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Dear JAOCD readership,

At the recent Council of Dermatology Editors meeting in Miami during the AAD Annual Meeting, we discussed an important issue that may be familiar to you: spam. In particular, we talked about invitations from obscure online journals that seem to be inundating all of our email accounts at alarming rates.

I’m sure most of us are victims of such unwanted attention from a variety of sources, and as authors, reviewers and readers of the JAOCD, this particular type of spam affects us all. Jeffrey Beall, an academic librarian at the University of Colorado at Denver, has begun cataloguing these questionable journals, and his full report, entitled “Beall’s List of Predatory, Online-Access Publishers,” can be found online at http://www.academia.edu/1151857/Bealls_List_of_Predatory_Open-Access_Publishers. Here is an excerpt of note:

“Predatory, open-access publishers are those that unprofessionally exploit the author-pays model of open-access publishing (Gold OA) for their own profit. Typically, these publishers spam professional email lists, broadly soliciting article submissions for the clear purpose of gaining additional income. Operating essentially as vanity presses, these publishers typically have a low article acceptance threshold, with a false-front or non-existent peer review process. Unlike professional publishing operations, whether subscription-based or ethically-sound open access, these predatory publishers add little value to scholarship, pay little attention to digital preservation, and operate using fly-by-night, unsustainable business models.”

-2012 Beall's List of Predatory, Online-Access Publishers

Of course, the JAOCD is not on this list, and it never will be; however, I want to highlight the dangers of submitting articles to these types of soliciting journals. If the soliciting journal is not immediately recognizable, I advise all potential authors to examine Beall’s list prior to submitting articles on which you have worked so hard.

As always, the JAOCD remains of sound academic orientation and invites you to continue submitting your scientific manuscripts (free of charge!).

We appreciate all of your hard work, support, and expertise, and urge you to protect yourselves from falling into these traps.

Warm Regards,

Karthik Krishnamurthy, DO, FAOCD
Greetings, everyone!

We recently welcomed a new member to the AOCD staff in Kirksville. Look for Jami Johnson’s article of introduction located in the next issue of Dermline.

Our 2013 Midyear Meeting has been completed, and outcome evaluation surveys have been sent to our attendees. By filling out this additional survey, our attendees become eligible to earn up to two additional CME credits. This is a NEW benefit available to members and is another reason we encourage everyone to attend the midyear meetings of the AOCD. Our next midyear meeting in 2014 will be at the Ritz Carlton in Dallas. Dr. Karthik Krishnamurthy is already hard at work planning this meeting.

OMED 2013
On February 2, 2013, I attended the AOA’s pre-OMED meeting in Las Vegas. At this year’s meeting, the AOCD will have various events in the Mandalay Bay Hotel, with the primary lectures and exhibits located in the Mandalay Bay Convention Center. Dr. Suzanne Sirota-Rozenberg has planned an exciting line-up of speakers and topics. A preliminary schedule will be in the upcoming issue of Dermline.

AOCD Office Update
The AOCD completed our move to the new office. Our post office box (P.O. Box 7525, Kirksville, Missouri, 63501) is our preferred mailing address, and all correspondence should continue to be sent there. All shipments, however, should be sent to our new street address: 2902 N. Baltimore St., Kirksville, MO, 63501. Please be sure to update your records.

ACGME Update
The AOA, the Accreditation Council for Graduate Medical Education (ACGME), and the American Association of Colleges of Osteopathic Medicine (AACOM) have entered into an agreement to pursue a single, unified accreditation system for graduate medical education programs in the United States beginning in July 2015.

At the recent AOA Board of Trustees Midyear Meeting held March 3rd to 6th in Maui, it was announced that the much-anticipated Memorandum of Understanding between the ACGME and the AOA would likely be available during the July House of Delegates meeting in Chicago. The AOA met with ACGME during the last week in February, and the two organizations agreed to hold more meetings on the subject of the unified accreditation system.

As developments and details unfold, information can be found at www.osteopathic.org/acgme. There, you can find answers to frequently asked questions, the AOA’s joint press release, a timeline of the issue, and other resources.

All the best,
Marsha A. Wise
Executive Director, AOCD
The JAOCSD relies on the participation of students, residents, Program Directors, and AOCD members. I believe, though, it is the AOCD dermatology residents who truly drive this journal to its continued success. And those residents will eventually become the leaders of our college.

Our JOACSD Editor-in-Chief, Karthik Krishnamurthy, DO, FAOCD, offers a prime example of how members of our college can take advantage of the myriad opportunities for involvement. Besides his duty as editor, Dr. Krishnamurthy is also the AOCD’s Third Vice-President and the Program Chair of the upcoming 2014 Midyear Meeting in Dallas. He also serves on several committees, including as Chair of the Editorial/Public Relations Committee. It wasn’t so long ago that Dr. Krishnamurthy was a resident in New York.

My point is that one can accomplish a lot if the desire to participate is there. At the American Academy of Dermatology Meeting in Miami, a team of dermatology residents from the PCOM/Lehigh Valley Health Network joined the AAD Dermpath Bowl, competing against other allopathic and osteopathic residents from residency programs across the country. These residents, under the direction of Program Director Stephen Purcell, DO, FAOCD, won first place in the competition! Congratulations to Tatyana Goysman, DO, Marie Lewars, DO, Luis Soro, DO, and Christian Oram, DO, for their fantastic performance against some of the top dermatology residents in the United States.

I was also very impressed with the resident presentations at our recent Midyear Meeting in Winter Park, Colorado. There was the talk by Ralph Fiore, II, DO, on iatrogenic infections, and a great case report on lamellar ichthyosis given by Steffany Steinmetz, DO. I also want to congratulate our Koprince Award winners, Aleksandra Brown, DO, Leilani Townsend, DO, Geeta Patel, DO, and Stacy Rosenblum, DO, for their presentations. I am encouraged to see the ever-improving quality of resident talks in general, and I hope that all of our talented presenters will continue speaking as they move forward in their dermatology careers.

So I end this message with a salute to our residents, their program directors and their trainers. May you continue to strive to be experts in the field of dermatology!

David L. Grice, DO, FAOCD
President, AOCD
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- Indicated for the topical treatment of acne vulgaris in patients 12 years or older.
- Suspended crystalline tretinoin in vehicle designed to deliver the active ingredients to the skin.
- Hydrogel alcohol-free aqueous base.

Important Safety Information for ZIANA Gel
- The most commonly reported adverse events were nasopharyngitis, pharyngolaryngeal pain, dry skin, cough, and sinusitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. ZIANA Gel should be discontinued if significant diarrhea occurs. Systemic absorption of clindamycin has been demonstrated following topical use of this product.
- If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued.
- Avoid exposure to sunlight and sunlamps. Patients with sunburn should not use the product. Use with caution in patients who require considerable sun exposure due to occupation or who are inherently sensitive to the sun. Avoid excessive exposure to the sun, cold, and wind, which can irritate skin. Daily use of sunscreen and protective clothing are recommended.
- Keep away from eyes, mouth, angles of nose, and mucous membranes.
- This drug is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.
- Concomitant use of topical medications with a strong drying effect can increase skin irritation. Use with caution.

To learn more, contact your Medicis, The Dermatology Company representative.
BRIEF SUMMARY
(see package insert for Full Prescribing Information)

ZIANA®
(clindamycin phosphate 1.2% and tretinoin 0.025%) Gel

RX ONLY
FOR TOPICAL USE ONLY

INDICATIONS AND USAGE
ZIANA® Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

CONTRAINDICATIONS
ZIANA® Gel is contraindicated in patients with regional entropion, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS
Colitis
Systemic absorption of clindamycin has been demonstrated following topical use of this product. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. When significant diarrhea occurs, ZIANA® Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death. Studies indicate a toxin(s) produced by clstridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure
Exposure to sunlight, including sunlamps, should be avoided during the use of ZIANA® Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., a hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with ZIANA® Gel.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use for approximating rates.

The safety data presented in Table 1 (below) reflects exposure to ZIANA® Gel in 1,853 patients with acne vulgaris. Patients were 12 years and older and were treated once daily for 12 weeks. Adverse reactions that were reported in ≥ 1% of patients treated with ZIANA® Gel were compared to adverse reactions in patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the vehicle gel alone.

Table 1: Adverse Reactions Reported in at least 1% of Patients Treated with ZIANA® Gel: 12-Week Studies

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ZIANA® Gel N=1,853</th>
<th>Clindamycin 1.2% N=1,428</th>
<th>Tretinoin 0.025% N=1,614</th>
<th>Vehicle Gel N=1,423</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>497 (27)</td>
<td>342 (24)</td>
<td>225 (27)</td>
<td>91 (22)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>65 (4)</td>
<td>64 (5)</td>
<td>16 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>29 (2)</td>
<td>18 (1)</td>
<td>5 (1)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (1)</td>
<td>7 (1)</td>
<td>4 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (1)</td>
<td>19 (1)</td>
<td>15 (2)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

Note: Formulations used in all treatment arms were in the ZIANA® vehicle gel.

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and 2, 1,277 subjects enrolled with moderate to severe acne. 854 subjects treated with ZIANA® Gel and 423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were slightly higher for the ZIANA®-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA® Gel showed a similar adverse reaction profile as seen in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

DRUG INTERACTIONS
Concomitant Topical Medication
Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution. When used with ZIANA® Gel, there may be increased skin irritation.

Erythromycin
ZIANA® Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. In vivo studies have shown antagonism between these two antibiotics. The clinical significance of this in vitro antagonism is not known.

Neuromuscular Blocking Agents
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ZIANA® Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA® Gel. ZIANA® Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ZIANA® Gel was tested for teratogenic and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA® Gel at 600 mg/kg/day (approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA® Gel for two weeks prior to artificial insemination and continuing until gestation day 18, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA® Gel applied daily to a 60 kg person.

Clindamycin
Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin up to 180 mg/kg/day (175 and 88 times the amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin
In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (~ 78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermatitis has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on a body surface area comparison.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of ZIANA® Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIANA® Gel is administered to a nursing woman.

Pediatic Use
Safety and effectiveness of ZIANA® Gel in pediatric patients under the age of 12 have not been established.

Clinical trials of ZIANA® Gel included patients 12–17 years of age.

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

Manufactured for:
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Scottsdale, AZ 85256
U.S. Patents 5,721,275 and 6,387,383
ZIANA is a registered trademark of Medicis Pharmaceutical Corporation.

Prescribing Information as of October 2008.

300-13B
Vera H. Price, M.D., Receives Dermatology Foundation Lifetime Career Educator Award

At its recent annual meeting of membership in Miami Beach, the Dermatology Foundation recognized the tremendous contribution Vera H. Price, M.D., has made to the specialty of dermatology by honoring her with the Lifetime Career Educator award. The award honors Dr. Price’s distinguished career and the high standard she has set for the next generation of teachers in all areas of dermatology.

Dr. Vera Price, widely recognized hair expert and Professor Emeritus of Dermatology at University of California, San Francisco (UCSF), has devoted her career of many decades to an area of dermatology in which there are few educators. Following her residency, Dr. Price came to the San Francisco area from Canada for “just one year.” Because she lacked a California license, she contacted the UCSF Dermatology Department for a one-year research position. This led to her study of the physical and chemical properties of human hair with the wool chemists at the USDA’s Wool and Mohair Laboratory in Berkeley. Three years later, recognizing that her move was permanent, Dr. Price resumed clinical dermatology at Kaiser-Permanente in San Francisco. She was encouraged to continue hair research studies in addition to patient care, and moved to the USDA’s Wool and Mohair Laboratory in Berkeley. Three years later, recognizing that her move was permanent, Dr. Price resumed clinical dermatology at Kaiser-Permanente in San Francisco. She was encouraged to continue hair research studies in addition to patient care, and established the UCSF Hair and Nail Clinic in 1970. During this time she taught medical students and residents and gave lectures about hair. In 1991 Dr. Price joined UCSF’s full-time faculty, establishing the UCSF Hair Research Center and then a one-year Clinical Hair Research Fellowship allowing her to mentor a young dermatologist annually. With one of her early fellows, Dr. Price coauthored the first textbook on scarring alopecia, Cicatricial Alopecia: An Approach to Diagnosis and Management. Since this subject is not covered in most residency programs, she devised a plan to fund and donate 600 CDs of the books to residents in the U.S. and Canada.

Dr. Price’s long list of accomplishments includes the establishment of two nonprofit patient organizations, the National Alopecia Areata Foundation (1981), and the Cicatricial Alopecia Research Foundation (2002). Her contribution to hair research has been significant. Dr. Price described several new hair disorders, was a founding member of the North American Hair Research Society (1991), and published well over 130 papers. She received the AAD’s Gold Triangle Award (1999, 2010) in honor of her public outreach, and the Women’s Dermatologic Society’s Mentor of the Year award in 2004 “in recognition of her outstanding role as a mentor to residents, dermatologists, other physicians, medical students, and undergraduates.” Dr. Price became an Honorary Member of the AAD in 2010, as well as several international dermatology societies. Described by a mentee as “a very skilled and knowledgeable clinician and researcher, and a wonderful mentor,” Dr. Price has always loved what she does. Of the awards she has received, “the DF Lifetime Career Educator Award is the one that makes me most humble. My students inspire me and keep me on my toes. I never stop learning from them.”

The Dermatology Foundation was established in 1964 and is the leading private funding source for skin disease research. It provides funding that helps develop and retain tomorrow’s teachers and researchers in dermatology, enabling advancements in patient care.
INTRODUCTION

A staggering one-third of the world’s population is thought to have latent tuberculosis, which is defined as the presence of Mycobacterium tuberculosis in the body without signs, symptoms, radiographic, or bacteriologic evidence of active tuberculosis infection.\(^1\)\(^2\) An estimated 5-10% of patients with latent tuberculosis infection (LTBI) will progress to active tuberculosis without treatment in their lifetime.\(^2\) Perhaps even more alarming is the fact that HIV patients have a 7-10% risk of progression to active tuberculosis per year.\(^2\) This is especially relevant in the field of dermatology, as many of the new pharmacologic therapies are effectively treating stubborn chronic dermatoses but at the same time categorizing our patients as chronically immunosuppressed (much like those infected with HIV). In all fields of medicine, the goals of testing for LTBI are to identify those patients who are at increased risk for the development of active tuberculosis, thus enabling early treatment.\(^3\)

Historical Perspectives

Before 2001, the tuberculin skin test (TST) was the only test available to help in the identification of Mycobacterium tuberculosis.\(^1\) In 2001, the CDC introduced the first in vitro blood test for diagnosis of LTBI: QuantiFERON TB.\(^1\) Then in 2005, the FDA approved QuantiFERON Gold, which measured the quantity of IFN-gamma released from cells after incubation with two antigens seen in Mycobacterium tuberculosis: ESAT-6 and CFP-10 (early secretory antigenic target 6 and culture filtrate protein 10, respectively).\(^1\) These two antigens are present in all Mycobacterium tuberculosis strains, but are also present in several additional atypical mycobacteria including M. kansasii, M. marinum, M. flavescentis, and M. szulgai, which can cause release of IFN-gamma (and thus false positive QuantiFERON Gold results).\(^1\)

In 2007, a third serum assay was approved for the identification of Mycobacterium tuberculosis called QuantiFERON Gold-in-Tube (QFT-GIT),\(^1\) an-ELISA based test. With the use of ELISA (enzyme-linked immunosorbent assay), three antigens are used: ESAT-6, CFP-10, and TB7. The quantity of IFN-gamma (released in response to these three antigens) is reported in IU/ml.\(^2\) The testing kit for QFT-GIT contains three heparinized tubes: a control tube (“nil, no antigens”), which determines the patient’s baseline level of IFN-gamma production; a tube containing “mitogen,” which is a stimulant of IFN-gamma production (and serves as a positive control to ensure functioning immune status); and a tube containing the three Mycobacterium antigens noted above.\(^2\) Table 1 shows QFT-GIT interpretation guidelines.

The latest IGRA (and perhaps the most useful from a dermatological perspective) is the T-SPOT.TB assay, which was approved for use in 2008.\(^1\) In contrast to the QFT-GIT, this new assay is performed by selectively isolating peripheral blood mononuclear cells, which has the tremendous benefit of “normalizing” differences in peripheral white blood cells.\(^5\) This added benefit is vitally important in dermatologic testing, as it theoretically performs better in patients with compromised immune systems.\(^2\) After the white blood cells are incubated with ESAT-6 and CFP-10, ELISpot (enzyme-linked immunospot assay) is used to detect individual, activated effector T cells that secrete IFN-gamma (once stimulated by the antigens).\(^1\) Each spot represents “the footprint” of an individual IFN-gamma-secreting T cell, and the results are reported as the number of spots (see Table 2).

Current Concepts

To date, both QFT-GIT and T-SPOT. TB interferon-gamma release assays are approved by the CDC for the detection of Mycobacterium tuberculosis infections.\(^1\) It is important to remember, however, that IGRA do not differentiate latent from active tuberculosis. Therefore, in the face of a positive IGRA, one must obtain a detailed review of clinical symptomatology, CXR and/or CT chest, and sputum gram stain/culture x3 to rule out active tuberculosis.\(^1,3\) It is also dermatologically relevant to realize that both of these approved tests react to other atypical mycobacteria due to the overlap of mycobacterial antigens, namely M. kansasii, M. marinum, M. flavescentis, M. gordoneae, and M.sulgai.\(^3\) Therefore, as dermatologists, it may also be prudent to do a thorough evaluation for the presence of other atypical mycobacteria in the presence of a positive IGRA if clinical suspicion for M. tuberculosis is low.
Apart from the known overlapping environmental mycobacterial antigens associated with the IGRAs, most of the confusion in the medical community regarding testing and interpretation has come from multiple trials that have studied the "concordance" of TST with IGRAs. A patient may have a negative TST and a positive IGR, or vice versa (disconcordance between tests), because TST and IGRAs are not interchangeable. TST measures delayed-type hypersensitivity 48-72 hours after placement of a PPD, whereas IGRAs measure the cell-mediated immune response by quantifying the IFN-gamma released (once serum is incubated with the mycobacterial antigens). Thus, the two tests are measuring different components of the immune response. Other factors that play a key role in the discordance of results include:

1. Prior BCG vaccination can cause false positive TSTs. BCG vaccination has no effect on the results of IGRAs.1

2. Prior positive TSTs affect a patient’s immune response with subsequent TST (called the “boosting” effect). There is no “boosting” effect with IGRAs.1

3. The presence of non-tuberculosis bacteria (namely M. kansasii, M. marinum, M. flavescens, and M. szulgai) can all cause false positive results in both TST and IGRAs due to the overlap of antigens in atypical mycobacteria.1

4. A certain percentage of patients who have a negative TST and subsequently a positive IGRA, without known TB risk factors, likely have encountered unrecognized TB exposure (raising a very important question: Should the definition of TB risk be re-evaluated?).

5. TST, QFT-GIT, and T-SPOT.TB all seem to be affected by decreased CD4+ counts, resulting in false negative TST, false negative QFT-GIT, and higher numbers of indeterminate results with T-SPOT.TB.1

6. Pediatric patients less than 5 years of age likely have a lack of immunologic maturity and thus may have a decreased IFN-gamma response, leading to more indeterminate IGRA results. Therefore, TST is still recommended for patients younger than age 5.1

7. In any given patient, there is a fluctuation in the IFN-gamma response (and subsequent quantity measured), possibly enough to cause positive IGRA results to become negative, or vice versa, with repeat serial testing. Therefore, there are likely yet-to-be-determined contributing immunologic factors playing a role in the results of and discordance between TST and IGRAs.

8. False negative TSTs, as well as falsely negative/indeterminate IGRAs, are commonly seen in patients who are immunosuppressed or who are on long-term immunosuppressant treatment. This adds an extra factor to the dermatologist’s use of IGRAs.

The CDC has taken into consideration countless studies in its current recommendations regarding the use of IGRAs, but there are several studies that are particularly worth mentioning with regard to the practice of dermatology. A variety of dermatologic disorders pose a serious challenge due to the increased risk of skin testing anergy. This is due to two main factors: intrinsic primary immune dysfunction and secondary immunologic blockade with the use of immunosuppressant medications. A recent cross-sectional study compared TST with QFT-GIT in diagnosing LTBI in patients with chronic inflammatory disease (including rheumatoid arthritis and spondyloarthropathy). This study also included patients who were using immunosuppressive medications (methotrexate, TNF-alpha inhibitors, and leflunomide). The results showed poor concordance between TST and QFT-GIT in this particular population of patients who had chronic immunosuppressive medications. Furthermore, the TST results were significantly suppressed in patients taking immunosuppressant medications (compared to those who were not on immunomodulating medications). This raises a still-unanswered question: Why are dermatologists still using TST, especially since the vast majority of patients being screened for LTBI fall into the category of “chronically immunosuppressed” or “currently taking an immunosuppressant medication”?

The flip side of this coin is that with QFT-GIT, there is a higher number of indeterminant results, found especially in patients with lower CD4+ counts; in patients receiving chemotherapy; in patients who have been previously treated with TNF-alpha inhibitors; and in patients who have lymphocytopenia secondary to other immunosuppressive therapy. It was also demonstrated by Soborg et al. that treatment with corticosteroids increases the risk for an indeterminant QFT-GIT.7

There may be a solution for the use of IGRAs in dermatology. A recent rheumatology article compared TST with the T-SPOT.TB assay in precisely the patient population dermatologists commonly encounter. A variety of immunosuppressed rheumatic-disease patients (including rheumatoid arthritis, SLE, vasculitis, scleroderma, sarcoidosis, polymyalgia rheumatica, dermatomyositis, polymyositis, and ankylosing spondylitis) on a vast array of immunosuppressive therapies (including corticosteroids, methotrexate, azathioprine, rituximab, TNF-alpha inhibitors, and cyclophosphamide) were enrolled in this study to compare TST with T-SPOT.TB assay for detection of M. tuberculosis. The findings suggest three critically relevant points:

1. This immunologically complicated patient population all had a strong response to the PHA control in T-SPOT.TB, suggesting that

<table>
<thead>
<tr>
<th>Nil control</th>
<th>Panel A (ESAT-6)</th>
<th>Panel B (CFP-10)</th>
<th>Positive control (PHA)</th>
<th>Results</th>
<th>What does it mean?</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or only a few spots</td>
<td>&gt; (or equal) 6 spots</td>
<td>&lt; (or equal) 5 spots</td>
<td>PHA</td>
<td>Both the test and the patient’s T cells are working properly</td>
<td></td>
</tr>
<tr>
<td>&gt; (or equal) 6 spots</td>
<td>&gt; (or equal) 6 spots</td>
<td>&lt; (or equal) 5 spots</td>
<td>PHA</td>
<td>Indeterminate</td>
<td></td>
</tr>
<tr>
<td>&gt; (or equal) 6 spots</td>
<td>&lt; (or equal) 5 spots</td>
<td>&lt; (or equal) 5 spots</td>
<td>PHA</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>if 5, 6 or 7 spots (close to cut-off)</td>
<td>if 5, 6 or 7 spots (close to cut-off)</td>
<td>Borderline/ equivocal</td>
<td>Due to biological and systemic variations. Retest and use clinical evaluation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2
these patients showed a sufficient response to release of IFN-gamma (despite being immunosuppressed).3

2. There were more false negative results with TST, likely due to skin anergy in immunocompromised patients.4

3. There were more false positive results with T-SPOT.TB assay, which may indicate a reaction to other atypical mycobacteria (from cross-reacting antigens).5

With all of the above in mind, one can take a more educated look at the updated CDC recommendations for the use of IGRAs. In general, the CDC recommends that an IGRA may be used in place of (but not in addition to) TST in all situations where diagnosing M. tuberculosis infection is needed and relevant. “1

To TST in all situations where diagnosing M. tuberculosis infection is needed and relevant. “1

Regardless of results, if a patient has symptoms of TB (even with a negative IGRA), the patient should be treated for latent (or active) tuberculosis.1

Even with additional clinical studies, and even with access to elaborate laboratory technology, physicians must always remember to stress the importance of a complete history and physical in diagnosis and treatment.

References


Case Report

Our dermatology service was consulted to evaluate a 41-year-old Caucasian male who was admitted with a chief complaint of a “burning rash” on the legs. The patient stated his cutaneous symptoms began about one to two weeks prior to admission, with lesions appearing on the lower legs and then progressing to involve the thighs, buttoks and abdomen. He described associated burning, itching and new-onset lower-extremity swelling. He was previously healthy, his only medicine being a non-steroidal anti-inflammatory agent, nabumetone, which he had taken as needed for several years for chronic low back pain. He denied any recent change in dosage or frequency of use. Prior to admission, the patient was started on 40mg of oral prednisone daily and a 10-day course of oral amoxicillin by his primary care physician.

On further questioning, he admitted to experiencing flu-like symptoms consisting of fatigue, body aches, chills and sore throat three to four weeks prior to admission. He did not experience a cutaneous eruption at that time. He denied any current fever, chills, abdominal pain, nausea, vomiting, diarrhea, hematochezia, melena, hematuria or dysuria. He admitted to stable low-back pain secondary to arthritis, but denied any new arthralgia. He had no past surgical history or known allergies.

On physical examination, vital signs were within normal limits, as they had been since admission. Examination of the lower extremities revealed 1+ non-pitting edema. An impressive dermatitis affecting the symmetric bilateral lower legs, thighs, buttocks, groin, and lower abdomen was easily appreciated, consisting of non-blanching petechiae, larger areas of palpable purpura and confluent areas of ecchymoses (Figure 1). Some of the larger purpuric lesions contained central hemorrhagic vesicles and bullae (Figure 2). Some of the lesions appeared targetoid and erythema multiforme-like (Figure 3). The lesions were confined to the lower half of the body, with no lesions apparent above the level of the umbilicus. The palms, soles, upper trunk, upper extremities, head, neck, mucous membranes and nails were spared. The differential diagnosis at this point included HSP, other forms of leukocytoclastic vasculitis, and erythema multiforme.

Routine labs were unremarkable. A CBC with differential was within normal limits with the exception of a slightly elevated neutrophil count, which was attributed to the patient having taken prednisone. Platelets and coagulation studies were within normal limits. A CMP including liver and renal function tests was within normal limits. A urinalysis revealed no evidence of proteinuria or microscopic hematuria. Anti-streptolysin O (ASO) and anti-DNase B titers were negative.

Two 4mm punch biopsies were taken from the right upper thigh. One was sent for routine processing with H&E staining and the other for examination with direct immunofluorescence (DIF). The epidermis showed mild spongiosis. The dermis was remarkable for a superficial and mid-dermal collection of neutrophils with karyorrhexis surrounding dermal capillaries and post-capillary venules. Extravasated erythrocytes, fibrin deposits and loss of endothelial cells were noted. These findings were consistent with a small-vessel leukocytoclastic vasculitis. Further examination with DIF revealed rings of IgA, C3 and fibrin deposits around superficial and mid-dermal capillaries, consistent with an IgA-mediated vasculitis.

The clinical, laboratory and pathologic findings were consistent with a diagnosis of HSP. We recommended completion of the patient’s course of amoxicillin. We also increased the patient’s dose of prednisone to 100mg daily for two weeks with a slow taper over an additional six weeks. The patient experienced cutaneous flares once to twice weekly as the prednisone was tapered down, but otherwise experienced no adverse effects. A glucose-6-phosphate dehydrogenase (G6PD) level was found to be within normal limits, and treatment with dapsone was initiated at a dose of 50mg daily.
At the time of this writing, our patient was first seen by our service about three months ago and has been off of corticosteroids for the last six weeks. His cutaneous symptoms are being controlled with dapsone, with plans to increase the dosage as needed and as tolerated. He still experiences intermittent cutaneous flares, but they are declining in frequency and severity. He has been referred back to his primary care physician with recommendations for monthly blood work and urinalysis for the next 12 months to monitor for potential delayed-onset renal insufficiency and hematuria.

Discussion

HSP is most commonly seen in children less than 10 years of age, with a peak age of onset of 4-7 years. It is the most common form of vasculitis in children. Adults have a much lower incidence of 3-14 per million versus 135-180 per million in children. Peak incidence occurs in the winter and spring, and there is a slight male predominance.\(^1\),\(^2\),\(^3\),\(^4\)

The etiology of HSP is unclear, but has been reported to be associated with numerous infections, medications, vaccinations, malignancies, and inherited conditions (Table 1).\(^5\) In spite of these many associations, no precipitating cause is ever found in the majority of children and adult patients. Children often present one to two weeks following an upper-respiratory-tract infection. A minority of HSP patients have positive ASO titers, though no causative role for group A β-hemolytic streptococci has been established.\(^6\) It is thought that antigens produced through these various processes stimulate the production of immunoglobulins, mostly IgA. Antigen-antibody complexes are subsequently formed, as in other forms of cutaneous small-vessel vasculitides. IgA levels are found to be increased both in circulation and in deposits in vessel walls of the skin, kidneys and GI tract. Immune-complex deposition in vessel walls results in activation of the alternate complement pathway, causing inflammatory cell activation and recruitment and ultimately resulting in vascular damage.\(^6\) The role of complement is further supported by reports of HSP in patients with inherited deficiencies of C2 and C4, as these molecules are believed to play a role in the clearance of immune complexes and/or antigens from apoptotic cells.\(^7\)

Clinically, HSP presents as an acute-onset of the classic tetrad of intermittent palpable purpura on the buttocks and extensor extremities, abdominal pain, arthralgias, and nephritis. Cutaneous lesions begin as macular erythematous papules that may resemble urticaria. They progress to non-blanching petechial pinpoint macules and purpuric papules. Lesions may coalesce into larger ecchymotic areas. Urticaria, hemorrhagic vesicles or bullae, and necrotic foci may be seen. Lesions are symmetrically distributed and commonly involve the buttocks and lower extremities. Rarely, lesions can occur on the upper extremities and face. The trunk is typically spared, but when involved is predictive of renal involvement. Individual lesions typically regress within 10-14 days. Complete cutaneous resolution typically occurs over weeks to months. Lesions tend to fade more quickly with bed rest and may recur more frequently with ambulation.\(^1\),\(^2\)

Common symptoms to specifically inquire about in the review of systems include colicky abdominal pain, nausea, vomiting, melena, hematochezia, arthralgia, and dependent edema. Fever occurs in 20% of adults and 40% of children, while 40-60% of patients experience GI symptoms. Abdominal symptoms occur more commonly in children, occasionally complicated by intussusception. Abdominal pain is also a significant predictor of delayed-onset renal insufficiency and hematuria.
Table 1: Possible triggers associated with HSP*
(Not a comprehensive list)

<table>
<thead>
<tr>
<th>Bacterial infections:</th>
<th>Medications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Group A beta hemolytic streptococci</td>
<td>• Non-steroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>• Staphylococcus aureus</td>
<td>• Angiotensin-converting-enzyme inhibitors</td>
</tr>
<tr>
<td>• Helicobacter pylori</td>
<td>• Angiotensin II receptor antagonists</td>
</tr>
<tr>
<td>• Mycoplasma</td>
<td>• Vancomycin</td>
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<tr>
<th>Viral infections:</th>
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<tbody>
<tr>
<td>• Hepatitis A, B, E</td>
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<tr>
<td>• Herpes simplex</td>
</tr>
<tr>
<td>• Parvovirus B19</td>
</tr>
<tr>
<td>• Coxsackievirus</td>
</tr>
<tr>
<td>• Varicella</td>
</tr>
<tr>
<td>• Adenovirus</td>
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<tr>
<td>• Cytomegalovirus</td>
</tr>
<tr>
<td>• Human immunodeficiency virus</td>
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<table>
<thead>
<tr>
<th>Parasites:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Toxocara canis</td>
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<thead>
<tr>
<th>Vaccinations:</th>
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<tbody>
<tr>
<td>• MMR (Measles, Mumps, Rubella)</td>
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<tr>
<td>• Pneumococcal</td>
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<tr>
<td>• Influenza</td>
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<td>• Meningococcal</td>
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<td>• Hepatitis B</td>
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<tr>
<th>Inherited:</th>
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<tr>
<td>• α1-antitrypsin deficiency</td>
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<tr>
<td>• Familial Mediterranean fever</td>
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<tr>
<td>• HLA-DRB1*01</td>
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<td>• HLA-B35</td>
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<td>• Cefuroxime</td>
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<td>• Quinolones</td>
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<td>• Clarithromycin</td>
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<tr>
<td>• Acetaminophen</td>
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<td>• CODEINE</td>
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<tr>
<td>• Etaacetoin</td>
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<td>• Ranitidine</td>
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<td>• Streptokinase</td>
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<tr>
<th>Malignancies:</th>
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<tbody>
<tr>
<td>• Non-small cell lung cancer</td>
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<tr>
<td>• Prostate cancer</td>
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<tr>
<td>• Lymphoma</td>
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<tr>
<td>• Multiple myeloma</td>
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<td>• Streptokinase</td>
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*Adapted from Sohagia et al.5

Table 2: Differential diagnosis of palpable purpura and plaques*

Arthropod bites
Morbiliform drug eruptions with hemorrhage in dependent sites
Erythema multiforme
Pityriasis lichenoides et varioliformis acuta
Infectious emboli (septic vasculitis):
  Infective endocarditis
  Neisseria meningococcus in acute meningococcemia
  Rickettsiae
  Fungi (e.g., Rhizopus)
Lichenoid capillaritis (pigmented purpura)
Papular urticaria
Systemic lupus erythematosus
Dermatitis herpetiformis
Acute hemorrhagic edema of infancy
Idiopathic thrombocytopenic purpura
Thrombotic thrombocytopenic purpura
Atypical cellulitis

*Adapted from Bolognia3

of nephritis. GI bleeding, if it occurs, is typically self-limited and does not require blood transfusions. Rare GI manifestations include intestinal perforation, pancreatitis, pseudomembranous colitis, acute acalculous cholecystitis, hemorrhagic ascites with serositis, and biliary cirrhosis. In one-fourth of patients, GI symptoms appear prior to cutaneous lesions, and HSP should be considered in the differential of an acute abdomen, especially in children.1,2,5,8

A non-migratory arthralgia is described in greater than 80% of patients, and is more commonly seen in adults. Joint pain is most likely the result of periarticular edema rather than actual inflammatory arthritis of the joint space. Typically involved joints include the ankles, knees, dorsal hands and feet. Arthralgias may precede the appearance of cutaneous findings and can be incapacitating, but are non-destructive and respond to non-steroidal anti-inflammatory agents.1,2,9

Renal involvement is common, but usually mild and self-limited, most often consisting of microscopic hematuria and minimal proteinuria. However, gross hematuria can occur. Nephritis occurs in 20-50% of children, and usually occurs within the first three weeks of disease onset. Adult patients experience more frequent and severe renal involvement, with 10-20% experiencing renal failure versus 1% in children.8 A recent history of infection, pyrexia, purpura involving the trunk, and elevated erythrocyte sedimentation rate (ESR) are all predictive of renal involvement. Nephritis may also be delayed for weeks to months following symptom onset. Progression to nephritic syndrome as well as acute crescentic glomerulonephritis and chronic renal failure is possible.1,2

Acute scrotal swelling may be the presenting manifestation in up to 15% of boys younger than 17 years of age with HSP. Ultrasound is useful to differentiate from surgical emergencies such as testicular torsion or incarcerated inguinal hernia. Other rare manifestations of HSP include involvement of the central and peripheral nervous systems, pulmonary system, and genitourinary tract.2

The differential diagnosis includes other entities presenting with palpable purpuric papules and plaques (Table 2). Evidence of medium-sized vessel disease (e.g., livedo reticularis) or widespread lesions (e.g., involving the face) may indicate an underlying IgA paraproteinemia.7

Children who present with palpable purpura, typical internal manifestations, and without thrombocytopenia may be diagnosed clinically (Table 3). In atypical cases, such as the adult patient lacking systemic features, a tissue biopsy is helpful in confirming the diagnosis.
Table 3: Diagnostic criteria for HSP*

<table>
<thead>
<tr>
<th>Required criterion</th>
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</thead>
<tbody>
<tr>
<td>• Palpable purpuric eruption</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Additional criteria (at least one is required)</td>
</tr>
<tr>
<td>• Diffuse abdominal pain</td>
</tr>
<tr>
<td>• Arthralgia</td>
</tr>
<tr>
<td>• Nephritis (hematuria or proteinuria)</td>
</tr>
<tr>
<td>• Histological evidence of IgA deposits in arterioles, capillaries and venules of the skin, kidneys or gastrointestinal tract</td>
</tr>
</tbody>
</table>

Table 4: Laboratory studies to consider in suspected HSP

<table>
<thead>
<tr>
<th>Required</th>
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<tbody>
<tr>
<td>• Platelet count</td>
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<td>• Coagulation studies</td>
</tr>
<tr>
<td>• UA</td>
</tr>
<tr>
<td>• BUN and creatinine</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Elective</td>
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<tr>
<td>• Lipase</td>
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<tr>
<td>• ESR</td>
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<tr>
<td>• Serum IgA</td>
</tr>
<tr>
<td>• ANA</td>
</tr>
<tr>
<td>• Serum immunoephoresis</td>
</tr>
<tr>
<td>• ANCA</td>
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<tr>
<td>• C3 and C4 levels</td>
</tr>
</tbody>
</table>

Table 5: Criteria for nephritic and nephrotic syndromes

**Nephritic Syndrome**

- **Required**
  - Hematuria (usually with dysmorphic RBCs)
  - Urinary sediment with RBC casts
- **Additional Features**
  - Mild to moderate proteinuria (< 3g in 24 hours)
  - Edema
  - Hypertension
  - Elevated serum creatinine
  - Oliguria (< 400 mL in 24 hours)

**Nephrotic Syndrome**

- Proteinuria (> 3.5 g in 24 hours)
- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Lupiduria
- Hypercoagulability

In a case such as ours, cutaneous punch biopsies should be sent for lesional H&PE and peri-lesional DIF. Additional confirmatory laboratory studies should include a normal platelet count and coagulation studies to exclude thrombocytopenic processes and coagulopathies, respectively. It is also necessary to perform a urinalysis to evaluate for microscopic hematuria and proteinuria, and BUN and creatinine levels to evaluate for renal insufficiency. If abdominal pain is present, a normal lipase level makes pancreatitis unlikely. An elevated ESR correlates with more severe renal involvement. Though not routinely checked, serum IgA levels would be elevated and C3/C4 levels would be depressed. ANA, serum immunoephoresis, ANCA testing, C3 and C4 levels, and genetic typing may be performed if overlap syndromes are suspected (Table 4). CBC is typically normal.1

Other studies not routinely ordered include abdominal ultrasound if gastrointestinal involvement is suspected and also to evaluate for intussusception. Routine abdominal radiographs are not recommended unless there is clinical suspicion for bowel perforation. A stool guaiac test might reveal an occult GI bleed, but may be of minimal clinical utility in the adult patient and as such is not routinely performed. Upper gastrointestinal endoscopy may be useful in demonstrating erythema, edema, petechiae, hemorrhage, erosions or ulcerations of the mucosa. Mucosal biopsies, if taken, would also show capillary deposition of IgA. Renal biopsy would also show the presence of IgA in the renal glomeruli.2,3

Histologically, HSP manifests as leukocytoclastic vasculitis of the small blood vessels (arterioles, capillaries, and post-capillary venules) of the upper to mid-dermis. The typical constellation of findings includes a perivascular infiltrate with neutrophils, neutrophil degeneration (leukocytoclasia) with nuclear dust, fibrinoid necrosis of the vessel walls with fibrin deposition, and extravasated erythrocytes. DIF demonstrates perivascular deposits of IgA, C3 and fibrin in the walls of these vessels. Other immunoglobulins may be seen to a lesser extent than IgA. However, intravascular IgA deposits are not specific to HSP and may also be seen in venous stasis, erythema nodosum, autoimmune connective-tissue diseases, acute hemorrhagic edema of infancy, Wegener’s granulomatosis, and drug-hypersensitivity reactions.10

Clinical correlation is therefore required to make the diagnosis.

Treatment is mainly supportive, utilizing acetaminophen and non-steroidal anti-inflammatory agents, as the symptoms of HSP are typically self-limited with spontaneous resolution occurring over weeks to months. More aggressive management depends largely on the severity of renal involvement, which is more commonly seen in adult patients. Controversy exists surrounding the use of more aggressive therapy, including systemic corticosteroids and/or cytotoxic agents (such as cyclophosphamide, cyclosporine or azathioprine), in patients with severe renal vasculitis in order to prevent progression to chronic renal failure and hypertension.9,11

Systemic corticosteroids are also effective in treating the arthralgia and abdominal pain associated with HSP as well as reducing the duration of cutaneous involvement; however, they do not prevent recurrences of new lesions.12 Dosing is typically 1-2mg/kg of prednisone or methylprednisolone daily for two weeks with a slow taper. Children treated with prednisone for a course of two to four weeks have exhibited more rapid resolution of skin lesions, renal disease, and arthralgia as well as improvement of abdominal pain; however, the risk of developing nephritis over a follow-up period of six to 12 months was not reduced.12,13 Dapsone and colchicine have been reported to decrease the duration of cutaneous lesions.14,15 Factor XIII infusions have been shown to improve arthralgias and gastrointestinal bleeding.16 Several small case series have suggested beneficial effects of plasmapheresis, aminocaproic acid, and...
intravenous immunoglobulin.\textsuperscript{17,18,19}

Outcomes are typically favorable for both children and adult patients. Complete recovery is expected in 94% of children and 89% of adults. One-third of patients have relapses, which are milder and shorter in duration, for several months.\textsuperscript{2} Five percent to 10% of patients experience cutaneous recurrences.\textsuperscript{20} Renal involvement determines long-term prognosis. Two percent of patients will develop chronic renal impairment, and this risk is 10-fold greater in patients who present with nephritic or nephrotic syndrome (Table 5). Adults are also more likely than children to develop significant chronic renal disease, especially if they experience pyrexia, arterial hypertension, purpura above the waist, hematuria/anemia at onset, high creatinine levels at disease onset, proteinuria >1g/day, arteri hypertension, purpura above the waist, hematuria/anemia at onset, high creatinine levels at disease onset, proteinuria >1g/day, an elevated ESR, renal biopsy showing high percentages of sclerotic glomeruli, interstitial fibrosis and fibrinoid sclerosis, persistent purpura, and/or progressively increased proteinuria during follow-up (Table 6).

Urinary abnormalities may persist for two to five years in patients who develop acute nephritis. When HSP presents with more than just microscopic hematuria, only 72% of cases proceed to complete recovery. Evidence of renal disease may reappear after apparent complete recovery, so long-term follow-up is necessary. Monthly urinalysis for at least 12 months is recommended.\textsuperscript{21,22,23} Children and young adults with a history of HSP may also be at increased risk for pregnancy-induced hypertension and/or proteinuria, and should be counseled and evaluated accordingly.\textsuperscript{2}

Conclusion

HSP is typically a vasculitis of childhood with an excellent prognosis; however, it rarely occurs in adults, and in those cases it can have more severe long-term complications. The prognosis depends mainly on the extent of renal involvement and its course, which may be delayed in appearance. The factors that portend a poorer prognosis have been discussed, and the need for continual follow-up and laboratory monitoring even in the absence of initial internal involvement is again restated.

Our patient was an adult male with a cutaneous eruption typical for HSP; however, typical systemic signs and symptoms of HSP were lacking, necessitating a skin biopsy for confirmation of the diagnosis. Our patient continues to lack any detectable sign of renal involvement, but will need to be followed to monitor for delayed-onset nephritis. Of interest, our patient did have a possible recent history of upper respiratory infection and was on chronic NSAID therapy, both counted as possible triggers for HSP.

Table 6 – Predictors of significant chronic renal disease (Adapted from Sohagia\textsuperscript{2})

<table>
<thead>
<tr>
<th>Predictors of significant chronic renal disease</th>
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<tbody>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Arterial hypertension</td>
</tr>
<tr>
<td>Purpura above the waist</td>
</tr>
<tr>
<td>Hematuria or anemia at onset</td>
</tr>
<tr>
<td>High creatinine levels at onset</td>
</tr>
<tr>
<td>Presenting with nephritic or nephrotic syndrome</td>
</tr>
<tr>
<td>Proteinuria &gt;1g/day</td>
</tr>
<tr>
<td>Elevated ESR</td>
</tr>
<tr>
<td>Renal biopsy showing high percentages of sclerotic glomeruli, interstitial fibrosis and fibrinoid sclerosis</td>
</tr>
<tr>
<td>Persistent purpura</td>
</tr>
<tr>
<td>Progressively increased proteinuria during follow-up</td>
</tr>
</tbody>
</table>

References

18. Prandota J, Pankow-Prandota L, Kotecki L. Impaired activation of the fibrinolytic


INTRODUCTION
Aquagenic wrinkling of the palms (AWP), also referred to as transient reactive papulotranslucent acrokeratoderma, is a rare condition that mainly affects adolescents and young women. It often occurs after just three minutes of immersion in water in patients with cystic fibrosis or those who are carriers of the cystic fibrosis gene. Normally, wrinkling of the palmar skin is seen after an average of 11 minutes of immersion in water. AWP has also been linked to COX-2 inhibitor use. We present a case of persistent, painful aquagenic wrinkling of the palms in a young female with no history of cystic fibrosis.

CASE REPORT
A 13-year-old female presented with a history of painful aquagenic wrinkling and edema of the palms that began when she was younger, as intermittent episodes with exposure to water, and thereafter became a chronic problem. She described her lesions as non-pruritic, edematous and painful, and denied involvement of her soles. Review of systems was negative for diarrhea, acholic stools, pneumonia, wheezing, palmar hyperhidrosis, nasal polyps, poor growth, and pancreatic insufficiency. Family history was negative for cystic fibrosis (CF) and excessive palmar wrinkling. The patient denied any use of cyclooxygenase (COX-2) inhibitors such as rofecoxib, celecoxib or aspirin.

On physical exam, the patient had erythema and swelling of palmar hands with small erythematous macules and wrinkling of the palms and digits (Figures 1-2). The patient’s palms were also hyperhidrotic and slightly tender to palpation.

Figures 1-2: Initial patient presentation

The patient was treated with glycopyrrolate 1mg PO BID for one month and had improved significantly when seen for follow-up. There was a 75% decrease in erythema, swelling and pain.

Figures 3-4: Post-treatment demonstrates marked reduction in wrinkling, swelling and pain.

Discussion
Aquagenic wrinkling of the palms (AWP) is a rare condition that mainly affects young women. It presents with exaggerated wrinkling...
of the palms with sharply demarcated small, white-to-translucent papules following brief immersion in water. Patients may experience pain, edema, discomfort, tingling, numbness, pruritus or a burning sensation during an episode. In most cases, the palmar skin returns to normal within a few hours after exposure to water. Plantar involvement of the hands is not observed in AWP; however, the soles of the feet may be involved.

The clinical findings associated with AWP were first described in 1974 by R.B. Elliot, who observed excessive skin wrinkling upon exposure to water in children with cystic fibrosis (CF). The majority of reported cases of AWP have been associated with cystic fibrosis, a mutation in the CFTR gene. Other contemporary theories for AWP include a weakness of the eccrine-duct wall, defective stratum-corneum barrier function, or occlusion of the eccrine-duct ostia. Drug-induced cases of AWP are known to be caused by the use of aspirin and rofecoxib. The most recent speculation regarding mechanism is COX-2 inhibition. COX-2 inhibition prevents the down-regulation of many renal water- and sodium-transport proteins also in keratinocytes. Therefore, this protein, when inhibited by aspirin and rofecoxib, leads to an increase in the sodium retention of these cells, causing increased water retention and wrinkling of the palms.

Histological studies show a hyperkeratotic, dilated eccrine ostia and a hyperkeratotic stratum corneum. In addition, an aberrant aquaporin-5 expression is seen. The association of AWP with cystic fibrosis, and cyclooxygenase-2 inhibitors, suggests that exposure of the skin to abnormally high concentrations of salt may play a role in AWP’s pathogenesis. It is important to recognize this association. In a patient with a CF gene mutation, there might be a lower threshold for developing AWP when taking certain medications such as aspirin or rofecoxib. In addition, in children and adolescents with forms of CF that might have previously gone unnoticed, recognition of this cutaneous manifestation may be the only sign of an underlying mutation. Patients presenting with AWP should be offered screening for both CF and the carrier state.

Treatment

Treatment for AWP is aimed at decreasing the hyperkeratosis and providing a water barrier to prevent exposure. Some patients have reported improvement with 12% ammonium lactate creams, petroleum jelly and glycopyrrolate 1mg PO daily. Other treatments include iontophoresis, antihistamines and acetic acid, but these have been shown to have only limited effects. Using 20% aluminum chloride applied nightly to the palms results in the most effective, rapid improvement of symptoms. Glycopyrrolate has also been shown to have a significant effect on AWP. It works as an anticholinergic drug, reducing certain secretions in different organs in the body. Oral glycopyrrolate tablets are very safe, and by blocking the actions of acetylcholine can help to reduce the stimulation of sweat glands in the hands.

Genetic testing was not recommended in our patient due to the negative family history of CF and lack of associated symptoms. However, with the diagnosis of AWP, the clinician should always further investigate the
patient’s family history and possible symptoms of CF, in addition to any medications used. Had there been a positive history and physical of a possible CF gene mutation, genetic testing and counseling would have been discussed and highly recommended.

References
Discussion
The differential diagnosis for a rash as described includes such entities as:

1. Acute generalized exanthematous pustulosis (AGEP)
2. Fixed drug eruption (FDE)
3. Hypersensitivity syndrome (HSS), also known as "drug rash with eosinophilia and systemic symptoms" (DRESS)
4. Serum sickness-like reaction
5. Systemic drug-related intertriginous and flexural exanthem (SDRIFE), also known as "baboon syndrome" in some reviews.12

Acute generalized exanthematous pustulosis
Acute generalized exanthematous pustulosis (AGEP) typically presents initially with an edematous erythodermic eruption in the body folds or on the face, with subsequent dissemination of primarily non-follicular, sterile pustules. The eruption is associated with high fever and leukocytosis with high neutrophil count. Pustules resolve spontaneously within a few days and are typically followed by a characteristic pinpoint desquamation. The whole episode lasts up to 15 days.

The estimated incidence is one to five cases per million per year. Occurring at any age, males and females are equally affected. More than 90% of the AGEP cases are drug-induced, with antibacterial medications being the most frequent triggers. In a minority of cases, viral infections have been suspected.

This is a self-limited disease with a favorable prognosis, although secondary infection might pose danger to patients in poor general condition, in which mortality can reach 5%

Fixed drug eruption
Fixed drug eruption (FDE) is a drug-induced disorder clinically distinguishable by its localized, often acral or mucosal, asymmetric, frequently pigmented, round-oval lesions. These lesions normally resolve with hyperpigmentation and typically recur at the same site with re-exposure to the offending drug. Fixed drug eruptions have been reported in patients as young as 1.5 years and as old as 87 years.

The prevalence of drug eruptions has been reported to range from 2-5% for inpatients and greater than 1% for outpatients.10 Fixed drug eruptions may account for as much as 16-21% of all cutaneous drug eruptions. The actual frequency may be higher than current estimates, owing to the availability of a variety of over-the-counter medications and nutritional supplements that are known to elicit fixed drug eruptions.

No deaths have been attributed to fixed drug eruptions. Widespread lesions may initially mimic toxic epidermal necrolysis, but they have a benign clinical course.12 Localized hyperpigmentation is a common complication; pain, infection, and, rarely, hypopigmentation also may occur.

Although the exact mechanism is unknown, research suggests a cell-mediated cytotoxic process.8 The process may involve an antibody-dependent, cell-mediated cytotoxic response.4 CD8+ effector/memory T cells play an important role in reactivation of lesions with re-exposure to the offending drug.4,5 The offending drug is thought to function as a hapten that preferentially binds to basal keratinocytes, leading to an inflammatory response.4 Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1).7 The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult.46

The newly arriving and resident CD8 cells likely perpetuate tissue damage by their production of the inflammatory cytokines interferon-gamma and tumor necrosis factor-alpha. Changes in cell-surface markers allow vascular endothelium to select CD4 cells for migration into active lesions. These regulatory CD4 cells likely produce interleukin 10, which has been shown to help suppress immune function, resulting in a resting lesion.7 As the inflammatory response dissipates, interleukin-15 expression from keratinocytes is thought to help ensure the survival of CD8 cells, helping them fulfill their effector-memory phenotypes. Thus, when re-exposure to the drug occurs, a more rapid response develops in the exact locations of any prior lesions.7

Hypersensitivity syndrome (DRESS)
Hypersensitivity syndrome (HSS), also known as drug rash with eosinophilia and systemic symptoms (DRESS), can often lead to lethal organ involvement such as fulminant hepatitis and must be diagnosed rapidly. In 1950, phenytoin was first reported in association with the constellation of symptoms that now characterizes HSS. The "phenotypic" diversity of this syndrome hampers the development of accepted diagnostic criteria. Its main clinical features, which include rash, fever and internal organ involvement, could be attributed to a wide range of other causes such as infectious diseases, neoplastic diseases, collagen vascular disorders and also adverse drug reactions. In addition, asymptomatic systemic involvement such as eosinophilia and atypical lymphocytes are often missed. Also, the clinical features of this syndrome are not all present simultaneously. Thus, long-term follow-up is needed to accurately identify patients with this syndrome. Since it appears following a long latency (2–8 weeks) after initiation of the culprit drug, and it has a prolonged course after cessation of the culprit drug, the symptoms are often not recognized as drug-related. The diagnosis, then, is made by exclusion.

General awareness of HSS is important due to the severity and life-threatening potential of this type of drug reaction, as the reported mortality rate is around 10%.

The lack of consensus regarding the definition of HSS has practical implications impeding the development of better diagnostic tests and treatment methods. Nevertheless, great strides have been made to elucidate the natural history and pathogenesis of HSS, and so far it can be concluded that HSS is characterized by: drug-induced immunological background, later onset than other drug reactions, longer duration than common "drug rashes," multiorgan involvement, lymphocyte activation, eosinophilia, and herpes virus reactivation.

Serum sickness-like reaction
Serum sickness-like reaction refers to an immune-complex disease following parenteral injections of therapeutic sera. The immune complexes consist of antigen and IgG, usually with antigen excess (type III reaction). As the amount of antibody formed increases, phagocytic mononuclear cells eliminate the antigen slowly. The immune complexes cause intravascular complement activation and subsequent immune complex–induced necrotizing angiitis, which is responsible for the diverse clinical symptoms of this syndrome. Eventually, the circulating complexes shift to antibody in excess of antigen, and the clinical signs subside.

Initial onset is after one to three weeks, but it may be as soon as two to four days after secondary exposure. Over 70 percent of patients with serum sickness manifest urticaria, often preceded by pruritus and erythema. Urticarial lesions are persistent, lasting a few days, and are sometimes tender or painful with bruising, unlike classical urticaria. Characteristically, a serpiginous, erythematous and purpuric eruption develops on the hands and feet at the borders of palmar and plantar skin, from the dorsa of the extremities (Wallace's line). Systemic features might include fever, joint pain and swelling, lymphadenopathy, and occasionally proteinuria, nephritis or endocarditis, with eosinophilia. In minor forms, fever, urticaria and transitory joint tenderness may be the only manifestations.

Serum sickness-like reactions may be produced by exposure to drugs such as penicillin, hydantoins, aminosalicylic acid,
streptomycin, thiazides, sulfonamides, streptokinase, tamoxifen, oral contraceptives, anti-influenza vaccine, and anti-snake venom serum. Other causes of serum sickness-like syndrome include radiopaque contrast media; infections (a serum sickness-like syndrome occurs in about 20 to 30 percent of patients with hepatitis B infection); and rarely, foods.

The diagnosis is mainly based on the time lag between initiating the offending agent and the appearance of the symptoms, the clinical manifestations, and the absence of other immunological or infectious causes. Prompt discontinuation of the offending agent and supportive care are the mainstays of treatment. Aspirin and antihistamines may relieve the symptoms. In case of severe symptoms, a short course of high-dose corticosteroids may be warranted. However, symptoms are usually self-limited, lasting for five to 28 days and resolving without sequelae. Avoidance of the offending agent is important.

Systemic drug-related intertriginous and flexural exanthem ("baboon syndrome")
The term "baboon syndrome" was originally introduced in 1984 to describe a mild systemic cutaneous reaction after oral exposure to type IV allergens, such as nickel, mercury or drugs. Recently, it has been proposed to replace this term by the acronym SDRIFE (systemic drug-related intertriginous and flexural exanthem). One hundred cases between 1984 and 2004 have been documented, with amoxicillin being the most common drug causing SDRIFE, followed by cephalosporins.

SDRIFE describes a special form of systemic contact dermatitis that occurs after systemically administered drugs. The proposed pathophysiology of SDRIFE is most likely a T cell-mediated reaction. The intertriginous and flexural areas are sites that are frequently stimulated mechanically. Mechanically stimulated skin exhibits enhanced expression of intercellular adhesion molecules on the keratinocytes, contributing to the accumulation of drug-activated lymphocytes there.

The diagnostic criteria for SDRIFE include:
1. exposure to a systemically administered drug
2. sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area
3. involvement of at least one other intertriginous/flexural fold
4. symmetry of affected areas
5. absence of systemic symptoms and signs

SDRIFE is self-limited, and treatment consists of avoiding the precipitating allergens as well as providing symptomatic relief and wound care. Medium-to-high-potency topical or systemic glucocorticoids may hasten recovery.

Summary
Our patient’s bullous intertriginous eruption had a short onset, no serious organ involvement, and complete resolution after cessation of offending medication, leading us to the conclusion that he had SDRIFE. Although no biopsy was performed due to the patient’s lack of systemic symptoms and signs and the classic clinical picture, histopathologic examination would have contributed to our report, as there is little data on this matter. Some authors indicate that the lesions demonstrate a non-specific dermatitis, while others have seen findings consistent with a toxic epidermal necrolysis (subepidermal bulla with confluent necrosis...
of the overlying epidermis, and perivascular infiltrate of lymphocytes which, if present at all, is usually sparse). As further information is gathered on the histopathologic and immunologic findings in the skin biopsy of a patient with SDRIFE, dermatopathologists will become important players in helping recognize this severe-appearing eruption as a reaction to medications. Dermatologists who are familiar with classic presentations of common drug-induced reactions will be essential contributors to the medical team caring for patients.

References

An 18-year-old female presented to our dermatology clinic with a three-month history of pruritic lesions extending from the right upper thigh to lower leg in a linear pattern. The patient was otherwise healthy and had no significant past medical history. She denied previous or concomitant history of herpes zoster infection or trauma at the site of the involved skin. Prior dermatologic history was significant for lichen simplex chronicus involving the forehead and submental area. Patient’s only medication was an oral control pill.

Physical examination of the skin revealed multiple violaceous and polygonal papules with Wickham’s striae along the L4 dermatome of the right lower extremity (Figures 1-3). The mucous membrane, hair, and nails were spared. Sections of the punch biopsy showed an irregularly acanthotic epidermis with a dense lichenoid band of lymphocytes and histiocytes in the superficial dermis and abutting the dermoepidermal junction. There were occasional melanophages in the papillary dermis and occasional dyskeratotic keratinocytes in the epidermis. There was overlying compact orthokeratosis and foci of wedge-shaped hypergranulosis (Figures 4-5). Serology for hepatitis C antibody was negative. Hepatitis B serology was reactive for hepatitis B surface antibody. Based on the clinical and histopathological findings, a diagnosis of zosteriform lichen planus was made. The patient was treated with topical triamcinolone acetonide (0.1% twice daily) for three months and subsequently switched to clobetasol propionate ointment (0.05% twice daily). Her itching improved, and her lesions are controlled. A regular follow-up with our clinic was suggested to see the course of the disease. She is followed by her primary care physician for the positive hepatitis B serology.

Discussion
Lichen planus (LP) is a relatively common skin disease of unknown etiology characterized by erythematous to violaceous, flat-topped, polygonal papules. A thin, transparent, and adherent scale may be present atop some lesions. Fine, whitish puncta or reticulated networks known as Wickham's striae is present over the surface of many papules. Symmetric involvement of the flexor surfaces of the wrist, arms, and lower extremities is common. Oral mucous membranes and the genitalia may also be affected. Lichen planus tends to be pruritic, although some patients are completely asymptomatic.

LP may exhibit numerous variations in pattern and are generally categorized according to the configuration of lesions, morphology, or the site of involvement. Variants of LP include annular, linear, hypertrophic, atrophic, vesiculobullous, erosive and ulcerative, follicular, actinic, and pigmentosus.1 Linear LP refers to LP with a unilateral, linear distribution. Histopathologically, linear LP is identical to LP. Key features include band-like infiltrate of lymphocytes at the epidermal-dermal junction, hyperkeratosis, focal areas of wedge-shaped hypergranulosis, and elongation of rete ridges that resemble a sawtooth pattern. Multiple apoptotic cells or colloid-hyaline (Civatte) bodies are present at the dermal-epidermal junction. The differential diagnosis of linear LP includes lichen striatus,2 linear verrucous epidermal nevus,1 and linear psoriasis.

Linear LP commonly presents secondary to trauma (koebnerization)4 or on the site of healed herpes zoster, an example of the Wolf’s isotopic response.5-7 In extremely rare cases, linear LP presents in a segmental fashion corresponding to one dermatome and is termed zosteriform LP. Zosteriform or linear distributions appear de novo on previously normal, non-traumatized skin, as in our patient. Although case reports of de novo zosteriform LP have been reported,8-10 this entity is controversial. Happle argued that in most reported cases of zosteriform lichen...
ZOSTERIFORM LICHEN PLANUS LIMITED TO L4 DERMATOME OF THE RIGHT LOWER EXTREMITY

In our patient, the distribution of lesions followed the L4 dermatome. The patient denied history of herpes zoster infection, and lesions did not occur on any previous site of trauma. The linear eruption seemed to follow a true dermatome rather than the lines of Blaschko on the lower extremity. Interestingly, reports of LP associated with hepatitis C infection, chronic active hepatitis, and primary biliary cirrhosis have been reported.

Our patient’s lesions and pruritus are currently controlled with topical corticosteroids. She will continue to follow up in our dermatology clinic for her skin lesions as well as with her primary care physician for the positive hepatitis B serology.

References

INTRODUCTION

Wells’ syndrome, or eosinophilic cellulitis, is a hypersensitivity reaction of unknown etiology. It is typically described as an acute, recurrent, pruritic skin reaction. While the etiology is unknown, this syndrome has been linked to a variety of allergic stimuli and arthropod bites,1 as well as cutaneous viral and fungal infections, parasitic infestations, and medication-hypersensitivity reactions.2 Familial cases have been described as well. About eighty cases have been reported in the literature.3 The syndrome has an excellent prognosis.

Case Description

A 17-month-old girl was referred to the dermatology clinic by her primary care manager for pruritic skin lesions of a few months’ duration that would resolve and then return. Her parents stated that the child had itchy, round lesions that appeared on her bilateral forearms, hands, plantar feet, and legs over the past month that would appear abruptly (Figure 1). Blistering was observed with some of the lesions (Figure 2). The lesions would resolve and then appear elsewhere, with random intervals of time between outbreaks. Some lesions appeared in areas where the mother stated she witnessed the child being bitten by mosquitoes a few hours earlier, while others had no clear association to anything and appeared in clothing-covered areas. The mother also reported the child had recurrent unexplained fevers for the last two to three months, which preceded skin symptoms. The child’s history was otherwise unremarkable, and she appeared healthy. No household family members shared similar symptoms. The mother reported sleeping in the same bed as the child a few times before the lesions were noted in the morning. The mother had no such symptoms. There were no pets in the household. The lesions did not respond to various courses of oral trimethoprim/sulfamethoxazole, topical mupirocin, permethrin treatment for presumptive scabies, chlorhexidine washes or oral antihistamine treatment. Skin bacterial cultures were negative. Initial complete blood counts (CBC) were unremarkable. The last CBC showed elevated band neutrophils but no leukocytosis. Punch biopsy of a lesion revealed compact orthokeratosis overlying an epidermis containing numerous eosinophils and a dermis with eosinophilic infiltrate with scattered flame figures (Figures 3 and 4). The patient’s blood work never revealed any hypereosinophilia.

Discussion

The clinical presentation along with histopathology led to a diagnosis of...
Wells’ syndrome, or eosinophilic cellulitis. Childhood cases are rare and may be associated with more severe blistering. A PubMed search revealed a review of 27 pediatric cases from 1979 to 2005, and a search of cases from 2005 to 2012 revealed 10 additional pediatric cases cited in the literature. This is a benign condition not usually associated with systemic manifestations, although a few cases have been linked to leukemia, myeloproliferative and lymphoproliferative disorders, and other underlying nonhematologic malignancies.

Clinically, most cases present with pruritic, erythematous, edematous plaques that appear over a few days and resolve in two to eight weeks. As the lesions resolve, they may indurate and discolor. Lesions most commonly present on the limbs, followed by the trunk, arms, and face. Lesions typically heal without scarring, although atrophy and hyperpigmentation can persist. Recurrence typically occurs over several years, with a mean relapse rate of four times in adults and three times in children. Seven clinical variants have been identified to include plaque-type, annular granuloma-like, urticarial, papulovesicular, bullous, papulonodular, and fixed drug eruption-like. The most common presentation in children is the classic plaque type, while adults most frequently exhibit erythematous annular lesions. While uncommon, systemic symptoms such as malaise and arthralgia can occur, and fever is even less common.

While the etiology is unclear, this hypersensitivity reaction is most commonly associated with a variety of allergic stimuli and arthropod reactions. In the spectrum of hypersensitivity disorders, Wells’ syndrome represents the benign cutaneous end, while hypereosinophilic syndrome represents the multiple-organ-system-dysfunction end. Histopathology may overlap between the two syndromes, but Wells’ syndrome lacks the persistent blood eosinophilia and multiorgan involvement.

Differential diagnosis includes allergic and contact dermatitis, drug reaction, granuloma annulare, candidiasis, Churg-Strauss syndrome, bullous arthropod bite reaction, and cellulitis. The history of spontaneous lesion eruption in multiple areas (including some clothing-covered areas), inconsistent blistering of lesions, lack of lesions in family members, and failure to respond to antihistamine treatment suggested this was a diagnosis other than an arthropod bite reaction. Of the differentials, cellulitis is the most likely diagnosis to be confused for Wells’ syndrome, as clearly demarcated erythematous indurated lesions can occur in both cases. However, cellulitic infections will rapidly expand in 24 hours and are more likely to be associated with systemic symptoms such as fever, chills, and malaise. Wells’ syndrome lesions are more typically pruritic than painful and tender. Wells’ syndrome should be considered in the setting of negative bacterial skin cultures and lack of response to antibiotic treatment. Clinicians should consider obtaining a CBC to check for eosinophilia, although it is not present in all stages of disease and is only present 50% of the time. Biopsy is necessary for diagnosis. Histology demonstrates a dense infiltration of eosinophils and histiocytes in the dermis in the acute stage, widespread degranulation known as “flame figures” in the subacute stage, and phagocytic histiocytes and few eosinophils in the resolving stage. Flame figures are not specific to Wells’ syndrome and can be seen in biopsies of eczema, herpes gestationis, scabies, prurigo nodularis, and Trichophyton rubrum infection.

The time course of Wells’ syndrome is variable, as is the response to treatment. Lesions will heal without treatment,
although reasons to treat include persistent lesions, patient comfort, and prevention of a secondary bacterial infection. Most localized disease is treated with topical corticosteroids. Isolated cases of successful treatment with tacrolimus, colchicine, antimalarial drugs, and immunosuppressive agents have been described in the literature. The mainstay of treatment remains oral corticosteroids, which have been shown to decrease the duration of symptoms in cases of widespread or persistent disease, alone or in combination with dapsone. Antihistamines are often given to reduce pruritus. The patient’s parents opted not to use oral steroid treatment as the lesions had lessened and the child appeared more comfortable. As of this writing, the patient was lost to follow-up.

References


INTRODUCTION

Periungual fibromas (Koenen tumors) present as flesh-colored or red papules arising from the proximal nail matrix. They usually lead to a longitudinal groove in the nail plate and may be painful. A periungual fibroma is one of the major clinical criteria for the diagnosis of tuberous sclerosis (TS) and, along with facial angiofibromas, is often considered pathognomonic of the disease. In some cases, Koenen tumors may be the only clinical manifestation of TS at the time of diagnosis. There are no reports in the literature to date of familial inheritance of Koenen tumors without the presence of multisystem disease.

We present a case of a mother and daughter with multiple Koenen tumors, no clinical evidence of systemic disease, and negative genetic testing for the TSC1 and TSC2 gene mutations.

Case Report

A 15-year-old girl presented with a skin-colored to reddish, painful periungual tumor on the left second finger (Figure 1). The tumor began to develop one to two years prior and had been increasing in size. The patient attempted treatment with over-the-counter wart remover and physical removal with nail files and clippers without success. She was otherwise healthy with no history of cardiac, renal, or neurologic disease. She was of normal intelligence.

The minor was accompanied by her 42-year-old mother, who reported multiple similar periungual tumors on both her fingers and her toes but was otherwise healthy (Figures 2 and 3). The patient’s 11-year-old brother and maternal grandmother were unaffected by these tumors, and further family history was negative. Physical exam of the patient and mother revealed no hypomelanotic macules, facial angiofibromas, shagreen patches, dental pits, or gingival hamartomas. Excisional biopsy was performed, and histology was consistent with fibroma, showing orthokeratosis and dense fibrotic tissue with atypical stellate fibroblasts. Molecular genetic analysis for gene mutations of the TSC1 and TSC2 genes was performed and was negative.
Discussion
Tuberous sclerosis is a genetic disease inherited in an autosomal-dominant manner; however, in up to 75% of affected individuals it is due to a spontaneous mutation. The genes responsible for tuberous sclerosis are TSC1 and TSC2, tumor suppressor genes, located on chromosome 9 and 16, respectively. Mutations in these genes lead to hamartomatous growths affecting the brain, skin, eyes, kidneys, heart, lungs, and bones. The expression of these gene defects and the clinical severity that results is highly variable among patients, even among patients within the same family. Diagnosis is typically made with clinical criteria set forth by the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association (USA). Table 1 is provided to list the required diagnostic criteria for TS. Genetic testing is now available and identifies mutations in the TSC1 or TSC2 gene in 75-80% of affected individuals. This test is most useful in questionable cases, prenatal diagnosis, and for screening family members of affected individuals.

We present a unique case of familial development of multiple Koenen tumors without apparent multisystem involvement or TS diagnosis. Sporadic appearance of Koenen tumors can occur, and acquired digital fibromas are clinically and histologically similar but are usually solitary and likely trauma-induced. Literature review revealed two cases of multiple acral and periungual tumors without TS association. In the first, Moulin et al. described a 70-year-old woman, her 50-year-old son, and his 27-year-old daughter all presenting with multiple mucinous fibrokeratomas on their palms and fingers, without the presence of a multisystem familial disease. Although they resembled Koenen tumors of TS, they differed in both location and histologic appearance. Dereure et al. described a case of multiple acral fibromas, mostly located in the subungual region, in a patient with familial retinoblastoma. This report hypothesized that multiple cutaneous fibromas may be a clinical marker of inheritable disorders with germ-line mutations of tumor suppressor genes, citing TS, neurofibromatosis, multiple endocrine neoplasia type 1, Li-Fraumeni syndrome and familial retinoblastoma as examples.

It is possible that these patients represent the very mildest clinical manifestation of TS, considering the extreme variability in clinical severity associated with the disease. This patient and her mother may be in the 20-25% of people affected by TS in whom current genetic testing is negative. Cardiac, neurologic, and renal manifestations of TS typically present in infancy or childhood, and pulmonary manifestations present in the second to third decade, but this is variable. The individuals we present here may not have yet developed the clinical manifestations of the hamartomatous growths that affect the brain, kidneys, lungs, and heart. Alternatively, this mother and daughter may represent a unique case of familial Koenen tumors without the association of any systemic involvement. Only time can elucidate this. In cases like this one, patients should be followed closely for clinical manifestations of systemic involvement so that early treatment can be initiated.

Acknowledgements
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References:
### Table 1: Diagnostic Criteria for Tuberous Sclerosis

#### Major Features
- Facial angiofibromas or forehead plaque
- Non-traumatic ungula or periungual fibroma
- Hypomelanotic macules (more than three)
- Shagreen patch (connective-tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant-cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

#### Minor Features
- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white-matter migration lines
- Gingival fibromas
- Non-renal hamartoma
- Retinal achromatic patch
- “Confetti” skin lesions
- Multiple renal cysts

#### Criteria
- **Definite TSC:** Either 2 major features or 1 major and 2 minor features
- **Probable TSC:** One major and one minor feature
- **Possible TSC:** Either 1 major feature or 2 or more minor features

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Abstract
Calciphylaxis is a rare but often lethal vasculopathic disorder that has a high predilection for patients with renal disease. It is most commonly recognized by the rapid progression of cutaneous ischemia and necrosis due to calcification, intimal fibroplasias, and pannicul ar thrombosis of arterioles. Commonly referred to as “metastatic calcification,” calciphylaxis has been attributed to the imbalance between serum calcium levels and phosphate levels. This imbalance has been largely associated with renal failure; more recently, it has been associated with hyperparathyroidism, diabetes mellitus, female sex, obesity, warfarin use, protein C and S deficiency, and a high phosphate level, as well. Additionally, a considerable number of patients with calciphylaxis have normal serum calcium levels or minimal to no renal impairment, suggesting an obscure causative factor to this condition. Evidence supporting the mechanism behind calciphylaxis is weak. We hope to shed light on its pathogenesis, risk factors, and other variables that may be implicated in its development and progression. Referencing these factors would open up additional discussions on future therapies for prevention and resolution of this often devastating disease process.

Case Report
A 61-year-old Hispanic female presented to the emergency department with altered mental status. According to the patient’s family, she was noted to have lesions on her bilateral lower extremities that began to appear two weeks prior. The lesions were initially red in color but changed to a black discoloration over the past “few weeks.” She had seen a doctor weeks prior and was told that she had cellulitis. She completed a one-week course of vancomycin. Blistering of the area and eschar formation were noted three days prior to her admission to the hospital.

Her past medical history was significant for hypertension, congestive heart failure and diabetes mellitus complicated by end-stage renal disease, and she was on dialysis. The patient was taking aspirin, ipratropium, vitamin B and C complex, folate, senna, metoprolol, hydralazine, esomeprazole, isosorbide mononitrate, metformin, lactulose, and sevelamer hydrochloride. She denied alcohol and drug use. Her family history was negative for any significant dermatologic disease or autoimmune disorders.

Physical exam revealed necrotic plaques with induration and bullae of the lower extremities, bilaterally. The area was surrounded by livido-like or retiform-like purpura (Figures 1 and 2) and scattered hemorrhagic bullae with large, violaceous borders on the right and left thighs with areas of necrosis. All sites were tender to palpation. Laboratory analysis was significant for hyperparathyroidism (PTH 438.7 pg/mL) with elevated serum calcium and phosphorous levels, 8.0mg/dL and 7.9mg/dL, respectively. Coagulation parameters were normal.

A 4-mm punch biopsy of the left lower calf was obtained, revealing subcutaneous calcium deposits with panniculitis and fat necrosis. Seldom, areas of calcification within the media of small- and medium-sized arterioles with intimal hyperplasia and fibrosis were also noted (Figures 3 and 4). The patient was diagnosed with calciphylaxis on the basis of clinical history, physical exam, and laboratory and histological findings.

Treatment was initiated with intravenous sodium thiosulfate after each dialysis. Daily wound care was introduced with application of mupirocin ointment, lidocaine ointment 5% and mometasone furoate ointment 0.1% to sites of necrotic tissue. The patient also underwent pain management. Unfortunately, due to progressive renal failure, the patient expired several weeks after her hospital admission.

Historical Perspectives on Calciphylaxis
The first-ever mention of the occurrence...
of calciphylaxis was by Bryant and White in 1898 as a subsequent effect of uremia. Nearly 70 years later, Selye et al. coined the term “calciphylaxis” for more-acute local calcification and related it to a local hypersensitivity reaction in a rodent model after exposure to various sensitizing agents. He referred to agents such as dihydrotachysterol, vitamin D2, vitamin D3, and parathyroid hormone as “calcifiers.” Although a noble attempt at explaining this condition, he later revoked his initial hypothesis and suggested instead that it was extensive calcification of soft tissues due to high doses of vitamin D.6,7 Subsequently, Selye et al. defined calciphylaxis as it was reported in humans as a syndrome primarily seen in uremic patients.6,7 Further evidence by Gipstein et al. strengthened Selye’s observations by thoroughly demonstrating that tissue calcification occurs with severely uremic patients undergoing hemodialysis. He noted that both initiation and progression of necrotic lesions were largely related to uncontrolled levels of calcium and phosphate. In the event that subcutaneous, necrotic lesions developed, a therapeutic parathyroidectomy was performed, demonstrating the importance of calcium balance.6 The benefits of a therapeutic parathyroidectomy in relationship to uremic calcification were further explored and encouraged in 1995 by Hafner et al. In that case, out of 100 patients diagnosed with end-stage renal failure, 58 patients underwent therapeutic parathyroidectomy, and of those, 38 patients survived; in the control group, only 13 of the 37 patients survived. Hafner described the development of these lesions as “uremic small-artery disease characteristic of skin necrosis and acral gangrene due to medial calcification and intimal hyperplasia in arteries of subcutaneous tissues” of the extremities.7 This served as additional evidence of the intricate relationship between end-stage renal disease, the administration of appropriate hemodialysis, and the consequence of subcutaneous calcification.

Clinical Presentations of Calciphylaxis
Several case reports have shown the clinical rarity that surrounds the diagnosis of calciphylaxis as well as the severity of the condition clinically. The majority of patients seen with clinical evidence of calciphylaxis have received a kidney transplant or are undergoing dialysis. The development of lesions begins as painful, symmetrical, violaceous discolorations of the skin that evolve into well-demarcated, non-healing ulcers.2 Most commonly, lesions on the shoulders, trunk, buttocks, and thighs have a poor prognosis due to the propensity for a larger degree of necrotic tissue. Chan et al. were able to confirm that patients undergoing dialysis who developed proximal lesions were more likely to die than those with distal lesions.8

In order to accurately diagnose this condition, one must have a high index of suspicion, as there are several differential diagnoses for necrotic ulcers.2,8 The typical presentation is a uremic patient with a characteristic necrotic lesion with abnormalities in laboratory values. Commonly, patients have hyperphosphatemia, increased serum calcium-to-phosphate level, moderately elevated serum parathyroid hormone, and a normal to slight increase in serum calcium levels.10,11 Additional studies do not aid in the diagnosis of this condition but may be warranted depending on other presentations of the disease.

Histological Profile of Calciphylaxis
The early stages of calciphylaxis include collagenous degeneration with erythrocytotic extravasation.11 Microcalcifications in small to medium-sized venules are often evident, as well as fine granular stippling of the vascular media. In addition to microvascular calcifications, the most consistent features are acute and chronic panniculitis in a septal pattern as well as slight to moderate inflammation. The dispersed infiltrate is usually neutrophils, lymphocytes, and rare eosinophils. In the early-phase lesions, neutrophils and lymphocytes can be seen within the dermis along with a deep perivascular infiltrate. Of note, there have been studies that have seen minimal to no inflammation and solely calcific venules.11-13

In late lesions, endovascular endothelial proliferation and intimal fibrosis in cutaneous blood vessels are seen, but these findings are not very common. Many cases also show the concomitant presence of micro-thrombi as well as thrombosis of larger venules. In one case studied by Essary et al., marked endovascular proliferation with luminal occlusion and partial re-canalization was seen in addition to dermoepidermal separation and epidermal devitalization. On a histological level, the most consistent finding is still intravascular calcium deposits within small and medium-sized venules and arterioles with or without necrosis using the confirmatory von Kossa stain.11 It is important to recognize that many conditions can mimic the histologic findings associated with calciphylaxis, and many diseases can stimulate the production of subcutaneous findings. As described by many other clinicians, peripheral vascular disease,
atheroembolus syndrome, septic emboli, oxalosis, protein C or S deficiency, Coumadin necrosis, lupus antiphospholipid syndrome and other calcifying disorders are convincing mimickers.4,7,10,11 Hence, clinical assessments as well as other pertinent laboratory values are essential in making this diagnosis.

Pathogenesis of Calciphylaxis: The Old and New Evidence

Determining the pathogenesis of calciphylaxis has been a challenging and speculative process.1 Although poorly understood, there are a number of associated diseases and biological triggers that play a convincing role in this condition.14 As stated previously, the first mention of human subcutaneous calcification was in relation to vascular calcification secondary to renal failure.1,4,5 More recently, there has been work in bone and cardiovascular diseases that has shown a reliable relationship with calcification.13 Several very crucial parts of bone mineralization are the molecular and cytochemical factors, receptor activator of nuclear factor-KB [RANK], RANK ligand, and osteoprotegerin. These also appear to regulate extraskeletal mineralization and could have a potential role in calciphylaxis.13,15 In a study by Luo et al., a specific matrix protein called mineral-binding ECM protein (Mgp) was shown to be a potential factor in arterial calcification. Shown in a mouse model, those animals that lacked this gene died within two months as a result of arterial calcification as well as inappropriate calcification of various cartilages. This revealed that to prevent calcification in soft tissues, there must be an inhibitory signal.13 This is a potential avenue of study to possibly correlate subcutaneous-tissue calcification with a potential causative mechanism, leading to a modality behind calciphylaxis.

However, there are other causative factors that could increase the expression of RANK ligand, in turn causing a decrease of the expression of osteoprotegerin. These factors include but are not limited to parathyroid hormone, corticosteroids, aluminum, liver disease, and various other forms of inflammation.13,15 Osteoprotegerin (OPG) is a protein that inhibits osteoclast formation and has a significant relationship to bone density and prevention of calcification in inappropriate areas of the body. Bucay et al. demonstrated that mice deficient in this protein exhibited a decrease in total bone density and high incidence of fractures. Unexpectedly, they also noted that mice deficient in this protein exhibited medial calcification of the aorta and renal arteries.16 This suggests a crucial role for OPG in calcification, once again showing the importance of gene regulation in extraskeletal calcification, leading to a potential correlation with calciphylaxis.

By far the most common disease associated with calciphylaxis is end-stage renal disease, a correlation that has increased in frequency in the last decade. In a retrospective study performed by Mazhar et al., patients diagnosed with calciphylaxis and end-stage renal disease over a 10-year period were observed and treated according to study designs. They collectively reviewed the risk factors for calciphylaxis and determined that female gender, low serum albumin, elevated serum phosphate, and higher serum alkaline phosphatase levels were all significant. They also determined that patients who developed calciphylaxis during their time in dialysis had an eightfold increase in risk of death. It was also determined that the increased risk associated with female gender was due to its relatively large proportion of adipose tissue compared to males due to hypoperfusion of the skin. Similarly, persons with more
abundant adipose tissue are also at increased risk, leading to an association between obesity and subcutaneous calcification.\(^9\)

One metal, aluminum, has been an unlikely culprit in the formation of calciphylaxis, backed by several pieces of supporting evidence.\(^{1,13}\) Aluminum is renally cleared from the body, and toxic levels of aluminum are often not reached without pre-existing renal insufficiency.\(^7\) Weenig et al. demonstrated that aluminum levels greater than 25ng/ml are much more common in calciphylaxis patients. To parallel this finding, aluminum, which is found to be deposited in the bone, is directly related to the severity of arterial calcification and acts directly on osteoblasts.\(^{1,13}\) Furthermore, the severity of bone aluminum deposition is directly proportional to the extent of arterial calcification in patients who are undergoing dialysis.\(^{17}\) Since it is unclear whether or not aluminum itself is related to dialysis, it is safe to assume that renal impairment is the leading cause of the accumulation of the metal.

Although there are many intricate pathways that seem to be involved in the pathogenesis of calciphylaxis, not one has been solely implicated. Therefore, it is important to take into consideration all the various data available but always consider the most common causes when suspecting this condition.

Past, Present and Future in Treatment Calciphylaxis is a condition that dermatologists are often called in to diagnose. When it comes to treatment options, it is difficult to take into consideration the multitude of co-morbidities associated with the condition as well as prescribe one adequate treatment. More commonly, nephrology, internal medicine, surgery, and dermatology must come together to treat this condition.

It is often a therapeutic challenge to balance the symptoms of this condition with its internal manifestations, which more often than not are related to dialysis. There has not been any optimal treatment for calciphylaxis determined, but many explored modalities have been partially therapeutic. There has been experimentation with low-dose tissue plasminogen activator, parathyroidectomy, hyperbaric oxygen, wound debridement, intravenous sodium thiosulfate, low-molecular-weight heparin, and zero-calcium dialysate.\(^{17}\)

By far and for many years, the first-line treatment for calciphylaxis has been sodium thiosulfate. When calciphylaxis is related to end-stage renal disease, the major aim of any clinician would be to decrease the calcium-phosphate product. When there is an absence of hyperparathyroidism, this sodium thiosulfate can be a very adequate adjunct to therapy. It is an inorganic salt that enhances and may restore endothelial-cell function through antioxidant effect. Often, 25g of sodium thiosulfate is given with dialysis three times per week, especially when Class II calcimimetics or bisphosphonates are of no avail. In a small case study, Ackermann et al. noted a marked decrease in livedo as well as normalization of calcium and phosphate levels. In that case, almost six weeks prior to the beginning of treatment, those lesions were well healed, and within two more weeks the patient was taken off therapy without relapse for several months.\(^{19}\) While sodium thiosulfate has been shown to reduce the level of rebound following dialysis sessions, it cannot be fully ascertained which part of the treatment, dialysis or sodium thiosulfate, played the greater role in the resolution of lesions.

Another adequate second-line agent, cinacalcet hydrochloride, has been utilized in multiple cases as well.\(^{24,17}\) Cinacalcet hydrochloride, a calciumimetic that lowers the levels of parathyroid hormone in patients receiving dialysis, may be utilized carefully. According to Robinson et al., 30 mg of cinacalcet hydrochloride every day can successfully treat the symptoms of patients with calciphylaxis. After treatment with cinacalcet hydrochloride for several weeks, patients reported less pain in the area, and the parathyroid level continued to decline progressively. There was also progressive re-epithelization of the wound area, and after five months of consistent therapy, ulcers markedly improved. Cinacalcet hydrochloride is generally well-tolerated, and the most frequently reported side effects were nausea and vomiting. During this treatment measure, calcium levels were adequately monitored to assess for the risk of hypocalcemia. Since it is a class II calcimimetic, it targets the calcium-sensing receptor of the parathyroid gland’s chief cells. It induces a conformational change that increases the sensitivity to circulating calcium. It has the additional use of treating secondary hyperparathyroidism.\(^{17}\) In view of the results demonstrated by Robinson et al., there could be some promise in treating calciphylaxis patients medically.

The most successful surgical treatment so far has been parathyroidectomy, which has not only reduced most of the external manifestations of the disease but also provided prolonged survival.\(^{17}\) For some, it has been a treatment of choice for those who have an unknown etiology associated with hyperparathyroidism. A parathyroidectomy lowers the parathyroid hormone levels and aids in the restoration of normal calcium-to-phosphorous homeostasis, helping to reduce the risk factors for calciphylaxis. Hafner et al. demonstrated that 38 of their 58 patients who underwent a parathyroidectomy had a prolonged survival compared to those that did not undergo the surgery. This treatment is still controversial to some practicing physicians as it also comes with side effects. Moreover, not all patients are candidates for this operation, and a proper medical evaluation must be performed prior to this treatment. A larger and more focused series looking at patients treated with parathyroidectomy is required, as current reports are anecdotal.

More recently, a focused approach that addresses hypercalcemia, hyperphosphatemia, and hyperparathyroidism has been implicated. Weenig et al. proposed a combination therapy that addressed the pathologic components of calciphylaxis, which are vascular thrombosis and the cutaneous ischemia related to it. By treating the vascular complications with thrombolytic agents and anticoagulation medications as well as hyperbaric oxygen therapy, there may be a way to decrease the regions of cutaneous ischemia. In addition, Weenig suggests the use of whirlpool therapy rather than manual debridement, which is far more painful and requires downtime. Although these are all valid options, it is important to involve the necessary additional medical services as well. Endocrinology, nephrology and dermatology are all key players in the treatment of these patients.\(^{19}\)

Conclusion The condition of calciphylaxis can no longer be avoided as an important area of study. While it is extremely rare, it is a potentially life-threatening condition, often related to dialysis. Understanding the key cutaneous findings and course of this disease is essential. The progressive nature of the disease has encouraged countless physicians to devote more time to uncovering its often indolent course. Since the first case in 1898, significant headway has been made in developing a more case-by-case approach to therapy, although larger patient populations must be studied. Hopefully, there will be further investigation into the particular cause and treatment of this devastating condition, which deserves significant physician attention and care.

References:


Klippel-Trénaunay syndrome: A case report and review of the literature

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Abstract

Klippel-Trénaunay syndrome (KTS) is a rare congenital malformation characterized by the triad of capillary malformations, atypical varicose veins, and hypertrophy of bone and/or soft tissue typically affecting one extremity. The extent of clinical involvement varies on an individual basis, and significant morbidity can accompany the disease. The exact etiology of KTS remains largely unknown, but may be related to inappropriate angiogenesis. We present a case of KTS occurring in a 73-year-old Caucasian female and discuss clinical features, diagnosis and management.

Case Presentation

A 73-year-old Caucasian female presented to the clinic with an ulcer on her right foot, present for approximately one month. She described it as exquisitely painful and noted occasional hemorrhage with the presence of serous crust. Additionally, she had increased edema localized to her right lower extremity. She had experienced multiple episodes of similar symptoms in the past for which she was treated with oral antibiotic therapy. Review of systems was negative for constitutional symptoms.

Her past medical history was significant for emphysema, hypertension, atrial fibrillation, phlebitis, and deep venous thrombosis. Current medications included atenolol, lisinopril, warfarin and lidocaine ointment. She was allergic to multiple medications including bacitracin, amoxicillin, clindamycin and sulfa drugs. No other family members were similarly affected.

Physical examination revealed a 10 mm ulceration with hemorrhagic crust on the dorsal right 4th metatarsal. The lesion was located within an erythematous and violaceous plaque spanning the digits and lateral aspect of the foot. A thick, adherent white scale was also present on the surface of the plaque. In addition, soft tissue and bony hypertrophy of the right foot and 1+ pitting edema of the right lower extremity were evident (Figure 1). Examination of the left lower extremity was benign and did not reveal findings similar to those of the right lower extremity. A large, erythematous and violaceous cutaneous hemangioma with multiple palpable varicosities encompassed the back, crossing the midline in an asymmetric pattern (Figures 2 and 3).

The findings of a cutaneous capillary malformation, venous varicosities, and hypertrophy of a single limb were consistent with a diagnosis of Klippel-Trénaunay syndrome. A venous ultrasound of the lower extremity was offered to assess for deep venous thrombosis, but the patient refused. Topical lidocaine ointment, topical garamycin ointment and oral cephalexin were prescribed for treatment. By the 10-day follow-up appointment, her condition had progressed, developing 2+ edema, increasing pain, and necrotic crust. After a thorough discussion with the patient, a vascular surgery consultation was requested, and she was admitted to the hospital for IV antibiotic therapy.

Upon admittance to the hospital, the patient's vitals were stable but did show a low grade fever of 100.1 degrees Fahrenheit (37.8 C). Laboratory testing revealed a mild leukocytosis (11.1 x 10^3/mL) and a slightly elevated D-dimer level (0.89 mcg/mL fibrinogen equivalent units). Fibrinogen and coagulation assays were within the normal limits, as were kidney and liver functions. A chest radiograph displayed hyperinflation of the lungs in the absence of infiltrates, and a recommended CT scan of the chest was refused. Venous ultrasound of the right lower extremity visualized multiple superficial varicosities with minimal calcification, and there was no evidence of acute deep venous thrombosis. Arterial Doppler ultrasound of the right lower extremity was also performed, displaying triphasic waveforms in all arteries except for the anterior tibial artery, which exhibited a biphasic waveform. At this time the vascular surgeon determined that our patient was not a candidate for surgical intervention.

After a three-day hospitalization, our patient's ulceration had significantly improved, and her fever and leukocytosis had resolved. She elected not to pursue any further testing to evaluate the extent of her disease, and we determined that she was not an appropriate candidate for invasive therapy secondary to her multiple medical comorbidities. Daily compression therapy with 30-40 mmHg pantyhose was recommended, and she was
instructed to continue her anticoagulation therapy with warfarin. After two months, the ulceration had completely resolved and our patient was doing extremely well with her therapy. Long-term follow-up with our patient was discontinued due to relocation.

Discussion

Klippel-Trénaunay syndrome was first described in 1900 by the French physicians Klippel and Trénaunay and was termed "naevus vasculosus osteohypertrophicus." KTS is a rare congenital malformation characterized by the triad of capillary malformations, atypical varicose veins, and hypertrophy of bone and/or soft tissue typically affecting one extremity. All three features of KTS need not be present to confer the diagnosis; the occurrence of two of these features is sufficient. The incidence is reported as <1:10,000, and the condition affects and females equally. In addition to the triad of KTS, lymphatic malformations and deep venous anomalies including venous incompetence, aneurysmal dilatation, hypoplasia, and aplasia are also associated with the disease.

The most common manifestation of KTS is the capillary malformation or port-wine stain, which occurs in 98% of patients. This is typically noted at birth and most frequently involves a single lower extremity. Ipsilateral involvement of both the upper and lower extremities is found in about 10% to 15% of cases, and rarely, contralateral extremities are affected. They can be further classified as having either a "geographic" or "blotchy/segmental" pattern. The geographic stains have confluent, well-defined borders throughout the extent of the lesion and typically display an intensely saturated, red-to-violaceous color. The most common location for geographic stains is laterally along the thigh, knee and lower leg. Conversely, the blotchy/segmental stains are pink to red in color and span large amounts of skin over the affected limb with poorly demarcated borders. Patients affected by blotchy/segmental stains tend to exhibit the other symptoms of KTS, such as hypertrophy and varicosities, at a later point in life than those with geographic stains.

It is important to clinically classify the capillary malformation of patients, as Maari and Frieden were able to correlate geographic stains with an increased presence of lymphatic malformations and risk of complications. As the patient matures, the geographic stains are prone to bleeding and may develop lymphatic macrocysts known as blebs. The presence of lymphatic hypoplasia with abnormal drainage increases the probability of cellulitis and gram-negative bacteremia in these patients. Geographic stains may actually represent a combined lymphatic-capillary/venous malformation. A higher rate of presentation of these lesions at birth than the segmental stains may help identify infants and children that need to be more closely monitored for complications.

Venous varicosities are present in 72% of cases of KTS. They may be recognized in early infancy but typically do not become prominent until the child becomes ambulatory or spends more time in the upright position. Varicose veins in KTS are most commonly located below the knee but may also present on the thigh and in the pelvic region. Persistence of the embryonic lateral marginal vein spanning the full length of the lateral limb is observed in 56% of patients. Local consumption of coagulation factors secondary to venous stasis leads to microthrombi that bind calcium and form a palpable phelolith. A large number of patients have recurrent bleeding in the subsynovial vascular plexus within the knee joint and may present with loss of knee motion, swelling or morning stiffness from knee arthropathy.

A wide spectrum of deep venous anomalies occurs and may impact internal organs such as the liver, kidney, gastrointestinal tract, heart and lungs. In patients with extensive vascular malformations of the lower limb that extend to the trunk, there is a three-fold greater likelihood of visceral anomalies. Absence of lesions on the trunk does not exclude visceral involvement, and patients may present with pain, hemorrhage, genital lymphedema, or gross hematuria. Recurrent or unresolved pulmonary embolism (PE) can lead to chronic thromboembolic pulmonary hypertension. In the absence of PE, pulmonary arterial hypertension (PAH) may occur from small-vessel abnormalities that lead to endothelial dysfunction and activation.
Hypertrophy of the bones or soft tissue of an affected limb is the most variable cardinal feature of KTS and occurs in 67% of patients. Hypertrophy of the soft tissue leads to an increase in the limb girth, while hypertrophy of the osseous structures leads to an increase in limb length. The type and location of vascular malformations have been shown to influence soft-tissue hypertrophy, and therefore clinical presentation is widely variable and the rate of progression is difficult to predict. Extent of the vascular malformation lesion is the single independent risk factor for leg-length discrepancies, regardless of the type or depth of the lesion. Common complications associated with leg-length discrepancies include vertebral scoliosis and gait abnormalities. Extensive vascular malformations, especially when situated deeply in soft tissue, may cause reactive changes in bone including demineralization leading to pathologic fractures.

**Etiology**

The etiology of KTS remains largely unknown. Recent findings in several case studies suggest a genetic component to the disease, with the possibility of several genes contributing to the pathogenesis in different patients. Somatic mutations in angiogenic factors that are critical during embryonic development may lead to an inappropriate angiogenesis and production of vascular malformations.

**Diagnosis and Imaging**

Evaluation is best performed with a variety of noninvasive imaging techniques. Initial evaluation of the extremities should include an arterial and venous Doppler ultrasound. In addition to providing hemodynamic information, this is non-invasive and economical. A greater than 50% change in arterial dynamics is a significant predictor of future limb-length discrepancies. A Doppler examination of arterial blood flow should be conducted in children > 1 year of age with extensive malformations of the lower limb. Changed vascular dynamics warrant evaluation with arterial/venous angiography. Although invasive, these studies provide a more detailed picture of anatomy. Magnetic resonance imaging (MRI) is the study of choice for soft-tissue evaluation, but also allows visualization of vascular malformations and lymphatic abnormalities. The development of a knee flexion contracture is an urgent indication for an MRI, even in young children. Irreversible knee arthropathy occurs from a chronic synovial inflammatory response and erosion of local articular cartilage and bone if surgical intervention does not occur early.

Multidetector computed tomography (MDCT) and three-dimensional magnetic resonance (3D-MR) venography may be most useful to assess the musculoskeletal extent of the malformation, characterize bone-density changes, study limb disassembly and thoracic or pelvic involvement, and verify the presence and patency of the deep venous system. However, there is radiation exposure and contrast administration. Indirect magnetic resonance venography provides precise volumetric extent while also depicting anatomy and patency. Given the young age at which these patients might present and the need for sequential follow-up and therapeutic planning, indirect magnetic resonance venography is now the most suitable imaging technique.

Lymphoscintigraphy with radionuclide tracers may be utilized in those individuals with significant girth discrepancy to determine the presence of abnormal lymphatic drainage and assess the risk of infection. Bone vascularity and regional blood flow can also be evaluated with scintigraphy.

Bone-involvement evaluation should include annual clinical and radiologic measurements of limb length with plain radiographs starting after age 2 until skeletal maturity is reached. Yearly evaluation will provide insight into the rate of progression and can aid in determining the timing of leg-length equalization procedures. A baseline D-dimer, fibrinogen, coagulation assay and platelet count should be measured. Elevated D-dimer levels are highly specific for venous malformations, and fibrinogen levels are usually low. Platelet count may be slightly reduced. Local intravascular coagulation (LIC) favors the production of thrombi. The continuous formation of thrombi consumes coagulation factors, which can then favor bleeding, and activation of disseminated intravascular coagulation can occur. Patients with KTS are known to be at a higher risk for PE and PAH, and a recent study revealed that statistically significant PAH correlated with levels of D-dimer when compared to a healthy control population. All patients with extensive slow-flow vascular malformations should be referred for an echocardiogram to exclude the presence of PAH.

**Treatment**

Patients with KTS are best initially evaluated and treated in a center with an experienced multidisciplinary team. Day-to-day treatment of low-flow vascular malformations leading to edema can be treated with compression garments. Lymphedema may be treated with manual technique combined with exercise and pneumatic compression garments up to 50-60 mmHg. Medical treatment is directed toward symptom relief and preventing complications. Cellulitis is a common problem, especially in patients with a geometric-pattern capillary malformation and associated lymphatic abnormalities. Prophylactic antibiotics are necessary for patients with recurrent episodes or persistent ulcers after bacterial culture and antibiogram. The administration of low-molecular-weight heparin in patients with localized intravascular coagulation and the clinical presence of phleboliths not only decreases thrombosis risk by reduction of D-dimer levels and normalization of fibrinogen levels, but also provides pain relief. Of note, pain is a prevalent morbidity factor in KTS and affects up to 88% of patients, with chronic venous insufficiency as the most frequent cause. Cellulitis, thrombophlebitis, DVT, vascular calcifications, growing pains, intraosseous vascular malformations, arthritis, and neuropathic pain have also been identified as common etiologies of pain. Sporadic use of analgesics and non-steroidal anti-inflammatory drugs may be effective, but treatment should be directed to the underlying cause of the pain.

Common procedures to reduce superficial varicosities include venous stripping, ligation, endovascular laser ablation, and sclerotherapy. Foam sclerants are recommended over traditional ethanol-based sclerosants, which may be too aggressive in large lesions. Despite a nearly 50% recurrence rate of varicosities following invasive procedures, patients reported an overall clinical improvement and decrease in symptoms.

Port-wine stains may be a cosmetic concern for patients, and pulsed dye laser is currently the first-line therapy. Generally, several treatment sessions are needed, and the response is worse for acral sites than in facial lesions, perhaps due to gravitational effects on capillary pressure. Laser treatment of venous malformations is limited to superficial lesions or may be combined with sclerotherapy. The most commonly used laser for this is the long-pulsed neodymium-doped yttrium aluminum garnet (Nd:YAG) 1064nm.

Orthopedic surgical intervention is indicated for projected leg-length discrepancies of greater than 2.0 cm. Although the most suitable age is around 11 years, determining the appropriate timing of intervention is crucial in achieving limbs of similar length at skeletal maturity, further emphasizing the need for yearly radiographs of the limbs. Procedures aim at either halting limb growth or elongating bone. In minor cases of leg-length discrepancy, shoe lifts or heel inserts may be instituted to avoid developing gait abnormalities and scoliosis. The current approach for knee arthropathy is synovectomy. Vascular surgery should be consulted when...
intense hemorrhage, refractory pain, recurrent infection, necrosis, and/or physical deformity are present, as partial amputation of the affected limb may be necessary.4

Conclusion

KTS is a rare congenital vascular malformation that requires complex evaluation and therapeutic planning due to its wide range of involvement. Early detection of clinical manifestations and intervention at the appropriate juncture may minimize the morbidity associated with KTS and lead to a significant improvement in quality of life. The psychological effects that KTS can have on the affected individual should not be dismissed. Treatment strategies must be individualized to address the needs and expectations of each patient. This is best accomplished with a multidisciplinary team.

References:

Birt-Hogg-Dubé Syndrome – A Case Report and Review

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Case Report

A 48-year-old Caucasian male presented to the dermatologist with a 10-year history of “white bumps” on his face and neck. The patient history included hypothyroidism, a pituitary tumor, and a family history of renal carcinoma of unknown type. Physical examination revealed numerous small, flesh-colored white papules on his face, neck, and chest (Figures 1 and 2). Shave biopsy of one of his lesions revealed findings consistent with a fibrofolliculoma. The pathology showed a hair follicle with thin extension of epithelium extending into the surrounding fibromyxoid stroma (Figure 3).

The patient was diagnosed with Birt-Hogg-Dubé syndrome (BHD) and was referred to a cancer center for a full work-up. CT scans of the chest, abdomen, and pelvis as well as a colonoscopy were obtained. The results were unremarkable. Further biopsies were performed, which showed evidence of a fibrofolliculoma and an acrochordon. He was referred for genetic testing and counseling for his syndrome. If a mutation is not identified, then it will not be necessary to refer his son for genetic testing. However, because BHD is an autosomal-dominant genodermatosis, his son should be aware of the likelihood of development of this disease in the future regardless of whether a gene is identified or not.

Discussion

Drs. Birt, Hogg, and Dubé first described BHD in 1977. They studied a family whose members were affected with numerous small, white and skin-colored, dome-shaped papules found on the face, neck, and chest. These benign hair-follicle tumors, termed "fibrofolliculomas," appeared after the age of 25. They discovered that this genodermatosis was characterized by a triad of fibrofolliculomas, trichodiscomas, and acrochordons and was inherited in an autosomal-dominant fashion. Since the original report, several cases of BHD have been described, but its incidence is yet to be established. Birt et al. made no mention of associated kidney, pulmonary, or gastrointestinal risks in their original report. Since then, several studies have shown that affected individuals may be at risk for developing renal neoplasms, multiple pulmonary cysts, and spontaneous pneumothorax. In the largest single study to date, Zbar et al. found almost a seven-fold increase in the risk for renal tumors and a 50-fold increase in the risk of pneumothorax in BHD-affected individuals, adjusted for age. The cutaneous manifestations of BHD tend to appear in the third or fourth decade of life. Fibrofolliculomas and trichodiscomas are clinically indistinguishable and require biopsy for differentiation. They present as 1 mm to 5 mm, smooth, skin-colored to grayish-white papules usually located on the face, neck, and upper trunk.

Kidney neoplasms associated with BHD are usually multiple and bilateral, and they typically occur earlier than sporadic tumors. The most common renal neoplasm associated with BHD is chromophobe renal carcinoma. Chromophobe renal carcinomas are uncommon and locally invasive, and they rarely metastasize. A mixed histologic pattern of chromophobe cancer and oncocytoma is a typical feature of BHD-associated renal cancer. At one time, BHD was also associated with an increased risk of colorectal polyps and cancers; however, recent studies do not indicate an increased risk for their development.

Pulmonary cysts associated with BHD are usually located basally in the lungs, and their histology has been shown to be consistent with emphysematous changes. Pneumothorax associated with BHD is typically secondary to ruptured pulmonary cysts and does not occur spontaneously. Recurrent episodes of spontaneous...
pneumothorax are more common than single episodes in patients with BHD. While the risk of spontaneous pneumothorax decreases with age, the risk of developing renal tumors increases with age.

A co-occurrence of various malignant and benign tumors can occur in BHD. These can include deforming lipomas, collagenomas, and oral fibromas. Other abnormalities such as internal carotid-artery aplasia and congenital cystic lung soft-tissue masses have been reported. However, no studies have proven a causal relationship.

The BHD gene locus was originally mapped to chromosome 17p12q11.2 by linkage analysis in 2001 by Khoo et al. and was later confirmed by multiple studies. Numerous truncating germline mutations have been reported in the BHD gene, and it is now possible to screen for these pathogenic mutations. Eventually named “folliculin” (FLCN), this gene was found in a variety of normal tissues, including kidney, lung, and skin. Its function remains unknown, but it is hypothesized to be a tumor-suppressor gene.

It is important to consider tuberous sclerosis in the differential diagnosis for BHD, as the angiofibromas associated with tuberous sclerosis may have overlapping features with the fibrofolliculomas in BHD. BHD may be associated with familial renal carcinomas and spontaneous pneumothorax; therefore, it is recommended that patients with BHD and their relatives undergo screening tests such as CT or MRI, as they may lack cutaneous manifestations and may be asymptomatic. Once a family-specific mutation is identified, genetic testing in asymptomatic at-risk relatives may also be appropriate for early detection.

Table 1. Diagnostic Criteria for Birt-Hogg-Dubé Syndrome

<table>
<thead>
<tr>
<th>Patients should fulfill one major or two minor criteria for diagnosis.</th>
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<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
</tr>
<tr>
<td>• At least five fibrofolliculomas or trichodiscomas, at least one of which is histologically confirmed, of adult onset (see note below)</td>
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<tr>
<td>• Pathogenic FLCN germline mutation</td>
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<tr>
<td><strong>Minor Criteria</strong></td>
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<tr>
<td>• Multiple lung cysts: bilateral, basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax</td>
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<tr>
<td>• Renal cancer: early onset (&lt;50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology</td>
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<tr>
<td>• A first-degree relative with BHD</td>
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</table>

Note: Fibrofolliculomas and trichodiscomas may be two presentations of the same lesion.

References
Case presentation

A 39-year-old, healthy Caucasian female presented to the dermatology office with a non-itchy, painless bump on her finger that had been increasing in size for the past few months. Physical examination revealed a 2 mm, flesh-colored, firm, hyperkeratotic, verrucous papule with disruption of normal skin markings and display of small black dots on the right middle finger, close to the nail. A clinical diagnosis of verruca vulgaris was made, and the patient received multiple treatment sessions using liquid nitrogen for wart destruction. However, she reported no improvement at her follow-up visits, and the wart remained the same size. Subsequently, the patient was prescribed topical treatments including imiquimod 5% cream, sinecatechins 15% ointment, and imiquimod 3.75% cream, but they did not significantly decrease the size of the wart. At her tenth visit to our office, the patient began to receive Nd:YAG 1064-nm laser therapy for wart treatment at two-week intervals. After the completion of the fourth laser treatment, the wart was completely resolved (Fig. 1).

Discussion

Verruca vulgaris is caused by HPV infection (subtypes 1, 2, 4, 27, 57, and 63) and occurs mostly in children and young adults. They are usually asymptomatic and are transmitted via skin-to-skin contact. Trauma and maceration may facilitate initial epidermal inoculation, and spreading may subsequently occur by autoinoculation.1 Common warts often present as well-demarcated, rough, hard nodules or plaques with irregular surfaces. Diagnosis of verrucae is based upon clinical appearance. Spontaneous remission of warts occurs in up to two-thirds of patients within two years; hence, observation is an option for all patients.2 However, since recurrence of verrucae is common, early intervention may be preferred to prevent wart spreading.

Treatment of verruca involves two approaches: destruction of the wart and induction of local immune reaction with immunotherapy. Destructive methods are most commonly used as initial therapy, and they include cryosurgery, electrocautery, curettage, excision, and laser therapy. Immunotherapy is aimed at eliciting an immune response to HPV, which may be achieved by applying a topical irritant such as salicylic acid, cantharidin, trichloroacetic acid, podophyllum resin, 5-fluorouracil, or tretinoin over the wart. These compounds can also be used in combination or with a destructive method.3,4 Cryotherapy is one of the most commonly used first-line treatments for verruca vulgaris. The wart is frozen with a thaw time of 30 to 45 seconds to produce a blister in one to two days. A sustained 10-second freeze with a spray gun has been found to be more effective than simply freezing to obtain a 2 mm to 3 mm halo around the wart. The ideal frequency of treatment is every two to three weeks, as the old blister desquamates. Complications of cryotherapy include hypopigmentation, scarring, and rarely, damage to the digital nerves from freezing too deeply on the side of the digit when treating a periungual wart.5

Immunotherapy may also be used for treatment of verruca vulgaris. Antiviral effect...
can be achieved with bleomycin and interferon alpha-2b, but they are reserved for recalcitrant warts. Imiquimod 5% cream may be used to induce local production of antiviral cytokines in the skin.\textsuperscript{3} Intralesional immunotherapy with skin test antigens (e.g., mumps, Candida, or Trichophyton antigens) and HPV vaccine have demonstrated success in treating warts.\textsuperscript{5} Lesions that have failed to respond to routine office modalities are often successfully treated with laser therapy such as carbon dioxide or pulsed dye laser.\textsuperscript{5,7} Nd:YAG 1064-nm laser has also been reported to be successful in treating verruca and has received FDA clearance for this indication (Fig. 2).

The Nd:YAG 1064-nm laser treatment involves the delivery of laser light irradiation at wavelength 1064 nm, which allows deeper penetration into thicker tissue compared to shorter-wavelength lasers without direct skin or verruca contact. This laser is also used for treating vascular and pigmented lesions, hair removal, skin rejuvenation, onychomycosis and many other aesthetic and medical treatments.\textsuperscript{8} A minimum of one to two treatment sessions is needed, with sessions spaced two to three weeks apart. Treatment sessions usually begin using a focused lens with a 2-mm spot under the settings of 1.5-ms pulse duration and energy mode of 8 or 9 (fluence of 255 J/cm\textsuperscript{2} to 287 J/cm\textsuperscript{2}). A Zimmer cooler is used upon the end of the laser treatment. In the case of our patient, a total of two passes over the wart was applied with each treatment session, and the patient tolerated the treatment very well. Upon the end of the fourth treatment session, the patient’s wart had completely resolved.

Conclusion
We have demonstrated the success of utilizing Nd:YAG 1064-nm laser in treating a verruca that had failed to respond to standard treatment. Dermatologists should consider using this laser therapy early in the course of treating resistant warts since it is well-tolerated by patients, and it provides timely, significant results that help to bring disease remission.

References
Abstract

Seborrheic keratosis is a benign skin tumor that can occur on almost any site of the body, with the exception of the palms and soles. Linear and dermatomal distribution is rare and may be associated with fibroepithelioma of Pinkus. We report a case of a 36-year-old woman who presented with itchy brownish papules and plaques on the left lower extremity with linear distribution for 10 years. Diagnosis was confirmed histologically as seborrheic keratosis. This case presents as a rare clinical variant with only four other reported cases in the current literature.

Case Report

A 36-year-old woman presented with a 10-year history of itchy brownish papules and plaques in a linear distribution on the anterior left lower extremity. Lesions gradually increased in size and number over time. Patient denied history of underlying disease, and family history was non-contributory. She stated that the lesions were treated with cryotherapy one year prior, providing temporary relief although some lesions recurred.

A biopsy was performed, and the histopathology showed hyperkeratosis and acanthosis with basaloid appearance and true and pseudo horn cysts in the epidermis. This is consistent with seborrheic keratosis.¹

Discussion:

Seborrheic keratoses are common, benign skin tumors and usually present as multiple oval, slightly raised, light brown to black, sharply demarcated papules or plaques with a scaly surface, rarely more than 3 cm in diameter. They are located mostly on the chest and back, but also commonly involve the scalp, face, neck and extremities, sparing the palms and soles. Occasionally, genital lesions are seen. The lesions appear to increase with age, and although the pathogenesis is unknown, they are thought to develop from the proliferation of keratinocytes of the epidermis.²³
Typical lesions of the trunk are much more common in white persons; however, the “dermatosis papulosa nigra” variant of the central face is common in African Americans and Asians.\(^2,3\) The lesions are usually asymptomatic, but can be itchy.\(^2,3\) The lesions tend to be self-limited, and the appearance of new lesions may continue for a few years.\(^2,3\) There have been no reports of malignant changes. Differential diagnosis includes linear verrucous epidermal nevus, lichen striatus, verruca plana and verruca vulgaris.

Linear verrucous epidermal nevi are verrucous, skin-colored, dirty gray or brown papules, which coalesce to form a serpiginous plaque. The age of onset is generally at birth, but it also may develop within the first 10 years of life. They follow the lines of Blaschko. Rarely, keratinocytic and adnexal malignancies occur in the epidermal nevi.\(^2\)

Lichen striatus presents as small, 1 mm to 3 mm papules that are erythematous and slightly scaly. They coalesce to form a band 1 cm to 3 cm wide, either continuous or interrupted, that over a few weeks progresses down the extremity or around the trunk, following the lines of Blaschko. Most frequently, it appears before age 6, but young adults, and more uncommonly older adults, may also be affected. Ten percent or fewer of cases occur on the face. Nail involvement can occur, such as nail-plate thinning, longitudinal ridging, splitting, and nail-bed hyperkeratosis. All lesions, including nail dystrophy, spontaneously resolve without scarring, although hypopigmentation may persist for several years.\(^2\)

Verruca plana, or flat warts, are most often caused by HPV-3, 10, 28 and 41. Children and young adults are primarily affected. Flat warts present most typically as 2 mm to 4 mm, flat-topped papules that are slightly erythematous or brown on pale skin and hyperpigmented on darker skin. They are generally multiple and grouped, most commonly occurring on the face, neck, dorsa of the hands, wrists, elbows or knees. Flat warts have the tendency to Koebnerize, forming linear, slightly raised, papular lesions. In men who shave their beards and in women who shave their legs, numerous flat warts may develop as a result of autoinoculation. Of all clinical HPV infections, flat warts have the highest rate of spontaneous remission.\(^2\)

Verruca vulgaris, also known as common warts, occurs largely between the ages of 5 and 20, with only 15% occurring after the age of 35. HPV-1, 2, 4, 27, 57 and 63 cause common warts. Common warts can occur anywhere on the skin but commonly arise on the hands, favoring the fingers and palms. They grow in size for weeks to months and

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Figures 4-6: Histology images showing hyperkeratosis and acanthosis with true and pseudo horn cysts in the epidermis.
usually present as elevated, rounded papules with a rough verrucous surface. Periungual warts are more common in nail blisters and may be confluent, involving the proximal and lateral folds. Common warts usually resolve spontaneously. 

In current literature, one 44-year-old female patient has been described as having multiple fibroepithelial basal-cell carcinomas (FEBCC) associated with seborrheic keratosis, distributed in a neviform fashion on the left side of the body. 

Differential diagnosis included Bazex-Dupré-Christol and Rombo syndromes and nevoid basal-cell carcinoma syndrome. There is one report of distribution along skin cleavage lines on the lower back and waist of a 65-year-old-woman, and another more recent report of 16-year-old female with linear and dermatomal seborrheic keratosis on the right side of the lower chest without underlying disease. 

Raindrop pattern on the back of elderly patients has also been described.

This case presents as a rare clinical variant of seborrheic keratosis, and although the patient did not report underlying disease, clinicians should be aware of the potential risk of associated BCC. In our office, the patient was treated with cryotherapy; however, further work-up and biopsies may be warranted. Unfortunately, she was lost to follow-up.

References:
6. Darjani A, Ramezanpour A. Seborrheic Keratosis: A Rare Clinical Appearance. The Internet Journal of Dermatology, 2000 Volume 1 Number 2
Abstract:
Multiple facial papules concentrated in the nasolabial folds are an important clue to an underlying genodermatosis and should initiate a thorough work-up. Basal-cell nevus syndrome (BCNS), or Gorlin’s syndrome, is an autosomal-dominantly inherited disorder with a mutation in the PTCH gene that predisposes to tumor formation. Patients classically have multiple basal-cell carcinomas, odontogenic keratocysts of the jaw, palmoplantar pits, calcification of the falx cerebri, medulloblastomas, and skeletal anomalies. Multiple hereditary infundibulocystic basal-cell carcinoma (MHHBCC) and generalized basaloid follicular hamartoma syndrome (GBFHS) are newly described syndromes that are also linked to a PTCH gene defect, but they have milder presentations. We describe a patient who meets the current criteria for BCNS, but due to her relatively indolent course we believe her condition is more likely to fit the diagnosis of MHHBCC. The following is a review of the differential diagnoses for multiple facial papules and a summary of current treatment options.

CASE
A 55-year-old white female presented to the office complaining of an irritated lesion at the left nasal ala and a cyst on the right upper arm that continually became infected despite repeated incision and drainage. Her medical history included anxiety and ovarian cysts. She was taking no medications and reported an allergy to penicillin. On exam, there was a flesh-colored nodule with a central punctum at the right upper posterior arm, which was later excised and found to be an epidermoid cyst. There was a crusted pearly papule at the left nasal ala which was biopsied and found to be a nodular basal-cell carcinoma. Incidentally, the patient was noted to have multiple firm, flesh-colored, 1 mm to 3 mm facial papules, especially concentrated in the nasolabial folds (see Figure 1). When the patient was questioned about the lesions, she said they had been present for many years and did not think they were of concern. Several of the facial papules were periodically biopsied, and the diagnosis of infundibulocystic basal-cell carcinoma was elucidated. The patient was also noted to have scattered small palmar pits on exam (see Figure 2).

Family history included a mother with infundibulocystic basal-cell carcinoma and basal-cell hamartomas. The patient’s brother had a history of BCC and a brain tumor of unknown type diagnosed at age 40. Another brother had frontonasal bossing and multiple facial papules, many of which were shown to be basal-cell carcinoma. The patient was sent for a panorex of the jaw, which was negative for odontogenic keratocysts. She was also referred to Mohs surgery for treatment of the nodular basal-cell carcinoma of the left nasal ala. The patient was referred to genetics to test for PTCH, PTEN and BHD genes.

As of this report, the patient has been temporarily lost to follow-up. When contacted she informed us that she needs to put her medical care on hold in order to tend to her 16-year-old niece, who has developed four brain tumors. The largest of the tumors was resected and found to be glioblastoma on pathologic examination. To further solidify our diagnosis we would like to obtain a skull X-ray to look for calcification of the falx cerebri and a chest X-ray to check for bifid ribs or vertebral abnormalities. We plan to treat the multiple infundibulocystic BCC with Levalulan photodynamic therapy, which is emerging as a promising treatment for this condition.

BASAL CELL NEVUS SYNDROME
Basal-cell nevus syndrome (BCNS) is also referred to as nevoid basal-cell carcinoma syndrome (NBCCS), Gorlin syndrome and Gorlin-Goltz syndrome. It is an autosomal-dominantly inherited disease linked to a gene defect in the sonic hedgehog signaling pathway that predisposes patients to...
A family with basal-cell carcinomas, jaw cysts and bifid ribs was first described to have this syndrome by Doctors Gorlin and Goltz in 1960. It appears, however, to date back to the Dynastic Period (3000-2575 BC), as shown by two Egyptian skeletons discovered to have the characteristic bony changes of Gorlin syndrome. The syndrome is now thought to affect 1 in 40,000 to 57,000 people.

Etiology and Pathogenesis
An inactivating mutation in the patched or PTCH1 gene located on chromosome 9q22.3 has been shown to be responsible for most cases of Gorlin syndrome. About 70% of these mutations are gene rearrangements that lead to truncated protein formation. PTCH1 mutations are autosomal-dominantly inherited in most cases, but 35% to 50% of cases are thought to be new mutations. There is almost complete penetrance of the PTCH1 mutation, but expression is widely variable. Inactivation of the gene has been proposed to be caused by a “two-hit” hypothesis, the first occurring in the germline and the second occurring postnatally. A few cases of NBCCS have been shown to be caused by mutations in the PTCH2 gene on chromosome 1p32 and the suppressor of fused (SUFU) gene on chromosome 10q24-q25. PTCH1, PTCH2 and SUFU are all tumor-suppressor genes of the Hedgehog (Hh) signaling pathway and regulate the production of growth-promoting transcription factors. A defect in PTCH leads to increased smoothened activity, which leads to increased Gli activity and finally causes uninhibited cell-cycle progression.

Clinical Presentation
Basal-cell carcinomas (BCC) arise in nearly all BCNS cases, but the frequency and age of onset of the tumors have not been fully established. The literature reports anywhere from 8% to 90% of BCNS patients developing BCCs before age 40, sometimes before age 10, with fair-skinned patients generally developing the tumors at an earlier age and in higher numbers. Previous criteria for BCNS have differed, with some sources listing “multiple BCCs or a BCC before age 20” as a major criterion, and others listing “greater than five BCCs in a lifetime or a BCC before age 30” as a criterion.

In 2005, the first international colloquium on basal-cell nevus syndrome was held at the Saint Louis University School of Medicine. The following guidelines were proposed after a literature review and roundtable discussion between 15 experts in the field: A patient must either (1) meet one major criterion and have molecular confirmation; (2) meet two major criteria; or (3) meet one major and two minor criteria (see Table 1).
Hypogonadism in males. Cysts in females, and hypogonadotrophic nevi, benign dermal cysts, chalazion, ovarian criteria above include coarse facies, multiple Other reported features not listed in the large calvaria. Frontal, biparietal, or temporal bossing and have abnormal skull configuration including bridging of the sella turcica; and about 70% of BCNS patients develop keratocysts of the jaw (usually by age 40); approximately 70% have lamellar calcification of the falk cerebri (less frequently of the tentorium cerebelli and bony bridging of the sella turcica); and about 70% have abnormal skull configuration including frontal, biparietal, or temporal bossing and large calvaria. Other reported features not listed in the criteria above include coarse facies, multiple nevi, benign dermal cysts, chalazion, ovarian cysts in females, and hypogonadotrophic hypogonadism in males.

Histology
Basal-cell carcinomas associated with BCNS cannot be differentiated from those in the general population. The most common types are the solid and superficial types. Other types of BCC may be seen less often. Odontogenic keratocysts typically have a thin, corrugated, stratified squamous epithelial lining with a surrounding thick, fibrous capsule. Varying degrees of keratinization can be noted.

Differential Diagnosis

Multiple Hereditary Infundibulocystic Basal-Cell Carcinoma (MHIBCC)

MHIBCC is a newly described syndrome in which patients present with pearly papules on the face, most densely concentrated within the nasolabial folds. On histology, the lesions are found to be infundibulocystic basal-cell carcinoma (IBCC), a more indolent form of BCC which tends to grow very slowly and rarely ulcerates.

Histologically, the lesions are well-circumscribed aggregates of basaloid buds and cords in a radial and anastomosing pattern located in the upper dermis. Sometimes necrosis, peripheral palisading, and cystic structures containing melanized and cornified cells can be seen. IBCC can be differentiated from trichoepithelioma, a benign follicular neoplasm, by the scant stroma consisting of wiry collagen bundles and few fibrocytes arranged in a compact fashion. See the photomicrograph from the above case presentation in Figure 3. In contrast, trichoepithelioma has abundant and densely fibrous stroma. Gorlin's syndrome and MHBCC are pathogenetically similar in that the inheritance of MHBCC seems to be autosomal-dominant and linked to the PTCH gene.

Generalized Basaloid Follicular Hamartoma Syndrome (GBFHS)

Basaloid follicular hamartoma is a benign tumor of abnormal follicular differentiation. Most patients present with one isolated lesion, but a rare multiple familial form has been described. The clinical presentation of GBFHS is variable, but the classic triad of findings consists of milium-like lesions, comedone-like lesions, and 1 mm to 2 mm hyperpigmented papules that resemble seborrhoeic keratosis, acrochordons or dermatosis papulosa nigra. Lesions usually start on the cheeks in early childhood and then spread to the scalp, ears, neck, shoulders, chest, axillae and upper arms. Patients may also have hypotrichosis of the scalp along with pinpoint, slightly hyperpigmented palmoplantar pits.

Upon biopsy the papules are shown to be basaloid follicular hamartomas (BFH). Histologic features include follicular-based, vertically oriented columns of squamous cells with buds and cords of basal cells at the periphery. The basaloid cells are uniform, small cells surrounded by scant fibrous stroma with clefting. Low mitotic rate, lack of necrosis, less than 10% of nuclei staining positively for PCNA, and less than 5% staining for Ki-67 markers prove that BFH has a low proliferative capacity and thus benign nature. Palmoplantar pits have been shown to represent malformed eccrine ducts on histology. Inheritance appears to be autosomal-dominant and, again, related to the PTCH gene, but with a lesser degree of dysfunction than MIBCC and BCNS.

Multiple Hereditary Trichoepithelioma (MHT)

Trichoepithelioma (TE) is a benign follicular neoplasm that is usually solitary and sporadic. MHT is a disorder presenting with multiple TE: 2 mm to 8 mm flesh-colored papules on the face, predominantly in the nasolabial folds. The histopathology of trichoepithelioma consists of aggregates of basaloid cells, often difficult to distinguish from BCC, IBCC or BFH. TE is characterized by groups of basaloid cells that look similar to hair bulbs. The tumor islands have peripheral palisading and multiple horn cysts seated in an inflammatory fibrous stroma. Abortive hair shafts and follicles are sometimes present. Features that differentiate TE from BCC include circumscription of the lesion, antler-like branching of basaloid cells and an epithelial tract that consists of multiple layers of basal cells. Inheritance is...
autosomal-dominant and linked to a mutation at chromosome 9p21 on the PTCH gene. Two additional syndromes with multiple TE and autosomal-dominant inheritance of a chromosome 9p21 mutation are Brooke-Spiegler syndrome and Rombo syndrome. Brooke-Spiegler syndrome is characterized by multiple trichoeiopheliomas, along with cylindromas of the nasolabial folds, nose, upper lip, forehead and scalp. Lesions usually appear at puberty and slowly increase in number over time. There is no known association with internal disease. Rombo syndrome consists of multiple TE, milia, basal-cell carcinoma, vermiculate atrophoderma, hypertrichosis, and peripheral vasodilation.7 Other Syndromes with Firm Facial Papules

The physical exam finding of multiple facial papules can be associated with many genodermatoses and should trigger the clinician to begin a detailed work-up. Histopathologic diagnosis of the papules is key to narrowing the search. The following syndromes were initially considered but have become low on the list of differential diagnoses for our patient due to the knowledge that the papules are infundibulocystic and nodular BCCs. Cowden syndrome is caused by an autosomal-dominantly inherited mutation of the tumor suppressor gene PTEN on chromosome 10q23. Characteristic findings include multiple benign tumors called trichilemmomas that appear around the mouth, nose, ears and neck around age 30 to 40 years. On histology, the lesions appear as well-circumscribed lobular epithelial proliferations with peripheral palisading and glycogenation. Clinically, patients are also found to have adenoid facies, craniomegaly, oral papillomas and keratoses of the dorsal hands and wrists. Cowden syndrome may be associated with gastrointestinal polyps, thyroid carcinoma, and fibroadenoma or adenocarcinoma of the breast.7

Birt-Hogg-Dubé syndrome (BHDS) is characterized by multiple fibrofolliculomas: 2 mm to 4 mm whitish, smooth papules (sometimes pedunculated) over the face, neck, oral cavity and upper trunk. The lesions usually appear after age 25. Histologically, the tumors are made up of anastomosing strands, two to four cells thick, of epithelial cells radiating from the hair follicle. The strands are circumscribed by loose mucinous connective tissue. The genetic defect is of the BHD gene on chromosome 17p11.2. There is generally autosomal-dominant inheritance, but the syndrome may be caused by a new mutation. BHDS has been associated with renal tumors, spontaneous pneumothorax and pulmonary cysts.7 Tuberous sclerosis presents with multiple angiofibromas or “adenoma sebaceum” on the nasolabial folds, cheeks and chin in early childhood. The lesions are clinically characterized as flesh-colored to pink, telangiectatic papules. They may also be found periungually, on the scalp and oral mucosa. Histology shows dilated blood vessels in a fibrous stroma with many stellate fibroblasts. Other skin findings include ash leaf macules and shagreen patches. Associated systemic findings are CNS tumors, seizures, mental retardation, schizophrenia, autism, ADHD, retinal phakomas, cardiac rhabdomyomas and aneurysms. The defect has been localized to the TSC2 gene on chromosome 9q34 and 16p13. Inheritance is classically autosomal-dominant, but 50% to 70% of cases are now thought to be caused by new mutations.7

Treatment

Electrodesiccation and curettage, cryotherapy, surgical excision and Mohs micrographic surgery are the conventional treatment options for basal-cell carcinomas. These treatments, however, are often impractical in Gorlin syndrome due to the extent of disease and concerns about scarring, especially with the preclusion for facial involvement. Non-surgical techniques such as topical 5-flourouracil or topical imiquimod may be used to cover larger areas of tumor involvement, but several weeks of treatment are necessary, which decreases patient compliance, and control rates are low for nodular lesions.7 Over the last decade, much evidence to support the use of photodynamic therapy (PDT) to treat basal-cell carcinoma has emerged. Photodynamic therapy involves the application of a photosensitizing precursor that is preferentially absorbed by tumor tissue and converted into phototoxic porphyrin. A light source is then used to excite the porphyrins, which leads to production of free radicals and thus causes targeted cell damage.4 In 2007, Braathen et al. developed an international consensus on the guidelines for use of PDT in nonmelanoma skin cancers. They report multiple large phase III studies of topical methyl aminolevulinic photodynamic therapy (MAL-PDT) on superficial BCC (sBCC) and nodular BCC (nBCC) lesions. In the sBCC studies, three-month complete resolution rates ranged from 80% (in complex cases, recurrent or large lesions, or lesions occurring in the “H-zone” of the face) to 97% in primary sBCC. Efficacy was also high in the nBCC group, with three-month complete response rates of 73% to 94%. Histologically controlled studies have confirmed these efficacy rates. Four-year follow-up of a phase III study of MAL-PDT on sBCC shows recurrence rates comparable with cryotherapy: 22% recurrence for MAL-PDT vs. 19% recurrence for cryotherapy at 48 months. Lesions 1 cm or less in diameter were shown to have just a 6% recurrence rate at 36 months. A five-year recurrence rate of 14% was found in nBCC patients who took part in a phase III study of MAL-PDT.5 For comparison, a review of available studies by Thissen, Neumann, and Schouten showed a five year cumulative recurrence rate of 5.7% to 18.8% with electrodesiccation and curettage and 3.2% to 8.0% with surgical excision.6 Overall, MAL-PDT is recommended as a first-line treatment for both sBCC and nBCC lesions, with supporting evidence for long-term efficacy.8 Several smaller open-label studies tested the efficacy of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) on primary sBCC lesions, showing initial clearance rates between 90% and 100%. ALA-PDT studies report variable efficacy in the treatment of nBCC, ranging from 61% to 92% clearance rates. Varying rates of clearance are likely due to inconsistency of lesion preparation with curettage and different light sources used (blue, red or laser). Although MAL and ALA have not been compared directly in clinical studies, it is known that ALA has poorer penetration into nBCC lesions as compared to MAL. MAL has a decreased charge and an increased lipophilicity, which aids in the delivery of sufficient photosensitizer to the full depth of the lesion. To facilitate penetration, nBCC lesions larger than 2 mm may be debulked before treatment, with re-treatment if necessary.7 Systemic photosensitization with the use of an intranasal optical fiber or laser ablation prior to PDT are some additional options for treatment of thicker lesions.4 Recurrence rates with ALA-PDT were shown to be 5% at a median of 17 months in a study by Soler et al.11 and 12% at 12 months in a phase II clinical trial by Wang et al.;12 however, more long-term follow-up is needed to prove lasting efficacy of ALA-PDT. Overall, ALA-PDT is recommended for the treatment of sBCC, but more research is needed before it can be recommended as a first-line treatment for nBCC. Along with efficacy, cosmetic outcomes and patient preference should be factors when choosing treatment for BCC. A prospective randomized trial of 97 patients with nodular BCCs showed a five-year local control rate of 96% for those treated with surgical excision, as opposed to 76% for those treated with PDT.13 Mohs surgery has shown the highest efficacy for facial BCCs, as all margins are examined intra-operatively.15 However, surgery is often impractical in Gorlin patients due to the multiplicity of tumors that develop on the face, often starting at a young age. In a randomized comparator study, 89% of sBCC patients were rated as having “good” or “excellent” cosmetic outcomes with MAL-PDT as compared to 50% in the cryotherapy group.10 In a review of current studies, cosmetic outcomes were
those treated with cryotherapy. In addition, treated with ALA-PDT and just 54% of 93% of patients with both sBCC and nBCC had "excellent" or "good" cosmetic outcomes in these mice when exposed to long-term UV radiation.

In a recent study, PTCH heterozygous mice were used as mouse models of Gorlin syndrome. Multiple MAL-PDT sessions were shown to prevent the development of BCC in these mice.

The selective COX-2 inhibitor celecoxib has recently shown some efficacy in NBCCS. A double-blind, placebo-controlled, randomized phase II study by Tang et al. proved celecoxib to be modestly effective in reducing the BCC burden and the rate of BCC formation in Gorlin patients and mouse models. In mice with the PTCH1 gene mutation, celecoxib was shown to reduce microscopic tumor burden by 35%. In Gorlin patients, the NSAID decreased the development of new BCCs by 50% in patients with milder disease (<15 BCCs). The concordance between the anti-BCC effects of celecoxib in human and mouse models for BCNS supports the hypothesis that the studies on chemoprevention in these mice can predict the effects of such treatments on humans. Although there were no serious adverse events during this study, the reported cardiac side effects should raise caution in its widespread use. Topical NSAIDs are a suggested area of study in order to decrease cardiac effects. Morpheaform BCCs have been shown to have elevated levels of COX2 and are inherently more aggressive tumors, so these patients may be good candidates for celecoxib.

Vismodegib is a novel small-molecule inhibitor of the transmembrane protein smoothened (SMO), a key player in the hedgehog pathway. A phase 1 trial showed a 58% response rate and a median response duration of 12.8 months in 33 patients with advanced BCC. The phase 2 trial was performed on 96 patients to further investigate the efficacy and safety of the drug. The majority of patients with both locally advanced disease and metastatic disease showed tumor shrinkage. Additionally, 54% of patients with locally advanced BCC had complete responses with no residual tumor cells on histology. Adverse events included muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite and diarrhea. Fatal events were reported in seven patients but were thought to be related to pre-existing risk factors. Tang et al. report success of vismodegib in the treatment and prevention of BCCs in BCNS patients. In a randomized, double-blind, placebo-controlled trial, 41 patients with BCNS were followed for a mean of eight months after enrollment. The mean per-patient rate of new surgically eligible basal-cell carcinomas was just two per year with vismodegib, as opposed to 29 in the placebo group. The percent change from baseline of existing clinically significant basal-cell carcinomas was -65% in the treatment group vs. -11% in the placebo group. Some patients had clinical regression of all tumors, and no tumors were shown to progress during treatment with vismodegib. Biopsy samples from sites of clinically regressed tumors showed no residual BCC at 83% of the time. After one month, patients treated with vismodegib had a 90% reduction in hedgehog target-gene expression in their BCC and a diminished rate of tumor-cell proliferation. Unfortunately, 54% of patients (14 of 26) receiving vismodegib discontinued treatment due to adverse events such as loss of taste, muscle cramps, hair loss and weight loss.

Discussion

The patient described in the above case meets two of the major criteria for BCNS: multiple BCCs and palmar pits. The findings of epidermoid and ovarian cysts also support the diagnosis. The pervasive family history of BCC and the history of frontal bossing and brain tumor in the brothers lead us to believe there is a family history of BCNS. If her family members were formally diagnosed, she would meet three of the major diagnostic criteria. The glioblastoma diagnosed in the patient's niece, though not the classically described medulloblastoma, is also thought to be caused by a dysfunction in the hedgehog signaling pathway and is thus suggestive of a Gorlin syndrome diagnosis. Despite technically meeting the BCNS criteria, it seems more likely that the patient may have MHBCC. Research shows that over 90% of BCNS patients develop odontogenic keratocysts of the jaw, which the patient did not. Also, her facial papules have remained stable for many years, and she was only first diagnosed with a nodular BCC at age 55. This is not out of proportion to her age or skin color. Crawford et al. described a similar case of a 67-year-old male with a history of BCC first diagnosed at age 50, who was found to have multiple infundibulocystic BCC, two infiltrative BCC on the nose and shallow palmar pits. The authors acknowledged that their patient met the criteria for BCNS syndrome but, due to the indolent course and lack of other organ involvement, likely had MHBCC. The case described by Crawford et al. and the case described here raise the question, are these diseases truly separate entities or a continuum of one disease? BCNS, MHBCC, GBFHS and MHT are all related in that they each represent a
defect in the sonic hedgehog/patched/smoothened (SHH/PTCH/SMO) pathway. As hypothesized by Crawford et al., it seems logical that milder phenotypes may be due to less severe gene defects, and vice versa. In this model, more deleterious gene defects like frameshift mutations or deletions would be responsible for severe disease, and a truncated protein would cause milder disease.\textsuperscript{3} Gerstenblith et al. disagree, reporting that phenotypic variation does not appear to be linked to the type of gene mutation present. In fact, 70% of PTCH1 gene mutations in Gorlin syndrome have been shown to be mere protein truncations.\textsuperscript{2} This then raises the question, why is there nearly 100% penetrance but with such clinical variability? More research is needed in this area. Overall, we believe that these diseases of SHH/PTCH/SMO dysfunction are a continuum of one disease and that our patient falls on the more benign end of the spectrum.

New treatment options with better cosmetic outcome have eliminated a great deal of morbidity associated with these conditions. There is a large body of literature supporting the use of MAL-PDT for BCC in the general population and recently in BCNS patients. ALA-PDT also seems like a promising treatment for BCC in BCNS with good cosmetic outcome, but more long-term efficacy data is needed. There is also some data to suggest that PDT helps prevent new BCC lesions in Gorlin syndrome, but more evidence is needed. It would also be helpful to compare the efficacy and cosmetic results of PDT vs. topical immunomodulators, as this has not been studied to our knowledge.

References:


Recurrent HSV-associated erythema multiforme: a case report of atypical morphology and distribution


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Introduction

Erythema multiforme (EM) is characterized by an acute polymorphous eruption of macules, papules, plaques, bullae, and targetoid lesions with an acral distribution pattern and limited mucosal involvement.1,2 It is usually a self-limited skin condition with resolution in three to five weeks,1 but it may recur in some individuals. The most commonly associated etiological factors are infections, such as herpes simplex virus (HSV) and Mycoplasma pneumoniae, and medications, notably barbiturates, penicillins, sulfonamides, thiazide diuretics, and nonsteroidal anti-inflammatories.3,4 Two common types of EM are HSV-associated erythema multiforme (HAEM) and drug-induced erythema multiforme (DIEM).

Clinically, HAEM lesions are commonly targetoid, located on the distal acral extremities and progress proximally; they have minimal mucosal involvement and may or may not have prodromal symptoms. DIEM lesions, on the other hand, consist of vesicles, bullae, erythematous plaques, and occasional targetoid lesions most often located centrally on the body, with prominent mucosal involvement and prodromal symptoms.1,3,5 Prodromal symptoms, if present, include a mild pruritis or burning sensation at the site of the eruption.

Histologically, HAEM lesions have a predominance of CD4+ T helper 1 (Th1) cells and moderate-to-pronounced dermal edema, whereas DIEM lesions have a predominately CD8+ T cell infiltrate with minimal dermal edema. Immunohistochemistry shows HAEM lesional skin is positive for HSV DNA and INF-γ, while DIEM lesions are negative for HSV deoxyribonucleic acid (DNA) and positive for TNF-α.6 We report a case of recurrent HSV-associated erythema multiforme with an atypical morphology and distribution.

Figures 1a, 1b. Multiple annular papules and plaques on shoulders and left arm.
Case Report

A 7-year-old Caucasian male presented to the office with a chief complaint of a rash occurring shortly after sun exposure to the trunk and upper arms. His mother described a several-month history of a pruritic, erythematous rash on the face and trunk occurring several minutes to several hours after sun exposure. On the initial physical exam, the patient had multiple annular plaques on his sun-exposed upper arms and shoulders (Figures 1a, 1b). Biopsy of a representative lesion revealed interface dermatitis with a lymphoid infiltrate along the dermo-epidermal junction and keratinocyte necrosis (Figures 2a, 2b). An Epstein-Barr virus in-situ hybridization test was negative. The initial differential diagnoses for this patient were juvenile spring eruption vs. HAEM vs. DIEM. The initial treatment involved a low-potency topical steroid to the affected area, sunscreen, and photo-protective clothing.

During the follow-up visit, three weeks later, the mother stated that the steroids were of no benefit. Upon further questioning, the patient’s mother admitted the patient suffers from frequent cold sores. On follow-up exam, the dermatitis had evolved to feature targetoid plaques (Figure 3). An HSV IgG level was ordered to aid in the diagnosis. Further biopsies and HSV-specific tissue studies were not performed. The HSV IgG was positive, which, along with the history of recurrent herpes labialis and an absent history of medication use, led to the diagnosis of HSV-associated erythema multiforme.

The patient was started on acyclovir at 20 milligrams per kilogram four times per day and counseled on strict sun avoidance. The rash cleared rapidly after several days of treatment, but upon discontinuation of the acyclovir, the rash returned. At that point, the patient was told to continue low-dose, 400 milligram daily acyclovir therapy, which prevented subsequent episodes.

Discussion

Erythema multiforme typically occurs in adults between the ages of 20 and 40, although all age groups can be affected. The Severe Cutaneous Adverse Reactions (SCAR) study concluded that EM patients are typically young and more commonly male, with males having as much as a 10-fold higher rate of recurrence compared with females. On the other hand, a retrospective review conducted by Wetter and Davis looking at 48 patients with recurrent EM showed a female predominance for the disease. The most commonly implicated etiological agents of EM are infections, notably HSV, M. pneumoniae, and fungi. However, multiple other infectious agents such as hepatitis C, cytomegalovirus, and human immunodeficiency virus have also been implicated. The medications most commonly associated with EM include barbiturates, penicillins, sulfonamides, and nonsteroidal anti-inflammatories, although numerous other medications have been associated with the disease as well. Other documented causes include malignancy, immunizations, sarcoidosis, connective-tissue diseases, and inflammatory bowel disease. In the present case, the clinical history and serology were both positive for HSV, helping to confirm the diagnosis of HSV-associated erythema multiforme.

Patients with HAEM can have a clinically evident HSV reactivation without an episode of EM, or they can have an episode of EM without a clinically evident HSV infection.
In our case, there was no direct link between the herpes labialis outbreaks and the EM episodes. It is possible that this patient had a subclinical HSV reactivation prior to the EM eruptions, and since these eruptions typically followed sun exposure, it stands to reason that ultraviolet (UV) radiation may have been the trigger for the subclinical HSV reactivation. Several case reports have shown that recurrent HAEM can be precipitated by sun exposure, and studies have shown that UV radiation is a causative factor of HSV reactivation. Our patient’s lesions were limited to the upper arms and shoulders, which is atypical, since classic HAEM lesions occur on the distal extremities and progress proximally. There are a handful of cases in the literature of patients presenting with photo-distributed lesions in HAEM, which seems less likely in our case, as the patient had no evident lesions on his sun-exposed distal extremities and upper chest.

HAEM is a delayed-type hypersensitivity reaction. The pathogenesis is believed to begin with a clinical or subclinical reactivation of HSV that leads to a transient viremia and the transport of HSV DNA fragments via peripheral blood mononuclear cells to the skin surface. This leads to recruitment of HSV-specific CD4+ helper T cells (T,1) and the T,1 release of interferon-γ, a pro-inflammatory cytokine, which initiates an inflammatory cascade that ultimately results in the prototypical skin manifestations. In addition, studies have shown that viral DNA can persist for up to one to five months after HAEM lesional skin has cleared, raising the possibility that these patients have an inability to clear the virus efficiently.

The treatment of recurrent HAEM involves the use of daily acyclovir, which has been shown to suppress recurring episodes. Valacyclovir or famciclovir, with a greater oral bioavailability than acyclovir, can be used if patients do not respond to acyclovir therapy. Our patient initially improved after several days with acyclovir therapy, but upon cessation of the medication and re-exposure to sunlight, the eruption returned. Consequently, we placed the patient on daily acyclovir, which suppressed antiretroviral therapy. Some patients unresponsive to suppressive antiretroviral therapy have been treated with hydroxychloroquine, dapsone, and even azathioprine, although the evidence for the use of these agents in HAEM is limited.

References

1. Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component.
Extranodal NK/T-cell Lymphoma, Nasal Type

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Abstract:
Extranodal natural killer/T-cell lymphoma, nasal type, is a rare and aggressive form of non-Hodgkin’s lymphoma (NHL), characterized by natural-killer (NK) cell phenotype, Epstein-Barr virus (EBV) positivity, and vascular damage and destruction. It is uncommon in the United States and more prevalent in Asia and in the native populations of Central and South America. Clinical presentation is non-diagnostic, and histologic examination with immunohistochemistry is necessary for diagnosis and staging. We report a case of extranodal NK/T-cell lymphoma, nasal type, arising on the back of a 66-year-old man.

Case Report
A 66-year-old man with no significant past medical history presented with a nodule on his left upper back of six weeks duration. He denied any symptoms other than mild pruritus. Physical examination revealed a 20 mm x 30 mm soft, fixed, and flesh-colored nodule on his left upper back (Figure 1). There were no enlarged lymph nodes.

A biopsy revealed an atypical lymphoid infiltrate. Immunohistochemical stains revealed a 19% population of small to medium-sized cells with the following immunophenotypes: CD1a(-), CD2(+), surface CD3(-), CD4(-), CD5(-), CD7(-), CD8(dim+), CD10(-), CD11b(-), CD16(partial dim+), CD25(-), CD30(-), CD34(-), CD45(+), CD34RO(dim+), CD52(+), CD56(+), and CD57(-). Also present were 12% small, mature T-lymphocytes, 5.2% mature, polytypic B-lymphocytes, and 0.27% plasma cells. In situ hybridization for Epstein-Barr virus showed almost 100% positivity of tumor cells. Molecular studies for T-cell gene rearrangement showed an atypical TCR-gamma DNA fragment pattern suspicious for clonality.

**Figure 1. 20 mm x 30 mm soft, fixed, and flesh-colored nodule on left upper back**
The findings of the hematoxyline and eosin, immunohistochemistry, molecular, and flow cytometry confirmed the diagnosis of Epstein-Barr virus related NK/T-cell lymphoma, nasal type. He was subsequently referred to oncology to further evaluate for systemic involvement, as well as for appropriate staging and treatment.

Discussion
Extranodal NK/T-cell lymphoma is a rare variant of non-Hodgkin’s lymphoma. It is most common in Asia and in the native populations of Central and South America, where it primarily affects men in their fifth decade.1 It is rare in the United States and Europe. The pathogenesis of extranodal NK/T-cell lymphoma, nasal type, is unknown. However, the strong association with EBV infection suggests a probable pathogenic role for the virus.1

Extranodal NK/T-cell lymphoma, nasal type, is characterized by a high incidence of nasal involvement with symptoms of nasal obstruction, epistaxis, nonspecific rhinitis or sinusitis.1 The tumor is locally invasive and can infiltrate the surrounding tissues. The skin, as in our case, is the second most common site of involvement and may be a primary or secondary manifestation of the disease. Other extranasal involvement includes lungs, testes, gastrointestinal tract, or central nervous system.1 Systemic symptoms such as fever, malaise, and weight loss may be present.

Bone marrow involvement is uncommon, though it may disseminate rapidly or be complicated by a hemophagocytic syndrome.3

Histopathologically, a diffuse infiltrate of polymorphous, atypical lymphocytes is seen in the dermis and often the subcutis. Prominent angiocentricity and angiodestruction are often accompanied by extensive necrosis.1

The key diagnostic features are the demonstration of NK- and T-cell markers on immunophenotyping, typically CD2, cytoplasmic CD3 epsilon (ε), and the NK-cell marker CD56. In addition, presence of EBV is demonstrated by in situ hybridization for EBV-encoded small nuclear RNAs (EBERs).4 The differential diagnosis of NK/T-cell lymphoma, nasal type, includes other NK and T-cell malignancies and EBV-associated T-cell or NK-cell lymphoproliferative disorders.

Although rare, extranodal NK/T-cell lymphoma, nasal type, is an aggressive lymphoma, characterized by rapid progression of disease, relapses, and extremely poor prognosis. The most important factor predicting poor outcome is the presence of extracutaneous involvement at presentation. A retrospective analysis of 53 patients with extranodal NK/T-cell lymphoma, nasal type, reported a median survival of 27 months in patients presenting with only skin lesions, compared with four months for patients presenting with both cutaneous and extracutaneous disease.5 Other predictors of poor outcome include high plasma levels of EBV DNA and tumor invasiveness.4 Systemic chemotherapy remains the initial choice of treatment, but the results have been disappointing.6

In conclusion, we present a rare case of extranodal NK/T-cell lymphoma, nasal type, arising on the back of a 66-year-old man. Diagnostic hallmarks include angiocentricity, angiodestruction, immunophenotype positivity for CD2, CD3ε and CD56, and evidence of EBV infection. Prognosis is poor despite chemotherapy as initial treatment of choice. Our patient was referred to oncology to further evaluate presence of systemic involvement for subsequent staging and therapy.

References:
Background:
Sinonasal mucosal malignant melanoma is an exceedingly rare entity, representing less than 1% of all melanomas. Compared to their cutaneous counterparts, mucosal melanomas have a much poorer prognosis. Due to their rare nature and benign symptomology, most mucosal melanomas are not found until metastases have occurred. A case report is presented with this rare finding.

Case Report:
An 85-year-old Caucasian female presented with chief complaint of “recurrent nose bleeds for the past year.” The patient described the bleeding as occurring a few times a week, consisting of bright red blood, and lasting a few minutes per episode. She denied any other symptoms such as headache, fever, or upper respiratory symptoms. Her past medical history was significant only for hypertension, hypothyroidism and hyperlipidemia. After a physical exam was completed, the patient was discharged with antibiotics to treat what was believed to be sinusitis.

The patient continued to have epistaxis after treatment and was referred to an ENT specialist, where she had CT images taken of her frontal and maxillary sinuses. The findings were consistent with what was believed to be sinus-wall thickening and hence a chronic sinusitis.

Nine months later, the patient, still with epistaxis, and with hopes of treating her “chronic sinusitis,” underwent an elective endoscopic left frontal sinusotomy, left ethmoidectomy, left maxillary antrostomy and septoplasty. Pathology results confirmed sinus...
contents containing lymphocytes, plasma cells and chronic inflammation, corresponding again to a diagnosis of chronic sinusitis.

The patient returned one month later with a new complaint of a small, skin-colored nodule on her right forehead, along with continued nasal bleeding. The patient underwent a right frontal sinusotomy and was found during the time of surgery to have a free passage of fluid from her previous left sinusotomy that tracked to her right anterior forehead, producing what seemed to appear as a mucocele. A revision of the left frontal sinusotomy was performed at this time as well as removal of the mass on her right forehead.

Better sampling technique due to the now greater involvement of both sinuses and forehead allowed for a different pathology to be shown. Gross description of sinus contents this time revealed multiple pieces of tan and pale, soft hemorrhagic tissue. Gross dissection of the forehead mass showed a 0.9 cm x 0.6 cm firm, tan piece of tissue.

Pathological examination of the new sinus contents via H&E stain revealed a very cellular spindle-cell neoplasm with an overlying chronic sinusitis with mild lymphocytes and plasma cells. The right forehead mass pathological exam showed the very same cellular spindle-cell neoplasm as produced in her sinus cavity (Figures 1 and 2).

Due to the new findings of a spindle-cell neoplasm, an all-inclusive immunohistochemistry panel for the work-up of spindle-cell tumors was obtained to rule out entities such as dermatofibrosarcoma, spindle-cell squamous carcinoma, and melanoma. S-100 stain was shown to be 1+ positive in all tumor cells, and the more-specific stain Pan-Melanoma (Melan A, tyrosinase, and S-100) was shown to be 4+ in all tumor cells (Figures 3 and 4). HMB45 stain also proved to be 4+ in all tumor cells. Immunohistochemistry stains confirmed the diagnosis of malignant melanoma in this spindle-cell neoplasm involving the patient’s forehead and subcutaneous tissues and extending into the sinus subepithelial and connective tissues.

After the diagnoses of malignant melanoma was established, the patient was sent to outpatient oncology and was found via PET to have metastatic lesions to multiple lymph nodes in her chest as well as multiple metastatic lesions to her liver. The patient denied any personal history of skin cancer or familial cases of melanoma. The patient currently reports being treated with postsurgical radiation to her sinus cavities.

Discussion
Melanomas are tumors derived from neuroectodermal cells called melanocytes. These cells are found in skin adnexa, basal layers of skin, and some mucosal membranes.
such as the conjunctiva, nasopharynx, sinonasal or genital mucosa. Primary mucosal melanoma of the head and neck is an uncommon neoplasm that represents 0.3% to 2% of all malignant melanomas. Specifically, sinonasal melanoma accounts for less than 1% of malignant melanomas. In contrast to its cutaneous counterpart, mucosal melanomas are not believed to be directly influenced by sunlight/UV light. This theory draws on the lack of sunlight/UV-light exposure to the affected areas. Although their roles remain unclear, irritants and carcinogenic compounds in the air, such as tobacco smoke and formaldehyde, have been implicated in the development of mucosal melanomas.

At presentation, the most common symptoms of patients with sinonasal melanoma are epistaxis and nasal congestion or obstruction. Discharge, facial pain, and edema are common in more advanced cases. These symptoms can easily be mistaken for the presenting signs of sinusitis. The major presenting signs of chronic sinusitis are nasal obstruction, facial pain, and nasal discharge. In sinonasal melanoma, the maxillary sinuses are most commonly involved, with the origin in frontal or sphenoid sinuses being extremely rare, which is what makes the case presented here even more interesting. Patients will typically present with these symptoms between the ages of 60 and 80 years, although diagnoses may occur at any age. Due to its rare nature and benign symptomology, most mucosal melanomas are not found until already in advanced stages of development, and prognosis is generally poor.

Compared to other mucosal melanomas, sinonasal melanoma shows vascular and deep-tissue invasion more frequently. Melanin pigment can be helpful in the diagnosis of mucosal melanoma, but in most cases pigment is absent. Pathologically, sinonasal-melanoma malignant cells are either epithelioid or spindled, with enlarged nuclei with prominent nucleoli; increased mitotic activity with atypical mitotic figures are commonly present. Immunohistochemical stains for S-100 protein, HMB-45, and Pan Melanoma stain are helpful for diagnosis and are characteristically positive.

Of note, distinct molecular features have been found in mucosal melanomas that differentiate them from their cutaneous counterparts. For instance, activating mutations of the BRAFV600E oncogene have been found in up to 75% of cutaneous melanomas and are absent completely in mucosal melanomas. New and promising BRAF-inhibiting agents such as vemurafenib, designed to combat metastatic melanoma, will not work for these mucosal melanomas, which lack the BRAF mutation. Fluorescence in situ hybridization shows that a c-KIT protein expression occurred in 96.9% of sinonasal mucosal melanomas, while mutations in NRAS occurred in over 22% of sinonasal mucosal melanomas. These newfound molecular fingerprints could lead the way to new treatment considerations for primary sinonasal mucosal melanomas targeting these specific NRAS and c-KIT mutations. Some experimental studies have shown marked tumor regression in patients with metastatic mucosal melanoma who were treated with single-agent imatinib, due to the inhibition of c-KIT. Further studies are needed to explore this treatment option.

Currently, no universally accepted staging system for mucosal melanoma exists. Due to the absence of histologic landmarks analogous to the papillary and reticular dermis, and the advanced stages of most cases at presentation, the prognostic value of various levels of invasion established in the Clark classification for cutaneous melanoma does not apply to mucosal melanoma. PET scans to evaluate the stage and extent of disease at diagnosis will best help to assess disease severity. The following is the system that suffices for staging:

Stage I – Localized disease
Stage II – Metastases to regional lymphatics
Stage III – Distant metastatic disease

Compared to its cutaneous counterparts, mucosal melanomas have a much poorer prognosis. In addition, sinonasal melanomas in particular have a dismal prognosis, specifically when there is infiltration into the skull or facial soft tissue. Wide excision is the primary treatment modality for sinonasal melanomas. A study conducted between 1963 and 1996 of 58 individuals with sinonasal melanoma showed that regardless of treatment modality, five-year survival rate remained the same, less than 30%, with a median survival of 21 months. Although radiotherapy improved regions of the melanoma locally, there was no statistical difference in survival time of patients being treated with excisional therapy alone versus those receiving surgery and radiotherapy. The addition of chemotherapy had no impact on survival, nor did the site of the tumor, the surgical procedure, the presence of lymph node metastases or the age of the patient. Additional studies have shown that even with adjuvant radiotherapy, up to half of patients will show sites of distant metastases and local recurrence. Nasal sinus melanomas have a 20% chance of metastases to overlying cutaneous tissue, with the most likely location of metastases being to the lungs or liver.

Conclusion:
Sinonasal melanoma is a severe and devastating disease. It is a rare entity that may present with benign symptoms. Physicians need to be aware of mucosal melanomas and include the oral mucosa, nasal mucosa, and conjunctiva when completing their full-body skin exams and looking for melanoma. Also, a clinical depiction of chronic sinusitis may be a more serious entity, such as a potential sinonasal melanoma. The best prognosis would result from early detection and early excision. Surgery is the mainstay of treatment, with no increase in survival rates with concurrent radiotherapy and chemotherapy. Despite current treatment modalities, the prognosis for these patients remains dismal. Staying aware of advances in immunotherapy, such as the creation of affordable medications against the c-KIT and NRAS mutations found in these tumors, is essential, as they may provide hope for mucosal-melanoma patients.

Consent: Informed consent was obtained from the patient for publication of this report and any accompanying images.

Competing interests: The authors declare that they have no competing interests.

Authors’ contributions: LB and WS participated in investigation and diagnosis. LB drafted the manuscript, while RR co-authored and reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgements
Thank you to Dr. Neil Goldberg for taking the time to share his insight and views on this case and our manuscript.

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5. Dauer EH, Lewis JE, Rohlinger AL,
64 AN UNEXPECTED FINDING OF SINONASAL MELANOMA IN A PATIENT BELIEVED TO HAVE CHRONIC SINUSITIS: A CASE REPORT
Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

**INDICATION & USAGE**

FINACEA® (azelaic acid) Gel, 15% is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea.

Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

**IMPORTANT SAFETY INFORMATION**

FINACEA Gel, 15% is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other components of the formulation. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation. FINACEA and its vehicle caused irritant reactions at the application site in human dermal safety studies. Skin irritation (e.g. pruritus, burning or stinging) may occur during use with FINACEA, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and/or persists during use with FINACEA, discontinue use and institute appropriate therapy.

In clinical trials with FINACEA, the most common local adverse events (AE’s) (inclusive of mild, moderate and severe categories) were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). Contact dermatitis, edema and acne were observed at frequencies of 1% or less.

Rarely reported AE’s included: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and exacerbation of recurrent herpes labialis. Post-marketing safety information: Skin (facial burning and irritation); Eyes (iritis on accidental exposure with FINACEA to the eyes). To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare at 1-866-463-3634 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

FINACEA is for topical use only. It is not for ophthalmic, oral or intravaginal use. In case of accidental eye exposure, wash eyes with large amounts of water and consult a physician if eye irritation persists. Wash hands following application of FINACEA.

See adjacent page for Brief Summary of full Prescribing Information. Model used for illustrative purposes only.

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
FINACEA Gel, 15%, is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema was present in patients with papules and pustules of rosacea occurred in clinical trials, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

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

WARNINGS
FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

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

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

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

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

• Avoid the use of occlusive dressings or wrappings.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (TG.AC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female TG.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male TG.AC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males.

Azelaic acid was not mutagenic or clastogenic in a battery of in vitro tests (Ames assay, HGPSRT in V79 cells (Chinese hamster lung cells), and chromosomal aberration assay in human lymphocytes) and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests. Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B
There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: Equilibrium dialysis was used to assess human milk partitioning in vitro. At an azelaic acid concentration of 25 μg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS
Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/ redness, were 19.4% (24/124) for FINACEA Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity

<table>
<thead>
<tr>
<th></th>
<th>Mild n=99 (22%)</th>
<th>Moderate n=61 (13%)</th>
<th>Severe n=27 (6%)</th>
<th>Mild n=46 (14%)</th>
<th>Moderate n=30 (9%)</th>
<th>Severe n=5 (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning/ stinging/ tingling</td>
<td>71 (16%)</td>
<td>42 (9%)</td>
<td>17 (4%)</td>
<td>8 (2%)</td>
<td>6 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29 (6%)</td>
<td>18 (4%)</td>
<td>5 (1%)</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Scaling/dry skin/ xerosis</td>
<td>21 (5%)</td>
<td>10 (2%)</td>
<td>5 (1%)</td>
<td>31 (9%)</td>
<td>14 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Erythema/ irritation</td>
<td>6 (1%)</td>
<td>7 (2%)</td>
<td>2 (&lt;1%)</td>
<td>8 (2%)</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>2 (&lt;1%)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (1%)</td>
<td>2 (&lt;1%)</td>
<td>0 (0%)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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

FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA Gel, 15%, caused significantly more irritation than its vehicle in a controlled irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety-Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA Gel, 15%, to the eye (see PRECAUTIONS).

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67068038S
Indication:
Kenalog® Spray (triamcinolone acetonide topical aerosol, USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Important Safety Information:
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

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

For more information, visit www.kenalogspray.com
KENALOG® SPRAY
Triamcinolone Acetonide Topical Aerosol, USP
(0.147 mg/g)
For dermatologic use only
Not for ophthalmic use

DESCRIPTION
The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. The steroids in this class include triamcinolone acetonide. Triamcinolone acetonide is designated chemically as 9-fluoro-11β,16α,17β-trihydroxy-16α,17α-ethylene-11β-(methyliminodiacetate)progesterone. Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.3%), and isobutane propellant.

CLINICAL PHARMACOLOGY
Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal skin intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted into the bile. Some of the topical corticosteroids and their metabolites are also excreted into the urine.

INDICATIONS AND USAGE
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

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

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, substitute a less potent steroid, or use a sequential approach. Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient
Patients using Kenalog Spray should receive the following information and instructions:
1. This medication is to be used as directed by the physician. It is for external use only; avoid contact with the eyes and inhalation of the spray.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
6. Do not use Kenalog Spray on the underarms or groin areas unless directed by your physician.
7. If no improvement is seen within 2 weeks, contact your physician.
8. Do not use other corticosteroid-containing products while using Kenalog Spray without first consulting your physician.

9. Kenalog Spray is flammable. Avoid heat, flames or smoking when applying Kenalog Spray.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone showed negative results.

Pregnancy: Teratogenic Effects
Category C. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

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

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

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

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

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

OVERDOSAGE
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION
Directions for use of the spray can are provided on the label. The preparation may be applied to any area of the body, but when it is sprayed about the face, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided. Spray is flammable; avoid heat, flame or smoking when using this product.

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

HOW SUPPLIED
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP)
63 g (NDC 10631-093-62) aerosol can.
100 g (NDC 10631-093-07) aerosol can.

Storage and Handling
Store at room temperature; avoid excessive heat. Contents under pressure; do not puncture or incinerate. Keep out of reach of children.

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1098 or www.fda.gov/medwatch.

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Jacksonville, FL 32257 USA

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