclear clear zone, suggesting smooth-muscle origin, are most apparent on cross section (Figure 8). Severe inflammation, significant cytologic atypia, necrosis, or encapsulation is not apparent. A trichrome stain will facilitate delineation of the brick-red smooth-muscle fibers from the blue-green collagen. If necessary, desmin, smooth-muscle actin, and muscle-specific actin may highlight the smooth-muscle origin of the tumor.

Mitotic figures are rare in cutaneous leiomyomas. The criteria often used to consider a cutaneous smooth-muscle tumor to be a leiomyosarcoma are a mitotic rate of two or more mitoses per 10 high-power field (HPF) or presence of necrosis. Atypia on its own has not been considered a definite diagnostic feature of leiomyosarcoma, unless accompanied by either of the former criteria. In comparison, angioleiomyomas are well circumscribed and often located in the deep dermis or extending into the subcutis. At higher magnification, thick-walled vessels are surrounded by bundles of smooth-muscle cells. The smooth-muscle cells have a fascicular arrangement, and the elastic lamina partly rim a representative vascular channel.

Some authors have divided angioleiomyomas into three histologic subtypes: solid, cavernous, and venous. All subtypes exhibit a proliferation of benign-appearing smooth-muscle cells and vascular channels. Tumors of the solid subtype are composed of closely compacted smooth-muscle and small, slit-like vascular channels. The cavernous subtype has dilated vascular channels with imperceptible blending of the blood-vessel wall with the smooth-muscle proliferation. Vascular channels distinct from intervascular smooth muscle are seen in the venous subtype of angioleiomyoma. Within the vascular-channel lumens of these tumors, recent or organized thrombi may be seen. Capsule and/or mucinous stromal alterations may be present. The smooth muscle has eosinophilic cytoplasm and cigar-shaped nuclei with minimal, if any, pleomorphism. Regarding the diagnosis of malignant leiomyosarcoma, additional use of immunohistochemical markers, such as p53, has been shown to be useful and reliable. In a study by Fernandez-Flores, results show tumor cells of leiomyosarcomas express p53; the marker was expressed by at least 80% of the tumoral cells. The authors concluded that expression of p53 by a high percentage of cells in a cutaneous smooth-muscle-cell tumor should be considered as highly suspicious for malignancy, leiomyosarcoma.

Management
Treatment options are limited. Excision is curative, but recurrence is common, reported in up to 50% of patients, especially in those who initially present with multiple lesions. Recurrence has been reported from six weeks to 15 years after surgery. Electrocoagulation, cryotherapy, and radiation therapy also have been utilized in treatment but have been shown to have little clinical benefit. A single report of carbon-dioxide laser ablation was recently published. This approach had previously been used successfully with uterine leiomyomas, where recurrence rates are much lower. Oral nitroglycerin, nifedipine, and phenoxybenzamine have been tried in an attempt to promote smooth-muscle relaxation; however, success has been limited. A study by Sahoo found that 10mg of nifedipine twice daily was remarkably effective in diminishing the pain in a patient with zosteriform cutaneous leiomyoma. Studies with treatment of intralesional 5-FU have not been found. After two sessions of intralesional injections of 5-FU, spaced six weeks apart, our patient's lesions have undergone minimal improvement in appearance and degree of tenderness.
Symptomatic treatment has been attempted with pain-blocking medications such as gabapentin, due to the neuropathic nature of the pain. This approach has met with variable but always incomplete pain resolution.18

Conclusion
The patient presented herein presented with multiple, biopsy-proven cutaneous piloleiomyomas on the shoulders, chest, and face. Due to the strong association of these cutaneous lesions with a genetic mutation in the FH gene and underlying renal-cell carcinomas, genetic testing and abdominal CT imaging for renal evaluation was warranted. This case stresses the importance of genetic testing and evaluation of renal-cell carcinomas in patients who have cutaneous leiomyomatosis. It is well documented that these patients are at increased risk for renal-cell carcinomas and thus should continually be monitored for this occurrence, as it could be a lifesaving management tool. Treatment with 5-FU was not completely successful in this patient; however, further evaluation and development of this therapeutic modality should be performed in future prospective studies of patients with piloleiomyomas. In addition, all cutaneous lesions thought to be smooth-muscle neoplasms should be further evaluated histologically, not only for the above reasons, but also for the possibility of the malignant variant, leiomyosarcoma.

References:

Figure 4: Low power histopathology piloleiomyoma
Figure 5: Higher magnification piloleiomyoma
Figure 6: Piloleiomyoma
Figure 7: Higher magnification piloleiomyoma
Figure 8: High Magnification Piloleiomyoma


34 MULTIPLE PILOLEIOMYOMAS ASSOCIATED WITH FUMARATE HYDRATASE GENE MUTATION: A CASE REPORT AND REVIEW OF THE LITERATURE
Case Study:

A nine-year-old male presented with complaints of a deep-red to purple growth on his right inguinal crease. Both the patient and the father noted gradual enlargement of the lesion over time. He reported painful episodes with spontaneous bleeding from the growth after minor trauma. Physical examination revealed a well-circumscribed, hyperkeratotic, red-blue nodule measuring 3.0 cm x 1.5 cm (Figure 1). Treatment options were discussed, and a course of imiquimod 5% cream was initially instituted but discontinued after a short time due to significant irritation. Recent cases have been described showing clinical resolution with a three- to five-month course of imiquimod therapy (1). Subsequently, the father of the patient elected for surgical excision of the lesion. A conservative margin with clinically normal skin was taken. Aggressive electrodessication was performed until complete hemostasis was achieved. The specimen was sent for histopathologic evaluation (Figure 2). The epidermis showed hyperkeratosis with a proliferation of blood vessels in the dermis possessing a thick wall and multilaminated basement membrane. There was hypergranulosis of the epidermis with the dermal vessels extending into the dermal papillae, fulfilling the criteria of verrucous hyperplasia of the epidermis (Figure 3). The superficial component resembled an angiookeratoma, and the deeper dermal component was akin to a lymphovascular malformation. Ulceration with scale crust was seen, as well as a superficial and deep perivascular and interstitial infiltrate of lymphocytes, eosinophils and extravasated red blood cells (Figure 4). The patient healed well with no post-surgical complications, despite deep margin involvement with the excision. He has continued to present to the clinic for follow-up over the last two years with no visible or palpable return of this lesion (Figure 5).

Discussion:

Verrucous hemangioma (VH) has long been plagued with terminologic confusion due to the difficulty in diagnosing and treating vascular birthmarks. On physical exam they are well circumscribed, red-blue, warty papules or plaques, often oriented in a linear configuration. Lesions typically present at birth or soon after and are found 95% of the time on the lower extremities (2). Often, the lesions begin as a bluish color and acquire a warty appearance due to reactive papillomatosis and hyperkeratosis. The presence of satellite lesions is typical (3).

VH have been met in the literature with various names including angiokeratoma circumscriptum, hemangioma unilateralis neviforme, unilateral verrucous hemangioma (4), keratotic hemangioma (5), and papulose angiookeratoma (6), to name a few. The term verrucous hemangioma was initially defined histologically in 1967 by Imperial and Helwig as they sought to detail the histologic differences between VH and angiookeratoma. The biologic classification of vascular lesions was then proposed in 1982 (7), and amended and accepted at the 1996 biannual meeting of the International Society for the Study of Vascular Anomalies (ISSVA) (8). It was proposed that vascular anomalies would be diagnosed and classified as either malformations or tumors.

The term “verrucous hemangioma” has recently been under scrutiny, replaced with the term “verrucous lymphovascular malformation” by many authors (9,10). This is secondary to verrucous hemangiomas having the clinical features of vascular malformations with presence at birth and proportionate growth. Histologically, verrucous hemangiomas look very similar to the tumor hemangioma of infancy in its involutive phase, sharing thick vascular walls, multilamellated basement membrane, uniform channels, and GLUT1 immunopositivity (9). In truth, the term "verrucous hemangioma" is a misnomer because the lesions are not neoplasms but instead are errors of morphology (11). Despite the potential for confusion, the term verrucous hemangioma should remain until a more precise designation becomes available.

Many treatment modalities have proved futile in preventing reoccurrence of VH. Cryosurgery, electrodessication, and laser therapy have all failed at controlling the disease, and complete surgical excision is often the treatment of choice. Larger lesions require wide, deep excision and may need grafting. Even with careful note of surgical margins, postsurgical recollection rate can be as high as 33% (12), and failed treatment is also a diagnostic clue for verrucous hemangioma (2). In some cases, the lesion proves not to be a good candidate for surgical excision due to size and should be treated symptomatically.

Given our patient’s clinical findings, along with histology showing deeper involvement extending far into the dermis, the more appropriate terminology may be verrucous lymphovascular malformation. Since the treatments of hemangiomas of infancy and of malformations differ greatly, the correct diagnosis is imperative in order to choose the best treatment course and optimize outcome.
References


Proteus Syndrome: A Case Series and Review of the Literature

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ABSTRACT

Proteus syndrome is a rare, sporadic disorder characterized by progressive, asymmetric, disproportionate overgrowth of multiple tissues. We describe two cases of this syndrome, one in a 16-year-old Hispanic female and another in a 25-year-old Hispanic female. Both patients presented with cerebriform connective-tissue nevi on the plantar surfaces of their feet. We also offer a literature review and further describe the lack of a definite correlation between Proteus syndrome and a mutation in the gene PTEN.

Introduction

Proteus syndrome (PS) is a rare, sporadic disorder that is characterized by progressive, asymmetric, disproportionate overgrowth of multiple tissues, bony hemihypertrophy, exostosis, cranial hyperostosis, visceral hamartomas (including lipomas), vascular anomalies, and epidermal and connective-tissue nevi. Cohen and Hayden reported the first two cases in 1979.1 Then in 1983, Weidemann, Burgio, and Aidenhoff named the syndrome after the Greek god Proteus, who changed shape to avoid capture.2 Many now believe that Joseph Carey Merrick, the “Elephant Man,” described by Dr. Frederick Treves in 1885, was afflicted by PS.3,4 In PS, an increased number of cutaneous findings have been thought to correlate with a poorer prognosis.5

Case #1

A 16-year-old Hispanic female of nonconsanguineous parents was referred to our dermatology clinic for evaluation of a lesion on her right foot. The patient reported an unremarkable past medical history except for scoliosis and varicose veins since she was approximately two years old, for which she underwent bilateral vein stripping three months prior to her presentation. She also complained of non-erythematous, non-pruritic papules that appeared on the plantar aspect of her right foot when she was approximately three years old. At the time of presentation, she stated that she was experiencing difficulty running due to pain that occurred on the bottom of her right foot. She also complained of occasional leg fatigue associated with long periods of standing. She denied visual disturbances or other medical problems. She had three healthy brothers and no family history of congenital conditions. On physical examination, there were bilateral varicosities and several large, red macules present on her lower extremities. On the right plantar surface of her foot, a cerebriform, flesh-colored plaque was noted. Her right anterior leg had an atrophic linear surgical scar. An MRI of her bilateral lower extremities and pelvis was obtained, showing multiple subcutaneous, dilated veins in both lower extremities. The soft tissues were within normal limits, and the osseous structures of the pelvis and lower extremities were unremarkable. The patient was diagnosed with Proteus syndrome based on the mosaic distribution of her lesions, sporadic occurrence, progressive course, and the presence of a cerebriform connective-tissue nevus.

Case #2

A 25-year-old Hispanic female was referred to our clinic to “rule out an infiltrative process such as Hansen’s disease.” She had previously been evaluated for gigantism of her hands and was ruled out for acromegaly at an outside institution. Her history included asymmetric overgrowth of her hands and digits, which was first noted in early childhood and had progressed over her lifetime. She complained of associated numbness and pain in her hands bilaterally. She also had overgrowth of the first three digits on her left foot and a soft-tissue mass on the plantar surface. She had required surgical intervention at age 4 to maintain function in her hands and left foot, and to remove a large lipoma from her right neck. She had no other family members with similar findings, and she had two healthy, unaffected children. On physical examination, the patient was of normal height and weight. She had normal facies and mentation. She had crowded dentition with extraanumerary teeth in the mandible and maxilla. Bony and soft-tissue overgrowth of multiple digits of her hands was noted and confirmed by radiologic studies. She also had a soft cerebriform mass on the plantar surface of her left foot. Her laboratory work-up was unremarkable. The patient was diagnosed with Proteus syndrome based on the mosaic distribution of her lesions, sporadic occurrence, progressive course, and cerebriform connective-tissue nevus.

Figure 1: Cerebriform mass on R plantar foot.

Figure 2: Varicosities.
Diagnosis
Diagnostic criteria were initially introduced in 1999 by Biesecker et al., who summarized the 1998 NIH-recommended criteria. Turner et al. in 2004 then revised the criteria due to over-reporting and misdiagnosis of the condition. Turner et al. reviewed 205 cases and found only 97 to be PS according to previously published criteria.

Clinical Manifestations
PS has manifold clinical manifestations, both cutaneous and extracutaneous. Of the cutaneous manifestations, cerebriform connective-tissue nevi (CCTN) are commonly seen and seem to be pathognomonic for PS. They are nearly always located on the plantar aspect of the foot and are generally not present at birth but manifest within the first three years of life. In one study, Nguyen et al. found 22 of 24 patients with PS to have CCTN (20 had them on soles of feet), and another study by Twede et al. found 12 of 16 patients with PS to have such findings (all 12 cases on feet). Other cutaneous manifestations include lipomas, which are usually not present at birth (helping to differentiate PS from hemihyperplasia multiple lipomatosis syndrome), cutaneous vascular and lymphatic malformations, hyperpigmented and hypopigmented patches, and epidermal nevi. Extracutaneous manifestations of PS include bony defects (hyperostosis of the skull, bony invasion of joint spaces, overgrowth of long bones), pulmonary cysts, early eruption of dentition, cystadenomas of the tunica albuginea and ovary, and, less commonly, other tumors. Systemic hemangiomas have also been reported. One patient who had previously been diagnosed with PS presented with intermittent rectal bleeding and was found to have multiple colonic hemangiomas. Ocular findings such as epibulbar cysts, optic nerve atrophy, strabismus, and chorioretinal atrophy were found in 42% of cases evaluated by Turner et al. in 2004. While most patients with PS have normal intelligence, patients with findings involving the head have a higher rate of mental impairment.

Pathogenesis
PS is hypothesized to result from mosaicism of a mutation that is lethal in the non-mosaic state. The molecular etiology, however, has remained elusive. It is speculated that phosphatase and tensin homolog (PTEN) gene mutations have a role in Proteus syndrome. PTEN plays a role in the regulation of P3 kinase signaling, which is involved in the control of apoptosis and cell-cycle progression. Hence, by removing the regulatory effects of PTEN on P3 kinase signaling, dysregulated cellular growth could occur. Zhou et al. in 2001 found PTEN mutations in 2 of 9 patients with PS, and in 3 of 5 patients with Proteus-like syndrome (PLS). Barker et al. in 2001 found no PTEN mutation in eight PS patients. Smith et al. reported a case of 16-month-old male with PS and a PTEN mutation in 2002. Cohen et al. reported in 2003 that in 19 PS patients, they found no PTEN mutations, and therefore their patients are distinctly set apart from another group of patients with the classification of PTEN hamartomatous-tumor syndrome. In 2006, Loffeld et al. reported a PTEN mutation in a three-year-old boy with PS, which in 2007 Happle suggested may have had a diagnosis of a type of Cowden syndrome. It is difficult to draw definitive conclusions from the above studies due to the small sample size and variability on how the PTEN mutations were screened. Three (8%) out of the above 35 patients with PS were found to have a PTEN mutation. A study with a larger subset of patients is needed. Unfortunately, such a study would be unlikely to happen given the rarity of PS.

Differential Diagnosis
PS has myriad phenotypes with features of many previously described hamartomatous diseases. Hence, it is imperative that physicians educate themselves on the differential diagnoses, which include: Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Klippel-Trenaunay syndrome, Parkes-Weber syndrome, hemihyperplasia, Maffucci syndrome, neurofibromatosis type 1, epidermal nevus syndrome, familial lipomatosis, and Proteus-like syndrome (PLS). PLS is diagnosed when a patient meets the minimum criteria of lipomas, any single hamartoma, and overgrowth of tissues (such as of the arms or legs) but does not meet the consensus diagnostic criteria of PS or the other differential-diagnosis syndromes.
Management

Management is primarily supportive. Serial medical photography, routine ophthalmologic exams, and skeletal surveys may be helpful. There have been a few cases of premature death secondary to pulmonary embolism reported in patients with PS. However, it is believed to be more likely due to decreased mobility rather than hypercoagulability.7 It may therefore be beneficial to screen patients with impaired mobility for deep venous thromboses and consider anticoagulation. Orthopedic surgery may be required to help debulk functionally restrictive bone malformations. There is some evidence supporting screening for malignancies. PS requires interdisciplinary management with multiple medical specialties for effective care. Referral to support groups should be done, as this diagnosis and its implications can place severe psychological strain on the patient and family.

References
Ms. J.W., a 41-year-old Caucasian female, presented to the dermatologist with a history of dermatomyositis that began in 2003 with severe muscle weakness along with the classical skin findings. Her myositis improved, well-controlled with methotrexate and prednisone; however, she continued to complain of severe pruritus due to her persistent skin involvement. Her records alluded to an allergic drug reaction to Plaquenil in 2005. More recently, her skin findings had remained unchanged, and she continued to experience significant pruritus and skin tenderness on her chest, arms and scalp. At this time, a desensitization regimen (Table 1) for Plaquenil was carried out, culminating in a daily dose of 400mg with no adverse effects. After only a few weeks of this therapy, her skin condition began to improve.

In regard to the course of DM in our patient: In 2003, after several months of fatigue, myalgias and muscle weakness, the patient became severely weak, was unable to walk, swallow without aspirating, or speak clearly. She had facial skin signs labeled as rosacea but also was noted to have a heliotrope periorbital rash. A subsequent muscle biopsy revealed myositis, and lab work showed elevated aldolase but normal CPK. The patient was initially treated with high-dose prednisone and hospitalized for supportive care until her weakness gradually improved. Once discharged, she was maintained on methotrexate and prednisone 10mg daily, though her skin findings never improved. Since 2003, she has been closely followed by her rheumatologist and has had several evaluations for systemic cancer, all of which have been negative.

Past medical history of the patient was significant for hypothyroidism, strabismus and infectious mononucleosis (1974), and current medications included Synthroid, Lexapro, folic acid, Zyrtec, alprazolam, and Oracea. Pertinent family history revealed a paternal grandmother with lupus and a maternal grandmother with breast cancer. Skin examination at the last office visit revealed poikilodema of the face, scalp, neck, chest and arms in a photodistributed pattern. Also of note was cuticular dystrophy and Gottron’s papules on both hands.

Treatment:

The patient is being managed with methotrexate 15mg weekly, prednisone 5mg every other day, triamcinolone 0.1% cream bid, Protopic 0.1% ointment bid, Plaquenil 400mg qd, and hydroxyzine 10mg q 6 hours as needed for pruritus.

Discussion:

Some of the first documented cases of dermatomyositis date back to the mid-late 19th century. It was at that time that Hans Unverricht, after witnessing several dramatic examples, coined the term that would come to name the condition itself – dermatomyositis. We now know that DM affects at least 1 in 100,000 people each year and tends to favor women in the 30- to 50-year-old age bracket. Most patients with dermatomyositis tend to have signs and symptoms that coalesce around a unique constellation, but individual cases may vary significantly. Classic findings include symmetric proximal weakness accompanied by elevations in creatine kinase. Muscle biopsies tend to show perifascicular atrophic, degenerating/regenerating myofibers with perivascular lymphocytic inflammation. Skin findings include pathognomonic heliotrope rash, periorbital edema, Gottron’s sign/papules and “shawl sign” poikiloderma. Additionally, facial erythema, periungal telangiectasias and cuticular hypertrophy are quite common. The order of onset for skin and muscle findings is not fixed, however. Muscular signs may proceed, coincide with, or follow skin manifestations, or they may be altogether absent (amyopathic dermatomyositis). Skin biopsy findings are varied as well but often reveal subtle interface dermatitis with increased mucin that is difficult if not impossible to distinguish from lupus erythematosus.

As with all connective-tissue diseases, serological testing has also proved to be of great benefit. One of the most well known autoantibodies found in some dermatomyositis patients is directed against histidyl-tRNA-synthetase (anti-Jo-1). Though this antibody is only found in less than one third of myositis patients, its specificity does appear to be relatively high. Interestingly, it has also been shown to be a marker for the development of interstitial lung disease and overall dermatomyositis activity. Clinicians can follow anti-Jo-1 titers to monitor disease improvement or relapse. Anti-Mi-2 antibodies are also seen in about 20-30% of DM patients and tend to prognosticate more severe cutaneous manifestations but a favorable prognosis. And finally, there are reports of new auto-antibodies to as-yet-unnamed 155 and 140 kDA proteins in DM patients. They seem to be fairly common, with a prevalence around 20%, and are a harbinger of much higher rates of malignancy. Without these markers, normal rates of malignancy associated with DM are approximately 10%-30% and represent cancers in virtually every organ of the body. Finally, though there is no consensus on cancer-screening methods or frequency, it has been shown that elevated CA-125 levels are associated with increased risk.

Oral steroids are the mainstay of treatment in DM, especially with muscle disease, but various other agents have been tried alone or in combination so as to lower the effective steroid dose. A partial list includes: antimalarials, methotrexate, azathioprine, chlorambucil, cyclosporine, and cyclophosphamide. Pertinent to this case, it is interesting to note that cutaneous reactions to hydroxychloroquine have been reported to occur in approximately 30% of DM patients. In 2006, Mates et al. published an oral desensitization regimen for Plaquenil successfully carried out on four patients with previous allergic exanthems caused by the drug. The mechanism for achieving this tolerance is...
poorly understood, but it appears to involve induction of CD4+ CD25+ regulatory T cells expressing IL-10 and (TGF)-B, which suppress inflammation.22 We present here another example of a case successfully and safely managed with this desensitization approach.

References


Table 1. Desensitization daily dosage for HCQ

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<th>Day</th>
<th>Suspension HCQ, mg/ml</th>
<th>Quantity given each day, ml</th>
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<tr>
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<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>2-7</td>
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<td>1</td>
</tr>
<tr>
<td>8-13</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>0.1</td>
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</tr>
<tr>
<td>16-22</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>2</td>
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<td>24</td>
<td>2</td>
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</tr>
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<td>Half a tablet</td>
</tr>
<tr>
<td>32-36</td>
<td>200 mg tab</td>
<td>One tablet</td>
</tr>
<tr>
<td>36-</td>
<td>200 mg tab</td>
<td>Two tablets</td>
</tr>
</tbody>
</table>

Table 1. Desensitization daily dosage for HCQ
Important Safety Information

Oracea® (doxycycline, USP) is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. In clinical trials, the most common adverse events reported were gastrointestinal upsets, nasopharyngitis/pain, and nasal congestion/sinusitis. Oracea® should not be used to treat microbial infections, and should be used only as indicated. This drug is contraindicated in people who have shown hypersensitivity to any of the tetracyclines, and, like other tetracycline drugs, may cause fetal harm when administered to a pregnant woman. Oracea® should not be used during pregnancy, by nursing mothers, or during tooth development (up to the age of 8 years). Although photosensitivity was not observed in clinical trials, Oracea® patients should minimize or avoid exposure to natural or artificial sunlight. All contraindications, warnings, and precautions associated with tetracyclines must be considered before prescribing Oracea®. The safety of Oracea® treatment beyond 9 months has not been established.
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**Case Report**

A four-month-old female was admitted with a one-day history of irritability, decreased appetite, and rash. The rash, which initially erupted on the face, resembled red insect bites and quickly (over a day) expanded into large, round, dark purple, ecchymotic lesions. At the same time, new lesions developed and progressed bilaterally down the upper and lower extremities. Swelling of lower extremities was also observed. The parents denied that the patient had any history of fever or recent illnesses (including upper respiratory or gastrointestinal illnesses), but they reported that the patient had received her four-month vaccinations one week prior to the eruption. No medications had been given.

On examination, the infant was afebrile, hemodynamically stable, and appeared well except for the multiple palpable, annular, targetoid, purpuric patches and plaques on her cheeks and distal upper and lower extremities. Oral and nasal mucosae were normal, and there were no signs of internal organ involvement. Over a three-day period following her admission, new ecchymotic lesions developed and progressed (distal to proximal) in her upper and lower extremities, reaching a 1-3 cm size. A mild, non-pitting edema developed below the knees (see Fig. 1).

The laboratory examination revealed an elevated white blood cell count (24,000/ mm³), an elevated platelet count (586,000/ mm³) and a mildly elevated CRP (1.7). The complete blood cell count, ASO titers, coagulation studies, chemistry profile, nasal pharyngeal viral culture, blood cultures, cerebral spinal culture and urine cultures were all negative. A skin biopsy sample from the right lower extremity exhibited leukocytoclastic vasculitis with eosinophil infiltration and early changes of fibrinoid necrosis. Direct immunofluorescence was negative. The clinical picture and the skin biopsy were consistent with AHEI.

The patient was managed conservatively with intravenous fluid administration and acetaminophen for pain control, and empirically with antibiotics (Rocephin) until the culture results were received and found to be negative. The patient was discharged with instructions to apply topical mupirocin to any lesions that ulcerated. The lesions resolved in 14 days without sequelae.

**Discussion**

Acute hemorrhagic edema of infancy (AHEI) is a leukocytoclastic, small-vessel vasculitis initially described by Snow in 1913 [1]. This condition was previously known as Finkelstein disease, Seidlmayer disease, cockade purpura and edema of young children, and acute benign leukocytoclastic vasculitis of young children [2,3]. The clinical hallmark of AHEI is the sudden appearance and spread of a purpuric rash with edema over the face and extremities of an otherwise healthy infant. The rash initially appears as multiple, red, macular or urticarial lesions that dramatically and rapidly evolve into large, target-like or cockade-appearing purpuric lesions that can measure 1 to 5 cm in diameter. The face and ears are commonly affected, while trunk and mucous membranes are usually spared. Edema of the face, dorsa of hands, feet, and proximal extremities develops early in the course of the disease. Fever is common but tends to be low-grade, and the patients usually do not appear toxic.

AHEI typically affects infants between four and 24 months of age [4]. The disease's etiology is unknown. In most cases reported in the literature, development of the disease was preceded by a prodromal period of bacterial or viral upper respiratory and gastrointestinal illnesses, UTI, use of medications (e.g., paracetamol or antibiotics), or immunizations [5]. Fiore et al. reported that 18 out of 294 total cases of AHEI occurred following recent (less than 15 days) immunization with combination vaccines such as DTaP and MMR, and also with vaccines for Hib, measles, and small pox [5]. The patient described in this case report received Pediarix (DTaP, IPV, Hep B) and Hib seven days prior to developing the rash.
The common differential diagnosis for AHEI includes Henoch-Schonlein purpura, meningococcemia, erythema multiforme, and drug eruption. All these entities are easily distinguished from AHEI by clinical examination. AHEI differs from Henoch-Schonlein purpura in that AHEI usually occurs in children under two years of age, is commonly accompanied with fever, has a rash distribution that includes the cheeks and ears, and almost always presents with edema, and perivascular immunoglobin A deposit is infrequent.

AHEI usually resolves spontaneously within one to three weeks without sequelae [6]. Recurrence is uncommon [4]. Because AHEI is typically benign and self-limiting, treatment is controversial. Despite reports that systemic corticosteroids and antihistamines fail to alter the course of the disease [4,8], some practitioners advocate the use of corticosteroids [9] and antihistamines [10] to hasten resolution.

It is important to recognize and correctly diagnose AHEI as a distinct clinical entity for appropriate prognosis to be made and to avoid unnecessary use of medications in this benign disease of infancy and early childhood.

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# Cutaneous Metastatic Thyroid Carcinoma: The Papillary Tall-Cell Variant

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**ABSTRACT**

Cutaneous metastases can represent the first sign of malignancy or indication of a malignant recurrence. Clinical characteristics, histopathologic features, and immunohistochemical stains may uncover the type of primary tumor. We report a case of the tall-cell variant of papillary thyroid carcinoma, metastatic to the skin, confirmed with thyroglobulin immunoperoxidase staining.

## Case Report

An 81-year-old male presented with an asymptomatic, 1 cm, subcutaneous nodule on the lower neck, superior to the medial aspect of the left clavicle. A shave biopsy was performed, demonstrating an atypical dermal neoplasm with features of adenocarcinoma (Figure 1).

Immuno histochemical studies revealed strong expression for cytokeratin 7 and EMA within the neoplasm. However, there was no expression of cytokeratin 20. Upon discussion of these findings with the patient, he reported having a history of thyroid carcinoma in the remote past, previously treated with 131I and thought to be in remission. Subsequent immunohistochemical studies for thyroglobulin were positive within the atypical papillary cells (Figure 2), supporting the diagnosis of metastatic thyroid adenocarcinoma to the skin. A PET/CT demonstrated multiple small, hypermetabolic cervical lymph nodes and pulmonary nodules. The patient remained asymptomatic and refused treatment.

**Discussion**

Cutaneous metastases from internal malignancies are rare, developing in 0.7% to 9% of patients.1,2 These rare skin lesions can be a manifestation of an occult malignancy from an internal organ, the development of a recurrence of a malignancy thought to be in remission, or the failure of therapy from a malignancy thought to be completely eradicated.1,2 Cutaneous metastases are often a sign that an internal malignancy has become widespread and disseminated.3

Papillary carcinoma of the thyroid is the most common thyroid cancer, accounting for 80% of all thyroid cancers.3 Overall, it has a 10-year survival rate of approximately 93%, but this is modified by several significant factors that are of importance to the dermatologist.4,5 While cervical lymph node metastases are common, other metastatic sites are uncommon, with the highest incidence in lung and bone.6

Cutaneous metastasis from thyroid carcinoma is very rare, but it is of vital interest to the dermatologist because of the potential for prognosis and treatment. In a review of 4,020 patients with cutaneous metastatic carcinoma, no thyroid carcinomas were detected.7 In a study by the same authors reviewing 7,316 cancer patients, 367 of those cases were found to involve the skin, but none of them involved thyroid neoplasms.8

A report of 724 cases of metastatic tumors of the skin found only four to be from thyroid neoplasms.9 In 1997, Dahl et al. reviewed the English literature from 1964 and found only 37 cases of thyroid carcinoma metastatic to the skin and reported six more cases in that review, totaling 43 patients.1 One report by Caron et al. in 1993 describes a patient with recurrence of metastatic skin nodules from primary thyroid carcinoma.10

Of the endocrine malignancies, thyroid carcinoma is the most common.11 Thyroid cancer is classified by the cell type from which it arises in the thyroid gland. The follicular cells arising from the embryonic endoderm give rise to papillary, follicular and anaplastic carcinomas.12 Follicular carcinoma accounts for 10% of thyroid cancers, whereas anaplastic carcinoma accounts for 2%.12 Papillary thyroid carcinoma, being the most common, accounts for 80% of thyroid malignancies and is especially of interest to the dermatologist because of the relatively higher potential incidence of cutaneous metastases from this form of thyroid cancer.12,15 Medullary thyroid carcinoma arises from the parafollicular C cells, which are derived from the neuroendocrine embryonic cell line.12 Medullary thyroid carcinoma accounts for 5% to 10% of all types of thyroid neoplasms.12,13,14

Intrathyroid lymphoid tissue gives rise to thyroid lymphomas, and sarcomas arise from intrathyroid connective tissue.12 Although metastases are generally lymphatic, thyroid lymphomas and sarcomas are very rare.

Multiple histologic variants of papillary thyroid carcinoma have been described in the literature. These patterns include the follicular variant, insular pattern, tall-cell pattern, diffuse sclerosing type, papillary thyroid carcinoma with Hashimoto’s thyroiditis, and multicentric papillary thyroid carcinoma.16 First described in 1976, the tall-cell variant has features of papillary carcinoma; however, it is more aggressive, with an enhanced propensity for extrathyroid extension and lymphovascular invasion.17

There is discrepancy in the literature involving the definition of the tall-cell variant of papillary thyroid carcinoma. The incidence of tall-cell variant of papillary thyroid carcinoma is between 3% and 19%.18,19 In 2008, Ghossein et al. explained the wide range in incidence as due to the inclusion criteria among studies.20 Some of these studies report inclusion of the tall-cell variant of papillary thyroid carcinoma to vary between papillary thyroid tumors with more than 30% of tall cells identified and tumors with more than 75% of tall cells identified.20 Other thyroid carcinomas have
been associated with the tall-cell variant. Spindle-cell squamous carcinoma, a form of anaplastic thyroid carcinoma, is almost exclusively associated with tall-cell variant of papillary thyroid carcinoma.

Controversy exists in the literature regarding the subtype of thyroid carcinoma with the highest propensity for skin metastases. Dahl et al. reports that papillary carcinoma accounts for 41% of skin metastases from thyroid carcinoma, follicular represents 28%, anaplastic represents 15%, and medullary represents 15%. However, another author found that medullary and giant-cell carcinomas of the thyroid have been reported more frequently. From a more recent study, the most common subtype associated with cutaneous metastasis was found to be follicular thyroid carcinoma origin, representing 42%. One study reports that the incidence of follicular carcinoma accounts for a range between 10-14% of all types of thyroid cancer, which is slightly higher than the 10% incidence reported in another study.

The location of metastases from thyroid carcinoma rarely includes the skin. Thyroid carcinoma most commonly metastasizes to the lymph nodes, lungs, and bones, but has also been found to metastasize to the liver and, rarely, the brain. Skin metastases in patients with thyroid carcinoma tend to occur on the scalp; however, involvement of the face, eyelid, neck, chest, torso, abdomen, scrotum and thyroidectomy scars have also been reported. While lymphatic spread is most common, clearly there is hematogenous dissemination, thought to be through the external carotid arteries. There have been rare cases of thyroid metastases to adrenal glands and oral mucosa.

The most common clinical presentation of cutaneous metastasis is an asymptomatic, solitary, flesh-colored nodule. However, lesions can manifest with pruritus and ulceration. Although rare, there have been cases of cutaneous seeding appearing along probable needle tracts of thyroid biopsies, which occur months to years following the procedure. Diagnosis can be made by biopsy or fine needle aspiration (FNA) cytology, and the extent of metastases can be determined through PET/CT imaging. FNA cytology can be helpful in providing clues for aggressive variants of thyroid carcinoma. These cutaneous tumors can be mistaken for primary adnexal tumors, as the histopathology is similar to that of hidradenoma papilliferum and syringocystadenoma papilliferum. However, immunohistochemistry stains are useful in making the distinction. Histopathologic features include papillomatous changes, fronding, and apocrine decapitation secretion. A characteristic feature of papillary thyroid carcinoma is psammoma bodies, which are observed in 25% of cases. Immunohistochemical staining describes why thyroglobulin and TTF-1 can be used. Thyroglobulin is specific to follicular and papillary types of thyroid carcinoma but not lung carcinoma, whereas TTF-1 is useful in distinguishing pulmonary and thyroid carcinomas.

Papillary thyroid carcinoma has characteristic nuclear features for histopathologic diagnosis including irregularity, clearing, overlapping, grooves, and pseudo-inclusions. Some authors refer to these nuclear features as “Orphan Annie eyes” on low-power fields. Histopathologic diagnosis of the tall-cell variant of papillary thyroid carcinoma is based on features such as nuclear stratification, exaggerated intranuclear inclusions, a low nuclear cytoplasmic ratio, and an eosinophilic granular cytoplasm. As previously mentioned, there is controversy within the literature regarding the number of tall cells needed to classify a tumor as a tall-cell variant. Some authors consider these tumors to be a “poorly differentiated thyroid carcinoma” instead of a separate variant. In 2008, Ghossein and Livolsi proposed standardized criteria for the diagnosis of papillary thyroid carcinoma tall-cell variant: composition of ≥ 50% tall cells, tall-cell height at least twice its width, eosinophilic tall-cell cytoplasm, and nuclear features of characteristic papillary thyroid carcinoma. The inconsistent definitions in the literature and the rarity of the tall-cell variant of papillary thyroid carcinoma can lead to a missed diagnosis of the tall-cell variant.

Prognosis
A study from 1997 found the average survival time after diagnosis for cutaneous metastasis was 19 months. More recent studies indicate the average survival time is between 7.5 to 19 months. Poor prognostic outcomes of the tall-cell variant of papillary thyroid carcinoma have been influenced by older age at presentation, larger metastatic tumor size, the ability to concentrate radioactive iodine, and high frequency of extrathyroid tumor expression. One study comparing the tall-cell variant to classic papillary thyroid carcinoma found patients with the tall-cell variant presented at a mean age of 54 years, had a 54% rate of extrathyroid extension, and had a worse five-year survival of 81.9%. The classic papillary thyroid carcinoma patients, on the other hand, presented at 46 years old, had a 30% rate of extrathyroid extension and had a 98% five-year survival rate. The mortality rate of the tall-cell variant of papillary thyroid carcinoma is 25% at 10 years. The tall-cell variant has a higher recurrence rate.

Treatment
Treatment includes total thyroidectomy, ablative therapy with radioactive iodine and chemotherapy. It is important for the dermatologist to note that most authors feel the metastatic lesions on the skin should be completely excised. Metastasectomy of skin lesions does not affect survival but does reduce morbidity. Palliative treatment is reserved for patients with widespread metastatic disease.

Classic papillary thyroid carcinoma has an indolent course and can be treated with thyroidectomy alone or with adjuvant radioactive iodine remnant ablation. The tall-cell variant of papillary thyroid carcinoma is the most commonly aggressive variant of papillary thyroid carcinoma. The aggressive nature of the tall-cell variant changes the treatment strategies.

Three molecular factors have been associated with the tall-cell variant that may help explain the aggressive biologic nature of this variant. Tall-cell variant papillary thyroid carcinoma has been found to have a high expression of Muc1, a transmembrane epithelial-cell surface glycoprotein that promotes cellular dissociation and oncogenic progression. There is also increased expression of type IV collagenase in the tall-cell variant, which begins the degradation of type IV collagen in the basement membrane. A higher prevalence of B-RAF serine-threonine kinase point mutations has been described in association with the tall-cell variant, nearing 80%. The tall-cell variant has also been found to be refractory to radioactive iodine therapy in many cases, thought to be directly related to the B-RAF mutation.

Conclusion
Cutaneous metastasis from most internal cancers commonly occurs in conjunction with extensive metastases. This case reminds physicians to include cutaneous thyroid metastasis in the differential diagnosis of solitary nodules. Diagnosis of the rare, more aggressive tall-cell variant of papillary thyroid carcinoma should not be missed, as it can change the treatment plan and the prognosis of patients diagnosed with classic papillary thyroid carcinoma.
from a cutaneous metastasis.

Acknowledgements

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**DRUG-INDUCED SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS CAUSED BY TERBINAFINE TREATMENT: A CASE REPORT AND BRIEF REVIEW**

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**Introduction**

Drug-induced cutaneous reactions are pathologies that dermatologists are all too familiar with, notably subacute cutaneous lupus erythematosus (SCLE). There are a wide variety of known causative agents that induce this condition, and it may be difficult initially to identify the etiology if the patient is on polypharmaceutical therapy. While some medications are notorious for causing the development of SCLE, others are uncommon. We present a case of SCLE secondary to terbinafine therapy, which is a rare causative medication.

**Case Presentation**

A 71-year-old woman presented to the dermatology clinic with a rash located over her back, chest, neck, face, and upper and lower extremities for the duration of two weeks. The rash suddenly began and aggressively spread over 14 days. The rash has an erythematous plaque with scaling in a photodistributed pattern. The initial papules start out small and later coalesce into larger plaques. The distribution of the rashes follows the typical photosensitivity pattern, involving the upper back, shoulders, chest, neck, lateral face, and extensor surfaces of the arms. After cessation of the offending agent, the lesions of SCLE usually resolve without scarring. It is possible, however, to develop vitiligo-like patches and/or telangiectasias where the original lesions were.

The patient was treated with a drug-induced subacute cutaneous lupus erythematosus. Due to the patient's history of initiating terbinafine therapy four weeks prior with a positive ANA titer, along with the drastic improvement when it was discontinued, it was concluded that terbinafine was the likely culprit of her reaction. She was advised to avoid terbinafine treatment and finish the prednisone taper. The patient's rash was 100% resolved on one-month follow-up with no recurrence.

**Discussion**

SCLE is a subtype of the well-known inflammatory autoimmune disorder systemic lupus erythematosus. Both SCLE and systemic lupus erythematosus can be induced by medications. Drug-induced systemic lupus erythematosus differs from drug-induced SCLE in several ways. First of all, drug-induced systemic lupus erythematosus involves diffuse systemic disease usually without a cutaneous presentation, while SCLE always presents with cutaneous involvement. While both forms may involve systemic effects such as serositis and arthralgias, the effects tend to be much more severe in drug-induced systemic lupus erythematosus than in SCLE. Furthermore, the pharmaceutical agents that initiate these two entities differ. While drug-induced systemic lupus erythematosus is often caused by minocycline, hydroalazine, and procainamide, SCLE is most often linked to hydrochlorothiazide, calcium-channel blockers, ACE-inhibitors, and some antimicrobials. Both SCLE and systemic lupus erythematosus are more common in women, and the average age of onset of SCLE is estimated to be 43 years.

SCLE is characterized by annular, scaly, erythematous papules and plaques that usually present in a photodistributed pattern. The initial papules start out small and later coalesce into larger plaques. The distribution of the rashes follows the typical photosensitivity pattern, involving the upper back, shoulders, chest, neck, lateral face, and extensor surfaces of the arms. After cessation of the offending agent, the lesions of SCLE usually resolve without scarring. It is possible, however, to develop vitiligo-like patches and/or telangiectasias where the original lesions were. Typical associated symptoms are fever, arthralgias, and myalgias, and it is estimated that 10-15 percent of patients may develop more serious internal manifestations such as nephritis, systemic vasculitis, or elevated liver enzymes as seen in our patient.
SCLE was first described in 1979 by Sontheimer and Thomas et al., and drug-induced SCLE was first recognized in 1985 secondary to hydrochlorothiazide use. Idiopathic SCLE is a variant of SCLE that is often difficult to differentiate from the drug-induced form. Both serological profiles are similar, and it has been suggested that the distribution of the lesions may be the only distinguishable factor. Idiopathic SCLE is generally only seen above the waist, while it is common for drug-induced SCLE to be located on the lower extremities, as seen in our patient. The development of SCLE has been noted with a variety of drugs, and hydrochlorothiazide is the most common. Other well-known initiators are statins, calcium-channel blockers, ACE-inhibitors, and a variety of antimicrobials. After initiation of the drug, eruptions usually occur within four to seven weeks.

When evaluating a patient with suspected SCLE, laboratory values are an essential diagnostic tool. Characteristic markers include high ANA titers and anti-Ro (SS-A) and anti-La (SS-B) antibodies, which are strongly associated with SCLE. In addition, anti-dsDNA, anti-ssDNA, and anti-histone levels should be drawn.

### Table 1: Antibody Panel Results

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>RESULTS</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA Screen, IFA</td>
<td>POSITIVE</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>ANA Titer</td>
<td>1:320</td>
<td>&lt;1:40 NEGATIVE</td>
</tr>
<tr>
<td>Anti-Ro (SS-A)</td>
<td>&gt;8.0 POSITIVE</td>
<td>&lt;1.0 NEGATIVE</td>
</tr>
<tr>
<td>Anti-La (SS-B)</td>
<td>&gt;8.0 POSITIVE</td>
<td>&lt;1.0 NEGATIVE</td>
</tr>
<tr>
<td>ANA Pattern</td>
<td>Homogenous</td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA Antibody</td>
<td>1</td>
<td>&gt;or equal to 10 (POSITIVE)</td>
</tr>
<tr>
<td>Anti-SCL-70 Antibody</td>
<td>&lt;1</td>
<td>&lt;1 (NEGATIVE)</td>
</tr>
<tr>
<td>Anti-Sm and Anti-Sm/RNP Antibodies</td>
<td>&lt;1</td>
<td>&lt;1 (NEGATIVE)</td>
</tr>
<tr>
<td>Anti-histone Antibodies</td>
<td>&lt;1</td>
<td>&lt;1 (NEGATIVE)</td>
</tr>
<tr>
<td>Anti-ssDNA Antibody</td>
<td>&lt;69</td>
<td>&lt;69 (NEGATIVE)</td>
</tr>
</tbody>
</table>

While anti-histone is an identifiable feature of drug-induced systemic lupus erythematosus, it is not pathognomonic for drug-induced SCLE. Some patients express it, while some do not. Reports vary as to its actual significance in diagnosis. A report by Bonsmann et al. followed five patients with terbinafine-induced SCLE, all of whom where anti-histone positive. Other case reports, such as one by McKellar et al., describe patients with SCLE who are negative for anti-histone. McKellar presents the case of a middle-aged male with a history of systemic lupus erythematosus who developed drug-induced SCLE after treatment with terbinafine. In this case, the typical anti-Ro (SS-A) antibody was positive, but anti-histone and ANA titers were both negative. The presence of anti-histone antibodies may be beneficial in distinguishing drug-induced SCLE from idiopathic SCLE, as it is not reported to be positive in the idiopathic form. Nuclear immunofluorescence should also be evaluated, and on skin biopsy, SCLE usually presents in a homogenous pattern. After cessation of the offending agent, levels of serum antibodies may be positive for some time. Anti-Ro has been reported to
remain positive for up to three years, and anti-La may stay elevated for up to one year. ANA titers typically return to normal limits by six or seven months.

There is also a positive correlation between SCLE and the presence of HLA-DR2 and HLA-DR3.

Treatment for patients with drug-induced SCLE begins with cessation of the offending agent. Oral and topical steroids are used initially to control the inflammatory response. It is also imperative that sunscreens be used, and avoidance of direct sunlight is highly recommended until there is resolution of the lesions.

In 1998, the first reported case of terbinafine-induced SCLE was described. Since that time, multiple reports have confirmed the link between terbinafine and SCLE. Terbinafine, also known as Lamisil, is an allylamine antifungal agent used commonly in the treatment of fungal infections of the skin and nails. Generally, it is considered to be well tolerated, with an estimated 11% of the patient population experiencing side effects, and 2.7% experiencing skin reactions. The adverse cutaneous reactions range from relatively benign pruritus to life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis. Rarely, terbinafine has even been reported to cause Sweet’s syndrome.

Other manifestations include fixed drug reactions, erythema annulare centrifugum, plaque and pustular psoriasis, exanthematous pustulosis, and erythema multiforme. Cutaneous manifestations secondary to terbinafine use typically occur three to four weeks after the initial dose is given.

Terbinafine-induced SCLE appears to affect women more than men. It is also evident that patients with a history of SLE, SCLE, or other autoimmune disorders have a predisposition to develop SCLE when receiving terbinafine treatment. A study by Callen and Hughes et al. followed a group of five patients who developed SCLE after commencement of terbinafine therapy for onychomycosis. Of those five, three had a history of SCLE, one had a possible episode of SCLE, and the other developed it de novo. There have been other reports that favor de novo development rather than an autoimmune predisposition. For example, the previously mentioned study by Bonsmann et al. followed a group of four patients with terbinafine-therapy-related SCLE, and of this group, only one had a history of possible autoimmunity with Raynaud's phenomenon. None of the patients had ever had an episode of SCLE, SLE, or cutaneous photosensitivity.

The pathogenesis by which terbinafine induces SCLE is not known; however, it is thought that it may deposit within the keratinocytes, leading to autoantibody formation that is seen in SCLE. It is therefore probable that those patients with a known history of autoimmunity may be more susceptible to developing terbinafine-induced SCLE. In addition, anti-Ro has been linked to the cytotoxic damage to keratinocytes that is seen in lupus.

In conclusion, drug-induced SCLE is a condition that tends to occur among patients with a history of autoimmune skin conditions. There are a multitude of medications that can induce the cutaneous eruptions seen in SCLE. Terbinafine is a rare cause of drug-induced SCLE, but it is important to consider due to its wide use in dermatology. While usually safe to use, it can be used with extreme caution in patients with a history of autoimmune disease, specifically SLE, photosensitivity, or elevated ANA titers. It is also advisable that patients with a history of positive anti-Ro antibodies avoid using terbinafine unless necessary. Subsequently, cases of dermatophyte infection should be confirmed by nail clippings and culture before initiation of terbinafine therapy in individuals prone to autoimmunity.

If SCLE does ensue after treatment, patients should be advised to discontinue the terbinafine and be assured that the skin manifestations are temporary and should resolve when the medication is eliminated. Terbinafine is, however, still considered to be a safe medication, and its use ultimately should depend on the physician’s clinical judgment.

References
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
FINACEA is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use. FINACEA is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation. In clinical trials, sensations of burning/stinging/tingling occurred in 29% of patients, and itching in 11%, regardless of the relationship to therapy. Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure to the eye. 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, these patients should be monitored for early signs of hypopigmentation.

Please see following page for Brief Summary of full Prescribing Information.
INDICATIONS AND USAGE
FINACEA 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. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

CONTRAINdications
FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS
FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use. 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, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS
General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of FINACEA Gel led to an increased number of tumors with papillomas at the treatment site (see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility). The clinical relevance of the findings in animal studies to humans is not clear.

Information for Patients: Patients using FINACEA Gel, 15%, should receive the following information and instructions:

• FINACEA Gel, 15%, is to be used only as directed by the physician.
• FINACEA Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
• Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA Gel, 15%. Avoid alcoholic cleansers, trictones and astringents, abrasives and peeling agents.
• Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
• The hands should be washed following application of FINACEA Gel, 15%.
• Cosmetics may be applied after FINACEA Gel, 15%, has dried.
• Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
• Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
• Patients should avoid abnormal changes in skin color to their physician.
• Avoid the use of excessive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear. Azelaic acid was not mutagenic or clastogenic in a battery of in vitro and in vivo tests. Azelaic acid was not mutagenic in the Ames bacterial test or in the mouse bone marrow micronucleus test. Azelaic acid was not teratogenic in in utero and in vivo studies with pregnant rats. pregnancy in the absence of papules and pustules has not been evaluated. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

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Case Report
A four-year-old female with an unremarkable medical history presented with an asymptomatic, enlarging mass on her scalp. It was first noticed approximately two years prior to her presentation. Her parents reported that it had been slowly increasing in size. The mass did not cause any discomfort. Her parents denied any limits in activity, range of motion, or gross neurologic defects. No growth or developmental delay was reported.

On physical exam, the patient was a healthy-appearing four-year-old with a 3 cm, firm, nontender, rubbery, fixed mass on her occipital scalp. There were no overlying skin changes or hair loss. Her range of motion was intact, and there were no neurologic deficits. She had no palpable lymphadenopathy. An MRI was obtained demonstrating a fatty mass confined to the subcutaneous tissue with no evidence of bony invasion (Figures 1, 2). The patient was subsequently taken to the operating room for excision of the mass. After complete resection, the specimen was sent for pathologic evaluation.

Pathology reported an encapsulated tumor composed of adipocytes in varying stages of maturation. This was present in a myxoid background. The cellular content varied from spindled to round cells, which were evenly distributed. Rare lipoblasts were identified with only one non-atypical mitotic figure noted (Figures 3, 4, 5). For the purpose of excluding a malignant neoplasm, a genetic analysis was performed using fluorescent in-situ hybridization for EWS, FUS and CHOP gene rearrangement. The results of these studies were negative. The above findings support a diagnosis of benign lipoblastoma.

Discussion
Lipoblastoma is a rare tumor with approximately 200 cases reported in the literature. It is generally considered a tumor of infancy, though several cases have been reported in adults. The majority of these tumors have occurred in children under three years of age with approximately a 2:1 male predominance. There was a higher reported incidence in Caucasians; however, more recent reviews suggest this prevalence may represent institutional demographics of this entity. Bing Tang et al. reported a case of a four-year-old who presented with abdominal swelling and intermittent pain. A 17x15x10 cm lipoblastoma was excised from the child’s abdomen. There are several cases in the literature reporting intrascrotal lipoblastomas, including a report by Robb et al. where the mass led to orchiectomy. McVay et al. reported a case series that included the case of a 7-month-old with an extensive tumor in the anterior triangle of the neck. The brachial plexus was draped over this mass. A recurrence five years after the initial surgery demonstrated a mass from the brachial plexus into the deep neck, mediastinum and chest. Speer et al. reported a case of a three-year-old who presented with an enlarging neck mass and hoarseness. They found a tumor extending from the right hemithorax to the patient’s thoracic inlet and neck. Another case was reported by Jimenez documenting a retroperitoneal tumor extending from below the liver to the inguinal region, and from the inferior vena cava to the lateral abdominal wall. This 12-year-old adolescent presented with low back pain, dyspnea and a mottled edematous lower extremity. O’Brien et al. reported a 10-month-old with an extradural cervical tumor resulting in quadraparesis.

The diagnosis of lipoblastoma/lipoblastomatosis is usually made by histopathologic examination after resection. Most lipoblastoma tumors have an encapsulated, well-circumscribed and encapsulated tumor. In contrast, lipoblastomatosis is a much deeper, infiltrative and poorly circumscribed tumor. Growth rate varies from slowly growing to rapidly expanding. The size of the tumors has been reported from 0.7 cm to as large as 21 cm depending on the series or case report reviewed. Early studies suggest most of the lesions have been located in the extremities and trunk; however, more recent case series contradict this.

Clinical presentation and symptoms depend on the morphologic form, size and location of the mass. Compression of adjacent structures is usually the cause of symptoms. Numerous case reports describe the wide variability in the clinical symptoms rather than a true prevalence.
hyperchromasia that would be present in liposarcoma. Lipoblastoma also lacks the microcystic spaces and hypercellularity that would be more pronounced in liposarcoma. Still, genetic analysis may be useful and necessary for distinguishing the two tumors. Lipoblastoma has a characteristic rearrangement of chromosomal region 8q11-13, whereas liposarcoma has a specific clonal chromosomal anomaly t(12;16).2,11,12

Management of lipoblastoma and lipoblastomatosis is by surgery. Recurrence estimates vary between 0-25%, with most being specifically from the lipoblastomatosis morphology. A review of 184 cases by Speer et al. reported an overall recurrence rate of 14.3%.2 Mognato et al. reported a case of complete spontaneous resolution of lipoblastomatosis in an infant.13 They performed a surgical biopsy, and after identifying the mass as lipoblastomatosis, chose observation because surgical resection would have resulted in a mutilating surgery for a benign lesion. This suggests that conservative observation may be a reasonable choice where surgery would be devastating.

Conclusion

We present a rare tumor to illustrate an important differential diagnosis in pediatric soft-tissue tumors. Lipoblastoma should be considered in the differential diagnosis of any pediatric soft-tissue tumor and must be clearly differentiated from a liposarcoma. As histopathology can be very similar, genetic analysis should be considered in difficult cases. Finally, evaluation and management will likely be a team approach involving radiology, pediatric surgery and subspecialty care as the location of the tumor can lead to a wide range of clinical symptoms and/or presentations.

References

Macular Arteritis: A Case Report and Review of the Literature

Jessica Newburger, DO,* David B. Kessler, DO, FAOCD**
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ABSTRACT
Cutaneous vasculitis traditionally presents with palpable purpura and erythematous nodules. Macular arteritis is a form of cutaneous vasculitis that presents with asymptomatic, hyperpigmented macules, which most often occur on the lower extremities. The disease runs a benign, chronic and indolent course. It may represent a latent, non-nodule forming, chronic variant of cutaneous polyarteritis nodosa (CPN). We present a case of a female with macular arteritis who presented with hyperpigmented macules on both legs without systemic involvement. There have been few cases reported to date.

We present a case and review the literature regarding macular arteritis.

Case report
A 32-year-old African-American female presented with a 10-month history of dark spots on both legs following an episode of lower-extremity tightness after exercise. The first lesion she noticed was an erythematous papule, and despite the initial tightness she felt in her legs, the lesions were asymptomatic and painless. They were limited to her lower extremities, but had increased in quantity and darkened in color over the past 10 months.

Another physician originally treated the patient for folliculitis with multiple topicals without improvement. She denied any associated fevers, malaise, joint pain or weakness. The patient’s past medical and surgical history consisted of a myomectomy for fibroids and endometriosis. She had surgery for temporomandibular joint arthropathy and a C-section in 2007. She denied any family history of autoimmune or systemic rheumatic disease. Her medications included only prenatal vitamins and vitamin D 50,000 IU daily. She had an allergy to penicillin. The patient also stated that she recently traveled to Jamaica.

On physical exam, there were hyperpigmented and erythematous macules on the patient’s anterior legs, distal thighs and dorsal feet, bilaterally (Figures 1 & 2). They measured 0.5 cm to 2.0 cm in size. The lesions were non-tender to palpation and non-pruritic. Additionally, the patient’s skin was noted to be very dry.

The patient was prescribed doxycycline and a topical steroid cream with minimal improvement. Laboratory testing revealed an ACE, ASO and ESR within normal levels. A complete blood count, liver function tests and renal function were all within reference range. A 4 mm punch biopsy of a lesion on the right leg was performed and showed leukocytoclastic vasculitis involving a small artery/arteriole, changes suggestive of polyarteritis nodosa (Figures 3 & 4). The histopathology further stated that in multiple sections there was a medium-sized artery/arteriole at the junction of the reticular dermis and subcutaneous fat which had a mixed cell infiltrate including neutrophils and neutrophilic karyorrhexis within its wall. The elastic-tissue stain did not show elastic tissue within the media of the vessel.

At that time, additional laboratory testing revealed a sedimentation rate of 5. The urinalysis was normal. Hepatitis serologies and RPR were non-reactive. The ANA, DNA, ENA, SS-A and -B, ANCA, rheumatoid factor and Lyme titer were all negative. Serum protein electrophoresis was normal, and cryoglobulins were not detected.

The doxycycline was discontinued. Topical ammonium lactate lotion was added to the topical steroid. Indomethacin 25 mg twice daily was initiated. The patient did not want to take systemic steroids. The NSAIDs showed no improvement, and pentoxifylline 400 mg three times daily showed no improvement. The patient was referred for a rheumatology consult, who agreed that the diagnosis of cutaneous polyarteritis nodosa was most likely.

Further lab evaluation included normal C3 and C4, negative anticardiolipin IgG, IgM, and IgA, and negative thyroid antibodies. Systemic immunomodulating therapy options were discussed with the patient, and although she declined initially, she was recently started on hydroxychloroquine and continues to be followed.

Discussion
Macular arteritis is a recently described form of cutaneous vasculitis that has unique clinical and histopathological characteristics. It presents with multiple, variably sized, asymptomatic, hyperpigmented or, less commonly, hypopigmented or erythematous macules. The lesions tend to favor the lower extremities and reveal lymphocytic arteritis in the deep dermis and subcutaneous fat at
various stages of evolution, ranging from fibrinoid necrosis to endarteritis obliterans. The disease runs a chronic, indolent course. This clinical presentation has not been reported previously in other forms of cutaneous vasculitis. Traditional stigmata of cutaneous vasculitis, such as palpable purpura and erythematous nodules, are not present.

The term “macular arteritis” was first coined by Fein et al. in 2003 for three African-American patients who presented with a rather uniform eruption of hyperpigmented macules on the lower extremities, which revealed a lymphocyte-mediated arteritis in the superficial subcutaneous fat. In 2005, Sadahira et al. reported two similar cases occurring in Japanese patients, followed by Al-Daraji et al. in 2008, who reported one case, and Saleh et al. in 2009, who presented three more cases.

As of 2009, 10 patients have been diagnosed with macular arteritis, and seven of the 10 cases were female patients. Five were African-American (50%), one biracial (African-American and Asian), two Asian (Japanese, 20%), and one Caucasian. The ethnicity of case 10 was not specified. The age of the patients at the time of diagnosis ranged between 6 and 73 years, with a mean age of 41 years. Lesions were asymptomatic to minimally pruritic and consisted, most often, of round to oval, discrete and confluent hyperpigmented macules that ranged in size between 0.5 and 3.5 cm. The site predominantly affected was the lower extremities, which was seen in all 10 patients.

The cause of macular arteritis is unknown. Extensive evaluation thus far has not revealed a consistent finding among cases. Despite weakly positive values of anticardiolipin antibodies (ACA) in two patients, ANA of moderate titer in one patient, anti-SS-A antibodies in one patient, and mildly elevated ESR in two patients, there was no evidence of systemic connective-tissue disease in any of these cases.

Histology has revealed similar findings in all reported cases of macular arteritis. The epidermis and dermis are unremarkable. There is a dense lymphocytic infiltrate around and within the wall of a small artery at the junction of the deep reticular dermis and subcutaneous fat. The artery shows intimal thickening. The lumen is sometimes narrowed by fibrinoid material along the luminal side of the vessel wall, though there is no evidence of vessel-wall destruction. One of the most striking features is the localization of the inflammation to the immediate vicinity of the affected vessel and the absence of infarction in the neighboring tissue.

Macular arteritis differs from traditional forms of cutaneous arteritis in that the primary lesion is a hyperpigmented macule. Vasculitides that affect small to large arteries in the skin, such as polyarteritis nodosa and temporal arteritis, typically present with erythematous nodules. In contrast to previously described forms of vasculitis, the lesions of macular arteritis are asymptomatic and show no tendency for progression.

Within the spectrum of arteritis that may affect the skin, numerous diseases have been described, including temporal arteritis, polyarteritis nodosa, Churg-Strauss syndrome, and Wegener’s granulomatosis. The primary lesions present in these forms of arteritis include erythematous nodules and papules. A variety of laboratory abnormalities have been reported in these various forms of cutaneous arteritis. The perinuclear pattern of antineutrophil cytoplasmic antibodies (p-ANCA) is present in at least 70% of patients with Churg-Strauss syndrome. The cytoplasmic pattern of ANCA antibodies (c-ANCA) is detectable in more than 80% of histologically proven cases of Wegener’s granulomatosis.

Al-Daraji et al. suggested that macular arteritis might represent a latent, non-nodule-forming, chronic variant of...
cutaneous polyarteritis nodosa (CPN) due to overlapping clinical-pathologic features. CPN similarly runs a chronic, benign course and is denoted by muscular vessel vasculitis, which can resolve with retiform hyperpigmentation. It is an uncommon form of vasculitis of the small- and medium-sized arteries in the reticular dermis and subcutaneous tissue and may encompass extracutaneous features such as arthralgias, arthritis, neuropathy and myopathy. In contrast, polyarteritis nodosa (PAN) is a form of nodular vasculitis that most frequently involves the medium-sized muscular arteries of the kidneys, liver, heart, and gastrointestinal tract.

In CPN, the site of involvement is primarily the legs, with over 95% of the lesions located in this region. A frequent manifestation is that of a painful subcutaneous nodule, which can be easily mistaken for erythema nodosum or panniculitis. Common generalized symptoms include malaise, fevers, myalgias, and sore throat. Myalgia, which clinically manifests as muscle aches, tenderness, and stiffness, is frequently observed over the calves.

For some authors, CPN is essentially PAN with cutaneous symptoms, whether or not other organs are involved. Another view is that CPN is only a stage in the evolution of the systemic disease. However, the majority of authors believe that CPN is a distinct entity with localized cutaneous vascular disease and runs a benign course with exacerbations and remissions that never seriously compromise the health of the patient. The etiology of CPN remains unknown, but presumably has an immune-complex mediated pathogenesis, as shown by IgM and C3 deposits in the biopsy specimens. Streptococcal infection is believed to cause this immune-complex mediated disease. No patient has died from CPN per se, and the tendency has been for the condition to slowly fade away. It runs a benign, chronic course lasting from months to years even though the acute symptoms may take two to eight weeks to resolve. Skin nodules take years to clear, with gradual decrease in frequency and severity.

Many healed lesions of CPN leave residual changes that are either violaceous livedoid or hyperpigmented and retiform in appearance, which can persist for months and even years. Although active lesions of CPN show a neutrophilic-mediated vasculitis with fibrinoid necrosis, resolving lesions of neutrophilic vasculitis progressively lose neutrophils, gain lymphocytes and macrophages with time, and show fibrous replacement of the injured vessel wall. The absence of neutrophil-mediated vascular inflammation in macular arteritis patients could be due to the older age of the lesions, as all patients to date have presented with long-standing rather than acute disease, of greater than two months duration. CPN is relatively uncommon, representing less than 3% of all cases of cutaneous vasculitis; however, its incidence may be higher due to underdiagnosis.

Although systemic disease is not a feature of CPN, renal aneurysms on selective visceral angiography have been identified in some patients, and providers should be aware of this. Corticosteroids remain the mainstay of treatment for CPN. The aim is to control the acute exacerbation and provide pain relief, rather than to suppress all manifestations of the disease. Usually a dose of 20 mg of prednisolone daily or less is needed to achieve this. Non-steroidal anti-inflammatory drugs (NSAIDs) may be helpful when used alone or together with systemic steroids. Pain relief is an added advantage besides the anti-inflammatory property of NSAIDs, and acetyl salicylic acid and indomethacin are commonly used. Aggressive treatment is not required in most cases of CPN, and symptomatic treatment with prednisolone or NSAIDs will suffice. Although conservative therapy with high-potency topical or intralesional corticosteroids is initially indicated in these patients, multiple anecdotal reports have also identified select patients responsive to salicylates, dipyridamole, sulfapyridine, pentoxifylline and dapsone. Patients who have chronic, painful skin lesions that are unresponsive to topical, intralesional, or low-dose corticosteroids may respond to low-dose methotrexate (7.5-20mg/week).

Regarding macular arteritis specifically, treatment is not required, as lesions tend to be asymptomatic and the disease has been shown to run a benign course.

References
MRSA Blistering Distal Dactylitis in an Elderly Patient: A Case Report

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ABSTRACT
Blistering distal dactylitis (BDD) is an infection of the anterior fat pad presenting as bullae that can evolve into erosions and is secondary to Gram-positive bacteria. Although initially reported in children, it is now known to also affect adults. The infection responds promptly to incision, drainage, and antibiotic treatment and is associated with low morbidity. We present an unusual case of BDD in an elderly man ending in medical-treatment failure, osteomyelitis, and amputation.

Introduction
Blistering distal dactylitis (BDD) is an infection of the anterior fat pad of the distal fingers that presents with tense bullae on an erythematous base. The entity was first described in 1972 by Hays and Mullard as a disease affecting children mainly due to beta hemolytic streptococcal infection with or without additional infection with staphylococcus aureus.1,2 Since then, cases have been reported in both infants and adults.3-7 Additionally, the spectrum of infectious agents reported has expanded to include group B streptococci and methicillin-resistant staph aureus (MRSA).4,5,8,9 BDD typically responds well to incision and drainage and antibiotic treatment and resolves without complications.2 The following is a report of MRSA BDD in an 89-year-old man.

Case Report
An 89-year-old man presented with a three-week history of a painless, tense bulla on his left 3rd finger. Patient also admitted to smaller recurrent blisters on his 2nd and 3rd fingers of his left hand over the past 12 months. Previous blisters were painless, flaccid, clear-fluid filled and had denuded and healed easily. This blister was larger, firm, and had a brown to red color surrounding it. He denied pain, pruritus, purulent drainage, and fever. He denied trauma and insect bites. Past medical history was significant for mild dementia, hypertension, chronic renal insufficiency, anemia, hyperlipidemia, MRSA-positive nasal swab, and amputation of the left fifth digit many years ago secondary to traumatic injury. Medications included docusate, lisinopril, omeprazole, and aspirin.

On physical exam, patient appeared well, and left middle finger revealed a 3 cm x 2.3 cm, violaceous, edematous change to finger pulp with a 3 mm x 5 mm clear, firm bulla on the distal anterior fingertip (Figure 1). Moderate erythema surrounded these changes and continued onto the dorsal surface of the finger. No nail changes or tenderness were appreciated. As the patient had no pain or systemic symptoms, treatment plan was for observation and return for follow-up evaluation in two weeks. On return, the bulla had eroded with drainage and crusting now present (Figure 2). Culture of purulent exudate grew MRSA. X-ray was negative for bone involvement. Lab work was unremarkable. Patient was started on minocycline but was unable to tolerate antibiotic due to vomiting. Doxycycline was prescribed, but patient was hesitant to begin another antibiotic. When he did, he was again unable to tolerate the medication due to vomiting. Patient was resistant to further treatment and only returned two months later due to pain in the distal finger. MRI was consistent with osteomyelitis, and the patient was started on oral trimethoprim/sulfamethoxazole. X-ray at this time showed destructive changes of the distal phalanx of the third digit consistent with osteomyelitis (Figure 3). Surgery was consulted, and the patient elected amputation rather than extended-course intravenous antibiotic treatment.

Discussion
Hays and Mullard first used the term BDD in a 1972 paper and later further delineated the disease in a 1975 report of 13 cases.1,2 They defined BDD as a distinct clinical entity manifested by a superficial blistering lesion over the anterior fat pad of the distal portion of a finger or thumb that may or may not have paronychial extension. The 13 patients they reported ranged in age from 2 to 16 years. All lesions were non-painful and drained thin, white, purulent exudate. Cultures grew beta hemolytic streptococcus in all cases, with three of the cases also growing staphylococcus aureus. Treatment consisted of incision and drainage, topical antibiotics, and systemic antibiotics and was effective in every case with no resultant morbidity or mortality. Since then, BDD has been reported multiple times in the literature with expansion of our understanding of the clinical presentation and infectious etiology. Apart from children, it has now
been reported in infants and adults and is known to affect proximal fingers, palms, toes and soles.\textsuperscript{3,6,10-12} Multiple bullae on different digits can occur.\textsuperscript{13} The organisms implicated in causing BDD have grown to include Group B strep, staph aureus alone, and methicillin-resistant staph aureus.\textsuperscript{4,5,8} We believe the patient we present is unique in his presentation in two ways: his age, and the morbidity associated with his infection.

Although BDD has not previously been expected to affect the elderly, we present a case of an 89-year-old man. It has been hypothesized that BDD infection in children is due to thumb sucking, and that infection in infants (<9 months old) may be secondary to exploration of the mouths of adults.\textsuperscript{3,6,11} One of the original 13 cases reported was associated with recurrent blisters, and BDD has since been reported in association with herpetic whitlow.\textsuperscript{2,11} Our patient is an elderly man who also reported recurrent blistering disease of unknown etiology preceding the BDD. In addition, he had a history of testing positive for MRSA by nasal swab during previous hospitalization. We propose that occurring together, these factors -- MRSA carriage and recurrent blistering -- contributed to the development of BDD in this elderly patient. Given the increasing prevalence of MRSA positivity, the aging of the population in general, and the susceptibility of the elderly to blistering disease (particularly autoimmune), the atypical presentation of BDD seen in this patient could become more common in the future.\textsuperscript{14}

The second significant aspect of this case of BDD was that it was associated with treatment failure and significant morbidity ending in osteomyelitis and amputation. Previously, it has been emphasized that BDD is a soft-tissue infection and is associated with low morbidity and no treatment failures.\textsuperscript{13,15} Our patient was unable to tolerate two antibiotic choices secondary to nausea and vomiting. In addition, he was resistant to attempting alternate antibiotic treatment following the initial reactions due to the apparently benign nature of the infection. As is typical of BDD, he had no pain, pruritus, or burning at the site of the bulla, and he had no systemic symptoms.\textsuperscript{13} He only returned to the clinic for further medical attention two months after his initial presentation due to the development of pain. Pain is typical of acute osteomyelitis secondary to contiguous spread of a soft-tissue infection, and staph aureus is the most common cause of this type of osteomyelitis.\textsuperscript{16} Diagnosis of osteomyelitis is most often by X-ray, MRI, or radionuclide scan. Conventional X-ray reflects the destructive process of the infection, showing periosteal thickening and elevation and focal osteopenia, but can lag two weeks behind the progress of the infection.\textsuperscript{16} Use of radionuclide studies and MRI in conjunction with X-ray can improve sensitivity and specificity when diagnosis is ambiguous. In the patient we present, initial X-ray was negative and may have accurately reflected lack of bone infection at that time or may have been a false negative due to being taken very early in the course of infection. Two months later, both X-ray and MRI showed changes consistent with osteomyelitis.

**Conclusion**

In summary, BDD is a blistering eruption on the acral areas that can be caused by beta hemolytic strep, group B strep, staph aureus, or MRSA. It presents as tense bullae that may progress to erosions and can affect infants, children, and adults. Diagnosis is clinical, based on a distinctive appearance, but culture of the bullae contents can direct antibiotic therapy. We present a case affecting an elderly man that ended in medical-treatment failure, osteomyelitis, and amputation. Although BDD is not customarily thought of as a disease of the elderly or one associated with significant morbidity, we present this case in order to broaden our medical awareness of the scope and possible consequences of the disease. In patients with BDD who fail to respond quickly to medical treatment, are unable to tolerate suitable medical treatment, or develop significant or progressive pain at the site of infection, the possibility of contiguous extension of the infection to bone should be considered. In these select patients, appropriate radiographic studies should be considered to evaluate for osteomyelitis so that treatment can be adjusted and potential morbidity can be avoided.

**References:**


LENZ, LEMOINE, NISENBAUM 61
Introduction

Cutaneous manifestations of internal malignancy are rare and are estimated in the literature to occur in 0.7% to 9% of patients with metastatic carcinoma (1). Moreover, Lookingbill et al. estimate that less than 5% of these cutaneous findings are of oral mucosa origin. We report a case of a male with a history of oropharyngeal carcinoma who presented with a metastatic lesion on his right mandible. To date, there are few literature reports looking at specific metastatic malignancies and the manner in which they may present in the skin. This report aims to reveal some of the cutaneous findings of metastatic oropharyngeal cancer. Recognizing these lesions and initiating therapies could aid in an earlier diagnosis and could potentially decrease mortality in these patients.

Case Report

A 55-year-old Caucasian male presented to the clinic as a referral from otolaryngology with a five-month history of an enlarging mass along the right mandible, thought to be a “cyst.” The patient admitted to swelling of the right side of his jaw as well as an intermittent, dull pain that was exacerbated with mastication. He denied having similar symptoms in the past or any associated trauma. Past medical history was significant for stage II squamous cell carcinoma in the midline of the soft palate that was diagnosed in 2006. The carcinoma was subsequently treated with localized radiation that was directed from an external position toward the right jaw line. Six months prior to his current visit, the patient had all of his lower teeth extracted due to radiation decay, replaced with a composite molding. Review of systems was negative for oral bleeding, drainage, and constitutional symptoms. He reported a 75 pack-year smoking history, drank two to three alcoholic beverages daily, and denied any chewing tobacco. Home medication included oxycodone 5 mg every 8 hours as needed for odynophagia. He denied any allergies or pertinent family history.

Physical exam revealed a cachetic male with bitemporal wasting and a thickened, hypertrophic, 1 cm, firm subcutaneous nodule noted along the right mandibular jaw line. Sensation to sharp and dull was decreased along the right mandible. The oral cavity featured halitosis, composite teeth that appeared within normal limits, and mild ulceration in the posterior pharynx but no evidence of a gross mass. Jaw movement included a left lateral deviation upon opening as well as limited range of motion. Right submandibular and subtonsilar lymphadenopathy was noted.

The differential was discussed with the patient and included malignancy of primary and metastatic nature, radiation dermatitis, infection, and idiopathic. The patient opted to have a 4-0 punch biopsy of the lesion along the right jaw line. The initial pathology report revealed chronic septal panniculitis with some changes suggestive of radiation dermatitis. This report did not correlate well with the clinical picture; therefore, we performed another punch biopsy for a second opinion. An MRI with and without contrast of his head and neck was also ordered to see if there were any other masses or evidence of metastasis. During the interim, his otolaryngologist and oncologist were contacted and past medical records were obtained.

The repeat biopsy revealed a deeply situated, infiltrative, poorly differentiated carcinoma with sclerosis. The morphologic features in conjunction with the immunohistochemical staining (AE1/AE3 +) results were compatible with poorly differentiated squamous cell carcinoma. MRI demonstrated a nodular necrotic mass with peripheral enhancement superficial to the angle of the right mandible as well as a similar focus in the left supraclavicular region, deep to the sternocleidomastoid.

PET CT imaging from skull base to the thigh was ordered by his oncologist and yielded an interval development of a right perimandibular soft-tissue nodule that was mildly hypermetabolic, possibly representing metastasis to a perimandibular lymph node. In addition, multiple poorly defined cavitary nodules were identified within the lungs that were non-hypermetabolic and measured 1-2 mm in size. The patient was sent to his oncologist for initiation of treatment.

Discussion

Malignancy of the oral cavity and oropharynx are the most common head and neck cancers in the United States (2). Soft palate cancers, an oropharyngeal subtype, comprise 2% and are predominantly squamous cell cancer (3). The greatest risk factor for head and neck cancer in American men and women is alcohol and tobacco use (3,4). Other risk factors include
Epstein-Barr virus, human papilloma virus, occupational exposure, radiation, diet, and genetics (3,4). Head and neck cancers are biologically aggressive and often spread to the lymph nodes of the neck (5). In comparison to oral cancer, oropharyngeal SCC demonstrates a more frequent regional lymph node and distant metastasis (2).

Researchers Chu-Sung Hu et al. evaluated the rates of cutaneous metastases of internal malignancy and proposed the idea that certain chemokines attract tumor cells more than others. CCR10 and CXCR4 were the investigated tumor markers, and immunohistochemical staining was performed on three cases of breast cancer with skin metastasis, three cases of lung cancer with skin metastasis, and one case of hepatocellular carcinoma without skin metastasis. It was found that the expression of CCR10 and CXCR4 had no correlation with cutaneous metastasis (1).

SCC extension beyond the soft palate occurs in greater than 50% of cases, with direct signs and symptoms corresponding to the invaded area. Some of the more common areas of expansion include the hard palate, retromolar trigone, inferior or superior alveolar process, base of tongue, and tonsils (3,4). As seen in our case, extension into the mandibular area may cause trigeminal nerve hypesthesia along the V3 distribution as well as wasting of the temporalis or masseter muscles. Furthermore, malocclusion, pain, and trismus indicate tumor involvement of the pterygoid muscles (3,4). Earlier stages may be asymptomatic, while advanced stages exhibit pain. In addition, later-stage soft palate SCC can feature altered speech, dysphagia, trismus, otalgia, neck mass, or velopharyngeal insufficiency (3,4).

To date, there is a scarcity of literature on cutaneous lesions arising in the setting of metastatic head and neck malignancies. The external depiction of what lies beneath is as important as the patient’s history itself, lending hints to a “visually literate physician” (8). With clinical suspicion and prompt diagnosis, one can take immediate steps toward properly managing the patient and offering palliative care. The rates of cutaneous metastasis of different types of cancer are still under investigation (1). From histologic subtypes to chemokine receptors, the enigmatic features of malignant superficial exhibition are what attracted us to present this case.

References
Introduction

Focal hyperhidrosis (excess sweating focused in a given area) affects approximately 2.8% of the population, with an estimated 7.8 million people in the United States suffering from this sweat-gland disorder. Given this high prevalence rate, it is surprising that there is not greater emphasis on focal hyperhidrosis and its treatment. Although often considered somewhat benign by many clinicians, recent studies indicate focal hyperhidrosis causes a substantially increased prevalence of bacterial, fungal, and viral infections and causes a profound effect on the patient’s quality of life. Changes in quality of life observed in focal hyperhidrosis are similar to those seen in other severe chronic disorders such as end-stage renal disease, multiple sclerosis and rheumatoid arthritis. This article will summarize the current state of knowledge concerning the mechanisms and regulation of sweating: prevalence, diagnosis, consequences, and etiology of excess sweating on the palms and soles of the feet (palmar-plantar hyperhidrosis) and armpits (axillary hyperhidrosis). We will then compare and contrast treatment options available for the focal hyperhidrosis patient.

Mechanisms and Regulation of Sweating

Sweating is a vital homeostatic process in the regulation of internal body temperature. Three sweat gland types exist: eccrine, apocrine, and apecocrine. The primary differences among the glands are where and how the sweat exits the gland (Figure 1). Eccrine glands make up the majority of the sweat glands and are the primary glands engaged for thermoregulation, although other non-thermal factors also influence sweating. Evaporative cooling of sweat from eccrine glands maintains our core body temperature in warm environments or during exercise. Eccrine sweating is also engaged by emotional stimuli, which is thought to be a primary trigger for focal hyperhidrosis. Eccrine glands are distributed over nearly the entire body, with the greatest density found on the palms, axillae, and soles of the feet. Interestingly, these are also the most common sites for focal hyperhidrosis. This review will focus on eccrine sweat glands because of their association with focal hyperhidrosis, but it is acknowledged that apocrine glands may contribute to axillary hyperhidrosis.

Structurally, the eccrine sweat gland consists of a bulbous secretory coil leading into the duct that opens onto the skin surface (Figure 2). Acetylcholine and norepinephrine are the primary neurotransmitters that stimulate eccrine sweat glands, allowing the bulbous coil to produce precursor fluid. This precursor fluid is formed by ion movement across and between cells, which osmotically draws water into the bulbous coil lumen. Pressure then builds within the coil until the pressure is great enough for the fluid to travel through the duct toward the skin’s surface. Modification of the precursor fluid occurs within the duct (reabsorption of sodium and chloride ions), resulting in hypotonic (i.e., lower ion concentration compared to blood) secreted sweat. Sweating can be quite profuse, and whole-body sweat rates have been recorded at over 3.7 liters per hour and 10-11 liters per day when exercising or working in hot environments. The nervous system controls and regulates sweating via skin sympathetic nerve activity to the eccrine sweat glands (Figure 3). It is these sympathetic nerve terminals that release the acetylcholine and norepinephrine to stimulate sweating. Because of the sympathetic nervous system involvement, sweating can be stimulated or modulated by other “fight or flight” factors.
appears first in childhood or adolescence. Sweating of focal hyperhidrosis usually being a rare disorder. The excessive misconceptions about focal hyperhidrosis data from this survey have helped to change and seek treatment at a higher rate. The may report their condition to physicians although it was acknowledged that women women reporting hyperhidrosis equally, age ranged from 25-64 years, with men and may vary between patients. A normal sweat rate is considered to be less than 1 mL/m^2/min of sweat production by the eccrine glands at rest and at room temperature. Morphologically, the sweat glands appear to be normal in focal hyperhidrosis patients; however, there are heightened responses to stimuli such as emotional or physical stress. Diagnostic criteria located in table 1. To quantify the extent of hyperhidrosis, a gravimetric or starch-iodine test is sometimes used. The gravimetric test quantifies the sweat rate (mg/min) and the starch-iodine test, completed during a thermoregulatory challenge, establishes the precise dimension of affected skin areas.

**Prevalence of Focal Hyperhidrosis**

Currently, 2.8% of the United States population is believed to have focal hyperhidrosis. This prevalence statistic was calculated by projecting the results of a nationally representative sample of 150,000 households (screened by mailed survey for hyperhidrosis) to the U.S. population based on U.S. census data. The data from this survey have helped to change misconceptions about focal hyperhidrosis being a rare disorder. The excessive sweating of focal hyperhidrosis usually appears first in childhood or adolescence but is normally not reported until later in life. Even current prevalence statistics may underestimate hyperhidrosis, as other research indicates that 2/3 of individuals with hyperhidrosis have not discussed the condition with their healthcare professional.

**Diagnosis of Focal Hyperhidrosis**

In a clinical setting, focal hyperhidrosis is usually diagnosed by patient history and physical examination. The perception of hyperhidrosis is an individual assessment and may vary between patients. A normal sweat rate is considered to be less than 1 mL/m^2/min of sweat production by the eccrine glands at rest and at room temperature. Morphologically, the sweat glands appear to be normal in focal hyperhidrosis patients; however, there are heightened responses to stimuli such as emotional or physical stress. Diagnostic criteria located in table 1. To quantify the extent of hyperhidrosis, a gravimetric or starch-iodine test is sometimes used. The gravimetric test quantifies the sweat rate (mg/min) and the starch-iodine test, completed during a thermoregulatory challenge, establishes the precise dimension of affected skin areas.

**Consequences of Focal Hyperhidrosis**

The seemingly harmless excessive-sweating component of focal hyperhidrosis has helped to mistakenly characterize this disorder as benign. However, as stated earlier, focal hyperhidrosis patients experience a significant morbidity, as the disease state interferes with nearly every aspect of daily life (Table 2). Individuals with focal hyperhidrosis often report physical discomfort due to wet clothing/shoes, and patients may go to considerable trouble to hide their excessive sweating, using different tactics such as pads, shields, absorbent tissues, and frequent clothing changes. The financial burden associated with the disorder can be costly when one accounts for dry cleaning and clothing replacement. It is likely that the major consequence of focal hyperhidrosis is the avoidance of social situations, which penetrates all person-to-person interactions, from relationships to choice of occupation. In one survey, social embarrassment was reported by 90% of patients with palmar hyperhidrosis, and 40% of respondents had psychological difficulties attributed to their symptoms. Previously, it was believed that individuals with hyperhidrosis suffer from other psychopathology; however, a more controlled analysis found that the anxiety, social avoidance, and depression in patients were secondary to the hyperhidrosis and not a primary diagnosis.

Individuals with focal hyperhidrosis are predisposed to fungal, bacterial, and viral site-specific secondary infections. This is due to constant moisture and skin maceration, which provides an excellent habitat for bacterial and fungal overgrowth and can contribute to bromhidrosis (foul-smelling sweat), especially in feet and the axillary regions. Pitted keratolysis, an infection of the plantar surface of the foot associated with pits and craters, and gram-negative bacterial macerative infection of the feet may also occur.

**Etiology of Focal Hyperhidrosis**

Local hyperhidrosis is a disorder that is not well understood. Focal-hyperhidrosis onset is normally between 14 and 25 years old. It is currently considered an idiopathic disorder that arises in otherwise healthy individuals. Between 30% and 65% of patients with focal hyperhidrosis have a positive family history, indicating a possible genetic component. Recent data identified the allelic probability that hyperhidrosis is heritable in an

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**Figure 3.** During whole-body heating, skin sympathetic nerve activity (SSNA) increases stimulatory signals to skin blood vessels to increase skin blood flow (SkBF) and to eccrine sweat glands to increase sweat rate (SR). Whole-body cooling suppresses SSNA and therefore SkBF and SR. Modified from Wilson, et al., *J Physiol*, 536: 615-623, 2005.
autosomal-dominant fashion with variable penetrance. Therefore, the child of a parent with hyperhidrosis has an approximately 25% chance of developing hyperhidrosis. Although many aspects of the pathophysiology of focal hyperhidrosis are not fully understood, patients with palmar hyperhidrosis have been shown to have greater sympathetic activity through the T2 and T3 ganglia.

### Treatment Options for Focal Hyperhidrosis

Many treatment options exist for the management of symptoms associated with focal hyperhidrosis. The risks, side effects, and benefits of each treatment are weighed with respect to the severity of the disease. Topical aluminum salts, systemic anticholinergics, tap water iontophoresis, and botulinum toxin are employed when the disease is not severe enough to consider the surgical options of endo-thoracic sympathectomy, liposuction, or subcutaneous axillary curettage. The side effects associated with the surgical options can be as debilitating as the disorder itself, so these treatments should be considered with caution. This review will focus on the non-surgical approaches of 1) topical aluminum salts, 2) systemic anticholinergics, 3) tap water iontophoresis, and 4) botulinum toxin.

#### 1) Topical Aluminum Salts

Over-the-counter antiperspirants are the first line of defense for focal hyperhidrosis, followed by prescription antiperspirants (e.g., Drysol) that can be applied to the axillae, palms, or soles of the feet. The active ingredient for most antiperspirants is a metal salt (e.g., aluminum chloride, GLY, aluminum chlorohydrate, aluminum chloride hexahydrate). These metal salts are thought to block the epidermal sweat duct or acrosyringium, which can cause atrophy and vacuolization of the glandular secretory cells with prolonged use. These products are designed to be applied at night, as excess sweating does not occur in these patients during sleep, for efficacious absorption of the aluminum salts into the sweat ducts. During the day, when sweat is actively being produced, the medication is not able to penetrate the sweat-gland pores. The solution should be applied to dried skin and washed off in the morning. Effectiveness appears to be increased if the area is covered, possibly allowing better metal salt penetration. The necessity of nightly application can be cumbersome for the patient, but the treatment is often effective in controlling sweating if applied diligently and as directed. Skin irritation is a common side effect. The skin may become extremely irritated and raw, which causes many patients to stop antiperspirant treatment. In some instances, aluminum chloride reacts with the excessive sweat and forms skin-irritating hydrochloric acid. Anhydrous ethyl alcohol added to 20% aluminum chloride hexahydrate may be prescribed to alleviate some irritation.

#### 2) Systemic Anticholinergics

Anticholinergics are competitive antagonists of muscarinic receptors located on the sweat glands. If these receptors are blocked, then sweat subsides. One study indicates that 75-80% of subjects were able to control sweating with anticholinergics, but 1/3 of the subjects were limited by side effects.

#### 3) Tap Water Iontophoresis

Tap water iontophoresis is a simple procedure that utilizes a battery-powered unit to deliver a current through tap water (i.e., water with a low concentration of ions) either through saturated wool pads separated by a non-conducting barrier or through a small tub. According to published reports, this treatment option is safe, non-invasive, efficient, cheap, and usually well-tolerated. The inhibitory effect of tap water iontophoresis on sweating is greater with the anodal current as opposed to the cathodal current and is dependent on the amperage used. The mechanism of action for tap water iontophoresis is not well understood; currently, the most compelling theory is that the anodal current causes H+ to accumulate within the sweat duct, which may cause lesions in the acrosyringium that inhibit sweating. The technique involves using the maximum amperage tolerated by the patient.

#### Table 1. Diagnostic criteria for focal hyperhidrosis.

**Primary criteria:** Focal, visible, excessive sweating of at least 6 months duration without apparent cause.

**Secondary criteria:**
1. Bilateral and relatively symmetric sweating
2. Impairment of activities of daily living
3. Onset < 25 years old
4. Family history
5. Cessation of sweating during sleep

#### Table 2. Patient burden of hyperhidrosis.

1. Change of clothing required 2+ times per day
2. Avoidance of social gatherings and/or hand shaking
3. Severe embarrassment associated with wet clothing or palms
4. Frustration with activities of daily living
5. Impaired work performance and productivity
6. Alteration in type of leisure activities
7. Depression and lack of confidence
8. Skin maceration
9. Increased bacterial, fungal, and/or viral infections
10. Difficulty with social and intimate relationships
employed in a stepwise fashion beginning with topical antiperspirants and progressing to botulinum toxin. Availability, cost, physician preference, and patient tolerance are factors that contribute to the patient's treatment for an individual. Topical antiperspirants, while effective, have the drawback of causing skin irritation. Oral anticholinergics are convenient but this may be hampered by the systemic side effects. Tap water iontophoresis is also effective but can be cumbersome to use for the patient. The relatively long-term effects of botulinum toxin make it an appealing treatment; however, pain and cost may be obstacles. Further studies to find the causes of focal hyperhidrosis will help to individualize and potentially improve treatment options for those with palmar-plantar and axillary hyperhidrosis.

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References

ADALIMUMAB FOR THE TREATMENT OF PITYRIASIS RUBRA PILARIS: CASE STUDY WITH AN OVERVIEW OF DISEASE CLASSIFICATION

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ABSTRACT

Pityriasis rubra pilaris (PRP) refers to a rare group of chronic, hyperkeratotic, papulosquamous diseases that can be acquired or inherited. It is commonly confused with other papulosquamous and erythrodermic disorders. The etiology is unknown, and treatment is often frustrating for both patient and clinician. In this case report we present and discuss a 64-year-old man with type I PRP, the most common variant. We discuss the nascent use of biologic therapy in PRP and report the successful use of adalimumab in treatment.

Clinical Case

A 64-year-old Caucasian male presented to the dermatology clinic with a chief complaint of rash for three weeks. The patient described a 48-hour period of intense head and upper trunk erythema followed by the development of an erythematous, pruritic, scaly rash on the scalp, face and arms. The patient denied any constitutional symptoms preceding development of the rash. The patient reported good overall health with a history of pre-diabetes only. The patient denied taking any medications prior to development of the current complaint and reported not using any medications on a regular basis. The patient denied alcohol or drug use but was previously a tobacco smoker with a 25 pack-year history and reported quitting 20 years prior. He denied any constitutional symptoms including: malaise, fever, chills, diarrhea, or weight loss. Prior to presentation, the patient was seen by his PCP and placed on a 40 mg daily prednisone burst for five days, hydroxyzine, and triamcinolone cream.

On physical exam, the patient had an erythematous, papulosquamous eruption with prominent scale over the back, shoulders, face, and head. The papules and plaques become confluent on the chest and back with prominent islands of sparing in some areas. There was diffuse erythema with fine scale over the face, scalp, and ears. Abdomen and lower extremities were without involvement. Our differential diagnosis was broad and included psoriasis, contact dermatitis, severe seborrheic dermatitis, pityriasis rubra pilaris, mycosis fungoides, and drug eruption.

A 4-mm punch biopsy was taken of the right shoulder revealing a broad, variably compact orthohyperkeratosis with patchy foci of parakeratosis. The granular cell layer was largely preserved, with some areas of hypergranulosis. Foci of incipient acantholysis were also noted. No intra- or extracellular neutrophils or spongiform pustules were seen. PAS-positive material was noted, but no definitive fungal hyphae were seen with GMS stain.

The patient showed little clinical improvement with initial treatment of isotretinoin 1mg/kg/day for 60 days. Additionally, the patient was using clobetasol ointment under occlusion at night and bland emollients for palmoplantar keratoderma (Figure 1), which developed subsequent to his initial visit. Tumor necrosis factor-inhibitor medications were considered owing to their efficacy and safety profile in treating psoriasis patients. Adalimumab was selected as a treatment option over etanercept due to its more convenient 2-week interval dosing schedule. Treatment was started with an initial subcutaneous dose of 80 mg followed by a 40 mg subcutaneous dose one week later. After just the initial two doses, the patient demonstrated a reduction in overall erythema and pruritus. Since then, 40 mg dosing has continued every two weeks for 20 weeks of total therapy. The patient was also treated concurrently with narrow-band UVB for a total of 28 treatments over a three-month period. The patient has experienced significant improvement with a total resolution of his palmar keratoderma (Figure 2) and reports considerable improvement in his quality of life.

We estimated the patient had nearly 40% total body involvement prior to treatment. Currently, we estimate the patient to have <5% of total body surface area involvement. In treating psoriasis, there exists an objective standard in the Psoriasis Area Severity Index (PASI) to measure extent of severity, giving the clinician the ability to quantify treatment effectiveness. There does not yet exist a similar index for pityriasis rubra pilaris. However, given the similar clinical features shared, a case could be made that the PASI score might be effective with PRP. Future work can be done in determining viability of the PASI score in PRP patients.

Discussion

Pityriasis rubra pilaris, also known as Devergie’s disease, was first described by Tarral in 1828 and later classified “pityriasis pilaris” by French professor of dermatology Alphonse Devergie in 1856. PRP refers to a group of chronic disorders...
characterized by reddish-orange plaques with pityriasisform scaling showing follicular keratoses and palmoplantar keratoderma. The disease may progress to erythroderma with areas of uninvolved skin called “islands of sparing” (Figure 3). The age of onset, behavior, clinical appearance, and prognosis are considered very important for its classification. The disease is sub-classified into six types, with both hereditary and acquired forms reported: classic adult type (I), atypical adult type (II), classic juvenile type (III), circumscribed juvenile type (IV), and atypical juvenile type (V); PRP has also been reported in patients with HIV, presenting with different clinical features and a poorer prognosis, designated PRP type VI.

The pathogenesis is unknown. It is generally inherited in an autosomal-dominant fashion with variable expression. Autosomal-recessive and X-linked inheritances have also been reported, but sporadic remains the most prevalent mode of inheritance. A familial subtype of the disease exists but is rare and usually presents as type V PRP. Though the etiology remains unknown, there have been multiple proposed hypotheses including vitamin A deficiency and an absence of retinol-binding protein. PRP has been associated with malignancy, trauma, infection and autoimmune diseases including myasthenia gravis and hypothyroidism. PRP occurs in all races and affects both sexes equally. The incidence of patients presenting to dermatology clinics in the United States has been reported to be 1 in 3,500-5,000 patients and as high as 1 in 50,000 in India in an outpatient setting. Prevalence has been reported at 1 in 400,000 in the UK. PRP occurs in a bimodal distribution, peaking in the first and fifth decades of life, although it may occur at any age.

Type I classic adult onset accounts for more than 50% of all cases of PRP and is consistent with our patient’s history and clinical findings. The disease typically starts on the head and face and spreads in a craniocaudal direction. The acquired form of the disorder has an acute onset. It is characterized by follicular hyperkeratotic papules that coalesce into large, scaly, erythematous plaques, palmoplantar keratoderma, and diffuse bran-like scaling of the scalp with progression to erythroderma. The palms and soles may acquire the appearance of a hyperkeratotic sandal. Palmoplantar keratoderma occurs in most patients, tends to have an orange hue, and may develop painful fissures. Nail changes include yellow-brown discoloration, subungual hyperkeratosis, longitudinal ridging, and splinter hemorrhages. Nail thickening is due to the accumulation of subungual keratin. Patients with extensive disease and prolonged facial erythroderma may develop ectropion, a dreaded complication. Oral mucosal involvement is a rarely reported condition.

Clinically, it may be difficult to distinguish PRP from other papulosquamous and erythrodermic disorders, particularly psoriasis. Histopathologic examination remains an essential diagnostic criterion, though there are multiple histologic features seen in both PRP and psoriasis including hyperkeratosis, parakeratosis, and acanthosis. PRP shows an acanthotic epidermis with alternating orthokeratotic papules that coalesce into large, scaly, erythematous plaques, palmoplantar keratoderma, and diffuse bran-like scaling of the scalp with progression to erythroderma. The palms and soles may acquire the appearance of a hyperkeratotic sandal. Palmoplantar keratoderma occurs in most patients, tends to have an orange hue, and may develop painful fissures. Nail changes include yellow-brown discoloration, subungual hyperkeratosis, longitudinal ridging, and splinter hemorrhages. Nail thickening is due to the accumulation of subungual keratin. Patients with extensive disease and prolonged facial erythroderma may develop ectropion, a dreaded complication. Oral mucosal involvement is a rarely reported condition.

The assessment of the value of treatment is difficult because the natural course of PRP is so variable. In many patients, the natural course of the disease is spontaneous resolution, making it difficult to appreciate the effectiveness of any single treatment. Because of the relative rarity of PRP, there
have not been any randomized, controlled trials published in the literature, only case reports and case series. Except for the non-classic form, PRP is a self-limiting disease with three out of four cases resolving in one to three years. Relapses are uncommon. Multiple treatment modalities have been used with varying degrees of success. Emollients remain a mainstay of treatment, reducing fissuring and dryness. Topical steroids may be beneficial for patient comfort but do not have long-term therapeutic effects. Systemic steroids are ineffective. The vitamin D analogue calcipotriene was reported to have shown benefit in three PRP patients.

Prior to the use of biologics for PRP, systemic retinoids appeared to be the most effective therapeutic agents. In a large study, it was found that 80 percent of patients had significant clearing within an average of 25 weeks of treatment with isotretinoin at a dose of 1 mg/kg/day. Low-dose weekly methotrexate alone or in combination with retinoids has shown efficacy, although the results have proven to be inconsistent. The extensive side effect profile of the oral retinoids, including xerotic skin, hyperlipidemia, ocular sicca, and teratogenic potential, has provided an impetus for finding a safer, more convenient treatment option. Treatment with cyclosporine, azathioprine, PUVA, and mycophenolate mofetil have all been reported with variable degrees of success. Newer biologic therapy has shown promise in the treatment of PRP. Tumor necrosis factor (TNF)-alpha inhibitors, first licensed for clinical use in 1998, is one class of biologic agent. TNF represents an important cytokine involved in normal inflammatory and immune responses. Elevated levels of TNF have been found in psoriatic plaque and in the synovial fluid of both psoriatic and rheumatoid arthritis. Not surprisingly, given the clinical and histological overlap with psoriasis, upregulation of TNF-alpha has been detected in punch biopsies of PRP lesions. Muller et al. reported nine patients with adult PRP successfully treated with the TNF inhibitor infliximab. Etanercept has shown promising results in the treatment of type I PRP in individual patients.

In 2009, Walling and Swick were the first to publish the use of adalimumab in PRP treatment. They reported a dramatic and rapid response in a 72-year-old male patient with near-complete resolution of PRP eruption after eight weeks of monotherapy. Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF. Adalimumab binds specifically to TNF-alpha and blocks its interaction with p55 and p75 cell-surface receptors, preventing the action of TNF on TNF receptors 1 and 2. The release of pro-inflammatory cytokines by macrophages and keratinocytes is prevented, and the production of acute phase proteins by hepatocytes is inhibited. Inflammation and hyperproliferation of keratinocytes are key features of PRP. Additional recent case reports have been published with encouraging findings showing prolonged efficacy with maintenance adalimumab dosing. Given the safety profile of adalimumab and its convenient bi-monthly dosing, it is anticipated that additional reports will be published on its successful use in PRP patients.

*Special thanks to our dermatopathologist, Keliegh Culpepper, M.D.*

References


70 ADALIMUMAB FOR THE TREATMENT OF PITYRIASIS RUBRA PILARIS: CASE STUDY WITH AN OVERVIEW OF DISEASE CLASSIFICATION
**A TOXIC CUT - A LEVAMISOLE-INDUCED, VASCULITIS-LIKE ERUPTION WITH WIDESPREAD BULLAE AND NECROSIS IN A 39-YEAR-OLD CRACK COCAINE ABUSER**

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**ABSTRACT**

In recent years, the use of levamisole, originally marketed as an antihelminthic agent, has been increasing as an adulterant in cocaine sold in the United States and Canada. This “cutting” agent may add bulk and potential stimulant effects to the cocaine, making it more marketable and profitable in the illicit drug trade industry. Unlike other largely innocuous substances added to illicit drugs, levamisole is known to cause many serious adverse effects, the most significant of which include agranulocytosis/neutropenia, vasculitis, skin necrosis, and death. We present a case of a 39-year-old female with levamisole-induced pseudo-vasculitis.

**Case Report**

A 39-year old female with a history of intravenous drug abuse (IVDA), hepatitis C, and hypertension presented to the St. Barnabas Hospital emergency department with a complaint of a painful “body rash.” The patient initially noticed a dark spot of “dead skin” on her left lower extremity three months prior, with no further skin changes, and reported a normal state of health until approximately five days before presenting to the ED. Within three days, a painful eruption began on her left thigh and then generalized to both of her legs, right ear, abdomen, and arms. The lesions started as purpuric macules and patches that progressed rapidly and developed overlying tender, hemorrhagic bullae as they extended. The patient admitted to experiencing flu-like symptoms for the previous three days with a low-grade fever of 100.3F, general malaise, and fatigue. She was currently taking oral ciprofloxacin and amoxicillin-clavulanate, prescribed by her primary care physician, for a MRSA+ skin abscess that was incised and drained the previous week. She denied arthralgia, myalgia, easy bleeding or bruising, headache, abdominal pain, chest pain, and difficulty breathing. Her only changes in medication were the oral antibiotics she was currently taking, and she denied any known drug allergies. Her social history included crack/cocaine use, although she was unsure of the date of her most recent use.

Upon admission, she was afebrile and her vital signs were within normal limits. On general exam she appeared moderately anxious but non-toxic. The skin exam revealed: three discrete, tender, nonblanchable erythematous macules on the right ear helix and lobe and right malar region; diffuse, well-demarcated, tender, nonblanchable, retiform purpura with an erythematous border and overlying tense hemorrhagic bullae on the mid-abdomen and bilateral upper and lower extremities; and a non-tender, necrotic eschar with a thin halo of erythema on the right pretibial surface (Figure 1). The mucous membranes, palms, and soles were uninvolved. The abdomen was obese with mild hepatosplenomegaly. The remainder of the physical exam was noncontributory.

Laboratory investigation revealed:
- white blood cell count 1.9, hemoglobin/hematocrit 10.5/34, platelets 80,000, D-dimer 36.3, fibrinogen 136, neutrophils 28,000, PT/PTT 13.8/32.6, and urinalysis protein 100.

A urine toxicology screen was positive for cocaine. Two 3-mm punch biopsies were obtained from a lower-extremity lesion. Hematoxylin and eosin staining revealed a leukocytoclastic-like vasculitis with numerous micro-thrombi in the dermis (Figure 2). Direct immunofluorescence testing was negative.

The patient improved clinically with supportive measures, and there was no progression of the eruption. Further comprehensive work-up for possible underlying infectious, hematologic, and autoimmune etiology as a cause of the vasculitis was negative.

**Discussion**

Levamisole is an antihelminthic agent used...
purposes. Recently, levamisole has been used, most importantly in the treatment of colorectal cancer. In North America, it is no longer available for use in humans due to its low therapeutic index, limited efficacy and serious side effects, most significantly vasculitis and agranulocytosis. It is, however, still available in the United States and South America for veterinary purposes. Recently, levamisole has received attention for its use as a “cutting” agent in cocaine, and according to a report by the U.S. Drug Enforcement Agency, it was found in nearly 70% of seized cocaine. While the reason for adding levamisole to cocaine is unclear, it is postulated that levamisole may increase dopamine levels in the brain and thus potentiate the addictive properties of cocaine. Additionally, it may add volume, making the product more profitable.

Unlike other more innocuous substances added to illicit drugs, serious adverse effects have been reported with levamisole use, most importantly agranulocytosis, which may occur in up to 20% of cases, and cutaneous vasculitis-like eruption. Other adverse effects include angioedema, urticaria, fever, infection, and variable CNS disturbances. Previous case reports describe a wide array of clinical presentations ranging from nonspecific flu-like symptoms to vasculitis, leukoencephalopathy, and other severe reactions. Patients may present with fever, generalized lymphadenopathy, mucosal ulcers, infections, prolonged sore throat, abscesses, thrush, or pneumonia. Cutaneous manifestations may include retiform purpura, where the purpuric lesions have a predilection for the ears, although they are commonly noted on the face, thighs, and buttocks as well. The lesions are often tender and appear as erythematous-to-purpuric, stellate plaques with or without necrotic centers. Of note, our patient presented with these characteristic cutaneous findings in addition to having leukopenia, elevated D-dimer, abnormal coagulation studies, low platelets, low fibrinogen, neutropenia, and mild renal insufficiency.

Figure 2. H&E staining demonstrating a focus of leukocytoclastic vasculitis with microthrombi within the vessel

Confirming levamisole toxicity in suspected patients currently remains a challenging task as a specific workup is lacking; however, the clinician should start with a thorough medical and social history. This is especially important in patients presenting with neutropenia of unknown etiology and/or a history of cocaine use, keeping in mind that patients are often reluctant to reveal their recreational drug-use habits. Details regarding the patient’s crack/cocaine use including type, method, frequency, amount, and most recent use are helpful. All other organic causes of vasculitis should be ruled out, as levamisole-induced pseudovasculitis remains a diagnosis of exclusion in the appropriate clinical setting.

Signs of infection, fever, skin abscesses or pulmonary infections should be noted, especially if they developed suddenly or progressed rapidly, as these may be signs of another underlying cause. A complete blood count (CBC) with differential is helpful initially to confirm neutropenia. Other helpful serologic tests if the history and physical exam are suggestive of crack/cocaine exposure include a urine toxicology screen and levamisole gas chromatography/mass spectrometry when available. These tests should be done as expeditiously as possible, ideally within 24–48 hours after crack/cocaine use, given the short half-lives of both cocaine and levamisole, which is 3-4 days and 5-6 hours, respectively.

While the exact mechanism of levamisole-induced toxicity is unclear, an immunologic etiology is speculated. Patients presenting with retiform purpura secondary to levamisole toxicity have been reported to demonstrate several nonspecific serologic markers. Autoantibodies such as lupus anticoagulant (LA), peri-nuclear antineutrophil cytoplasmic antibodies (pANCA), and cytoplasmic antibodies (cANCA) have been reported. Other helpful serologic tests if the history and physical exam are suggestive of crack/cocaine exposure include a urine toxicology screen and levamisole gas chromatography/mass spectrometry when available. These tests should be done as expeditiously as possible, ideally within 24–48 hours after crack/cocaine use, given the short half-lives of both cocaine and levamisole, which is 3-4 days and 5-6 hours, respectively.

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Table I: Suggested laboratory work-up when levamisole-induced toxicity is suspected

1. CBC with differential
2. Complete metabolic panel
3. Urine toxicology
4. Coagulation profile (PT/PTT/INR)
5. ESR
6. ANA
7. C3/C4
8. Cryoglobulins
9. Hepatitis panel
10. HIV serology
11. Lupus anticoagulant
12. Anticardiolipin antibody
13. Antithrombin 3
14. Protein C & S
15. Russel viper venom antibody
16. pANCA, cANCA
17. ANCA subsets: myeloperoxidase (MPO), proteinase 3 (PR3), anti-human neutrophil elastase antibody (HNE), cathespin G, lactoferrin, azurocidin, bacterial permeability increasing (BPI) protein, catalase K, defensin, lysozyme
cytoplasmic antibodies (pANCA), and rheumatoid factor (RF) have been reported to be positive findings in the literature.\textsuperscript{7,8,9,12} In one recent case report, it was noted that anti-human neutrophil elastase antibody (HNE), an uncommon serologic marker for levamisole-induced neutropenia, appears to be specific to cocaine-induced pseudovasculitis and may be helpful in differentiating it from a true autoimmune vasculitis.\textsuperscript{7} Genetic susceptibility may also play a role, as agranulocytosis associated with levamisole use has been reported more frequently in patients with the HLA-B27 genotype.\textsuperscript{4} The presence of the HLA-B27 genotype is also strongly associated with various autoimmune disorders, further supporting the theory that levamisole-associated agranulocytosis may be immunologically linked.

Since cocaine-induced pseudovasculitis can mimic numerous autoimmune disorders both clinically and serologically, it is important to rule out a true autoimmune vasculitis secondary to Wegener’s granulomatosis, Churg-Strauss granulomatosis, pANCA-positive necrotizing vasculitis, limited scleroderma, antiphospholipid syndrome, or another condition.\textsuperscript{5,11} Conventional autoimmune serologic studies cannot reliably distinguish between cocaine-related syndromes and primary autoimmune etiologies. As most of the current knowledge of this disease entity is derived from case reports and anecdotal findings, there is currently no consensus for the exact proposed laboratory work-up. A proposed serologic work-up is presented in Table I.

Histologic examination of the skin lesion in levamisole toxicity can be helpful when used in conjunction with the history and laboratory findings. Typically, hematoxylin and eosin staining may show a vasculopathic reaction pattern including leukocytoclastic vasculitis with or without microvascular occlusion or thrombotic vasculitis. Varying ages of histologic thrombosis, if seen, may correlate with a time course of crack cocaine use.\textsuperscript{9,12} Direct immunofluorescence will be negative and can aid in ruling out other causes of true vasculitis. Although the histologic findings associated with levamisole-induced toxicity are non-specific, when evaluated together with serologic studies and a thorough history in the appropriate clinical setting, it may be effectively diagnosed and treated.

Although optimal treatment for levamisole-induced toxicity is yet to be defined, immediate withdrawal of the offending agent is crucial to prevent disease progression.\textsuperscript{59} Primary treatment should be supportive, and broad-spectrum antimicrobial coverage is recommended in severely neutropenic patients.\textsuperscript{5} For patients who are at risk of methicillin-resistant Staphylococcus aureus, vancomycin should be administered. For febrile patients with an active infection and an absolute neutrophil count less than 1 k/ul, an urgent consultation with the on-call hematologist/oncologist is recommended. Such patients should be admitted, an infectious work-up including blood cultures should be ordered, and intravenous broad-spectrum antibiotics, such as piperacillin/tazobactam, imipenem or ceftazidime, should be given.\textsuperscript{11} Filgastim, a granulocyte colony stimulating factor, should be started in the interim before consultation with a hematologist is made.\textsuperscript{3,11} Optimizing supportive care for complicating infections as well as wound care is helpful in decreasing morbidity and mortality.

The majority of patients recover spontaneously over the ensuing weeks without long-term sequelae. Neutrophil counts will begin to shift back to normal within five to 10 days.\textsuperscript{8} Complete resolution of skin lesions usually occurs within two to three weeks after discontinuing the offending agent but can take longer in some cases.\textsuperscript{13} Serologic markers can be expected to return to normal within two to 14 months after stopping the drug.

## Conclusion

This case report demonstrates the significant hematologic and cutaneous aberrations in a non-toxic appearing patient with a history of crack cocaine use. The cutaneous manifestations can be striking, most commonly presenting as retiform purpura on the lower extremities and ears. Detecting levamisole in the serum is difficult, but as yet, anti-HNE antibody appears to be the most specific serologic marker for levamisole-induced pseudovasculitis. Of note, it is important to remember that although patients may not immediately reveal their recreational drug histories, it is always prudent to consider possible toxicologic etiologies when forming a differential diagnosis if the clinical picture warrants. Further investigation is needed for better understanding of the immunomodulator-related hematologic and cutaneous adverse effects of levamisole. As its illegal use as an adulterant in cocaine production increases, it is important to recognize the signs and symptoms associated with levamisole toxicity as well as create awareness in the community and educate patients about its potentially toxic effects.

## References

NODULAR AMYLOIDOSIS: A CASE REPORT

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ABSTRACT
Primary cutaneous amyloidosis (PCA) is a spectrum of disease that is characterized by the dermal deposition of amyloid in the absence of systemic involvement. PCA encompasses macular, lichen, and nodular amyloidosis. Primary cutaneous nodular amyloidosis (PCNA) is the rarest form of PCA and is differentiated by its pathogenesis and clinical presentation. It is also associated with progression to systemic amyloidosis, and up to 40% of patients with primary systemic amyloidosis can present with cutaneous findings identical to PCNA. It is vitally important to rule out systemic involvement before making the diagnosis, and these patients require regular evaluations to screen for progression to systemic disease. While the course of PCNA is generally benign, an effective treatment regimen has not been established; and recurrences rates are high. We present a case of PCNA in a 76-year-old Caucasian female and discuss both the clinical and histological characteristics of the disease.

Case Report:
A 76-year-old Caucasian female presented to the clinic with a chief complaint of multiple lesions located on her right lower extremity. The lesions had been present for an unknown period of time, and the patient denied any pain, pruritus, or hemorrhaging associated with the lesions. She admitted to a recent history of intentional weight loss attributed to diet, as well as recent fatigue. Upon further inquiry she denied fever, night sweats, paresthesias, dyspnea, syncope, lower extremity edema, neuropathy, xerostomia, or ecchymosis formation with minimal trauma. Her past medical history was positive for asthma and allergic bronchitis. Her past surgical history included an appendectomy, lumpectomy, carpal tunnel release, and an unknown foot surgery.

The physical examination revealed three pearly, flesh-colored, dome-shaped nodules that measured 4 mm in size on the right pretilial surface (Figure 1). There was no obvious peripheral edema, and oral examination was negative for macroglossia. Physical-examination testing demonstrated a negative Tinel’s, Phalen’s and reverse Phalen’s test. Neuromuscular examination demonstrated 2/4 reflexes and 5/5 strength of all four extremities. The initial differential diagnosis included cutaneous sarcoidosis, lymphoma cutis, nodular pretibial myxedema and granuloma annulare.

Two 4 mm punch biopsies were taken from the right lower extremity with nearly identical histopathologic findings. Each biopsy demonstrated large nodular aggregates of amorphous, pale, eosinophilic-to-gray-staining material in the papillary and reticular dermis extending to the deep margins of subcutaneous fat (Figure 2). A patchy infiltrate composed of plasma cells was found adjacent to the amorphous material. The material stained positive for amyloid on Bennhold Congo red and thioflavim T stains, and the periodic acid-Schiff stain was faintly positive. Elastic-tissue stain was also performed but was unable to provide any diagnostic information. At this point, a diagnosis of primary cutaneous nodular amyloidosis was conferred (PCNA), but the involvement of systemic amyloidosis was yet to be excluded. Therefore, the patient was referred to an internal-medicine specialist for a more extensive work-up with the recommendation to perform serum protein electrophoresis and immunofixation electrophoresis, as well as a 24-hour urine protein electrophoresis and immunofixation electrophoresis.

Discussion:
Primary cutaneous amyloidosis (PCA) is a process in which amyloid, a non-functional protein arranged in beta-pleated sheets, is deposited into the skin in the absence of internal organ involvement. It is classically divided into three groups: macular amyloidosis, papular or lichen amyloidosis, and nodular amyloidosis. Primary cutaneous nodular amyloidosis (PCNA) is the rarest form of PCA, with approximately 60 documented cases in the medical literature published through 2008. The amyloid deposits found in PCNA are derived from monoclonal immunoglobulin light chains produced by local plasma cells, and are thought to be the result of a reactive or neoplastic process. PCNA differentiates itself from the other variants of PCA in that the amyloid deposits found in the lichen and macular forms are derived from degenerated keratinocytes and not from plasma cells. PCNA occurs equally in men and women, with an average age of 60 at the onset of cutaneous lesions. There has not been an established predilection of PCNA for any ethnic group.

The diagnosis of primary cutaneous...
amyloidosis is based on both the clinical morphology of lesions and on the histologic presence of cutaneous amyloid deposits. Clinical, PCNA presents as solitary or multiple, waxy, erythematous, yellow-orange nodules or plaques. The asymptomatic lesions are most commonly found on the trunk, extremities, face, scalp, and genitals. The clinical differential diagnosis includes cutaneous sarcoidosis, lymphoma cutis, pseudolymphoma, pretibial myxedema, granuloma annulare, reticulohistiocytoma, multicentric reticulohistiocytosis, and granuloma faciale. Performing a punch biopsy of a representative lesion is essential in obtaining a definitive diagnosis. Histologic examination will reveal a homogeneous eosinophilic deposition situated in the dermis, subcutis, and perivascular tissue.

A sparse-to-dense plasma-cell infiltrate is located adjacent to this eosinophilic deposition, and these plasma cells may also adopt a perivascular or perineural disposition. Special stains are utilized in the identification of the eosinophilic deposits, with a Congo red stain resulting in an apple-green birefringence of amyloid under polarized light. Amyloid will also fluoresce an intense yellow-green color when stained with thioflavin T or purple with crystal violet staining. Immunostains for light-chain deposition and γ light chains and β2-microglobulin are also performed for confirmation. Due to this correlation, it is prudent to inquire about the symptoms of SS. Anti-Ro and anti-La antibody testing may be performed to screen for SS if clinical suspicion exists. Other disease associations have been reported such as CREST syndrome, primary biliary cirrhosis, systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis.

Conclusion:
PCNA is an uncommonly encountered disease that results from the deposition of amyloid in the dermis and subcutaneous tissue. The amyloid protein is derived from monoclonal immunoglobulin light chains produced by local plasma cells, and while the cause of the disease has been postulated, it remains largely unknown. The pearl of this disease lies in its ability to either mimic or progress to systemic amyloidosis. It is imperative for the diagnosing physician to perform the necessary evaluation to screen for systemic involvement, as failure to diagnose may result in fatal consequences for the patient. The extent of cutaneous involvement in PCNA is variable, and treatment should be tailored to suit the therapeutic needs of each individual patient. In our case, the 4 mm punch biopsies of the pretibial lesions provided a suitable cosmetic result for our patient, and there has not been an observed recurrence. None of the testing has yielded evidence of systemic involvement, and we will continue to monitor our patient at six-month intervals or as needed.

References: