Why is Skin Cancer Still on the Rise?
A standardized survey exploring screening behaviors, tanning attitudes, and sun-protective measures in a general U.S. sample population

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Dear Readers,

Yet another year has passed, and the JAOCD is celebrating its 14th year in publication. It was founded by Dr. Jay Gottlieb in 2003 and has attracted many talented and dedicated editors and reviewers over the decades. As our current Editor-in-Chief, Dr. Karthik Krishnamurthy, assumes the responsibilities of the AOCN presidency, I will be piloting the ship.

As early as this spring, you should be able to claim category 1B credit for reading the journal and taking a brief quiz. Rather than reinventing the wheel, we have been working with other specialty DO organizations to ensure our CME credits are valid and recognized by the AOA. My hope is that this helps our members attain the few category 1 hours sometimes unavailable at our meetings. Of course, I also hope it incentivizes more of us to include the JAOCD in our regular reading regimen.

We also have published our last printed issue. Going forward, all issues will be online and always available for you to peruse. In an era of shrinking sponsorship, it no longer makes sense to continue printing and mailing our journal. This decision also allows us to practice good environmental stewardship and will help us to more accurately assess our true readership, allowing us to approach more sponsors and tweak our journal to better fit your needs.

Many of us, myself included, first published in the JOACD, and I wish to keep this option open for future authors. We need your help, though, to make this happen. The residency requirement of a yearly publishable paper has not produced the volume of quality submissions we need to become a suitably prestigious reflection of our College and our profession. We rely on Program Directors to thoroughly review their residents’ papers, a responsibility that may be getting lost in the shuffle. I kindly ask that Program Directors take this task seriously, as subpar submissions clog our review process and continue to hinder our bid for MedLine indexing. We ask that authors honestly assess their work to determine whether it represents the thoughtfulness and professionalism required of great physicians -- and if not, change it. We want to see the best you have to offer.

Finally, I would like to invite submissions that broaden our scope. We receive plenty of case reports. Consider producing original research and in-depth reviews, and focusing on topics specifically related to osteopathy. We also welcome opinion pieces, letters to the editor, comments on current or historical events, clinical pearls and tidbits of wisdom, and comments and opinions on AOA/ AOCN policies and procedures.

I hope you find increased value in our new electronic format, and I look forward to seeing what our authors produce for upcoming issues.

Stay well,

Derrick

Derrick Adams, DO
Co-Editor-in-Chief, JAOCD
Hello, Everyone,

Welcome to the first online issue of the JAOCD!

The new year will hopefully open up new opportunities for our members to obtain CME credits. We applied to award category 1B credit for reading the JAOCD, and we have now received approval from the AOA. We will begin to offer 1B credit for reading the journal on March 1, 2017. We also plan to begin offering online category 1A credit.

The AOCD staff has been working to obtain ACCME accreditation in order to provide AMA credit for our CME meetings. The application has been submitted, and we learned recently that we are scheduled for our initial interview in March 2017. By August 1, we will have an official determination from the ACCME on whether the AOCD qualifies to provide AMA credit. Wish us luck!

We hope you will make plans to attend our Spring 2017 meeting in Atlanta, GA, from March 29 through April 1. The meeting will take place at the Ritz-Carlton Atlanta. More information on the meeting can be found on our web site at www.aocd.org and in our weekly Thursday Bulletin email blasts.

Save The Dates!

• 2017 Fall Meeting: October 24-28 at the Intercontinental New Orleans
• 2018 Spring Meeting: March 19-25 at the Hilton West Palm Beach
• 2018 Fall Meeting: October 9-13 at the Westin San Diego, Gaslamp Quarter

We would like to remind everyone that the Foundation for Osteopathic Dermatology is accepting applications for research grants. For more information, visit the Foundation page at https://aocd.site-ym.com/?page=Foundation.

As always, please call (1-800-449-2623) or email (dermatology@aocd.org) the AOCD office if you need assistance.

Here’s to a happy and healthy 2017!

Sincerely,

Marsha Wise
Executive Director, AOCD
Happy New Year! January 1, 2017 ushered in new opportunities and challenges. Last year is but a vapor. With the new year comes a change in leadership in the White House. We witnessed an election season like no other in history. As with any change in leadership, we and our practices will all experience some form of change and growth as a result of that election. Let us remain true to our practice of medicine, regardless of political view.

As President of the AOCD, I welcome you to the winter edition of the Journal of the American Osteopathic College of Dermatology. It seems but yesterday we gathered in Santa Monica for our Fall meeting. In March, we will gather in Atlanta to learn, develop fellowship, and share new knowledge and ideas. I encourage all of our membership to make a special effort to join us in Atlanta. The cast of presenters is both broad and deep in knowledge and experience.

You have all honored me with your support throughout this year, and Dr. Lin, our Immediate Past President, continues to guide me through some unchartered waters as we move into the future. Please continue your invaluable support of all our AOCD leadership.

During this holiday season, I pondered my own professional and personal accomplishments and goals. I realized I had not updated my plan over the last several years, mostly because it remains grounded in my core values. Although a few of the desired outcomes of those values have changed, I determined I must become more proactive in shaping those outcomes.

I decided I will be a verb in 2017!

As humans, we declare resolutions with conviction. We begin with such steadfastness, but soon, our persistence wanes, with the ever-present pressures of life. I believe that is why so many New Year's resolutions come and go before the end of winter (or even before January 31!). Our goals are descriptive of what we want, and perhaps not what we need to be to accomplish what we want. Our goals are but nouns and adjectives to describe success, health, happiness, or anything else upon which we set our sights.

Conversely, “being” requires conscious choice. Being a verb communicates a commitment to action. Assuming the role of a verb means honoring whom we want to be. Try “being a verb” in this wonderful new year!

Let’s keep the AOCD strong as a provider of service and support to dermatologists who chose the path of osteopathy. As you read this edition of the JAOCD, think about how we can keep the vision and legacy of DO dermatology alive and well. Keep the main thing the main thing. Let me know the verb you choose.

See you in Atlanta!

Alpesh Desai, DO
President, American Osteopathic College of Dermatology
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Understanding Skin Cancer Screening Behaviors, Tanning Attitudes, and Sun Protective Measures of a General U.S. Sample Population Using Standardized Skin Cancer Survey Questions

Miguel Villacorta, DO, MPH,* Simona Bartos, DO, MPH,** Cyril Blavo, DO, MS, MPHTM,*** Patrick Hardigan, PhD,**** Tracy Faveu, DO*****

* Dermatologist Resident, 1st year, Broward Health Medical Center, Ft. Lauderdale, FL
** Traditional Rotating Intern, Broward Health Medical Center, Ft. Lauderdale, FL
*** Director and Professor of Public Health, College of Public Health, Nova Southeastern University, Ft. Lauderdale, FL
**** Executive Director of HPD Research, College of Osteopathic Medicine, Nova Southeastern University, Ft. Lauderdale, FL
***** Dermatologist, Ft. Lauderdale, FL

Disclosures: None
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Abstract
Skin cancer is the most commonly diagnosed cancer in the United States, and its incidence is increasing over time. Despite this, screening guidelines are not agreed upon, and there are few standardized tools to analyze sun-exposure attitudes and behaviors. This study examines the frequency of self-reported burns, tanning attitudes, sun-protection behaviors, self-skin exams (SSE), and clinical skin exams (CSE) and aims to contribute to skin cancer screening research through the use of this standardized skin-surveillance survey measure. Through these measures, this study aims to add to the growing body of research in skin surveillance as well as improve the validity of comparisons between studies.

Introduction
Skin cancer, the most common form of cancer in the United States, is divided into three main categories: melanoma, basal cell carcinoma and squamous cell carcinoma. Over the last few decades, the number of cases of skin cancer has increased.2,3 Melanoma is among the most aggressive and hard-to-treat cancers. In 2014, an estimated 76,100 new cases and 9,710 deaths were expected in the United States, with melanoma accounting for 75% of all skin cancer deaths.2

One in five Americans may develop skin cancer in their lifetime.5 More than $8.1 billion is spent on treating skin cancer annually.6

Despite the increasing incidence of skin cancer, it is one of the most preventable types of cancer.7 While fair skin complexion is a risk factor, the major modifiable risk factor is exposure to ultraviolet radiation (UV).8 Public health efforts have focused on reducing UV exposure, increasing adoption of sun-protective habits, promoting regular skin cancer screenings, and educating patients on the dangers of UV exposure. Despite these efforts, skin cancer rates continue to increase in the United States.9

Understanding skin-screening habits, ultraviolet-exposure risk, tanning attitudes, and perceptions are essential for implementation and evaluation of interventional efforts. However, there are no clear guidelines to guide the practitioners.

Early detection of melanoma offers the best chance for a cure.10 Melanoma invades vertically and becomes metastatic over time, with the best prognostic indicator being tumor thickness (Breslow depth).10 A retrospective study found that full skin examination increases the detection of melanoma, decreases overall Breslow thickness at diagnosis, and decreases patient morbidity and mortality.9

In light of the variability present in the published literature, the benefit of skin examinations continues to be debated. Many organizations, including the American Association of Dermatology (AAD), the Skin Cancer Foundation and the American Cancer Society, recommend routine skin cancer screenings.11-13 However, the U.S. Preventive Task Force has concluded that there is insufficient evidence for these screenings.14 This lack of agreement demonstrates the need for additional research in this area.

To our knowledge, the only skin-screening program that has led to a significant reduction in mortality occurred in 2004, when Germany implemented the first effective population-based skin cancer screening program. It decreased mortality by about 50% after five years.11 Germany went on to implement a nationwide skin cancer screening initiative in 2008.

Further complicating this area of research are the variations in study design and methods used in different skin cancer screening studies. These variations make it difficult to draw clear conclusions. Recent studies have begun to take steps to streamline this area of research by creating standardized skin screening survey items.12 Most studies involving skin cancer screening have sampled data from patients that have recently had a clinical skin exam.13 The use of convenience samples may be a source of bias in the literature. The variability in the data from non-standardized question sets and the lack of generalized sample population studies have contributed to the underdevelopment of formal skin cancer screening guidelines. Standardized questionnaires and studies involving skin-screening behaviors in the general population are needed.8

Purpose
The aim of this study is to report the frequency of self-reported self-skin exams (SSE), clinical skin exams (CSE), tanning attitudes, and sun protection behaviors in a U.S. general population sample of adults utilizing standardized skin-surveillance survey measures.

Research Design and Methods
Our study utilized a survey that was designed and administered using the web-based SurveyMonkey.com platform. For security measures, the web-based questionnaire was conducted using standard web-based https security protocols. Prior to the deployment of our survey, the Nova Southeastern University Institutional Review Board (IRB) granted exempt IRB status for the study on December 15, 2014. The survey was open for data collection during a three-day period between March 9, 2015 and March 11, 2015.

Before completing the questionnaire, the participants were informed that their participation was voluntary and anonymous. Participation in the survey implied informed consent. Participants were recruited using the SurveyMonkey.com Audience service. This service consists of a diverse group of over 45 million members utilizing multiple channels to attract diverse participants and incorporates multiple data sources to reduce bias.15 In addition, SurveyMonkey utilizes profiling and screening as well as TrueSample Validation to validate each respondent. Gallup, a proven and reputable full research business service, conducts phone interviews with 1,500 people each day.16 SurveyMonkey, like Gallup’s metrics, fall consistently within a 5% margin of error.15

SurveyMonkey Audience members participate in surveys via the Internet and can participate only in a limited number of surveys each week. Participants do not receive direct compensation for answering surveys, but receive non-monetary incentives including contributions to charities of their choice.16,17

Criteria for survey participation included (a) adults between 18 years of age and 100 years of age; (b) English proficiency; (c) residence in the United States; (d) a participating member of SurveyMonkey.com Audience service; (e) unmet survey participation quota according to SurveyMonkey’s policies; and (f) acceptance of informed consent.

Various definitions of skin examinations exist in the literature, and for this study we used the Sharon Manne and Nadine Kasparian definition.8,18 It states that the skin examination is “the careful and deliberate checking for changes in spots or moles on all areas of your skin, including those areas rarely exposed to the sun.”8,18 Self-skin examination was defined as “a skin examination performed by yourself."
with the help of a partner or a mirror.” A clinical skin examination was defined as “a skin examination performed by a health care professional.”

In 2005, a collaborative research group led by Karen Glanz worked toward developing standardized care measures to evaluate sun exposure and sun-protection habits.7 This group established a set of consensus-based, standardized skin survey items for adults, adolescents, and children. The current study used the research group’s standardized skin cancer screening questions in addition to survey questions developed based on the work of Kasparian. Efforts were made to maintain the question type, answer choices, and formatting of the standardized questions wherever possible.

The survey questionnaire was divided into various sections. Demographic information included gender, age, ethnicity, and self-assessed Fitzpatrick skin type obtained by utilizing a photographic reference and text. The skin phenotype is commonly classified using the Fitzpatrick classification system, which combines constitutional skin color and tanning ability.8 Skin history was assessed by questions regarding prior personal or family history of skin cancer. Family history was defined as a first- or second-degree relative such as a parent, sibling, or grandparent.

The survey also included questions about annual sunscreen usage, clinical skin examinations, self-skin examinations, sun-protection behavior, and use of indoor tanning. Tanning attitudes as well as social perceptions of the perceived frequency of skin exams by friends and family were assessed.

Table 1. Survey responses: demographics, Fitzpatrick skin type, online platform.

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<td>30</td>
<td>3.0%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Fitzpatrick VI</td>
<td>8</td>
<td>0.8%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>207</td>
<td>21.0%</td>
<td>21.0%</td>
</tr>
<tr>
<td>30-44</td>
<td>230</td>
<td>23.3%</td>
<td>44.3%</td>
</tr>
<tr>
<td>45-60</td>
<td>283</td>
<td>28.7%</td>
<td>72.9%</td>
</tr>
<tr>
<td>61+</td>
<td>267</td>
<td>27.1%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Income</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0 to $9,999</td>
<td>55</td>
<td>5.6%</td>
<td>5.6%</td>
</tr>
<tr>
<td>$10,000 to $24,999</td>
<td>91</td>
<td>9.2%</td>
<td>9.2%</td>
</tr>
<tr>
<td>$25,000 to $49,999</td>
<td>91</td>
<td>9.2%</td>
<td>9.2%</td>
</tr>
<tr>
<td>$50,000 to $74,999</td>
<td>42</td>
<td>4.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td>$75,000 to $99,999</td>
<td>33</td>
<td>3.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>$100,000 to $124,999</td>
<td>19</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>$125,000 to $149,999</td>
<td>56</td>
<td>5.7%</td>
<td>5.7%</td>
</tr>
<tr>
<td>$150,000 to $174,999</td>
<td>133</td>
<td>13.5%</td>
<td>13.5%</td>
</tr>
<tr>
<td>$175,000 to $199,999</td>
<td>148</td>
<td>15.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>$200,000+</td>
<td>157</td>
<td>15.9%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>159</td>
<td>16.1%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>U.S. Region</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>East North Central</td>
<td>140</td>
<td>14.2%</td>
<td>14.2%</td>
</tr>
<tr>
<td>East South Central</td>
<td>28</td>
<td>2.8%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>176</td>
<td>17.8%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Mountain</td>
<td>60</td>
<td>6.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>New England</td>
<td>45</td>
<td>4.6%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Pacific</td>
<td>282</td>
<td>28.6%</td>
<td>28.6%</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>110</td>
<td>11.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>West North Central</td>
<td>54</td>
<td>5.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>West South Central</td>
<td>79</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Device</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Android Phone/ Tablet</td>
<td>98</td>
<td>9.9%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Mac Desktop/ Laptop</td>
<td>148</td>
<td>15.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>1.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Other Phone/Tablet</td>
<td>2</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Windows Desktop/ Laptop</td>
<td>538</td>
<td>54.5%</td>
<td>54.5%</td>
</tr>
<tr>
<td>iOS Phone/Tablet</td>
<td>189</td>
<td>19.1%</td>
<td>19.1%</td>
</tr>
</tbody>
</table>

Results
A total of 1,044 respondents initiated the survey, and 1,026 completed it, for a completion rate of 98.2%. There were 987 total surveys included in our analysis after 39 were excluded of the basis of age. Of these respondents, 54% (529) were female and 46% (458) were male. Most respondents were White/Caucasian (82%, 810), from the Pacific region (29%, 282), and of Fitzpatrick Skin Type III (37%, 368). Of note, Fitzpatrick Skin Types V and VI accounted for only 3% (30) and 1% (8) of the responses, respectively (Table 1).

A total of 64% (628) of respondents reported no familial or personal history of skin cancer. The second largest group reported a family history of skin cancer (28%, 278). The remaining respondents reported a personal history (6%) or both family and personal history (3%). Most respondents reported that they have never visited a dermatologist (74%, 734) and have never used an indoor sun bed (94%, 929) (Table 2).

Regarding skin cancer screenings, 59% (586) reported they have never received a clinical skin screening examination, and 34% (331) reported yearly clinical skin examinations. Also, 58% (570) reported they have never performed self-skin examinations with or without partner assistance, while 11% (109) reported annual self-skin examinations, and 16% (158) reported yearly self-skin examinations (Table 2).

In this study, 63% (618) of the respondents had not experienced a sunburn during the previous 12 months, 23% (225) experienced one sunburn, 10% (100) experienced two sunburns, and 4% (44) experienced three or more sunburns.

There were some differences in the prevalence of sun-protective behaviors. The most common behavior, wearing sunglasses, was reported by 42% (413) of respondents. In addition, 29% (285) of respondents reported “sometimes” wearing sunscreen, and 40% (398) of respondents reported never spending time in the sun to get a tan.

Most respondents (56.1%) agreed that tanning makes them look better. However, most respondents (83.1%) disagreed that their skin was healthier when tanned. Most (59.9%) disagreed that tanning makes them feel better about themselves, and most (55.3%) reported avoiding tanning due to the associated risks of skin cancer and premature aging (Table 3).

Discussion
The Healthy People 2020 goal for number of U.S. adults experiencing a sunburn over a 12-month period is 33.8%.2 The data from this study suggest that 37.4% of U.S. adults have had at least one sunburn in the last 12 months. This data is comparable to the 37.5% of U.S. adults experiencing at least one sunburn over the last 12 months as reported by the 2010 NHIS report.2 The 2000 National Health Interview Survey (NHIS) also found that 36.2% of U.S. adults experienced a sunburn in the last 12 months.2 This increase of 1.2% represents a negative trend that may suggest current public-health efforts remain largely ineffective.

Sunburns and episodic UV exposure increase the risk of melanoma and basal cell carcinoma, while squamous cell carcinoma is associated with cumulative UV exposure.24–26 The number of...
TABLE 2. Survey responses: skin cancer history, UV light exposure, frequency of skin exams.

<table>
<thead>
<tr>
<th>History of skin cancer</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family and personal</td>
<td>26</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Neither family nor personal</td>
<td>628</td>
<td>63.6%</td>
<td>66.3%</td>
</tr>
<tr>
<td>Family only</td>
<td>278</td>
<td>28.2%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Personal only</td>
<td>55</td>
<td>5.6%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sunburn in past 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical skin exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
</tr>
<tr>
<td>Daily</td>
</tr>
<tr>
<td>Monthly</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Twice a year</td>
</tr>
<tr>
<td>Weekly</td>
</tr>
<tr>
<td>Yearly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-skin exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
</tr>
<tr>
<td>Daily</td>
</tr>
<tr>
<td>Monthly</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Twice a year</td>
</tr>
<tr>
<td>Weekly</td>
</tr>
<tr>
<td>Yearly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dermatological patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Cosmetic</td>
</tr>
<tr>
<td>Medical</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use of tanner/ sunbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
</tr>
<tr>
<td>Daily</td>
</tr>
<tr>
<td>Monthly</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Twice a year</td>
</tr>
<tr>
<td>Weekly</td>
</tr>
<tr>
<td>Yearly</td>
</tr>
</tbody>
</table>

TABLE 3. Survey responses: sun safety measures, tanning attitudes, and social perceptions of friends and family.

For the following questions, think about what you do when you are outside during the summer on a warm sunny day.

<table>
<thead>
<tr>
<th>Question</th>
<th>Always (%)</th>
<th>Often (%)</th>
<th>Sometimes (%)</th>
<th>Rarely (%)</th>
<th>Never (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you wear SUNSCREEN?</td>
<td>159 (16.1%)</td>
<td>270 (27.4%)</td>
<td>285 (28.9%)</td>
<td>175 (17.7%)</td>
<td>98 (9.9%)</td>
</tr>
<tr>
<td>How often do you wear a SHIRT WITH SLEEVES that cover your shoulders?</td>
<td>338 (34.2%)</td>
<td>369 (37.4%)</td>
<td>177 (17.9%)</td>
<td>73 (7.4%)</td>
<td>30 (3.0%)</td>
</tr>
<tr>
<td>How often do you wear a HAT?</td>
<td>121 (12.3%)</td>
<td>217 (22.0%)</td>
<td>239 (24.2%)</td>
<td>236 (23.9%)</td>
<td>174 (17.6%)</td>
</tr>
<tr>
<td>How often do you stay in the SHADE or UNDER AN UMBRELLA?</td>
<td>66 (6.7%)</td>
<td>313 (31.7%)</td>
<td>356 (36.1%)</td>
<td>174 (17.6%)</td>
<td>78 (7.9%)</td>
</tr>
<tr>
<td>How often do you wear SUNGLASSES?</td>
<td>413 (41.8%)</td>
<td>262 (26.5%)</td>
<td>160 (16.2%)</td>
<td>83 (8.4%)</td>
<td>69 (7.0%)</td>
</tr>
<tr>
<td>How often do you spend time in the sun in order to get a tan?</td>
<td>18 (1.8%)</td>
<td>91 (9.2%)</td>
<td>214 (21.7%)</td>
<td>266 (27.0%)</td>
<td>398 (40.3%)</td>
</tr>
</tbody>
</table>

Please state whether you agree or disagree with each statement.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Agree (%)</th>
<th>Disagree (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanning makes me look better</td>
<td>554 (56.1%)</td>
<td>433 (43.9%)</td>
</tr>
<tr>
<td>Tanning makes me look more attractive</td>
<td>490 (49.6%)</td>
<td>497 (50.4%)</td>
</tr>
<tr>
<td>Tanning improves the appearance of my skin</td>
<td>449 (45.5%)</td>
<td>538 (54.5%)</td>
</tr>
<tr>
<td>My skin is healthier when tanned.</td>
<td>167 (16.9%)</td>
<td>820 (83.1%)</td>
</tr>
<tr>
<td>Tanning makes me feel better about myself</td>
<td>396 (40.1%)</td>
<td>591 (59.9%)</td>
</tr>
<tr>
<td>I avoid tanning due to the risk of skin cancer.</td>
<td>594 (60.2%)</td>
<td>393 (39.8%)</td>
</tr>
<tr>
<td>I avoid tanning due to the risk of aging.</td>
<td>546 (55.3%)</td>
<td>441 (44.7%)</td>
</tr>
</tbody>
</table>

The following questions are related to your belief of the frequency of skin exams by friends and family.

<table>
<thead>
<tr>
<th>Question</th>
<th>All (%)</th>
<th>Most (%)</th>
<th>Few (%)</th>
<th>None (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>What proportion of your family do you think currently performs self-skin exams?</td>
<td>40 (4.1%)</td>
<td>149 (15.1%)</td>
<td>500 (50.7%)</td>
<td>298 (30.2%)</td>
</tr>
<tr>
<td>What proportion of your friends do you think currently performs self-skin exams?</td>
<td>3 (0.3%)</td>
<td>97 (9.8%)</td>
<td>608 (61.6%)</td>
<td>279 (28.3%)</td>
</tr>
<tr>
<td>What proportion of your family do you think currently performs clinical skin exams?</td>
<td>26 (2.6%)</td>
<td>143 (14.5%)</td>
<td>455 (46.1%)</td>
<td>363 (36.8%)</td>
</tr>
<tr>
<td>What proportion of your friends do you think currently performs clinical skin exams?</td>
<td>8 (0.8%)</td>
<td>83 (8.4%)</td>
<td>550 (55.7%)</td>
<td>346 (35.1%)</td>
</tr>
</tbody>
</table>

Understanding skin cancer screening behaviors, tanning attitudes, and sun protective measures of a general U.S. sample population using standardized skin cancer survey questions.
as the daily use of sunscreen. These interventions should take into account the factors associated with adherence to sun-protective practices and screening, which include female gender, sun-sensitive skin type, greater perceived risk, greater perceived benefits, and a recent physician recommendation. Published studies report that the percentage of adults engaging in annual clinical skin examinations is between 8% and 21%. In this study, 59.4% of respondents reported never receiving a clinical skin examination, while 33.5% reported annual clinical skin examination by a health care professional. In contrast, the percentage of adults engaged in annual self-skin examinations, as reported in the published literature, is between 23% and 61%. In this study, 57.8% of adults reported they never perform self-skin examinations, 11.0% perform biannual self-skin examinations, and 16.0% perform yearly self-skin examinations.

The variations in the data from skin cancer studies may also be influenced by different definitions of clinical and self-skin examinations and by variations in the frequency and thoroughness of examinations, making comparisons between studies difficult. One of the clearest findings from a literature review by Kasparian et al. was the variation among reported behaviors across 91 studies. A strength of the current study was the use of standardized skin screening tools. This tool can be used in future studies to better describe the prevalence of sun protection, exposure, and skin cancer screening behavior.

Most studies assess the frequency of clinical skin examinations by sampling attendees of skin cancer screening clinics. Many studies utilize a convenience sample of dermatological patients, which introduces a selection bias. In contrast, most of the respondents in this study were non-dermatological patients. Only 25.6% of the respondents in this study had seen a dermatologist.

Unlike other studies that utilize convenience samples, this study surveyed a large sample of the general population. Other strengths of this study include the use of standardized definitions of clinical and self-skin examinations. These definitions included criteria for frequency as well as thoroughness of the examination.

A limitation to this study is the use of self-reported samples limited to those with an internet connection and access to SurveyMonkey’s services. Most surveys on sun-exposure and sun-protection behaviors utilize verbal reports and self-reported surveys. These are practical and feasible tools for population surveillance. Social desirability bias may have played a role in this study. Other limitations of the study are the low sample of minorities and individuals with a darker skin complexion as well as those without internet access. Future studies can focus on gathering additional data with a higher representation of these groups.

**Conclusion**

This study implemented standardized core measures and aims to add to the growing body of research on skin screening behaviors. It is our opinion that the continued use of standardized survey measures will improve the validity of comparisons between studies.

A future study is planned to analyze correlations and perform subset analysis on the collected data. A copy of our standardized questionnaire is available by request.
References


Atypical Fibroxanthoma: A Case Report and Literature Review
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** Osteopathic Medical Student, 4th year, Ohio University Heritage College of Osteopathic Medicine, Athens, OH
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Disclosures: None
Correspondence: Jacqueline C. Fisher, DO; JacquelineFisherC@gmail.com

Abstract
Atypical fibroxanthoma (AFX) is a rare, rapidly growing mesenchymal neoplasm that often presents on sun-exposed head and neck regions of older individuals. The diagnosis relies on knowledge of its clinical and histological features combined with immunohistochemistry markers used primarily to exclude other cutaneous neoplasms that may share a similar clinical presentation. Current treatment guidelines recommend wide local excision or Mohs micrographic surgery to prevent local recurrence and, on rare instances, metastasis of AFX, combined with long-term clinical monitoring. We report the case of an 88-year-old male presenting with a rapidly growing atypical fibroxanthoma and discuss diagnosis and treatment of this rare cutaneous neoplasm.

Introduction
Atypical fibroxanthoma (AFX) is a rare, rapidly growing, mesenchymal neoplasm that comprises 0.2% of skin tumors.1,2 AFX was first described in 1963 by Helwig et al. as a low-grade dermal tumor consisting of atypical spindle cells with an uncertain etiology.3 Since then, research has supported that AFX likely arises from a fibroblast or myofibroblast-like cell. The most widely agreed upon predisposing factor for development of AFX is ultraviolet (UV) radiation exposure.1,2 Additional risk factors include a history of radiation exposure, previous burn or trauma to the area, immune suppression, and a history of xeroderma pigmentosum.4,5 In a recent review, Koch et al. determined that the majority of cases occur on sun-exposed head and neck regions in males in their 5th to 7th decade of life, with a mean age of 75.8.1 Fewer cases occurred on non-sun-exposed regions, such as the trunk and limbs, of a slightly younger population. Other reports have indicated that AFX occurs in patients ranging from 3 to 115 years old.1,6

Clinically, an atypical fibroxanthoma (AFX) manifests as an asymptomatic, solitary, rapidly growing, exophytic papule or nodule.1 The overlying skin may be smooth and intact with a yellow hue, or it may ulcerate and bleed. AFX is rarely pigmented.2 Typically, the diameter of the nodule is less than 2 cm, but can range in size from 0.3 cm to 10 cm. Due to its nonspecific clinical appearance, diagnosis of AFX is challenging. Other pathologies to consider based on physical examination include squamous cell carcinoma, basal cell carcinoma, pyogenic granuloma, malignant melanoma, adnexal tumor, cutaneous soft tissue sarcoma, and Merkel cell carcinoma.2,5 Therefore, biopsy is imperative to achieve the correct diagnosis.

AFX was once considered benign secondary to its excellent prognosis. However, reports of metastatic AFX resulting in death have challenged this claim.1,2 Herein, we report the case of an 88-year-old male who presented with a rapidly growing atypical fibroxanthoma and provide a discussion regarding diagnosis and treatment of this rare cutaneous neoplasm.

Case Report
An 88-year-old Caucasian male presented to our dermatology clinic for evaluation of a rapidly enlarging solid cutaneous tumor present for approximately six months on his posterior neck. He denied associated symptoms of pain, pruritus, tenderness, or bleeding. His past medical history was significant for basal cell carcinoma, squamous cell carcinoma, metastatic prostate carcinoma, atypical fibroxanthoma, cutaneous soft tissue sarcoma, and prostate cancer. Family history was noncontributory.

On clinical examination, his left posterior neck had a solitary, fixed and firm, nontender, red to slightly blue, indurated nodule measuring 1.0 cm x 0.8 cm (Figure 1). Significant solar elastosis of surrounding skin was observed. A saucerization biopsy was performed to remove the bulk of the tumor, which was sent to a dermatopathology laboratory for tissue processing. The differential diagnosis included basal cell carcinoma, squamous cell carcinoma, metastatic prostate carcinoma, atypical fibroxanthoma, cutaneous soft tissue sarcoma, and Merkel cell carcinoma.2,5 Therefore, biopsy is imperative to achieve the correct diagnosis.

On histopathology examination, the tumor was composed of atypical spindled epithelial cells with mitosis and multinucleated giant cells. (Figures 2a, 2b). H&E stain demonstrating atypical spindled epithelial cells with mitosis and multinucleated giant cells.

Figure 1. AFX on left posterior neck with background of solar elastosis.

Figure 2a

Figure 2b
sarcoma, leiomyosarcoma, amelanotic malignant melanoma, and dermatofibrosarcoma protuberans. The dermatopathology report described sheet-like and fascicular proliferation of atypical spindled cells with admixed multinucleate giant cells using hematoxylin and eosin (H&E) staining (Figures 2a, 2b). Atypical mitotic figures were readily observed along with focal intralobular hemorrhage with siderophage accumulation. Immunohistochemistry demonstrated strong positivity of spindle cells for CD10 and some associated smooth muscle actin (SMA) positivity (Figures 3, 4). Immunohistochemistry was negative for S-100 protein, SOX10, cytokeratin 5/6, high molecular weight keratin and desmin. The surgical margins were positive.

Our patient was referred for Mohs micrographic surgery, which required two stages for tumor clearance. The resulting defect measured 4.5 cm × 4.0 cm and was reconstructed with a complex linear closure. The patient is currently followed in our dermatology clinic monitoring for AFX recurrence and metastasis.

Discussion

Atypical fibroxanthoma (AFX) is typically a diagnosis of exclusion that requires histopathologic and immunohistochemical analysis to distinguish it from tumors with similar clinical and microscopic appearances. Histopathologically, AFX appears extremely abnormal, with a dermal proliferation of haphazardly arranged spindle cells, multinucleated giant cells, or epitheloid cells that demonstrate pleomorphism with frequent mitotic figures, giant cells, or epithelioid cells that demonstrate pleomorphism with frequent mitotic figures, hyperchromatic nuclei, and intracytoplasmic lipidization.4,5 There are several AFX variants based on microscopic morphology. These include spindle cell, desmoplastic, granular, angiomatoid, histiocytoma), known as myxofibrosarcoma or malignant fibrous histiocytoma.6

Due to a lack of distinguishing morphological features, immunohistochemical analysis is required to differentiate AFX from spindle cell and squamous cell carcinoma, malignant melanoma (specifically the desmoplastic variant), leiomyosarcoma, and undifferentiated pleomorphic sarcoma (UPS) (formerly known as myxofibrosarcoma or malignant fibrous histiocytoma).7 There is no immunohistochemical stain specific for AFX; however, this tumor should stain positive for vimentin, CD10, CD68, and smooth muscle actin. Additionally, AFX should stain negative for CAM5.2, CD34, Melan-A, S100, HMB-45, cytokeratin AE1/AE3, and cytokeratin 5/6. If a tumor stains positive for cytokeratins, it helps differentiate a spindle cell SCC from AFX. Furthermore, if S100 and SOX-10 stains positive, this frequently distinguishes desmoplastic melanoma from AFX. Finally, a staining pattern positive for desmin, smooth muscle actin, and h-Caldesmon discards a leiomyosarcoma from AFX (Table 1).

Although the goal of immunohistochemical analysis is to distinguish AFX from other tumors in its histopathologic differential diagnosis, clinical correlation is required because of the potential for cross-reactivity and/or aberrant staining among neoplasms. Moreover, undifferentiated pleomorphic sarcoma (UPS) is argued to be histopathologically and immunohistochemically indistinguishable from AFX.4,8 In fact, some argue that AFX is a superficial type of UPS. However, a study by Lazova et al. suggested LN-2 stain may be specific to UPS (Table 1).9 It is also proposed that identification of H-ras, K-ras, and N-ras mutations by gene analyses is diagnostic of UPS since these mutations are absent in AFX.4,8 Additionally, analyzing the deep component of a biopsy may be helpful in differentiating AFX from UPS, as evidence of subcutaneous fat invasion, perineural or vascular invasion, or necrosis favors the more aggressive UPS neoplasm.3 Distinguishing between AFX and UPS is critical because the latter has significantly higher rates of recurrence and metastasis.4 Still, there have been limited cases of metastatic AFX with aggressive characteristics indicative of a poorer prognosis.2

Other primary tumor characteristics of an AFX that may indicate a more aggressive course include increased tumor size, depth, ulceration, and necrosis.10 Patient status is also important when predicting the clinical course of AFX. Patients with a history of radiation therapy or those who are immunocompromised have a higher risk for AFX recurrence or metastasis.10 Previously reported locations for AFX metastases include parotid gland (most common), subcutaneous fat, lymph nodes, lungs, and abdomen.5,10 Because AFX has the potential to recur and metastasize, initial treatment should focus on complete excision with clear margins.

Treatment

Due to the rarity of AFX, there are no standardized treatment recommendations. Previously reported treatments include wide local excision, Mohs micrographic surgery, modified Mohs micrographic surgery (slow Mohs), radiation therapy, cryotherapy, and electrosurgery.4,6 Since the majority of cases of AFX occur on the head and neck, tissue conservation is a priority.

Mohs micrographic surgery is recommended because it is an efficient treatment modality to spare tissue and obtain tumor-free margins. Most treatment studies focusing on wide local excision or Mohs have shown recurrence rates ranging from 0% to 16%. Furthermore, most of the recurrences occurred within one to two years post-surgery.11-15 For example, Davis et al. (n=44) showed a 16% recurrence and 0% recurrence in AFX cases treated by wide local excision or Mohs surgery, respectively.

The patients treated by wide local excision were followed for an average of 73.6 months, and the Mohs patients were followed for an average of 29.6 months.11 Huether et al. (n=33) showed patients with AFX treated by Mohs surgery had a 6.9% recurrence rate over an average follow-up of 3.3 years.16 Finally, Seavolt and McCall treated 13 AFX patients with Mohs surgery and reported

| Table 1. Immunohistochemical staining patterns for AFX vs. tumors in histopathologic differential diagnosis |
|---------------------------------------------------------------|---------------------------------|---------------------------------|-------------------------------------------------|-------------------------------------------------|
| **AFX Fibroxanthoma** | **Spindle/Squamous Cell Carcinoma** | **Melanoma** | **Leiomyosarcoma** | **Undifferentiated Pleomorphic Sarcoma** |
| Positive Vimentin | Positive Cytokeratins | Positive S100 | Positive Desmin | Positive CD74 |
| CD68, CD10 | P63 | CD10 | M-Actin | CD74, CD10 |
| Procollagen 1 | S100 | Melan-A/Mart1 | HMB-45 | CD99 |
| CD2A | Desmin | CD99 | CD99 | CD99 |
| Fascin | HMB-45 | CD10 | M-Actin | CD99 |
| A1At | Melan-A/Mart1 | CD10 | M-Actin | CD99 |
| CD99 | EMA | CD15 | CD15 | CD74 |
| CD34 | CD34 | NGFR | CD34 | CD34 |
| CD31 | CD31 | CD15 | CD15 | CD74 |
| NGFR | CD15 | CD74 | CD74 | CD74 |
| CD12 | CD12 | CD74 | CD74 | CD12 |

Figure 3 (1x). Positive CD10 showing significant brown staining of AFX on left posterior neck.

Figure 4 (5x). Positive SMA showing light brown staining of AFX on left posterior neck.
no recurrences; however, the follow-up period was noted to be short.17

Radiation or chemotherapy is recommended once an AFX has recurred or metastasized.2,3 There are rare cases where AFX recurrences or metastases resulted in death. A recent review by Koch et al. showed a 0.7% mortality rate in 1,488 patients with metastatic AFX.1 Since the literature supports a risk of recurrence or metastasis, and subsequent death from an AFX, regular follow-up is highly encouraged for five years after initial treatment.5 Although Mohs micrographic surgery is favored for primary AFX, physicians must use their clinical judgment to determine treatment based on patient status, comorbidities, and life expectancy.

Conclusion
Atypical fibroxanthoma is currently considered to have an intermediate malignant potential requiring timely diagnosis and treatment. It is a rare neoplasm that commands a multi-step diagnostic process including a biopsy with histopathologic analysis, immunohistochemical staining, and potentially genetic analysis. Once identified, Mohs micrographic surgery is supported as the best treatment modality for obtaining tumor-free margins and conserving healthy tissue. If treated appropriately, AFX has an excellent prognosis. However, there is a low risk of recurrence, metastasis, and death from a primary AFX. Therefore, regular long-term monitoring for AFX recurrence and metastasis is required.

References
Childhood Exanthems: A Differential Challenge

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Abstract
Childhood exanthems are frequently related to recent viral or bacterial infection. Other causes involve medications and inflammatory conditions such as immune-mediated vasculitis. We present a challenging case of an asymptomatic 7-year-old girl with an atypical exanthem and discuss differential diagnoses, focusing on common viral and bacterial causes.

Introduction
Viral and bacterial infections are common causes of generalized rashes in children, and patients may present with systemic signs and symptoms such as pharyngitis, fever or malaise. Common infectious agents include adenovirus, echovirus, coxsackievirus, EBV, HHV6, HHV7, parvovirus B19 and streptococcus pyogenes.1,3 Determining the underlying pathogen relies heavily on characteristic skin findings and detailed history gathering of timing, progression and immunization status. The morphology and distribution of cutaneous and mucosal lesions are also essential diagnostic clues that help distinguish between childhood exanthems. We present a challenging exanthem diagnosis in a 7-year-old female, providing insights into diagnostic tools that can help guide diagnosis and treatment in patients who present with atypical physical exam findings. We review characteristic features of several childhood exanthems and discuss appropriate workup and treatment for each condition.

Case Report
A 7-year-old female presented to our dermatology clinic with a two-day history of a generalized erythematous pruritic eruption. She stated the lesions first appeared on her face, and spread to her trunk and extremities after one day. The patient denied cough, fever, chills, sore throat, abdominal pain, arthritis, dysuria, hematuria, diarrhea, bloody stools, sick contacts or recent travel. On physical exam, there were generalized, bright red, erythematous, blanchable macules and confluent patches affecting the malar cheeks, torso, arms, palms and legs, with sparing of the eyelids, chin, axilla and antecubital fossae (Figure 1). Oral exam revealed a white strawberry tongue (Figure 2). There were no lesions on the buccal or palatal mucosa. Pharyngeal erythema, tonsillar enlargement and exudates were also absent. There was no cervical or axillary lymphadenopathy.

Two punch biopsies were performed on the lower back. Histopathology showed polymorphous dermatitis with neutrophils, nuclear dust and red cell extravasation. Fibrinoid necrosis was not observed (Figure 3).

Vasculitis protocol, which included a complete blood count, complete metabolic panel, urinalysis, stool guaiac, anti-streptolysin O titer (ASO), antinuclear antibody, erythrocyte sedimentation rate, antineutrophil cytoplasmic antibodies, rheumatoid factor, hepatitis panel, complement levels, antiphospholipid antibodies, cryoglobulins, and serum protein electrophoresis, were all within normal limits except for the anti-streptolysin O titer. The ASO titer was markedly elevated (1248), and throat culture was positive for Group A beta-hemolytic streptococci. Parvovirus B19 IgG and IgM anti-bodies were not detected.

Biopsy and lab findings were consistent with streptococcal toxin-mediated exanthem. Due to a history of penicillin intolerance, the patient was treated with cefadroxil 30 mg/kg for 10 days, hydrocortisone 2.5% cream twice daily as needed for two weeks, and camphor/menthol lotion as needed. On follow-up, 14 days after initiating treatment, the eruption had completely resolved (Figure 4).

Discussion
Exanthematous eruptions occur most commonly in school-aged children. In the early 1900s, six classical infectious childhood exanthems were described. These include measles, scarlet fever, rubella, Duke’s disease, erythema infectiosum and roseola infantum. Physicians no longer recognize Duke’s disease as a distinct entity, but rather an atypical presentation of another classical exanthem.2,3 Overlapping and atypical exanthematous clinical presentations are often encountered. In order to establish a prompt diagnosis, it is important to have a detailed
understanding of the clinical characteristics that help distinguish between various viral, bacterial and inflammatory cutaneous eruptions.

In the following sections, we discuss identifying features such as cutaneous distribution and progression, associated signs and symptoms, and appropriate laboratory workup of common viral and bacterial exanthems.

**Streptococcal infection**

Scarlet fever (scarlatina) is caused by infection with group A beta-hemolytic streptococcus (GABHS), mainly Streptococcus pyogenes, which produces pyrogenic exotoxins A, B and C. These exotoxins produce local inflammatory mediators and alterations of the cytokine milieu, leading to dilation of blood vessels and delayed-type skin reactivity. Streptococcal infections are most commonly seen in children between 1 year old and 10 years old. The infection is spread person-to-person via respiratory droplets and is typically easy to contract in close-contact settings, such as schools, daycares, and households.2

Unlike in our case, once infected, patients typically develop an abrupt onset of fever with sore throat, tonsillar enlargement, headache, nausea, vomiting, abdominal pain, myalgia, and malaise. The rash typically appears 12 hours to 48 hours after the onset of fever and is classically characterized by a sandpaper-like texture.6,7 Our patient did not develop sandpaper-like skin findings, nor did she experience associated pharyngitis or tonsillar enlargement. Her lesions also lacked the lacy reticular pattern classically observed in parvovirus eruptions. Laboratory testing confirmed diagnosis with a positive throat culture and elevated anti-streptolysin O antibody titer, strongly supporting a streptococcal etiology. In addition, parvovirus B19-specific IgM and IgG antibodies were absent.

Scarlatina classically begins in the skin folds and then rapidly expands to cover the trunk and extremities; the palms and soles are usually spared. The skin-fold lesions often exhibit a linear petechial rash that is particularly notable on the lower extremities; the palms and soles are usually spared.8

The skin-fold lesions often exhibit a linear petechial rash that is particularly notable on the lower extremities; the palms and soles are usually spared.8 Strawberry tongue is another distinct finding of scarlatina. By day four or five, the white coating sloughs off, leaving red, edematous papilla that produce a “white strawberry tongue.”

**Gianotti-Crosti syndrome**

Gianotti–Crosti syndrome (CGS), or papular acrodermatitis of childhood, is a type IV hypersensitivity reaction to viral antigens. The most common viral triggers include hepatitis B and EBV, but other causes include hepatitis A and C, rotavirus, EBV rubella, CMV, coxsackievirus (A16, B4 and B5), adenovirus enterovirus, respiratory syncytial virus, parainfluenza virus (types 1 and 2), parvovirus B19, HHV 6, echovirus, poxvirus, and HIV.24

CGS is typically an abrupt eruption of erythematous, flat-topped papules affecting the face, extensor extremities and buttocks. These papules may coalesce into hemorrhagic plaques and are either asymptomatic or pruritic.25 Diagnosis relies exclusively on clinical presentation. Recent studies have proposed diagnostic criteria for GCS, which include the clinical findings described above along with symmetrical distribution, duration of 10 days, and a lack of truncal lesions and scaled lesions.26 GCS is self-limiting, and treatment is supportive.

**Epstein-Barr virus**

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is best known as the causative agent of infectious mononucleosis. Transmission occurs via saliva. In the United States, 50% of the population is infected by the age of 5.27 Cutaneous involvement is usually seen in children and may be the only symptom present. The eruption is described as an erythematous macular rash in a scattered, haphazard distribution. Cutaneous findings are seen in 3% to 15% of those infected with EBV. Additional symptoms include fever, hepatomegaly, splenomegaly, posterior cervical lymphadenopathy and pharyngitis.27 These symptoms are rare in children but may be seen in adolescents and adults.

Patients with EBV mistakenly diagnosed as streptococcal infection and treated with amoxicillin or ampicillin will also present with a cutaneous eruption. This rash is typically described as a...
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Measles

Measles is a highly contagious, single-stranded RNA virus that primarily affects children and infants. The virus spreads through multiple routes, including fecal-oral and respiratory droplets. Cases of measles can be severe, particularly in children, but generally resolve with supportive care. The disease is characterized by a distinctive rash that appears on the face and spreads downward to the trunk and extremities. The rash usually begins as a macular eruption that occurs in patients who have previously had measles immunization. Unlike typical presentation, the rash begins on the face and trunk and then spreads downward to the extremities.

Infectious mononucleosis is self-limited and only requires supportive care.

Coxackievirus

Coxackievirus is a single-stranded RNA enterovirus that most commonly affects children and infants. The virus is spread through multiple routes, including fecal-oral and respiratory droplets. Cases of coxackievirus A16 are associated with a variety of clinical manifestations, including upper respiratory tract infection, vesicular eruptions, meningitis, and non-specific cutaneous eruptions. Coxackievirus A16 is responsible for the exanthem hand, foot, and mouth disease (HFMD) and the exanthem herpangina.

HFMD begins as vesicular lesions typically on the palms, soles, and oral mucosa but can also present on the extremities, trunk, and neck. Herpangina, on the other hand, presents as vesicles in the posterior oropharynx. In HFMD and herpangina, patients often report sore throat, fever, and headache.

Diagnosis of HFMD and herpangina relies primarily on clinical exam findings; however, viral culture of vesicular fluid may be performed for confirmatory purposes. Both conditions are self-limited, and treatment consists of supportive care.

Measles

Measles, also known as rubella, is a highly contagious, single-stranded RNA virus most commonly seen in children, though it can occur at any age. Individuals who are susceptible to the virus have a 90% chance of becoming infected upon exposure. Transmission occurs through respiratory droplets, either airborne or on a surface. People immunized with the live-attenuated vaccine are typically protected from contracting the virus upon exposure.

In 2000, the virus was considered to be eliminated in the United States, but due to a decrease in childhood vaccinations, measles has been on the upsurge. Between 2000 and 2014, 288 cases were confirmed by the CDC. Of those infected, patients were either unimmunized or had an unclear vaccination history.

The clinical manifestation of measles occurs in four stages: incubation, prodromal, exanthematosus, and recovery. In the incubation period, which lasts for up to three weeks post exposure, patients are typically asymptomatic or may begin to show signs of fever, respiratory symptoms, and rash. The prodromal period usually lasts for two to four days and marks the stage of characteristic symptoms, including cough, coryza, and conjunctivitis. Fever, malaise, and anorexia are also seen in this stage. The cutaneous outbreak occurs two to four days after the fever begins, whether in the incubation or prodromal phase. The rash is described as blanchable, erythematous, maculopapular lesions that begin on the face and spread downward to the trunk and extremities. The soles and palms are typically spared. The rash usually lasts for two days and then begins to improve, indicating the recovery phase. Although the description, distribution, and time frame of the rash fits our case, the prodromal characteristic findings were absent.

There are also two variants of the measles: modified and atypical. Modified measles is a milder presentation with a longer incubation period, and it occurs in patients who have preexisting measles immunity. Atypical measles occurs on the other hand, occurs in patients who received the previous killed-virus vaccine rather than the live-attenuated vaccine. Because the killed-virus vaccine was distributed between 1963 and 1967, the atypical variant occurs in the current adult population.

Measles can be diagnosed by clinical presentation alone, but confirmation by laboratory testing is required due to the necessity of reporting any measles case to public health officials. Tests should include a complete blood count, liver enzymes, serological markers (IgG and IgM antibodies), viral cultures, and reverse transcriptase polymerase chain reaction testing. The measles virus is self-limited, but patients should be given supportive care and vitamin A supplementation. Vitamin A has been shown to reduce mortality in up to 50% of cases, as well as prevent ocular damage and blindness.

Kawasaki disease

Kawasaki disease is a febrile vasculitis affecting small- and medium-sized vessels. It is the leading cause of acquired cardiac disease in children. Although the cause of Kawasaki disease is unknown, it is theorized to be an infectious process worsened by genetic components.

Patients with Kawasaki disease go through three clinical phases: acute, subacute, and convalescent. In the acute phase, patients initially present with an abrupt onset of fever that does not subside with antibiotic or antipyretic treatment. This phase may last for up to four weeks. The cutaneous findings of perianal, palm, and sole erythema and desquamation are present in the acute phase, as well. The rash begins to evolve into a macular, morbilliform eruption on the trunk and extremities. Bilateral non-exudative conjunctivitis, anterior uveitis, strawberry tongue, palpable purpura, marking the convalescent phase. When the fever begins to subside, the patient has entered the subacute phase. The hallmark of this phase is desquamation on the digits and a risk of coronary aneurysm that may lead to sudden death. Once the clinical signs and symptoms have cleared, with the exception of Beau’s lines, the patient is considered to be in the convalescent phase.

The diagnosis of Kawasaki disease is clinical; laboratory tests and imaging are confirmatory. The diagnostic criteria, created by Tomisaku Kawasaki, include a fever that lasts for at least five days and at least four out of the five following signs: bilateral conjunctival injection, mucosal changes (erythematous or fissured lips, erythematous pharynx, or strawberry tongue), extremity changes (erythematous or edematous palms or soles, or desquamation), polymorphous cutaneous eruption, and cervical lymphadenopathy (measuring greater than 1.5 cm). Patients who do not meet the criteria but prompt high suspicion for the diagnosis are considered to have incomplete Kawasaki disease.

Appropriate laboratory testing includes complete blood count, liver enzymes, C-reactive proteins, erythrocyte sedimentation rate, and urinalysis. In studies, urine proteins filamin C and meprin A have shown promise as confirmatory biomarkers.

The gold standard of treatment includes the full dose of intravenous immunoglobulin (IVIG) and high-dose aspirin. It is also imperative to screen for coronary artery aneurysms with EKG at the time of diagnosis, at two weeks, again at six to eight weeks, and finally at one year after the onset of symptoms.

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP), a vasculitis mediated by immunoglobin A (IgA), affects small vessels mainly of the skin, kidneys, joints and gastrointestinal tract. Although there is a confirmed role for IgA in HSP, infectious, genetic, antigenic, and environmental factors are all thought to play a role in the disease. HSP is the most common vasculitis in children, with 90% of cases presenting between the ages of 3 years and 10 years, but it can also occur in adults.

The cutaneous eruption is usually the complaint upon presentation. It typically occurs symmetrically and in crops, with new crops occurring for up to three weeks. The rash usually begins as a macular or urticarial eruption on the lower extremities and buttocks. The initial lesions coalesce and form petechiae and palpable purpura, marking the hallmark finding of HSP.

The American College of Rheumatology has developed clinical diagnostic criteria for HSP, which include: palpable purpura, presentation before age 20, abdominal pain, and a cutaneous biopsy showing granulocytes in the walls of arterioles or venules. If suspicion is present, the vasculitis workup should also be completed as a confirmatory measure. In our patient, the maculopapular rash distribution and absence of abdominal pain made the diagnosis of HSP unlikely. Furthermore, our biopsy did not show granulocytes on the walls of the vasculature.

Because HSP is self-limiting, treatment is supportive. If gastrointestinal or renal complications are present, hospitalization is required to monitor patients to prevent further complications. Those who do not require hospitalization need close follow-up with urine studies to confirm the disease has run its course without further systemic complications.

Erythema multiforme

Erythema multiforme (EM) is considered a type IV hypersensitivity reaction to infection, drugs, radiation, autoimmune diseases, malignancies and various other factors. Of reported cases, 90% were caused by an infectious process, and of those, HSV was the most common. Mycoplasma pneumoniae is also a common cause, mainly in children.

As the name implies, erythema multiforme has a wide range of cutaneous presentations; however, the hallmark of EM is a target lesion. This may be the initial presentation, or it may start as an erythematous macule, papule or urticarial plaque that later morphs into a target lesion. A target lesion has a central clearing and/or blistering, along with an edematous and pale periphery surrounded by an erythematous halo.

The diagnosis is based on clinical findings; however, a skin biopsy is warranted in the case of uncertainty due to atypical presentation or suspicion of underlying autoimmune disease. Due to the high incidence of HSV and mycoplasma pneumoniae, serological testing for both is also warranted.
The diagnostic workup should further assist in finding the cause, which will drive the treatment plan for EM. This may entail antibiotics, antivirals, or withdrawal of a causative drug. Additionally, supportive treatment is necessary and includes antihistamines, topical corticosteroids, and wound care.51

Rocky Mountain spotted fever
Rocky Mountain spotted fever (RMSF) is a tick-borne disease caused by *Rickettsia rickettsii*. It is commonly found in the south-central and southeastern United States. Patients usually present with prodromal symptoms, which may include fever, headache, nausea, abdominal pain, myalgia and arthralgia, approximately three days prior to cutaneous involvement. The rash typically occurs on the third to fifth day post exposure. Ninety percent of patients have the rash, which is classically described as a maculopapular eruption starting at the extremities and moving toward the trunk, with the palms and soles affected last. The macules evolve into petechiae; at times, they may present only as petechiae.52

The initial diagnosis is clinical, based on the patient's symptoms and risk of exposure. Without immediate treatment, the disease is lethal; therefore, treatment should be started immediately if the clinical picture fits RMSF. Confirmatory testing can also be done, but will take time to return, so treatment should not be based on these tests. The standard for confirmatory testing involves serologic testing with the indirect fluorescent antibody.53 Skin biopsy is an option for a more time-sensitive response, with a 90% sensitivity rate.54

Doxycycline is the standard of treatment for both children and adults. If antibiotics are started within the first five days of exposure, mortality rates drop from 20% to 5%, and complications may be prevented.55

Conclusion
Exanthematous eruptions can be difficult to diagnose when classic clinical findings are absent or when features of several conditions overlap. A detailed understanding of commonly encountered exanths is necessary in order to establish a comprehensive differential diagnosis and appropriate diagnostic tests. This case illustrates how the use of simple and inexpensive laboratory tests can help narrow differential diagnoses and guide appropriate treatment to prevent complications and long-term sequela.

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CHILLOD EXANTHEMS: A DIFFERENTIAL CHALLENGE
Chronic Inflammation and Vascular Density in Sun-Exposed Skin

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Abstract

Introduction: Prior studies have identified increased chronic inflammation in sun-exposed sites compared to sun-protected sites. Ultraviolet radiation has also been found to promote angiogenesis. We propose a possible relationship between inflammation, angiogenesis and photocarcinogenesis. Materials and Methods: Two elliptical biopsies from sun-exposed skin and sun-protected skin were taken from 13 Caucasian cadavers. Dermal vessels and inflammatory cells were counted in H&E stained slides per 10 consecutive high-power fields (400 X). Results: Sun-exposed biopsies showed a significant increase in mean numbers of both chronic inflammatory cells and vessels compared to sun-protected biopsies (p < 0.001). No statistically significant correlation was found between mean number of vessels and mean number of chronic inflammatory cells in either exposed and protected specimens (r = -0.37; p=0.21 and r =0.24; p=0.43, respectively). Conclusion: Sun-exposed skin demonstrates an increase in chronic inflammatory cells and vessels compared to sun-protected skin.


Introduction

Cutaneous photoaging and carcinogenesis induce microscopic and macroscopic changes resulting from short-term and long-term exposure to ultraviolet light type B (UVB). Clinically, chronic exposure may result in fine lines, wrinkles, fragility, and malignant neoplasms. Acute exposure to UVB radiation has been found to cause epidermal hyperplasia, dilation and enhancement of the dermal vasculature. In addition, biochemical alterations with decreased levels of IFN-beta, an anti-angiogenic mediator, and increased levels of vessel-endothelial-growth factor, TNF-alpha, IL-8, and fibroblast growth factor have been reported following UV radiation. The most commonly documented histological changes in chronic sun-exposure include accumulation of glycosaminoglycan, loss of collagen fibers, and production and laying down of abnormal elastin fibers, resulting in solar elastosis. These changes may be due to UVB induction of fibroblasts, mast cells, keratinocytes, endothelial cells, and infiltrating inflammatory cells.

The goal of our study was to observe inflammatory and vascular changes in sun-exposed versus sun-protected skin areas, and determine if these findings of chronic inflammation and vascular changes associated with chronic sun-exposure are consistent in a simple model. The use of cadaver skin allowed for larger specimen sampling. Based on this information and data from other studies, the implications of chronic inflammation and angiogenesis in chronic sun exposure and associated lesions will be discussed. We used a quantitative approach with hematoxycin and eosin (H&E) stained specimens from cadavers.

Materials and Methods

Institutional review board approval for exempt status based on work with cadavers was obtained.

From each of 15 randomly selected Caucasian cadavers, two 2-inch elliptical skin biopsies were obtained: one from a sun-exposed site, defined as the area from the face anterior to the ear, inferior to the hairline and superior to the chin and jaw line; and one from a sun-protected site, designated as the upper and inner thigh regions. The tissue underwent routine processing and staining with H&E. Only data from 13 cadavers were statistically analyzed due to poor tissue preservation from two cadavers.

Chronic inflammatory cells (lymphocytes, macrophages, and plasma cells) were manually counted from 10 consecutive high-power fields at 400x magnification, with field placement immediately below the basal layer of the epidermis. In addition, superficial dermal vessels including arterioles, veins, and lymphatic vessels were counted within each field at the same magnification. In sun-exposed skin, we observed solar elastosis as evidence of UV exposure. We were able to perform multiple field counts due to the amount of tissue available.

Statistical evaluation was performed with IBM SPSS Grad Pack 22. A paired t-test was used to compare mean numbers of inflammatory cells between sun-exposed and sun-protected specimens. A paired t-test was also used to compare the mean numbers of dermal vessels from sun-exposed and sun-protected specimens. A Pearson’s correlation was performed to assess the relationship between mean vessel quantities and mean number...
of inflammatory infiltrates of the two cohorts. For both statistical analyses, \( p < 0.05 \) was used to designate statistical significance.

**Results**

Determination of age and gender as covariates was not statistically significant, allowing for justified comparison. Paired samples t-test between the mean inflammatory cell counts in the upper thigh (5.86, [2.50]) and the inner thigh (6.98, [5.43]) revealed no statistical significance (\( p = 0.40 \)).

Based on this, the mean value of both inner thigh and upper thigh were used to represent the sun-protected value. Comparison of the mean number of inflammatory infiltrates between face (sun-exposed) (19.17, [8.08]) and the average of upper thigh and inner thigh (sun-protected) (6.42, [3.56]) biopsy specimens was statistically significant (\( p < 0.001 \)). More chronic inflammatory cells were present in sun-exposed skin versus sun-protected skin (Figures 1-3).

Comparison of the mean vessel quantity between face (5.69 [1.71]) and inner thigh (4.15 [1.52]) biopsy specimens was statistically significant (\( p = 0.011 \)), with a greater number of vessels in sun-exposed versus sun-protected skin (Figures 1-3).

A direct relationship between inflammatory-cell quantity and dermal-venue quantity was not established. Correlation of mean inflammatory cell count and mean dermal vessel count in sun-exposed specimens was not statistically significant (\( r = -0.37, p = 0.21 \)), nor was correlation of mean dermal vessel count and mean inflammatory cell count in sun-protected specimens (\( r = 0.24, p = 0.43 \)).

**Discussion**

A limited number of studies have examined the relationship between chronic sun exposure and inflammation. A French study examined specimens of pre-auricular (sun-exposed) and post-auricular (sun-protected) skin for comparative differences in inflammation. They identified a greater number of mononuclear cells in the dermis of pre-auricular specimens, specifically around areas of elastolysis and perifollicular areas, whereas inflammatory infiltrates of post-auricular skin showed greater evidence of intrinsic aging and were perivascular, perifollicular, and interfollicular in nature. Immunohistochemical studies with anti-Cd68 antibodies to detect macrophages, and tryptase to detect mast cells, have identified a greater number of dermal macrophages and mast cells in sun-exposed skin compared to sun-protected skin. Specific T-cell antibodies identified a greater number of CD4+ T cells and fewer CD8+ T cells in sun-exposed skin sites compared to sun-protected skin sites. These results, combined with our results, support an association between chronic UV exposure and inflammation. In our study, we designated sun-protected skin as the upper and inner thigh rather than post-auricular skin. It’s possible post-auricular skin may have some degree of sun exposure, whereas the inner and upper thigh were less likely to be sun-exposed in a general elderly population.

Inflammatory cells play many roles in the skin, covering both destruction and repair. One study found a greater number of mast cells in sun-exposed skin specimens. These cells, along with other inflammatory cells, secrete cytokines and metalloproteinase (MMP), specifically interstitial collagenase (MMP-1). MMP-1 is primarily responsible for the collagen damage found in photodamaged skin. One study employed the use of sunscreen, compared to sunscreen and anti-oxidants, and noted a 43% and 60% decrease in MMP-1 expression, respectively. Of greater clinical significance is the role of inflammatory cells, MMPs, and photocarcinogenesis. MMP gene expression is evident in many cell types, including macrophages, T-cells, monocytes, fibroblasts, keratinocytes, and endothelial cells. Ultraviolet radiation stimulates growth factor and cytokine receptors located on keratinocytes and fibroblasts, further upregulating transcription of AP-1, a nuclear transcription factor, which then stimulates the production of collagenase (MMP-1), stromelysin 1 (MMP-3), and 92-kda gelatinase (MMP-9). Metalloproteinases act to degrade the extracellular matrix basement membrane, altering cellular architecture and facilitating tumor invasion and metastasis.

A Chinese study compared MMP-12 expression in 298 melanoma specimens to MMP-12 expression in 60 normal skin specimens, and found elevated levels of MMP-12 expression in melanoma specimens with a significant association with tumor invasion and metastatic potential. It has been reported that increased expression of MMP-1 and MMP-3 in melanoma metastases correspond with significantly shorter disease-free survival periods. Although the relationship between inflammatory-cell counts/types, MMP expression, and cutaneous progression have not been completely ascertained, together these individual findings may point to a clearer mechanism for photoaging and photocarcinogenesis in chronic inflammation.

NSAIDs target a group of pro-inflammatory enzymes known as cyclooxygenases, COX-1 and COX-2. COX-2, although not present in normal skin, can be produced in the presence of UVB radiation. UVB is a known environmental carcinogen that allows for the formation of (6-4) pyrimidine-pyrimidine cyclobutane pyrimidine dimers, which initiate and promote photocarcinogenesis. UV-induced COX-2 has been shown to induce prostaglandin-E2 synthesis (PGE-2), resulting in elevated PGE-2, which is capable of binding various EP receptors on the surface of cells. EP-1, EP-2, and EP-4 have been identified as playing a role in photocarcinogenesis in murine models. Through its diverse action on various receptors, PGE-2 has been determined to cause an inflammatory response, aid in tumoral invasion, and inhibit apoptosis. COX-2 has been identified in epithelial cells of UVB-induced SKH-1 tumors in mice, in addition to dermal fibroblasts and macrophages within the tumor stroma. One study found COX-2 expression significantly increased in actinic keratosis, Bowen’s disease, and squamous cell carcinoma lesions, compared to normal skin, with normal skin having no expression based on study-specific staining standards.

Another study found COX-2 expression in 90%, 100%, and 88.9% of basal cell carcinomas, squamous cell carcinomas, and actinic keratosis, respectively, with expression not only in the epithelial components of the tumors but also in vessel walls and inflammatory cells. The presence of COX-2 within inflammatory cells may be
related to tumorigenesis. The cellular presence and role of COX-2 remains questionable, as studies have shown that mice with COX-2 deletions in epithelial cells are not devoid of UVB-induced skin tumors.

Diclofenac sodium 3% gel, an NSAID with preferential activity on COX-2, has been FDA-approved in the United States for actinic keratoses. A review of 18 articles studying diclofenac 3% gel in the treatment of actinic keratoses has suggested it is effective. The evidence for NSAIDs in the management of basal cell carcinoma is weaker; however, a recent meta-analyses identified a 10% risk reduction in basal cell cancer in patients deemed high-risk (history of skin cancer and/or high prevalence of AKs) who were taking any oral NSAID. Another meta-analysis determined, despite significant study heterogeneity, a significantly reduced risk of SCC among people taking any NSAIDs. Our results bolster these findings, as inflammation resulting from chronic sun exposure may play a role in inflammatory and angiogenic changes of photocarcinogenesis. The use of NSAIDs has helped elucidate the possible roles of chronic inflammation in chronic sun-exposed skin lesions, further lending support to their pathogenetic role.

Vascular changes occur, as well, both in photoaging and carcinogenesis. Traditionally, a noted reduction in vascularity has been described in elderly skin. Most elderly individuals have some evidence of cumulative sun damage in commonly sun-exposed regions, such as the head and neck, compared to relatively sun-protected areas like the inner thigh. One case series from South Korea examined biopsies form 21 patients from the face and buttocks, performing immunohistochemical and computer-assisted morphometric analyses of dermal vessels. The authors identified a significant reduction in the number of dermal vessels in photodamaged skin compared to sun-protected skin in patients 70 years of age and older. A reduction in vessel size was noted in patients 40 years of age and older. Linear regression revealed a negative correlation between age and vessel density, vessel size, and vessel area. They theorized that repeated, acute exposure to UV radiation causes inflammation, angiogenesis, and extracellular matrix degradation, cumulatively causing an unfavorable physical environment for dermal vessels. However, it should be noted that sun exposure may be avoided in many Asian countries as an effort to prevent tanning.

In contrast, a murine study subjected skh-1 hairless mice to UVB radiation, gradually increasing minimal erythema doses over a 10-week period to reach 4.5, in an effort to examine the angiogenic changes that occur with chronic UVB exposure in actinically sun-damaged skin. Irradiated mice had evidence of UV exposure, with wrinkling of skin compared to non-irradiated mice. CD31 immunostaining of irradiated skin specimens revealed not only an increased number of vessels, along with significantly increased size and density, but also an inflammatory infiltrate in the upper dermis. This may indicate a direct relationship between inflammatory cells and dermal vasculature changes that occur in response to chronic UVB exposure. The authors subjected transgenic mice with skin-specific overexpression of thrombospondin-1 (TSP-1), an angiogenic inhibitor, to the same UVB radiation regimen. They reported an absence of clinical wrinkling in transgenic mice subjected to the same UVB regimen as wild type mice, in addition to reduced numbers of dermal inflammatory cells and vessels and a reduction of more than 55% in average vessel size of dermal vessels compared to wild-type mice. Of note, ki-67 and CD31 immunostaining of specimens of irradiated transgenic mice revealed a reduced number of proliferating dermal endothelial cells compared to exposed wild type mice. It has been reported that thrombospondins may inhibit zymogens of MMP-2 and MMP-9. This may indicate COX-2 plays an indirect role in angiogenesis in skin cancers without increasing vessel numbers. However, COX-2 expression has been significantly associated with microvessel density in colorectal and breast cancers.

Our subjects were from any elderly Caucasian population, representative of an at-risk skin cancer population in the general U.S. population. Limitations of our study include a small sample size and lack of data on actual cumulative sun-exposure, personal and family history of pre-cancer and cancerous skin, and presence of risk factors for increased incidence of skin cancer. Skin cancer was not a cause of death in any of the subjects. Prospective studies examining pre-cancer-prone skin and inflammation might help determine an effective time to intervene with topical NSAID therapy to treat and prevent photocarcinogenesis.

**Conclusion**

Vessel density and chronic inflammation were increased in sun-exposed skin compared with sun-protected skin. These changes could play a role in photoaging and photocarcinogenesis.

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Figure 4. Scatter-plot and linear correlation between mean inflammatory cells and mean vessels.

![Figure 4](image_url)

**Face**

![Graph](image_url)\[r = -0.37\] \[p = 0.21\]

**Inner thigh**

![Graph](image_url)\[r = 0.24\] \[p = 0.43\]
References


Clear Cell Acanthoma:
A Clinical, Dermoscopic and Histological Review
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Abstract
Clear cell acanthoma (CCA) is an uncommon, benign epidermal tumor that may be easily misdiagnosed on a clinical basis alone. Although biopsy is commonly performed for diagnosis, perceptive clinicians may suspect a CCA with the use of clinical and dermoscopic findings. We present a case of a suspected clear cell acanthoma confirmed by biopsy along with a clinical, dermoscopic and histological review of the condition.

Introduction
CCA was first described in 1962 and was also known as “Degos acanthoma” and “acanthome cellules claires of Degos and Civatte.”1 There are currently no known risk factors, and the etiology is unknown. It is theorized that the cause may be an inflammatory reaction secondary to an unknown trigger.2 Yet further investigation is necessary to conclude the actual cause. CCA typically presents as an erythematous, solitary papule with a peripheral scale, usually on the lower extremities. Because this description clinically coincides with a multitude of other lesions, our aim is to describe how dermoscopy can distinguish CCA from its differentials, making diagnosis biopsy-free.

Case Report
A 68-year-old white female presented to our outpatient clinic for a full-body skin exam. Her past medical history was significant only for chronic obstructive pulmonary disease. She denied personal or family history of skin cancer. Physical exam revealed a sharply demarcated, 0.3 cm x 0.3 cm, shiny, pink, moist, blanchable papule with a collarette scale located on the left anterior distal shin in conjunction with varicose veins (Figure 1). Dermatoscopic evaluation showed dotted vessels arranged in a linear “string of pearls” distribution, revealing the characteristic dermoscopic vascular pattern seen in clear cell acanthoma (CCA) (Figure 2).3,4

Discussion
CCA is a rare, benign lesion that is oftentimes difficult to diagnose with clinical observation alone. CCA shares clinical features that overlap with a variety of other lesions, making the differential diagnosis extremely broad. Dermoscopically, however, this lesion has unique and specific features, which greatly improves diagnostic accuracy. The dermoscopic features show a stereotypical vascular pattern composed of dotted vessels distributed linearly in a “string of pearls” configuration.

Clinical Findings
CCAs are generally solitary, asymptomatic, red or brown, dome-shaped papules or nodules. They may be covered by scaled edges or appear moist. The size of lesions can range from approximately 3 mm to 20 mm, and they can slowly grow for up to 10 years. When closely examining the surface of the lesion, vascular puncta are present, which easily bleed following minor trauma. These lesions are usually found on the lower extremities in middle-aged to elderly adults, with both sexes affected equally.5,6

Although this is the most common presentation, there are a variety of clear cell acanthoma types, creating a large list of differential diagnoses. These

![Figure 1. Clinical presentation of CCA.](image1)

![Figure 2. Dermoscopic presentation of CCA under contact polarized light with isopropyl alcohol immersion medium.](image2)

![Figure 3. H&E (10x): CCA demonstrating circumscribed area of psoriasiform epidermal hyperplasia with cytoplasmic pallor, overlying parakeratosis containing neutrophils and papillary dermal telangiectasia.](image3)

![Figure 4. H&E (20x): Shave biopsy showing abrupt border between pale and normal cells in epidermis.](image4)
types include giant, polypoid, pigmented, eruptive, atypical and cystic. In addition, there have been three recent literature reports detailing "atypical CCA," which some authors argue is a malignant counterpart of CCA. These cases were clinically described as erythematous, moist nodules, all of which were located on the face. Dermoepitheliocytologically, these lesions portrayed a dot-like pattern of globular capillary vasculature, similar to benign CCA. The literature is still pointing toward calling them benign lesions, secondary to the lack of recurrence. Further research is required for atypical CCA.7

Differential Diagnosis
CCA has a vast differential diagnosis that includes actinic keratosis, lichenoid keratosis, pyogenic granuloma, dermatofibroma, basal cell carcinoma, squamous cell carcinoma, inflamed seborrheic keratosis, eccrine poroma, clear cell hidradenoma, amelanotic melanoma, and psoriasis. When considering non-pigmented skin lesions such as these, dermoscopic vascular structures are often helpful in making a correct diagnosis. Among this wide differential base, clear cell acanthomas are unique in their dermoscopic distribution of dotted or globular vessels, arranged in a curvilinear pattern.

Diagnosis
CCA may be suspected on physical exam, especially when combined with the clues and patterns visualized with a dermatoscope. Confirmatory diagnosis of clear cell acanthoma requires a skin biopsy. Dermoscopically, these lesions are set apart from their differentials by the pattern of their vasculature, rendering a skin biopsy practically unnecessary. Under a dermatoscope, clear cell acanthomas portray pinpoint vessels in a linear pattern, described as pearls on a string.8

Histopathology
Typically, CCA are characterized by well-demarcated epidermal hyperplasia made up of large keratinocytes and basal cells full of a glycogen-rich cytoplasm positive to periodic-acid-Schiff staining. An abundance of densely packed, dilated capillaries is seen in a well-demarcated distribution that correlates with the dermoscopic vascular features or red dots and globules outlined above. Parakeratosis, neutrophilic exocytosis and mild spongiosis are also present (Figures 3 and 4). 4,6

In the atypical variant of CCA, histological findings consist of cytological atypia of tumor cells with enlarged nuclei, some of which show mitotic figures. In one study, these tumor cells were positive for p63.7

Management and Therapy
Management of a solitary CCA lesion is by excisional removal. This can be done through a variety of methods including, but not limited to, standard surgical excision, Mohs micrographic surgery, cryotherapy, electrolaser, electrofulguration, curettage and carbon dioxide laser. For cases of multiple or larger lesions, cryotherapy and carbon dioxide laser have been successfully used.6 In addition, in line with a theorized inflammatory reactive cause, one case report showed regression of CCA after a two-month trial of calcipotriol.2 In the case of our patient, shave excision combined with electrofulguration was used for diagnosis and treatment.

Conclusion
CCAs have a large differential including many lesions that are less benign and occur with much higher frequencies in the population. Under these conditions, the diagnosis of CCA is usually made histologically, after a biopsy has been performed. Since the features of this lesion are dermoscopically distinct, this may afford the clinician more diagnostic confidence. The use of routine dermoscopy may therefore reduce the number of biopsies performed on this benign dermatologic entity.

References
Guaifenesin-induced Acute Generalized Exanthematous Pustulosis (AGEP): A Case Presentation and Discussion

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Abstract

Guaifenesin is an expectorant medication available as a single-ingredient formula or combined with pseudoephedrine or dextromethorphan to serve as an over-the-counter cold and cough medication. Cutaneous adverse reactions, albeit rare, have been attributed to pseudoephedrine and dextromethorphan.1-4 We present a case of cutaneous pustular eruption secondary to ingestion of guaifenesin 1200 mg extended-release bi-layer tablets consistent with acute generalized exanthematous pustulosis (AGEP). To our knowledge, this is the first reported case of AGEP associated with single-ingredient guaifenesin.

Introduction

Acute generalized exanthematous pustulosis (AGEP), also known as pustular drug eruption, is a rare cutaneous adverse reaction characterized by the rapid development of numerous non-follicular, sterile, pinpoint pustules on an erythematous base, commonly associated with high fever and leukocytosis.1,3,4,10 Incidence is estimated as one to five cases per million per year.4 The eruption can be pruritic or painful.1-3 It generally begins on the face and extends to the trunk, with a predilection for the major intertriginous regions. Mucosal membranes, most commonly the oral mucosa, may be affected. When this occurs, it is often confined to a single site. Severe AGEP, with mucous membrane and systemic organ involvement (hepatic, renal, or pulmonary insufficiency), accounts for approximately 20% of the affected areas is common.1-10

Table 1. Medications reportedly associated with AGEP

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication(s)</th>
</tr>
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<tbody>
<tr>
<td>Antibiotics</td>
<td>Pristinamycin*</td>
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<tr>
<td></td>
<td>Aminopenicillins*</td>
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<tr>
<td></td>
<td>Quinolones*</td>
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<tr>
<td></td>
<td>Sulfonamides*</td>
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<td></td>
<td>Macrolides</td>
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<tr>
<td>Antifungals</td>
<td>Terbinafine</td>
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<td></td>
<td>Fluconazole</td>
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<tr>
<td></td>
<td>Ketoconazole</td>
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<tr>
<td></td>
<td>Nystatin</td>
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<tr>
<td></td>
<td>Amphotericin B</td>
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<tr>
<td>Decongestants</td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
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<td>Diuretics</td>
<td>Hydroxychloroquine</td>
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<td>Chemotherapy agents</td>
<td>Imatinib</td>
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<tr>
<td>Alpha-1-blockers</td>
<td>Terazosin</td>
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<td>Calcium channel blockers</td>
<td>Diltiazem</td>
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<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
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<td>Proton pump inhibitors</td>
<td>Omeprazole</td>
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<tr>
<td>Antiplatelet agents</td>
<td>Clopidogrel</td>
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<tr>
<td></td>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Analgesics</td>
<td>NSAIDs (Oxicam)</td>
</tr>
<tr>
<td></td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Stimulant laxatives</td>
<td>Senna glycoside (sennoside)</td>
</tr>
</tbody>
</table>

*Most commonly reported offending antibiotics in AGEP cases

The time interval between drug exposure and presentation of symptoms varies by offending agent, but it often occurs within 48 hours of ingestion.5-7 AGEP should be suspected in patients with characteristic cutaneous features presenting within hours or days after starting a new drug.5 Discontinuation of the causative agent results in rapid resolution of eruption within four to 10 days, and subsequent post-inflamatory desquamation of the affected areas is common.1-10

Case Report

A 67-year-old, febrile, Caucasian female was admitted to the hospital for a painful, erythematous, pustular eruption that evolved over a four-day period after ingesting guaifenesin 1200 mg for congestion. The patient noted the rash appeared within a few hours of ingesting the medication and began as erythema involving the intertriginous areas of the groin. The rash worsened and rapidly spread to the trunk, eventually evolving into pustules. The patient stated she had experienced flu-like symptoms two weeks prior. She did not take any medications regularly and had no personal or family history of psoriasis or other skin disease.

Physical examination displayed intertriginous erythema with numerous, coalescent pustules most prominent under the breasts and axilla, as well as mucous membrane involvement (Figure 1). Petechial lesions were appreciated on the upper extremities and at the periphery of the erythematous patches. No scaling or desquamation of the post auricular skin or scalp was noted. An erosion on the right labia was noted, likely secondary to trauma of the pustular eruption.

Admission laboratory analysis revealed a marked increase in white blood cell count (37.6 K/mm3) with neutrophilia (36% band neutrophils),
hypokalemia (3.3 mmol/L), hypocalcemia (7.3 mg/dl), and hypoalbuminemia (2.0 g/dl). Rapid influenza and beta hemolytic strep tests were negative. Throat culture and blood cultures were also negative at 48 hours.

Based on gross clinical appearance and laboratory findings, AGEP secondary to guaifenesin was diagnosed. After discontinuation of the offending medication, the eruption rapidly improved. Routine wound care and supportive therapy was recommended.

Discussion

The pathophysiology of AGEP is not well understood. Cultured peripheral blood studies suggest a T-cell-mediated disease; it is postulated that following exposure to the offending agent, drug-specific CD4 and CD8 T cells are activated, proliferate and migrate into the epidermis and dermis. The CD8 cells induce keratinocytes to undergo apoptosis via perforin and granzyme B mechanisms, leading to tissue destruction and epidermal vesicle formation. Keratinocytes release neutrophil-attracting interleukin-8 (IL-8) or CXCL8, causing neutrophils to enter vesicles, with resultant formation of sterile pustules. Analysis of AGEP patients’ CD4 T cells reveals a Th1-dominant cytokine profile with increased interferon-γ and granulocyte-macrophage colony stimulating factor (GM-CSF) production, which promotes neutrophil survival and enhances pustule formation. A Th2 pattern with high IL-4 and IL-5 production causes eosinophil proliferation and resultant eosinophilia in 30% of reported AGEP cases. It is also suspected that Th17 cells may lead to the release of IL-17 and IL-22, further promoting keratinocyte production of CXCL8.

Histological findings can help differentiate AGEP from other clinically similar, severe, acute cutaneous eruptions such as acute pustular psoriasis, drug reaction with eosinophilia and systemic symptoms, Steven’s Johnson syndrome, and toxic epidermal necrolysis. AGEP is characterized by intracorneal, subcorneal, and intraepidermal spongiform pustules. Papillary dermal edema with a perivascular neutrophil and eosinophil mixed infiltrate is suggestive of AGEP. Leukocytoclastic vasculitis (LCV) and necrosis of keratinocytes may also be seen on histology. In comparison, characteristic histologic findings of acute pustular psoriasis include papillolaneanthosis, increased mitotic figures, and dilated blood vessels typically absent in AGEP.

While severe cutaneous adverse reactions to guaifenesin have not been previously documented in the literature, there are three well-documented cases of AGEP associated with exposure to pseudoephedrine, a sympathomimetic agent found in nasal decongestants such as guaifenesin 600 mg / pseudoephedrine 60 mg. Despite extensive use of pseudoephedrine, reported adverse reactions are rare.1

Conclusion

To our knowledge, this is the first reported case of AGEP secondary to guaifenesin 1200 mg extended-release bi-layer tablets. This case demonstrates the importance of recognizing guaifenesin as a possible offending agent in patients presenting with acute cutaneous eruptions characteristic of AGEP. It is critical for internists and emergency physicians to be aware of these potential offending agents in order to promptly recognize significant dermatologic reactions, elucidate the diagnosis of severe drug eruptions and initiate appropriate treatment measures.

References


Leser-Trélat Sign Presentation with Mediastinal Squamous Cell Carcinoma

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Abstract

The sign of Leser-Trélat is a rare dermatological manifestation of a paraneoplastic syndrome. It is characterized by an abrupt onset of numerous seborrheic keratoses in association with adenocarcinomas and lymphoproliferative disorders. Herein, we review a case of a 59-year-old female with the classic cutaneous presentation of the sign Leser-Trélat. Our patient's cutaneous expression coincided with a mediastinal squamous cell carcinoma.

Introduction

European surgeons Edmund Leser and Ulysse Trélat first independently associated internal malignancies with these skin lesions in 1890. In addition, Eugen Holländer first associated “verrucae seborrhoeicae,” with internal malignancy in 1901. Leser-Trélat sign is a rare dermatological manifestation of a paraneoplastic syndrome characterized by an abrupt onset of numerous seborrheic keratoses. Associated symptoms often include pruritus and velvety, lichenified skin characteristic of acanthosis nigricans. Typically, the sign of Leser-Trélat presents in the elderly, and it has been associated with adenocarcinoma as well as lymphoproliferative disorders. The adenocarcinoma most frequently originates from the colon, breast, or stomach. Although potentially paraneoplastic, the eruptive seborrhoeic keratoses in Leser-Trélat occur in malignancies of other organs and in non-malignant ailments. The validity of this dermatological phenomena has been challenged due to the fact that seborrhoeic keratoses and neoplasms are both common in the elderly population.

The exact pathogenesis of Leser-Trélat sign is unknown; however, it is theorized that it may be related to an overproduction of growth hormone, epidermal growth factor (EGF) and transforming growth factor alpha (α-TGF). The latter is not found in normal adult cells, but in fetal cells and transformed cell lines. Both EGF and α-TGF bind to the EGF receptor found in keratinocytes, especially in actively proliferating cells of the basal layer of normal epidermis. Normal EGF receptors are present mainly on basal keratinocytes and decrease as keratinocytes differentiate in the upper epidermal layers. However, acanthosis nigricans, seborrhoeic keratoses, and acrochordon contain a dense population of receptors in all layers of the epidermis except for the stratum corneum. The similarity in hyperactivity of these growth factors during cutaneous malignancies and cutaneous paraneoplastic syndromes could provide the link between the expression of Leser-Trélat sign and squamous cell carcinoma. In many reported cases, the removal of the malignancy greatly reduced the appearance of the Leser-Trélat sign.

Case Presentation

A 59-year-old Caucasian woman, Fitzpatrick type III, with history of mediastinal squamous cell carcinoma, Ehlers-Danlos syndrome, molar pregnancy, COPD, osteoarthritis, chronic fatigue and smoking, presented with several lesions of concern on her back and submammary region. The lesions were numerous, stuck-on plaques that were waxy brown to dark brown in coloration (Figures 1, 2). Dermoscopically, they presented with comedone-like openings, milia-like cysts, and bulbous projections. The lesions were first noted nine years prior and appeared rapidly, but the patient became concerned with a more recent development of plaques. The patient could not correlate the exact onset of her seborrhoeic keratoses with her malignancy, although she denied significant keratotic lesions prior to her diagnosis. The patient denied change in size and color but admitted to intermittent pruritus. In addition, she displayed generalized hair thinning and non-scarring alopecia of the scalp. On remaining physical exam, the patient appeared generally thin, with aphasia, but no palpable lymphadenopathy was appreciated.

Two lesions suspicious for atypical processes were biopsied, by shave removal, from the mid back and left submammary regions. The biopsy revealed findings characteristic of seborrhoeic keratoses. Several other lesions on the back and submammary region suspicious for irritated benign growths were treated with cryotherapy.

The patient initially sought medical assistance in September 2012 for aphasia. A CT of the neck and chest noted a hypodense 0.8 cm nodule in the lower left lobe of the thyroid and a 3.8 cm left anterosuperior mediastinal mass and adenopathy. Biopsies of both lesions determined that the thyroid nodule was benign; however, the mediastinal mass was consistent with squamous cell carcinoma (TxN2M0, stage IIIA). Mass effect caused aphasia secondary to left vocal cord paralysis resulting from recurrent laryngeal nerve involvement.

The mass was treated with stereotactic body radiation therapy (SBRT), and the patient underwent CyberKnife radiosurgery in five fractions. The patient was not offered chemoradiation therapy nor neoadjuvant chemotherapy. In May 2013, a PET scan showed the mediastinal mass had reduced to 2.5 cm in size.

The follow-up PET scan on November 2013 noted a hypermetabolic lesion in the region of the aortic arch on the mediastinal mass, with no change from prior imaging. In addition, the patient had an elevated CEA of 11.52 ng/ml. CT of the chest in February 2014 demonstrated a gradual increase of the mediastinal mass in the left mid lung zone that measured 3.5 cm x 2.5 cm. A stable subcentimetric nodular density along the lateral aspect of the left major fissure was noted, as well. No abnormal hilar or mediastinal adenopathy were noted, but it was subsequently determined that the malignancy was unresectable.

A CT-guided biopsy and Theros CancerType ID noted a persistent primary keratinizing squamous cell carcinoma of the lung, with necrosis and calcifications. Further evaluation included whole-body radiological imaging, and results showed no additional areas of focus or abnormality. The patient denied palliative chemotherapy and elected to be closely monitored.

Discussion

We report a case with a characteristic presentation of Leser-Trélat sign associated with mediastinal squamous cell carcinoma. Although our patient's case has an unusual origin, there are several cases of Leser-Trélat sign in the literature with similar features. Heaphy et al. presented a case of a 58-year-old woman who was not only similar in age to our patient but also experienced fatigue and had a smoking history. However, in their case, the Leser-Trélat sign was caused by adenocarcinoma of the lung, which is commonly associated with...
this cutaneous manifestation. The similarities in presentation support our conclusion that our patient’s dermatologic manifestation is the sign of Leser-Trélat. In both cases, the patients are not elderly, and therefore the onset of seborrheic keratosis and malignancy cannot be attributed to age alone. In addition, Mukherjee et al. described a case of squamous cell carcinoma of the lung with a paraneoplastic presentation. However, in that case, the paraneoplastic type was acanthosis nigricans.

The variation in ailments that present with eruptive seborrheic keratosis makes the criteria for Leser-Trélat sign a controversial topic in the medical community. Several studies have been conducted that analyze the ailments of patients who present with eruptive seborrheic keratosis and compare them with a control group. These case-control studies reveal no significant association of specific internal malignancies with eruptive seborrheic keratosis versus other ailments.

Conclusion
Although widely debated and disputed in multiple studies, there continues to be a large database of literature validating the sign of Leser-Trélat as a paraneoplastic syndrome. In order to gain a better understanding of this condition, it is essential to continue documenting all possible presentations. Regardless of cause, it is critical to be aware of the presentation of the sign of Leser-Trélat and its implication of malignancies, internal or cutaneous.

References
Locally Advanced Basal Cell Carcinoma with Subtle Skin Findings
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Disclosures: None
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Abstract
Osseous destruction of the cranium by basal cell carcinoma (BCC) is extremely rare. A case of a 73-year-old man with multiple recurrences of morpheaform BCC involving the right nasal ala is presented. Years after his last re-excision, he presented with a small erosion along the supra-alar crease. He additionally reported intermittent epistaxis and nasal congestion. He was subsequently found to have infiltration of the right orbital floor, hard palate, and anterior maxillary sinus by basal cell carcinoma. Due to the size and extent of infiltration of the tumor into the orbital floor and hard palate, the patient was considered a poor surgical candidate. He was placed on daily vismodegib, and follow-up CT scan has demonstrated a partial tumor response.

Introduction
While basal cell carcinoma (BCC) is the most common malignancy found in humans, with more than 2 million cases diagnosed each year in the United States, the disease remains localized in the great majority of cases.1 Locally advanced and metastatic disease is quite rare, with an incidence ranging from 0.18% to 3%.2 Complications of local disease include local tissue destruction, functional impairment, and cosmetic disfigurement.3

There are many risk factors contributing to the development of recurrent, locally advanced, or metastatic basal cell carcinoma. Anatomical locations with higher risk of recurrence include the eyelid, periorcular region, nose, lip, temple, ear, hands, feet, and genitalia.1 Increased recurrence rates are further observed when poorly defined borders are present, in tumors larger than 2 cm in diameter, in tumors with aggressive histologic patterns (morpheaform, micronodular, metatypical, basosquamous), in tumors with perineural involvement, and in patients with prior history of recurrent BCC.3

Very few cases of osseous destruction of the cranium by advanced basal cell carcinoma have been reported. The incidence is estimated to be approximately 0.03%.4 The majority of reported cases involve longstanding lesions on the scalp or face. Presenting symptoms vary depending on the location and extent of infiltration. In one case, the patient presented with cerebrospinal fluid otorrhea, facial nerve palsy, and trigeminal nerve impairment secondary to destruction of the petrous bone by recurrent auricular BCC.5 The primary tumor had been excised three years prior, and there were no signs of recurrent disease on the skin surface at the time of presentation. Here we present an additional case of basal cell carcinoma with extensive bony infiltration but very subtle skin findings.

Case Report
A 73-year-old Caucasian male presented for evaluation of a 4 mm, non-healing erosion at the site of a prior excision. He had an extensive history of recurrent basal cell carcinoma involving the superior aspect of the right nasolabial fold. This was initially resected with frozen sections in 1998. The surgical defect was closed with an advancement flap. In July 2003, he presented with a large recurrence, which was resected. Two subsequent re-excisions (August 2003 and October 2003) were necessary due to positive margins and were again performed with frozen sections. His nose was then reconstructed with a paramedian forehead flap and right auricular cartilage graft.

In addition to the non-healing area involving the right supra-alar crease, the patient also admitted to intermittent bleeding from the right naris. He denied facial numbness, paresthesia, weakness, change in vision, or epiphora.

Physical exam demonstrated a well-healed forehead flap donor scar along the left paramedian forehead. Due to the extensive past excisions, most of the right nasal ala was gone. The right soft tissue triangle and most of the right nasal sidewall were replaced by a flap (Figure 1). A superficial, 3 mm x 4 mm erosion was noted in the supra-alar crease. There was no obvious recurrent cancer externally either on the nose or on the paranasal cheek. A 3 mm punch biopsy was performed. Pathology demonstrated morpheaform BCC extending to the margins.

The patient was evaluated by Otolaryngology for further delineation of the epistaxis. On anterior rhinoscopy, the right nasal cavity was significantly narrowed and obstructed by amorphous masses of yellowish, irregular granulation tissue. The patient was subsequently sent for a CT scan, which demonstrated an irregular, infiltrating, enhancing mass along the right side of the face, centered along the right nasal soft tissues and nasal ala. The mass extended from just below the frontal sinus, at the level of the upper orbits, and crossed the midline, involving the anterior olfactory recesses and the right nasolacrimal duct. Significant osseous destruction was identified, including the orbital floor, hard palate, and anterior maxillary sinus. The first four maxillary teeth were encompassed by soft tissue. Overall, the mass measured approximately 7 cm craniocaudally x 4.4 cm transversely x 3.8 cm anterior-posterior (Figures 2-4).

A multi-disciplinary conference was held, including specialists from dermatology, otolaryngology, oncology, pathology, radiology, and dentistry. Due to the size and infiltration of the tumor into the orbital floor and hard palate, the patient was considered a poor surgical candidate. After a discussion with the patient, he was placed on vismodegib 150 mg daily. His treatment course was complicated by non-compliance. Over the course of six months, he took 103 doses. He reported muscle spasms, a 30-pound weight loss, dysgeusia, fatigue, hair loss, and diarrhea. A repeat CT scan was performed and demonstrated a modest tumor response to treatment. This study showed that the tumor was approximately 6.2 cm craniocaudally x 2.5 cm transversely x 1.4 cm anterior-posterior (Figures 5, 6). For the time being, the patient is continuing vismodegib in hopes that the tumor will continue to shrink. In the future, surgery may become a treatment option.

Discussion
Treatment of locally advanced and metastatic basal cell carcinoma is managed on a case-by-case basis. Standard therapy does not exist due to the rarity of cases and the variations in presentation. Treatment...
is mostly individualized, depending on the patient’s co-morbidities, anatomical location of the lesion, extent of infiltration, previous treatment history, and patient preference. For advanced localized disease, surgical excision followed by radiation therapy is commonly performed if the lesion is amenable and there are no contraindications. A patient may not be a surgical candidate for a number of reasons including co-morbidities, inoperable disease, substantial anticipated disfigurement, or a low likelihood of surgical cure due to history of multiple recurrences. Inhibitors of the hedgehog signaling pathway, including vismodegib, offer an alternative treatment in metastatic or unresectable BCC.

In the majority of basal cell carcinomas, both sporadic and those arising in Gorlin’s syndrome, alterations in the hedgehog signaling pathway have been identified. Most commonly, a loss of function mutation in patched homologue 1 (PTCH1) leads to unopposed activity of smoothened homologue (SMO). Smoothened signal transduction leads to activation and nuclear translocation of GLI transcription factors and induction of genes involved in cell proliferation, survival, and differentiation. In approximately 10% of basal cell carcinomas, there is an activating mutation in SMO that results in constitutional activation.

Vismodegib is a small-molecule inhibitor of smoothened. In 2012, it was approved by the Food and Drug Administration (FDA) for the treatment of metastatic or locally advanced BCC. Phase 1 studies from 2009 showed an objective response to treatment in 18 out of 33 patients; two had a complete response, and 16 had a partial response. This study combined data from 15 patients with locally advanced disease and 18 patients with metastatic BCC. In the phase 2 study (ERIVANCE BCC), 27 of 63 patients with locally advanced disease responded to vismodegib, with 13 patients having a complete response. The Safety Events in Vismodegib (STEVIE) trial, a large, ongoing, multicenter, open-label study, is monitoring the safety and efficacy of 150 mg vismodegib daily in patients with locally advanced or metastatic BCC. While this study is not yet complete, interim analysis of 499 patients was performed. Of the patients with locally advanced disease, 66.7% responded to the drug; Of 453 patients, 153 had complete responses, and 149 had partial responses. Partial response was defined as at least a 30% decrease in the sum diameters of target lesions. In those who did respond, the median time to best response was 2.6 months.

The optimal duration of treatment with vismodegib has not been defined. Studies have typically continued patients on vismodegib until they experienced intolerable side effects, progression of disease, complete cure, or the end of the study. In the interim analysis from the STEVIE trial, 80% of patients had discontinued treatment at clinical cutoff. The median duration of treatment was 36.4 weeks. The reasons for cessation included: adverse events (36%), progressive disease (14%), patient request to stop treatment (10%), investigator request, and death.

Drug intolerance can potentially present an obstacle in treatment of advanced basal cell carcinoma. Ninety-eight percent of patients from the STEVIE interim analysis experienced an adverse event. The most commonly reported side effects included muscle spasms, alopecia, dysgeusia, weight loss, asthenia, decreased appetite, ageusia, alopecia, nausea, and fatigue. Most of the adverse events were grade 1 or 2. Pretreatment counseling regarding possible medication side effects is essential.

For patients who are refractory to vismodegib or develop resistance, few treatment options exist. Sonidegib, another smoothened inhibitor, was approved by the FDA in 2015 for locally advanced BCC recurring after surgery or radiation therapy, and for patients who are poor candidates for surgery or radiation therapy. The BOLT study, a phase 2 trial of 230 patients with locally advanced BCC, found an objective response rate in approximately 35% of participants. The side effect profile is similar to that of vismodegib. A recent study was undertaken using sonidegib 800 mg daily in nine patients with advanced BCC previously resistant to treatment with vismodegib. The study did not find better outcomes with sonidegib. Of the nine patients, five experienced progressive disease, three remained stable, and one was not able to be evaluated. In the future, therapies with targets in the hedgehog pathway downstream of SMO may prove more beneficial for refractory or resistant cases.

**Conclusion**

Advanced basal cell carcinoma with intracranial invasion is rare. Once the tumor has infiltrated and destroyed the facial bones, treatment becomes extremely challenging. This case highlights the importance of closely monitoring patients who have a history of multiple recurrences, especially in high risk anatomic locations or with more aggressive histologic subtype. A detailed review of systems should be elicited at each follow-up visit. Based on the history and physical exam, imaging studies may be warranted to rule out progressive disease. Hedgehog pathway inhibitors should be considered in patients with unresectable disease.
References


Oculocutaneous Albinism, A Family Matter

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Abstract

Oculocutaneous albinism (OCA) is a group of autosomal-recessive conditions characterized by mutations in melanin biosynthesis with resultant absence or reduction of melanin in the melanosomes. Herein, we present a rare case of two Caucasian sisters diagnosed with oculocutaneous albinism type 1 (OCA1). On physical exam, the sisters had nominal cutaneous evidence of OCA. This case highlights the difficulty of diagnosing oculocutaneous albinism in Caucasians. Additionally, we emphasize the uncommon underlying genetic mutations observed in individuals with oculocutaneous albinism.

Introduction

Oculocutaneous albinism (OCA) is a group of autosomal-recessive conditions characterized by mutations in melanin biosynthesis with resultant absence or reduction of melanin in the melanosomes. Melanin-poor, pigment-poor melanocytes phenotypically present as hypopigmentation of the hair, skin, and eyes.1,2

There are four genes responsible for the four principal types of OCA. OCA type 1A (OCA1A) and OCA type 1B (OCA1B) are caused by a mutation in the tyrosinase gene (TYR) on chromosome 11q14.3.3,4 OCA type 2 is caused by a mutation in the OCA2 gene.2,3 OCA type 3 is caused by a mutation in the tyrosinase-related protein 1 gene (TYRP1), and OCA type 4 is caused by a mutation in SLC45A2 (a.k.a. MATP).5,6 OCA1A is considered the most severe type of OCA due to a complete absence of melanin production. OCA1B, OCA2, OCA3 and OCA4 are considered less severe, as they often show small amounts of pigment accumulation over time.4 Overall, there is significant clinical overlap between the variants of OCA. Thus, molecular diagnosis is often necessary to establish the specific OCA subtype. The clinical characteristics found in individuals afflicted with OCA type 1 include hypopigmentation of the skin and hair and the distinctive ocular changes characteristic of all forms of albinism.4 Decreased melanin production does not alter the development of skin, but it does alter the color. The absence of melanin in the eye, on the other hand, leads to anomalous development and function.2 The ocular changes associated with OCA include severe nystagmus, prominent photophobia, reduced pigmentation of the retinal epithelium and reduced visual acuity.2 A pathognomonic finding of albinism is misrouting of the optic nerve at the optic chiasm, resulting in strabismus and reduced stereoscopic vision.1,4 Mutations in the TYR gene may entirely abolish tyrosinase activity, resulting in OCA1A, or decrease the activity of the tyrosinase enzyme, resulting in the development of OCA1B. Clinically, the difference between OCA1A and OCA1B is seen over time, as OCA1B individuals often accumulate minor quantities of melanin and begin to display small amounts of pigmentation.2

Ultimately, OCA is considered a clinical diagnosis. The diagnosis is made if the individual has hypopigmentation of the skin or hair in conjunction with the aforementioned characteristic ocular signs. Molecular genetic testing is often used in combination with the clinical diagnosis to establish the specific genetic mutation and thus the OCA subtype.2 Approximately one out of every 17,000 people has one of the four types of albinism.5,6 We present a rare case of sisters diagnosed with oculocutaneous albinism type 1, emphasizing the uncommon genetic mutations we observed in these two individuals.

Case Report

Two Caucasian sisters were referred to our dermatology clinic after receiving a diagnosis of oculocutaneous albinism type 1. Patient A was a 2-year-old Caucasian female, and Patient B was a 5-year-old Caucasian female. On physical exam, the sisters had nominal cutaneous evidence of OCA (Figures 1, 2). Patients A and B were diagnosed with OCA after a retinal specialist recommended genetic testing to identify the cause of the sisters' underlying optical impediments. The mother initially identified optical difficulties in her younger daughter, patient A, around 8 weeks of age. She noticed the infant displaying nystagmus and an inability to track. At seven months, patient A began crawling, and it quickly became evident the infant could not see more than a few feet in front of her. The mother became increasingly concerned when, at one year of age, her daughter had difficulty seeing beyond 20 feet (6 m). At that time, the child was evaluated by an ophthalmologist, who told the mother nothing was structurally wrong. The mother insisted on further workup. The mother's primary clue to the underlying abnormality was her older daughter, patient B, who did not display these apparent optical difficulties. Patient A was referred to a neuro-ophthalmologist at the University of Michigan. An electroretinogram (ERG) and magnetic resonance imaging (MRI) were conducted for the initial ruling out of Leber congenital amaurosis (LCA). The MRI displayed no abnormalities. The ERG identified normal cones but decreased rods. Patient A was referred to a retinal specialist, who recommended genetic testing.

Both children underwent molecular analysis for underlying genetic anomalies. The genetic testing was performed using PCR amplification and DNA sequencing in two directions. Quantitative PCR analysis was performed using the ABI TaqMan copy number assay and Copy Caller software. qPCR primers for the OCA1 gene were used for amplification and detection, namely Hs03778472_cn (intron 4), whereas RNAse P was used as the reference.

Patient A was found to possess a heterozygous mutation and a heterozygous deletion in the OCA1 gene, namely c.1217C>T, and deletion of exon 4. Additionally, patient A was found to possess the c.21delC frameshift mutation in the C10orf11 gene. Patient B was found to possess the same heterozygous mutation and deletion in the
OCA1 gene, but she did not possess the c.21delC frameshift mutation in the C10orf11 gene. Both girls were found to have clinical and molecular findings consistent with OCA1. Both mother and father underwent molecular genetic testing. The mother was found to possess the c.1217C>T mutation and the father the deletion of exon 4.

To date, both patients are doing well and being monitored with close follow-up.

**Discussion**

To date, 12 genetic mutations have been identified in the development of albinism. OCA type 1 is caused by a mutation in the tyrosinase gene (TYR) on chromosome 11q14.3. The TYR gene consists of 529 amino acids and five exons that span 65 kb of genomic DNA. The gene encodes tyrosinase, an enzyme that catalyzes the first two steps in the melanin biosynthesis pathway. Tyrosinase converts tyrosine to L-dihydroxyphenylalanine (DOPA) and then to dopaquinone. The TYR gene mutation causes a complete or partial loss of the catalytic activity of tyrosinase.

The current case emphasizes a rare molecular presentation of OCA type 1, increasing awareness of the condition's varied clinical manifestations. Current literature on albinism suggests 90% of OCA1A patients have two mutations. Among OCA1B patients, 37% have two mutations, and 63% have only one. In both forms, less than 1% of patients have an exonic or whole-gene deletion identified after molecular review. Both of our patients possessed a deletion of exon 4. Additionally, patient A had a distinctive mutation in the C10orf11 gene. A mutation in the gene C10orf11 on chromosome 1q22.2-q23.1 is associated with a new form of OCA, known as OCA7. However, the specific structural and functional behaviors of C10orf11 remain an enigma. The C10orf11 gene encodes a protein containing three leucine-rich repeats (LRRs) that have a variety of functions including cell adhesion, extracellular matrix assembly, neuronal development and RNA processing. The C10orf11 mutation was observed in patient A but is not sufficient for the diagnosis of albinism. It is currently unknown what effect, if any, this mutation will have on patient A's clinical symptoms. It is our hope that case reports like this will inspire continued research to identify the relationships between genetic and phenotypic variations in the development of OCA. Identifying the significance of unique genetic mutations causing OCA will be vital to the development of personalized medicine for patients with albinism.

An essential component of medical management for these individuals involves genetic counseling. As in all types of autosomal-recessive inheritance, these sisters will pass on one non-working copy of the OCA1 gene to all of their offspring. At minimum, their children will be carriers of the condition. Additional patient education and future partner genetic counseling should be encouraged. The optimal time to determine genetic risk and clarification of carrier status is before pregnancy occurs. This case highlights the value of a dermatology consultation in young patients with clinical features of hypopigmentation and/or ocular findings. As in this case, the initial diagnosis of oculocutaneous albinism was delayed until confirmed by an ophthalmologist aware of the spectrum of its clinical features. Delays can result in years of unprotected solar exposure in individuals at greater risk for the harmful effects of UV radiation. Patients with OCA type 1, due to a pigment reduction in hair and skin, often develop solar keratosis, basal cell carcinoma and squamous cell carcinoma. Additionally, and arguably most commonly, these patients may develop numerous actinic keratoses, predisposing them to squamous cell carcinoma. Morbidity is influenced by phenotype, education and resource availability. Dermatologic consultation is essential, as patients (and in juvenile cases, their parents) must be made aware of the importance of sun-protection in patients with OCA1. Extensive solar exposure without protection results in a cumulative increase in the risk of cutaneous neoplasms. Five to 10 minutes of sun exposure in individuals with OCA1 is considered substantial.

It is also important to emphasize that while melanoma is rare in individuals with OCA, it does occur. In one case, a patient with OCA was found to have malignant amelanotic melanoma that developed from an intradermal nevus.

Patients with OCA need to be screened regularly for changes to their skin. Ongoing surveillance is imperative, particularly in those whose visual impairments make it difficult to appropriately assess and monitor their own skin. Finally, patients and families should be assured that persons with OCA have normal intelligence, fertility and, with proper skin protection, natural lifespans.

**Conclusion**

As with any genetic condition, a patient's morbidity and mortality can be vastly improved with identification, education and support. In this case report, we showcase a rare genetic mutation observed in individuals with oculocutaneous albinism, aiming to provide additional information on an uncommon clinical entity to assist with early diagnosis and management.

**References**

Porphyria Cutanea Tarda: A Case Presentation and Discussion

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Abstract

The porphyrias are metabolic disorders caused by altered activity of enzymes in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common subtype, with a prevalence of about 1 in 10,000 people, and is due to deficient activity of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme biosynthetic pathway. Cutaneous findings are common and include photosensitivity, bullae, skin fragility, erosions, scarring, and milia in sun-exposed areas. The cause of PCT may be multifactorial, related to genetic and environmental factors. Generally, there is a strong association with liver disease, and one should consider possible triggers including but not limited to alcohol abuse, iron overload including possible hereditary hemochromatosis, hepatitis C virus infection, and estrogen use.

The diagnosis can be made through screening of serum, urine, and fecal porphyrin levels. We present a case of a 57-year-old female with PCT and secondary hemochromatosis.

Introduction

Porphyria cutanea tarda (PCT) is a complex and multifactorial disease. PCT results from subnormal activity of uroporphyrinogen decarboxylase (UROD) in the liver, with subsequent decreased conversion of uroporphyrinogen to coproporphyrinogen in the heme biosynthetic pathway (Figure 1). Uroporphyrin, the oxidized form of uroporphyrinogen, circulates in plasma, accumulates in various organs including the skin, and is excreted in urine. Due to uroporphyrin's fluorescent properties and ability to form free radicals, it results in a delayed photodermatitis (PCT). Porphyria cutanea tarda is the most common porphyria, presenting with various cutaneous findings including painful blistering, atrophic scars, hypertrichosis, hyperpigmented macules, and milia in sun-exposed areas. Since it was first described by Waldenstrom in 1937, there has been increasing interest in the relationship between PCT, iron overload, UROD activity, and the possible link to hereditary hemochromatosis.

Case Report

A 57-year-old white female presented to our outpatient dermatology clinic with complaints of blisters and bumps on her hands for three months’ duration. She stated the lesions would start out as little blisters that would easily break open, leave her with painful sores, and heal with “little white, pimple-like” bumps. The patient reported she had not developed any new blisters for a few weeks. She didn’t recall any inciting triggers and denied any other affected areas. She reported starting nabumetone a few months earlier for arthritis but admitted taking it only as needed. She denied any other medications. Past medical and family histories were unremarkable. She reported a long history of alcohol consumption, consuming five to six “shots” of whisky a night for 15 years.

Two weeks prior to our visit, she had previously been seen by a nurse practitioner who diagnosed her with dyshidrotic eczema. She was given an intramuscular corticosteroid injection, which she reported did not help.

On physical exam, there were multiple hyperpigmented macules, with areas of shallow scarring and multiple milia on her bilateral dorsal hands (Figures 2, 3). No onycholysis was noted. Her skin appeared bronze in nature, but she denied using tanning beds, and she reported having the darkest skin in her family. Examination of her face revealed noticeable hypertrichosis (Figure 4). The rest of her physical exam was unremarkable.

Given the lack of new bullae, no biopsy was performed, and she agreed to return for a biopsy if a new one arose. Based on history and clinical presentation, her case seemed most consistent with pseudoporphyria or porphyria cutanea tarda (PCT). She was instructed to hold her nabumetone, avoid other NSAIDS, and start decreasing her alcohol intake and sun exposure.

Laboratory workup, including a CBC, complete metabolic profile, iron studies, hepatitis B/C, HIV screen, HbA1C, CRP, and ANA, was unremarkable except for mildly elevated AST/ALT in a 2:1 ratio and a significantly elevated ferritin at 637 ng/ml (reference interval 15 ng/ml to 115 ng/ml). A urinary porphyrin screen was performed, which showed considerably elevated uroporphyrins (uroporphyrin 1 – 794.0 mcg [normal 4.1 mcg...
decarboxylase (UROD) enzyme, the fifth enzyme in the heme biosynthesis pathway leading to the formation of porphyrins. The overproduction of porphyrins by sun exposure leads to the creation of reactive species such as singlet oxygen and free radicals that cause tissue damage.

Porphyria cutanea tarda (PCT) is the most common type of heritable porphyria, accounting for 75% to 80% of PCT cases. Type II is familial. Familial PCT is inherited autosomal-dominantly and accounts for 15% to 20% of PCT cases. UROD enzymatic activity is reduced by at least 50% in both the liver and erythrocytes. Multiple mutations have been found that produce the same phenotype. A familial PCT usually presents in a clinically similar manner to sporadic PCT, but usually earlier in life, and is precipitated by similar factors (e.g., alcohol, estrogen). Co-inheritance of UROD and HFE mutations can cause accelerated presentation of PCT. A type III PCT has been observed in which a combination of UROD and HFE mutations together cause the disease.

Type II is familial. Familial PCT is inherited autosomal-dominantly and accounts for 15% to 20% of PCT cases. UROD enzymatic activity is reduced by at least 50% in both the liver and erythrocytes. Multiple mutations have been found that produce the same phenotype. A familial PCT usually presents in a clinically similar manner to sporadic PCT, but usually earlier in life, and is precipitated by similar factors (e.g., alcohol, estrogen). Co-inheritance of UROD and HFE mutations can cause accelerated presentation of PCT. A type III PCT has been observed in which a combination of UROD and HFE mutations together cause the disease.

Elevated estrogen levels have been found in many PCT patients, with one study finding up to 66% of female PCT patients using exogenous estrogen. Oral contraceptives, postmenopausal hormone replacement, and tamoxifen are common precipitating factors for PCT in women. Infrequently, PCT has also been stimulated by pregnancy and childbirth. A possible mechanism by which estrogen might cause PCT is via increased estrogen quinone formation leading to increased free-radical production. Hepatic iron overload is found in nearly all patients with PCT, but the mechanism is somewhat unclear. Iron may increase production of peroxides and free radicals, leading to oxidation of uroporphyrinogen in the cell, liver damage, inhibition of UROD or enzyme modification. Most patients with iron overload have HFE gene mutations, and HFE mutations are found more commonly in PCT patients than in the general population, so gene testing should be considered if clinical suspicion is high. The two most common types of mutations are C282Y and H63D. Heterozygous C282Y causes iron overload in an estimated 50% of patients. HFE mutations are a common precipitating factor for PCT, most patients with hemochromatosis never develop the disease.

Hepatitis C and HIV infection have both been found to precipitate PCT. HCV is a very common precipitating factor. Two possible mechanisms by which HCV causes PCT are its triggering of increases in free hepaticatolipid iron and free radical oxidation due to increased oxidative stress. HIV can play an independent role in the development of PCT, but it is often found with HCV coinfection. The mechanisms by which HIV produces PCT are altered porphyrins, direct hepatic damage, impaired cytochrome oxidase, and increased iron levels. PCT has been associated with many other conditions such as diabetes mellitus, dialysis-dependent chronic renal failure, and discoid porphyria cutanea tarda as a case presentation and discussion.
lupus erythematosus, myeloproliferative diseases, lymphoproliferative diseases, and hepatic disease.\textsuperscript{6,19} Clinical presentation usually provides strong evidence to suspect PCT, and a variety of studies help improve diagnostic accuracy. Total plasma or urine porphyrin is the initial exam to confirm porphyria. A 24-hour urine specimen with fractionation reveals elevated uroporphyrins and a uroporphyrin-to-coproporphyrin ratio of 3:1 to 5:1, which distinguishes PCT from other cutaneous porphyrias, including pseudoporphoria, which would have normal urinary porphyrins.\textsuperscript{3,20} Urinary delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels also aid in differentiating between porphyrias.\textsuperscript{21} PCT has normal urinary ALA and PBG levels. In office, the urine sample examined under Wood’s light will fluoresce pink or coral-red.\textsuperscript{4} Normal erythrocyte total porphyrins help distinguish PCT from hepatocellular porphyria (HEP), which has markedly elevated erythrocyte porphyrins.\textsuperscript{20} Decreased measured erythrocyte UROD activity points to familial PCT, as sporadic PCT has normal erythrocyte UROD activity.\textsuperscript{3} A detailed history will help reveal some possible precipitating factors such as alcohol consumption, oral estrogen use, or smoking. Liver studies, including serum bilirubin, prothrombin time, and hepatic enzymes, should be performed. Complete blood count, metabolic panel with creatinine, and iron studies with an emphasis on serum ferritin levels will help in management. HFE genetic testing looking specifically at C282Y and H63D mutations should be used for hemochromatosis diagnosis.\textsuperscript{2,5,12} UROD mutation testing improves diagnostic accuracy for PCT type. Viral serology will help find the possible precipitating presence of HCV or HIV infection.\textsuperscript{2,16,22} Histopathology of PCT reveals a subepidermal bulla with little to no inflammatory infiltrate and an undulating, festooning dermal papilla projecting into the bulla.\textsuperscript{3,4,23} Thickened blood-vessel walls in the dermis occur due to deposition of PAS-positive material.\textsuperscript{4,23} Caterpillar bodies, a common, but not diagnostic, characteristic of PCT consist of PAS-positive cosinophilic, elongated, wavy structures usually found in the epidermis above the bulla.\textsuperscript{4,6,23} Direct immunofluorescence shows IgG, IgM, fibrinogen, and complement (C3) in the basement membrane and around vessels of the upper dermis.\textsuperscript{3,4,6,23} Management of PCT begins with avoidance of all possible precipitating factors like alcohol and estrogen.\textsuperscript{2,24} Physical barriers and sun protection, such as clothing and sunscreens containing zinc oxide, and avoiding skin trauma protect against worsening skin disease. This initial approach may be sufficient to treat PCT.

Phlebotomy is the preferred treatment for PCT. Phlebotomy of 450 mL (one unit) at two-week intervals is performed until serum ferritin falls below 25 ng/mL, or until hemoglobin falls below a preset point, to prevent anemia.\textsuperscript{2,25} Clinical improvement may take several months. Skin fragility and bullous formation will be the first clinical symptoms to improve. More chronic symptoms such as hypertrichosis and sclerosis will improve at a slower rate.\textsuperscript{26} Antimalarial medications (chloroquine and hydroxychloroquine) can be used as an alternative to phlebotomy. Low-dose treatment with hydroxychloroquine (100 mg) or chloroquine (125 mg) given twice a week has shown similar results as phlebotomy.\textsuperscript{27} While treating with antimalarials, monitor urine and plasma porphyrin levels.\textsuperscript{2,4,6,16} Therapy is discontinued when porphyrin levels are normal. Treat underlying HCV and/or HIV infection if found to be present.\textsuperscript{18} Iron chelation can be used if other treatments are contraindicated, but is not as effective as phlebotomy or antimalarials.

**Conclusion**

Porphyria cutanea tarda should be suspected in patients with bullae and increased skin fragility in sun-exposed areas. The diagnosis can be confirmed biochemically by characteristically elevated uroporphyrins and coproporphyrins in the urine. Given the diagnosis of PCT, investigations may include, but are not limited to, liver function tests, iron studies, HCV and HIV serology, alcohol intake, and current medication review. With the possible association of hereditary hemochromatosis, one may consider gene screening if PCT is clinically suspected. The patient should continue to be monitored closely, both clinically and biochemically, to ensure response to treatment and monitor for possible relapse. Of the various treatment options available, the preferred modality is phlebotomy combined with avoidance of sunlight and other precipitating factors.
References


Abstract

We present a case of a pre-adolescent female with neurofibromatosis type 1 (NF1) who developed squamous cell carcinoma (SCC) on the dorsum of the nose. This rare presentation has been reported in the literature only twice, and both instances involved adult patients. SCC itself is very rare in children and is usually seen in those with a predisposing condition like immunosuppression, radiation exposure or genodermatoses, none of which our patient had. We also discuss the possible pathogenesis of epithelial tumor development in patients with NF1, a historically non-epithelial tumor-producing disorder.

Introduction

Neurofibromatosis type 1 is an autosomal-dominant genetic disorder characterized by the presence of café-au-lait macules (CALMs), neurofibromas, nerve sheath tumors, Lisch nodules and freckling in the axillary or inguinal region. Almost every organ system in the body can be affected by renal dysfunction, from essential hypertension and learning difficulties to scoliosis. Skin manifestations like CALMs and plexiform neurofibromas will usually appear congenitally or within the first year of life, whereas other skin findings, like simple neurofibromas, appear later in childhood. Generally, all criteria for diagnosis of NF1 are met in 97% of patients by age 8 and in 100% of patients by age 20. Patients are at increased risk of developing a number of different central nervous and non-epithelial neoplasms. It is very rare for patients with NF1 to develop cutaneous squamous cell carcinoma.

Case Report

An 11-year-old female with a past medical history of NF1 and positive family history of NF1, including mother and sibling, presented to the dermatology clinic for evaluation of a lesion on the dorsum of the nose that was present for the past six months. There was no bleeding, pain or change in size. She denied similar lesions elsewhere. On physical examination, the patient had a smooth, pink papule measuring 7 mm in diameter on the dorsum of the nose. The patient is being followed by Ophthalmology, Neurology and Dermatology, and she has been offered genetic counseling for her underlying NF1. We recommended yearly follow-up for full skin exams to monitor for further skin cancer development.

Discussion

NF1 is an autosomal-dominant genetic disorder resulting from mutations in the NF1 gene at chromosome 17q11.2. Tumors in NF1 are predominantly derived from connective tissue, and neurofibromas are the most common type of benign tumor in these patients. Patients with NF1 are at increased risk of developing non-epithelial tumors including optic gliomas, astrocytomas and malignant peripheral nerve sheath sarcomas.

The NF1 gene codes for neurofibromin, a protein that acts as a GTPase-activating protein. This leads to negative regulation of Ras-mitogen-activated protein kinase, which is involved in cell survival and proliferation. Neurofibromin acts as a tumor suppressor by hastening the transition from GTP to GDP, causing Ras to be nonfunctional. With Ras nonfunctional, tumor formation does not occur.

While evidence linking NF1 to epithelial tumors is scant, there have been some studies investigating a possible role for the gene in their carcinogenesis. It is known that neurofibromin can be found in normal human epidermis. A Finland study by Hermonen et al. used reverse transcriptase PCR, immunohistochemistry, and molecular hybridizations to characterize the expression of NF within keratinocytes. They found evidence supporting its involvement in epidermal tumors like basal cell carcinoma and squamous cell carcinoma. Another study in mice by Atit et al. showed further evidence for NF1's role in epithelial carcinogenesis. They studied mice who were heterogeneous for null mutations in NF1 and exposed them to known carcinogens. Heterogeneous mice developed papillomatous growths as well as sustained increases in keratinocyte proliferation, while wild types with the same exposure did not. In addition, all mice with papillomas were shown to have activation of Ras, a crucial step in the process of carcinogenesis, supporting its involvement in epidermal tumors.

There are very few reported cases of epithelial tumors, specifically cutaneous squamous cell carcinoma (SCC), in patients with NF1. Ishida and Okabe reported a case of SCC of the forehead in an 80-year-old female patient with a history of NF1. Friedrich et al. reported a case of SCC arising on the sole of the foot in a 67-year-old male patient with NF1. Squamous cell carcinoma is the second most common cutaneous malignancy in adults. Classically, it occurs in older adults on chronically sun-exposed areas as well as in those with radiation exposure, chronic wounds, arsenic exposure and immunodeficiency. Children rarely develop any cutaneous cancers, with an incidence of 1.4 per
1,000 patients. One study by a large pediatric hospital showed that out of about 36,000 dermatology patients, 53 cutaneous malignancies were diagnosed. Of that number, 6% were squamous cell cancer. In children, cutaneous malignancies are mainly seen in association with underlying skin conditions like albinism, xeroderma pigmentosum, nevus sebaceous, and Gorlin syndrome, although all of the classic predisposing factors can come into play. According to one article, pediatric squamous cell cancer of all types appears to have increased in prevalence over the past two decades. They believe it to be caused by multiple factors, including recurrence of SCC after radiation treatments years later and increased HPV infection prevalence.

Cutaneous malignancy should be considered early on in any child with predisposing factors and atypical presentation. It is important to use a dermatopathologist comfortable with diagnosing pediatric lesions. Clinicians may also consider performing a second, wider biopsy, so as not to miss or delay diagnosis. Treatment of these lesions is recommended, and full excision is warranted, as squamous cell cancers in children have poor prognoses.

Conclusion
This is the third reported case of cutaneous SCC in a patient with NF1, and the first reported case in a pre-adolescent patient. To our knowledge, this is also the first documented case of SCC of the nose diagnosed in a patient with NF1. Due to the rarity of the condition, there are no clear guidelines for management of pediatric squamous cell cancer; with its increasing incidence, this issue may be addressed in the future. Our case, along with prior studies, suggest a potential increase in risk for developing epithelial tumors in patients with NF1, warranting further study. With this knowledge, clinicians can be more informed about all the risks pertaining to NF1 and consider SCC when they come across any abnormal lesions in predisposed individuals.

References
Sclerotic-Type Chronic Graft-Versus-Host Disease: A Case Presentation and Discussion

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Abstract
Background: Hematopoietic stem cell transplants (HSCT) are becoming more common; therefore, graft-versus-host disease (GVHD) is becoming a more prevalent dermatologic condition. Objective: To educate current dermatologists on the most current recommendations for chronic GVHD (cGVHD), specifically sclerotic-type chronic GVHD (ScGVHD). Methods: A patient with ScGVHD is presented. A literature review was performed for ScGVHD. Results: A discussion is provided on the presentation, treatment, and management of ScGVHD. Limitations: This is a case report of one patient. The mechanism of action of ScGVHD is not well-known, and there are no FDA-approved therapies with indications for cGVHD. Conclusion: Due to the increased morbidity and mortality of ScGVHD patients, research on the mechanism of action and optimization of currently used therapies is imperative.

Introduction
Hematopoietic stem cell transplants (HSCT) are becoming more common for treatment of multiple medical conditions. One of the most common complications of HSCT is graft-versus-host disease (GVHD). GVHD is distinguished as either acute or chronic, and both types frequently affect the skin. Due to the increased prevalence of GVHD patients, dermatologists need to be aware of the multiple presentations and the current recommendations for treatment and management. This case presentation and discussion focus on chronic GVHD (cGVHD), specifically sclerotic-type chronic GVHD (ScGVHD), and the difficulties of its treatment and management.

Case Presentation
A 61-year-old male presented with a past medical history of multiple myeloma, status post autologous stem cell transplant with subsequent allogeneic sibling peripheral stem cell transplant. One year later, the patient was diagnosed with acute graft-versus-host disease (aGVHD) of the esophagus and small and large intestines. Two years after the aGVHD, the patient presented with symmetrical diffuse, bound down, woody plaques with hypopigmentation and alopecia of the upper and lower extremities (Figure 1). Involving the bilateral anterior lower legs were multiple pink-colored papules (Figure 2). On the plantar surface of the left foot, there were punched-out ulcerations with yellow adherent film (Figure 3). There was decreased capillary refill of the fingers and toes. Wrist dorsiflexion was 15 degrees, and hand grasp was 75 percent of normal. Pathology revealed mild epidermal changes, thickening of dermal collagen bundles, and dermal fibrosis extending into the subcutis resulting in septal hyalinization (Figure 4). These findings were consistent with sclerotic-type chronic graft-versus-host disease.

The patient has been treated aggressively by Oncology with multiple immunosuppressive therapies, including topical ointments (tacrolimus and triamcinolone), oral corticosteroids, imatinib, cyclosporine, sirolimus, narrow-band UVB phototherapy, extracorporeal photopheresis, intravenous immunoglobulin (IVIG), and rituximab infusions. Long-term oral corticosteroids and cyclosporine usage resulted in adrenal insufficiency and hypertension, respectively. The patient is currently receiving rituximab infusions. In addition, the patient follows a strict exercise and stretching regimen to maintain his upper and lower extremity range of motion, uses compression stockings to assist with his chronic lymphedema, and receives wound care for his chronic plantar wounds.

Discussion
In 1968, the first successful allogeneic bone marrow transplant was performed. There are now approximately 25,000 allogeneic hematopoietic stem cell transplants (HSCT) performed worldwide each year.1 One of the most severe sequela of HSCT is graft-versus-host disease, specifically chronic GVHD, which occurs in 30 percent to 70 percent of HSCT patients.2 The skin is the most frequently affected organ in both acute and chronic GVHD.3

In the past, acute and chronic GVHD were distinguished by time of onset following HSCT,
with acute appearing in fewer than 100 days, and chronic presenting more than 100 days after HSCT. However, this changed with the NIH consensus conference on cGVHD in 2005, where the acute and chronic GVHD definitions were reclassified based on clinical and histologic findings. The NIH definitions can now better indicate prognosis, guide treatment, and define eligibility for clinical trials.

Cutaneous cGVHD is a polymorphic condition that often has multiple presentations within one patient. Non-sclerotic cGVHD can resemble lichen planus, poikiloderma, psoriasis or papulosquamous lesions, subacute cutaneous lupus, and keratosis pilaris. Sclerotic-type cGVHD manifestations appear more bound down, and can resemble lichen sclerosus, morphea, and eosinophilic fasciitis.

Although sclerotic-type cGVHD is not an acute, life-threatening condition, widespread involvement may lead to significant disability and morbidity. Deep-seated fibrosis of the subcutaneous tissue and fascia may result in loss of range of motion. Longstanding fibrosis may result in skin ulceration and proliferation of benign angiomatous nodules. Due to the increased risk of developing cutaneous malignancies secondary to immunosuppression, chronic scarring, and potentially photosensitizing agents, the importance of sun protection and regular skin examinations should be emphasized.

Because the exact mechanism of action of cGVHD is unknown, it is difficult to treat. Cutaneous sclerotic type cGVHD is particularly resistant to systemic immunotherapy. First-line therapy for chronic GVHD includes systemic corticosteroids with or without a calcineurin inhibitor, which is based on controlled trials; however, at least 50 percent of these patients will not respond adequately. For steroid-refractory cGVHD, there are no therapies with level I evidence from randomized, controlled trials. There are a few with level II evidence from clinical trials without randomization, including photopheresis, rituximab, pentostatin and thalidomide. Steroid-refractory cGVHD therapies all have level C recommendations, where evidence is insufficient to support for or against treatment, or evidence may not outweigh adverse consequences or cost of treatment. The second-line therapies for steroid-refractory cGVHD are generally approached through trial and error. More than 10 years after the initial NIH Consensus Conference in 2005, there are still no FDA-approved agents with indication for cGVHD. Therefore, there is a strong need for clinical trials to optimize the currently used therapies or to develop new agents.

A recent study using the new NIH cGVHD definitions revealed a possible association between ScGVHD and the presence of total body irradiation (TBI) conditioning prior to transplantation. It also suggested that elevated C3 may stimulate fibrotic processes, and that increased platelets may act as acute-phase reactants, triggering synthesis of collagens and other matrix proteins. These predictors were either unknown or absent in our patient. Of note, previous acute or chronic GVHD did not predispose patients to an increased risk of ScGVHD.

This study also revealed that ScGVHD patients with a body surface area (BSA) sclerosis greater than the median 37.4 percent had poorer survival than those with less than median BSA sclerosis. In this population, it is possible that restriction of the chest and abdominal wall secondary to sclerosis may lead to decreased lung vital capacity and therefore decreased survival. Although cGVHD is not generally viewed as an acute, life-threatening condition, it can be lethal for ScGVHD patients.

**Conclusion**

As cGVHD becomes a more common dermatologic condition, resulting from the increased prevalence of HSCs, dermatologists must be aware of the diverse presentations of cGVHD, as early involvement can greatly decrease the sequelae of cGVHD. However, due to the unknown exact mechanism of action of cGVHD, it is very difficult to treat. There are no FDA-approved therapies with indications for cGVHD, and most steroid-refractory treatments are approached through trial and error. Therefore, it is imperative that our community supports increased research on the mechanism of action and optimization of currently used therapies for cGVHD.

**References**


Abstract

Syphilis has been called “the great imitator” due to its wide range of variable symptoms that often mimic other disease processes. The painless syphils chancre can easily go unnoticed, or be mistaken for a folliculitis, abrasion, or benign papule. The non-pruritic, diffuse rash that develops in secondary syphilis, characterized by dissemination and multiplication of the microorganism in different tissues, typically presents anywhere from simultaneously to six months after the healing of the primary chancre.

We present a challenging case of secondary syphilis that masqueraded as connective-tissue disease, granuloma annulare, and tinea corporis for years despite initial treatment.

Introduction

Syphilis, an entity with origins dating back to the 1530s, was first formally described in 1905. It is a chronic disease with varying presentations and a waxing and waning course. Sexual contact is the main mode of transmission, with the causative organism being Treponema pallidum, a spirochete. The gold standard of diagnosis is serologic testing, and penicillin G remains the treatment of choice.

Syphilis is commonly misdiagnosed as connective-tissue disease, granuloma annulare, lupus vulgaris, psoriasis, tinea corporis, and other dermatological diseases. Several case reports in the literature highlight the similarities between these diseases and the importance of accurate diagnosis and early treatment to prevent progression of syphilis to cardiovascular and neurologic sequelae. A high clinical suspicion of disease, coupled with clinical, serologic, and histologic evidence, is optimal for diagnosis and early management of syphilis.

Case Report

A 63-year-old Caucasian male with no documented past medical history presented in April 2015 for evaluation of a pruritic, diffuse rash of seven months’ duration. The patient denied any constitutional symptoms. The patient had diffuse annular, granulomatous, erythematous papules coalescing into plaques with central clearing on the trunk, back, bilateral biceps and forearms (Figures 1-4). The rash was treated with oral terbinafine and steroids and initially improved.

Four weeks later, the patient returned without significant improvement, and a punch biopsy was performed with a clinical suspicion of a gyrate erythema or granuloma annulare. Biopsy showed superficial and deep perivascular dermatitis with abundant perivascular lymphocytes and plasma cells. There was focal patchy vacuolar interface change and increased reticular dermal mucin confirmed with Alcian blue/PAS stain (Figures 5 [4x], 6 [20x]).

With further interrogation of the patient and review of the medical record, the patient had been seen in 2010 for a similar rash, also treated with oral terbinafine and biopsied, with results indicating drug eruption versus arthropod-bite reaction. At that time, an ANA, Lyme titer and RPR were performed. The RPR came back positive for syphilis, and the patient was referred to Infectious Disease. He had undergone an extensive workup at that time for Histoplasma, HIV, ANA, Lyme, Blastomyces, and Cryptococcus. The patient was started on cefuroxime 500 mg twice a day for the syphilis.

Upon further questioning in 2015, the patient reported he may have been partially treated by the Centers for Disease Control (CDC) for syphilis.
The patient denied any extramarital affairs. We performed another RPR, with a result of 1:128. The patient was referred to Infectious Disease for workup of tertiary syphilis and treatment. Infectious Disease treated the patient with ceftriaxone 2 g IV every 24 hours for two weeks, and he was worked up again for HIV and hepatitis. He also underwent a lumbar puncture to rule out neurosyphilis. Results from the HIV and hepatitis labs and the lumbar puncture were negative. The patient was treated successfully for secondary syphilis.

**Discussion**

Syphilis is a chronic disease with varying presentations and a waxing and waning course. While sexual contact is the main mode of transmission, with the causative organism being Treponema pallidum, a spirochete, transmission across the placenta is thought to be the second most common mode. Numerous studies have investigated the transmission probability among partners and have estimated it to be around 60 percent. Three stages of syphilis have been described: the primary stage, presenting with a painless chancre at the site of inoculation; the secondary stage, characterized by a polymorphic rash; and the tertiary stage, characterized by cardiovascular and neurologic sequelae and gumma formation. The tertiary stage is the most destructive.

Syphilis is divided into early (< 1 year) and late (> 1 year) stages, with the early stages (primary, secondary, and early latent) believed to be infectious. Late manifestations of disease involving all organ systems have given syphilis its name as the "great imitator," with the key to diagnosis remaining a high index of suspicion.

A single, painless, indurated ulcer with a clean base characterizes primary syphilis. These primary chancre also typically present with a sharply margined border. Up to 80 percent of patients with primary syphilis have painless regional lymphadenopathy. The incubation period for primary syphilis ranges from three to 90 days. In men, the penis is the most common site affected, while in women, it is the labia majora. Anorectal chancre are common in homosexuals. Extranodal chancre involving the fingers, tongue, anus, and mouth are rare, but when affected, they are typically painful lesions. The most common extragenital chancre location is the mouth, most specifically the lip.

Secondary syphilis is often subtle and is a cutaneous manifestation of the disease. A primary chancre can be found in up to one-third of patients with secondary syphilis. Skin lesions can often mimic other dermatologic diseases, making syphilis easy to misdiagnose. The rash can have variable morphology, ranging from macular to maculopapular, follicular, and occasionally pustular. Classically, however, lesions are non-pruritic and are universally distributed with a "raw ham" or copper-colored appearance. The palms and soles are typically involved. In up to 7 percent of patients, a patchy, "moth-eaten" pattern of alopecia has been reported. Systemic symptoms of secondary syphilis may include malaise, prostration, cachexia, headache, low-grade fever, asymptomatic meningitis, cranial nerve palsies, gastrointestinal symptoms, painless adenopathy, and vague bone and joint pain, among others.

Tertiary syphilis consists of cardiovascular and neurologic involvement. It is estimated that approximately one-third of patients with untreated primary syphilis develop tertiary syphilis. Cardiovascular symptoms usually present between 10 years and 30 years after the initial infection. The most common cardiovascular manifestation of disease is syphilitic aortitis, typically involving the ascending aorta. Clinical signs and symptoms of neurosyphilis include "focal central nervous system ischemia and stroke, tabes dorsalis (progressive ataxia, bladder incontinence), and general paresis (altered mental status, depression, forgetfulness, confusion)." Cutaneous tertiary syphilis typically presents with nodular lesions that can easily mimic other dermatologic diseases such as granuloma annulare, lupus vulgaris, psoriasis, and sarcoid.

Diagnosis of syphilis is based on both clinical and laboratory findings. The gold standard for the diagnosis of primary syphilis continues to be visualization of spirochetes under dark-field microscopy. For secondary, latent, and tertiary syphilis, serologic testing is the method of choice for diagnosis. Nontreponemal tests, including VDRL, are often indicated for screening, while treponemal tests, including RPR, FTA-ABS (the serum fluorescent treponemal antibody absorption test), and MHA-TP (microhemagglutination test for T. pallidum), are used to confirm the diagnosis. Nontreponemal tests, however, can lack sensitivity and can give a high rate of false-positive reactions. This is particularly true in patients of increased age, patients who are pregnant or drug-addicted, and those with malignancy, autoimmune diseases (SLE), and viral (EBV and hepatitis), protozoal or mycoplasmal infections. Neurosyphilis is often diagnosed based on a combination of results from serologic testing, abnormalities of CSF cell count and protein levels, or a reactive CSF VDRL.

The first-line therapy for syphilis remains intramuscular benzathine penicillin G. Due to the devastating sequelae of syphilis, it is recommended that patients allergic to penicillin be desensitized and subsequently treated with penicillin.

Despite serologic testing for the diagnosis of syphilis, atypical clinical presentations and false-negative laboratory tests, particularly in HIV-positive individuals, complicate accurate and early diagnosis of disease. This, in turn, has led to an increase in dermatological specimens for the diagnosis of syphilis. In addition to the variability in clinical presentation and mimicry of other disease processes, the histopathological features of syphilis also exhibit a wide spectrum, with features ranging from interface dermatitis to granulomatous diseases. However, several well-recognized histologic patterns characteristic of the papulosquamous eruption of secondary syphilis have been described. These include interstitial inflammation, endothelial swelling, irregular acanthosis, and elongated rete ridges. Although not diagnostic, they should raise suspicion for syphilis, particularly in the absence of clinical features. Although a variety of diagnostic tests are available for accurate diagnosis, the incidence of false-negative laboratory tests as well as clinical features resembling other etiologies make it one of the most commonly misdiagnosed entities in the field of dermatology. The tragic outcomes that can result from misdiagnosis of syphilis, including but not limited to cardiovascular and neurologic sequelae, demonstrate the importance of early and accurate diagnosis.

Bittencourt et al. report a different case of secondary syphilis in an HIV patient with palmoplantar lesions masquerading as granulomatous psoriasis. They present a 32-year-old male with bilateral asymptomatic erythematous-scaly plaques on palms and soles for three months, associated with periangual erythema, subungual hyperkeratosis and onychodystrophy of toenails. This case demonstrates the challenge of diagnosing syphilis, in that clinically, it can mimic psoriasis and dermatophytosis. However, the unusual alterations typical of syphilis in the case by Bittencourt et al., coupled with a negative result of mycological examination and improvement after treatment, led to the actual diagnosis of syphilis over its mimickers. This validates the importance of clinical suspicion, particularly in the case of atypical manifestations of secondary syphilis.

**Conclusion**

Syphilis is a disease that skillfully mimics other dermatological diseases in both clinical and histologic features. Furthermore, it is a disease with multisystem effects, one that allows a dermatologist to "highlight the relationship of skin diseases to the rest of the body." The cases by Wu and Bittencourt et al., along with the present case, exemplify this mimicry and the need for a high clinical index of suspicion for syphilis. Although a variety of diagnostic tools are available for accurate diagnosis, the incidence of false-negative laboratory tests as well as clinical features resembling other etiologies make it one of the most commonly misdiagnosed entities in the field of dermatology. The tragic outcomes that can result from misdiagnosis of syphilis, including but not limited to cardiovascular and neurologic sequelae, demonstrate the importance of early and accurate diagnosis.
References


Segmental Speckled Lentiginous Nevus Exacerbated by Pregnancy in an Otherwise Healthy Female: A Case Report

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Abstract
Speckled lentiginous nevi (SLN), or nevus spili, are seen in 0.2% to 2.3% of the population, presenting as tan patches with overlying hyperpigmented macules or papules in a speckled arrangement. Segmental SLN represent a small subset of SLN, with the segmental type comprised of larger, unilateral lesions that may rarely give rise to melanomas and have been reported to proliferate in response to ultraviolet light exposure. We present the case of a 40-year-old woman who presented with dark brown macules and papules scattered in a sharp, unilateral distribution over her back, chest, and abdomen. The lesions had been present for 10 years but had enlarged and darkened during her previous pregnancies. A clinical diagnosis of segmental speckled lentiginous nevus was made, and the patient was given appropriate instructions for sun protection and proper follow-up. This is the second reported case of segmental SLN with morphologic changes during pregnancy, suggesting an underlying hormonal component in its pathogenesis.

Introduction
Speckled lentiginous nevus (SLN), also referred to as nevus spili, is a relatively common skin lesion, occurring in 2.3% of adults.3 SLN lesions present as numerous, hyperpigmented macules and papules over tan-brown patches.2 SLN has recently been categorized into macular and papular subtypes, known as nevus spili maculosus and nevus spili papulosus, respectively.3 Segmental SLN are large lesions that present in a unilateral or zosteriform distribution. Such cases typically present at birth or in infancy and may worsen secondary to ultraviolet (UV) light exposure.4 These have been reported to give rise to single or multiple melanomas, although this is rare.14 In this case report, we present a 40-year-old female with adult-onset segmental SLN that worsened during pregnancy, review the disease’s pathogenesis and management, and provide diagnostic pearls.

Case Report
A 40-year-old, otherwise healthy woman presented with a 10-year history of dark brown macules and papules on the right side of her torso. The lesions were asymptomatic but were noted to become darker and larger during past pregnancies. No previous workup or treatments had been attempted. A full review of systems, including visual changes, hearing loss, neurologic abnormalities, and musculoskeletal changes, was negative.

Physical examination revealed a female with Fitzpatrick type IV skin with a unilateral distribution of brown macules and papules on the right side of her torso (Figures 1, 2). No epidermal nevi or port wine stains were noted. Due to the asymptomatic nature of the lesions and their clinical presentation, a clinical diagnosis of segmental speckled lentiginous nevus was made. The patient was educated on the importance of sun protection and close monitoring of her skin lesions with annual skin examinations.

Discussion
Despite continuing debate over the nosology of speckled lentiginous nevi (SLN) among melanocytic lesions, the etiology is likely multifactorial, with genetic and environmental factors playing a role.5 Approximately 80% are present at birth or shortly after,7 leading some authors to categorize SLN as a congenital melanocytic nevus, while others believe it to be an acquired process because the characteristic speckled hyperpigmentation may take years to develop.6 Segmental or "zosteriform" presentations of SLN are also believed to be caused by somatic mosaicism, which consists of genetically distinct populations of cells that result from post-zygotic somatic mutations. Recently, activating mutations of HRAS were identified in smaller SLN lesions, whereas an activating missense NRAS mutation was identified in a case of congenital segmental SLN.8,9 Environmental factors also influence established SLN lesions. Ultraviolet (UV) light exposure has been reported to darken the lentiginous background hyperpigmentation and cause proliferation of the speckled macules and papules.4 Additionally, in one case series, melanomas arising within segmental SLN occurred only in sun-exposed areas, which may be explained by epigenetic modification of tumor suppressor genes in lesional skin.4 Our patient reported darkening and enlargement of her SLN during pregnancy, which is our knowledge has been reported in only one other case.10 Of note, the other case of SLN worsened by pregnancy had a congenital onset, whereas our patient reported adult-onset of her SLN. There are similarities between the SLN in our patient and general characteristics of melasma, a hyperpigmentation disorder that commonly affects women's faces secondary to hormonal changes, including those associated with pregnancy or oral-contraceptive use. Melasma occurs more frequently in darker pigmented individuals (Fitzpatrick III-V), may be triggered by sun exposure and pregnancy—suggesting hormones may have played a role in the hyperpigmentation component of our patient’s SLN—and has a genetic component, with 40% of affected patients reporting relatives also affected by the disease.11

A meticulous physical examination can give the clinician several important clues for the diagnosis of SLN and associated disorders. The underlying patch, a key finding in SLN, is absent in clinically similar disorders like agminated nevus (Figure 10). The clinician several important clues for the diagnosis of SLN and associated disorders. The underlying patch, a key finding in SLN, is absent in clinically similar disorders like agminated nevus (Figure 10).
presentations of SLN are also important clinical distinctions. Macular SLN are more likely to have an evenly spaced distribution, and they have a higher likelihood of malignant changes, whereas nevus spilus papulosis more often presents in an uneven, “star map” distribution and may be associated with phakomatosis pigmentokeratotica. SLN have also been associated with phakomatosis pigmentovascularis (PPV) types III and IV and speckled lentiginous nevus syndrome, which is characterized by SLN along with ipsilateral muscle weakness, hyperhidrosis, or sensory changes. Type III PPV may be associated with multiple granular cell tumors. Therefore, a thorough skin examination for port wine stains or nevus flammeus, an additional finding of PPV, should be performed. Other differential diagnoses to be considered for SLN-like lesions include café au lait macules, congenital nevi, lentigo simplex, and melanoma.

The diagnosis of SLN is often clinical, and management is similar to that of other large melanocytic nevi. On biopsy, the macules and papules are consistent with small junctional and compound nevi, respectively, with histology of background hyperpigmentation representing lentigo simplex. The darkening of SLN lesions in response to UV exposure may be explained by these lentiginous features. Management of segmental SLN patients is similar to that of patients with large or numerous nevi. Patients should be followed with annual skin examinations and be educated on the importance of sun protection to prevent malignant changes within the lesion. Further treatment of lesions is often for cosmetic purposes and has been performed using Q-switched (QS) Nd:YAG, QS ruby, and QS alexandrite lasers.

**Conclusion**

SLN typically present as smaller patches, though they may also have larger, segmental or zosteriform distributions. Such segmental cases are believed to be the result of somatic mosaicism affecting RAS proteins in the skin. SLN may worsen secondary to UV light exposure and have been reported to give rise to melanoma, which is more common in macular subtypes. We presented a case of segmental SLN in an otherwise-healthy, 40-year-old woman whose disease worsened during pregnancy; to our knowledge, this is only the second reported case in the literature of segmental SLN worsened by pregnancy.

**References**

INDICATIONS AND USAGE: ULTRAVATE® (halobetasol propionate) Lotion, 0.05% is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older. Treatment beyond 2 weeks is not recommended, and the total dosage should not exceed 50 grams per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Discontinue therapy when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

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ULTRAVATE (halobetasol propionate) lotion

1. INDICATIONS AND USAGE
ULTRAVATE lotion is indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.

2. DOSAGE AND ADMINISTRATION
Apply a thin layer of ULTRAVATE lotion to the affected skin twice daily for up to two weeks. Rub in gently. Discontinue therapy when control is achieved. If no improvement is seen within two weeks, reassessment of diagnosis may be necessary. Treatment beyond two weeks is not recommended and the total dosage should not exceed 50 grams (50 ml) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis [see Warnings and Precautions (5)]. Do not use with occlusive dressings unless directed by a physician.

ULTRAVATE lotion is for external use only.

Avoid use on the face, scalp, groin, or axillae.

ULTRAVATE lotion is not for ophthalmic, oral, or intravaginal use.

4. CONTRAINDICATIONS
None.

5. WARNINGS AND PRECAUTIONS
5.1 Effects on Endocrine System
ULTRAVATE lotion is a topical corticosteroid that has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression, with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid. The potential for hypothalamic-pituitary-adrenal (HPA) suppression with ULTRAVATE lotion was evaluated in a study of 20 adult subjects with moderate to severe plaque psoriasis involving > 20% of the body surface area. ULTRAVATE lotion produced HPA axis suppression when used twice daily for two weeks. In 5 out of 20 (25%) adult patients with plaque psoriasis, recovery of HPA axis function was generally prompt with the discontinuation of treatment [see Clinical Pharmacology (12.2)].

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

5.3 Concomitant Skin Infections
Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of ULTRAVATE lotion until the infection has been adequately treated.

5.4 Allergic Contact Dermatitis
Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue ULTRAVATE lotion if allergic contact dermatitis is established.

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

During randomized, controlled, blinded clinical trials 277 adults with plaque psoriasis were treated with ULTRAVATE lotion twice daily for up to two weeks (up to approximately 50 grams/week). Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ULTRAVATE lotion twice daily for up to two weeks, and more frequently than in vehicle-treated subjects. Table 1, Adverse Reactions Occurring in > 1% of Subjects Treated with ULTRAVATE Lotion for up to Two Weeks.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Vehicle Lotion (N=259)</th>
<th>ULTRAVATE Lotion (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Application site atrophy</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hand edema</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Rhema</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
| Less common adverse reactions (incidence less than 1% but greater than 0.1%) that occurred in subjects treated with ULTRAVATE lotion included application site discoloration, herpes zoster, influenza, nasopharyngitis, otitis media acute, throat infection, wound, and increased blood pressure.

6.2 Pediatric Use
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULTRAVATE lotion and any potential adverse effects on the breastfed infant from ULTRAVATE lotion or from the underlying maternal condition.

Clinical Considerations
Advise breastfeeding women not to apply ULTRAVATE lotion directly to the nipple and areola to avoid direct infant exposure. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids.

Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see Use in Specific Populations (8.4)].

6.3 Geriatric Use
Clinical studies with ULTRAVATE lotion included 860 subjects aged 65 years and over. Overall differences in safety or effectiveness were observed between these patients and those younger than 65 years. Clinical studies of ULTRAVATE lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

6.4 Drug Interactions
Topically applied ULTRAVATE lotion can be absorbed in sufficient amounts to produce systemic effects [see Warnings and Precautions (5.1)].

6.5 Overdose
In patients with severe uncontrolled plaque psoriasis, systemic absorption of corticosteroids may result in manifestations of adrenal suppression which may require that patients be evaluated periodically for evidence of HPA axis suppression. Discontinue use in cases of systemic HPA axis suppression.

6.6 Information for Patients
Inform patients that systemic absorption can occur when ULTRAVATE lotion is used on large areas of the body, when the medication is used during extended periods of time, or when the medication is used in combination with other corticosteroids or other drugs that may increase the systemic effects of corticosteroids. Instruct patients to report to the physician any signs and symptoms of systemic absorption.

7. PATIENT COUNSELING INFORMATION
This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all administration instructions or all possible adverse or unintended effects.

Advise patients using ULTRAVATE lotion of the following information and instructions:

Instruct patients to discontinue ULTRAVATE lotion when psoriasis is controlled. ULTRAVATE lotion should not be used for longer than 2 weeks. Advise patients to contact the physician if no improvement is seen within 2 weeks. Inform patients that total dosage should not exceed 50 grams per week [see Dosage and Administration (2)].

Instruct patients to avoid bandaging, wrapping or otherwise occluding the treatment area, unless directed by a physician. Advise patients to avoid use on the face, scalp, groin, or axillae [see Dosage and Administration (2)].

Inform patients that ULTRAVATE lotion is for external use only. Advise patients that ULTRAVATE lotion is not for oral, nasal or ophthalmic use [see Dosage and Administration (2)].

Breastfeeding women should not apply ULTRAVATE lotion directly to the nipple and areola to avoid direct exposure of the infant [see Lactation (8.2)].

Rx Only