An Osteopathic Approach to Raynaud’s Phenomenon

Also in this issue:
Tinea Faciei Presenting as a Perioral Dermatitis
Cutaneous Pili Migrans Misdiagnosed
Vicks VapoRub™ for Onychomycosis?
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Dear JAOCN readers,

Thank you all for your continued support and great submissions, as well as for your patience as we revamp the format and appearance of the journal. We have had four different styles this year, and we'd love to get your feedback on which is most appealing.

I would also like to take this opportunity to invite my fellow members to the 2014 Dallas meeting, being held February 20-24 at the Ritz Carlton. This is an exciting meeting for many reasons. First, as Program Chair, I have scheduled 26 Category 1-A CME credits! The speaker line-up is refreshing and high-impact, with medical/surgical experts such as Ron Rapini, MD (“Unusual Infections”), David Fivenson, MD (“What’s Under that Ulcer?”), Jennifer Cather, MD (“Managing Psoriasis Patients Across the Life Course”), and James Q. Del Rosso, DO (Pharmacologic Q&A).

There will also be an emphasis on less-visible issues we face as physicians -- answers to questions we cannot find in textbooks, journals, or labs. Clifford Lober, MD, JD, will be talking about “Legal Dilemmas in Dermatology,” including real-life cases and scenarios. Kelly Nelson, MD, will shed light on “Issues in Patient Safety.” I have invited the web-blog phenomenon James Dahle, MD, the “White Coat Investor,” to share tips and strategies specifically aimed at physicians and practices in a non-proprietary information session between colleagues. Lloyd Cleaver, DO, will be updating and demystifying OCC requirements. Finally, Faith McNicholas, the manager for Coding & Reimbursement / Governmental Affairs for the AAD, will give us an extended, interactive update on the implementation of ICD-10. She recently gave a similar talk at our Einstein Grand Rounds, and I can attest to her expertise and approachability. Rounding out our meeting, topics in melanoma, Mohs, dermatopathology, and cosmetic dermatology will be covered.

This meeting will be our first to implement the feedback from member surveys, taking into account preferences in content, accessibility, and increased number of offered CME hours. I urge you not to miss out on this unique opportunity to attend such a well-rounded and innovative program line-up.

Happy holidays to all,
Karthik Krishnamurthy, DO, FAOCD
Editor-in-Chief, Journal of the American Osteopathic College of Dermatology
2nd Vice President, American Osteopathic College of Dermatology
Program Chair, 2014 Dallas Meeting
Greetings, everyone!

The 2013 Annual Meeting is now behind us, and new officers were elected at our annual business meeting on October 1, 2013. The AOCD has many committees working for the entire AOCD membership. If you would like to be a member of a committee, please contact the AOCD office for more information (www.aocd.org).

The AOCD has grown tremendously over the last decade. We had many exciting changes during 2013 with the move to our new, spacious office, and the website update. We encourage everyone to log on to the new site (www.aocd.org) and explore the wealth of information located on it. If you have username or password problems, please let us know. We are happy to assist!

2014 AOCD Dues Renewal

It’s time to renew your dues for 2014. Your membership in the AOCD and participation in our CME events are greatly appreciated, and your continued support helps us to achieve the AOCD’s objectives:

1. To maintain the highest possible standards in the practice of dermatology.
2. To stimulate study and to extend knowledge in the field of dermatology.
3. To promote a more general understanding of the nature and scope of the services rendered by osteopathic dermatologists to the other divisions of medical practice, hospitals, clinics, and the public.
4. To contribute to the best interests of the osteopathic profession by functioning as an affiliated organization of the American Osteopathic Association.

Meetings Update

AOCD Midyear 2014 will be held February 20-23, 2014, in Dallas, TX, at the Ritz Carlton. You must contact the Ritz Carlton directly for room reservations (www.ritzcarlton.com/en/Properties/Dallas/Default.htm).

Meeting Evaluations and Surveys

AOA requirements for CME continue to evolve. Thank you to everyone for participating in the various surveys throughout the year and for returning meeting evaluations. The results are tabulated and reviewed by the Board of Trustees and the CME committee. Locations for future AOCD Midyear Meetings will be chosen based on survey results.

The AOCD Board of Trustees and National Office wish you a happy and healthy holiday season.

Best,
Marsha A. Wise
Dear Colleagues,

What an interesting start to my tenure it has been. If you think being President is a quiet job, think again. In the first six weeks, we’ve been addressing the many exciting events and goals on our agenda for the coming year.

First, our JAOCD is on the forefront with its high standards and increasing visibility. Our peer-reviewed journal showcases our residents, members and program directors. No article is unchecked. The design is evolving. Karthik and the rest of the journal team are doing a great job.

Our college is hard at work for you. Marsha Wise, with a click of a button, has all of the answers you need. John Grogan keeps our residents in check, and Shelly Wood is recruiting those sponsors. Our annual convention showcased local and across-the-country talent. As our college grows, our own talent will be even more present. The new CME rules for conferences require 50 percent DO lecturers. I know our future program chairs are already working toward this goal. If anyone is interested in lecturing, touch base with Rick Lin and Dan Ladd. Our Dallas meeting is set to go, and I hope to see you all there. Over 100 members have signed up already. Come get your CME and socialize with your colleagues!

The finance committee has been extremely effective, with Marsha keeping us fiscally responsible. Nice work! Your EEC committee, too, is always at it. Basic standards for the residencies are constantly being reviewed and revised. Thank you to the in-training exam committee for all your efforts. We strive to produce the best dermatologists in the country.

So, what’s on the horizon? The AAD ad hoc task force is working to bridge the gap between DO and MD dermatologists. Our goal is to work together, not separately. It is also working to dispel the incorrect perceptions of DOs amongst the MDs. We have a real friend in Dirk Elston. I ask all of you to be our advocates. Educating our colleagues and patients about DO dermatologists is essential. Striving for excellence in practice and residencies should be everyone’s goal.

Please don’t be a stranger to our college. Be on a committee, come to our meetings, advocate for us. You will find it highly rewarding.

Fondly,
Suzanne Sirota Rozenberg, DO, FAOCD
President, AOCD
YOUR PATIENTS’ PROBLEMS ARE
itchy, goopy, burning, red, flaky, irritated, messy, sticky, hard-to-reach, peeling, greasy

sensitive-to-touch

AEROSOLVED

NO-TOUCH RELIEF
The Only Mid-Potency Topical Steroid Aerosol Spray

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 those patients with a history of hypersensitivity to any of the components of the preparations.

For external use only. Please see full Prescribing Information on reverse and also at KenalogSpray.com.


Kenalog® is a licensed trademark of Bristol-Myers Squibb Company.

KNGJ11  09/13
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, 21-trihydroxy-1, 4-diene-3, 20-dione cyclic 16, 17β-acetate with alcohol. The structural formula is:

\[
\text{HO} - \text{C}_2\text{H}_4\text{O} - \text{CH} - \text{C}_2\text{H}_4\text{O} - \text{C}_1\text{H}_3\text{CH}(\text{CH}_3) - \text{OH}
\]

A two-second application, which covers an approximately the size of the hand, delivers an amount of triamcinolone acetonide not exceeding 0.2 mg. After spraying, the nonvolatile vehicle remaining on the skin contains approximately 0.2% triamcinolone acetonide. 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 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 by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

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 those 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 fontanelles, headaches, and bilateral papilledema.

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

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, hirsutism, prolonged exposure to occlusive dressings). The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, hirsutism, prolonged exposure to occlusive dressings.

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

DOSE 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 more applications daily of Kenalog Spray (Triamcinolone Acetonide Topical Aerosol) are generally adequate.

HOW SUPPLIED
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP) is a 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-1088 or www.fda.gov/medwatch.

RANBAXY
Jacksonville, FL 32257 USA

Revised August 2011

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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.

See reverse side for a Brief Summary of the Full Prescribing Information.


ZIANA is a registered trademark of Medicis Pharmaceutical Corporation.

ZNA 12-024 06/30/13
studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis.

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 clostridia 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 assays for C. difficile toxin may be helpful diagnostically.

Adverse reactions

Clinical Studies Experience

BRIEF SUMMARY

(see package insert for Full Prescribing Information)

RX ONLY

FOR TOPICAL USE ONLY

INDICATIONS AND USAGE

ZIANA® Gel is indicated for the topical treatment of acne vulgaris in patients 12 years and older.

CONTRAINDICATIONS

ZIANA® Gel is contraindicated in patients with regional enteritis, 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 clostridia 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.

Ultrasound 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 sun 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 at least 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>
<thead>
<tr>
<th>ZIANA® Gel</th>
<th>Clindamycin</th>
<th>Tretinoin</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>N=1,853</td>
<td>N=1,428</td>
<td>N=846</td>
<td>N=423</td>
</tr>
<tr>
<td>PATIENTS WITH AT LEAST ONE AD</td>
<td>49 (7)</td>
<td>34 (2)</td>
<td>22 (3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>65 (5)</td>
<td>64 (5)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>29 (2)</td>
<td>18 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (1)</td>
<td>7 (1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Cough</td>
<td>18 (1)</td>
<td>21 (2)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (1)</td>
<td>19 (1)</td>
<td>15 (2)</td>
</tr>
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</table>

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

Cautions and safety tolerance evaluations were conducted at each study visit in all of the clinical trials by assessment of erythema, scaling, itching, burning, and stinging:

| ZIANA® Gel-Treated Patients with Local Skin Reactions |
| Local Reaction | Baseline N=1,835 N (%) | End of Treatment N=1,814 N (%) |
| Erythema | 638 (35) | 416 (26) |
| Scaling | 237 (13) | 280 (17) |
| Itching | 189 (10) | 70 (4) |
| Burning | 38 (2) | 56 (4) |
| Stinging | 33 (2) | 27 (2) |

Adverse reactions reported in at least 1% of patients treated with ZIANA® Gel: 12-Week Studies

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 water 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 vitro studies have shown antagonism between these two antimicrobials. 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 maternal 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.

Dermal tretinoin 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.

Pediatric 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:

Medicis, The Dermatology Company
Scottsdale, AZ 85256

U.S. Patents 5,721,275 and 6,387,383

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Prescribing Information as of October 2008.

300-138
Definition, Epidemiology, Presentation
Raynaud’s phenomenon is characterized as episodic, paroxysmal vasospasm and ischemia of the extremities, usually involving the fingers and toes, on exposure to cold or a stressful stimulus. It was first described by Maurice Raynaud in 1862 as “a local asphyxia of the extremities.” It is a triphasic color change of the digits -- from white (vasoconstriction), to blue (tissue hypoxia), to red (reperfusion) -- accompanied by severe pain. Attacks vary in frequency and duration among individuals. In those with severe disease, ulceration and gangrene of the digits can occur.

Raynaud’s phenomenon can be further classified as primary (idiopathic) or secondary to underlying disease. Underlying conditions can include, but are not limited to, systemic sclerosis, mixed connective-tissue disease, and systemic lupus erythematosus. Raynaud’s phenomenon affects 3% to 5% of the general population, with a higher predominance in women. Some well-known triggers include a positive family history, estrogen exposure, emotional stress, smoking, and hand-vibration syndrome.

Pathophysiology
The pathophysiology of Raynaud’s phenomenon is not clear. It is believed to be due to an imbalance of vasoconstriction and vasodilation. In primary disease, there is excess activation of the sympathetic nervous system directly affecting the vascular tone in the extremities it supplies. The usual disturbance involves thoracic vertebral segments 1 through 3. There is also a decrease in vasodilators, including calcitonin-gene-related peptide, which is released by nerves. In patients with both primary and secondary Raynaud’s phenomenon, skin biopsies have revealed diminished release from neurons.

Endogenous levels of nitric oxide, a potent vasodilator activated by high levels of cyclic guanylyl nitro peptide (cGNP), are also decreased in primary and secondary disease. Prostaglandins, whose role is to inhibit platelet aggregation and increase fibrinolysis, are also found to be deficient in patients with Raynaud’s phenomenon. Individuals consuming large quantities of prostaglandin inhibitors on a regular basis may thus be at risk.

Two key players that increase vasoconstriction and are likely involved in the pathogenesis of Raynaud’s phenomenon are endothelin-1 and angiotensin-II. Endothelin-1 is not only involved in vasoconstriction but also in structural vascular changes and remodeling, which can further contribute to the ischemic process that occurs in this disease. Angiotensin II is part of the renin-angiotensin system (RAS) in the kidney. Circulating levels of angiotensin II are increased in primary and secondary disease. Therefore, inhibition of angiotensin II, via angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, is a potential future treatment for Raynaud’s phenomenon.

Treatment
There are several treatment options available for primary and secondary Raynaud’s phenomenon. First-line treatment involves lifestyle modifications including avoiding stress, hand and leg warmers, avoiding cold environments or rapid changes in temperature, and smoking cessation if applicable. Patients can perform the swing-arm maneuver, which involves rapidly windmilling the arms around the body with the goal of increasing blood flow distally to the fingers.

First-line medications are the noncardioselective dihydropyridine calcium-channel blockers. Nifedipine, a short-acting agent, is most commonly prescribed at 10 mg to 30 mg doses three times daily. These drugs cause relaxation of the vascular smooth-muscle cells via inhibition of the voltage-gated channels. This in turn promotes vasodilatation and increased blood flow to the periphery. These have been aggressively studied and are routinely prescribed by physicians. However, when prescribing these drugs, patients are to be cautioned about side-effects including headache, flushing, and reflex tachycardia.

Topical nitrate therapy is also a relatively common agent used in the treatment of Raynaud’s phenomenon. Sustained release patches of glycerol trinitrate were shown in clinical trials to decrease the number (P<0.05) and severity (P<0.05) of attacks in primary and secondary Raynaud’s phenomenon. However, use may be limited due to the high potential for side effects like headache and hypotension, which can be disabling to patients.

Prostaglandins have a side-effect profile similar to calcium-channel blockers, but their mechanism of action differs. They have the combined ability to inhibit platelet aggregation, increase fibrinolysis, and simultaneously promote vasodilation. Despite the multitude of beneficial effects, no oral prostaglandin is as effective as intravenous prostaglandins in the treatment of Raynaud’s
and B. After four months of treatment with bosentan, there was a 48% reduction in digital ulcers compared to placebo. Current use of this drug is still limited as more insight is sought into this class of drugs. Additionally, there is potential for increased hepatic transaminases with bosentan, which can occur in 10% of patients. Alpha-adrenoreceptors play a key role in temperature regulation and sympathetic-nervous regulation of vascular tone. Prazosin, which inhibits the alpha-1 postsynaptic receptor, has been used in several trials to see if there is an improvement in patients with secondary Raynaud’s phenomenon. Though found to reduce the severity of Raynaud’s attacks, side effects including dizziness, headache, palpitations, nausea, and hypotension are common and limit the use of these agents in patients. Several other experimental agents have been used in the treatment of primary and secondary Raynaud’s phenomenon, such as HMG-CoA-reductase inhibitors, aspirin, serotonin-reuptake inhibitors, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and botulinum toxin A. However, more research needs to be done before any of these agents can be implemented in treatment for this disease.

Osteopathic Approach
Primary Raynaud’s phenomenon, unlike secondary forms, is mainly a functional disease. Thus, along with medical management of the patient, osteopathic medicine may play an integral role in decreasing the severity and number of attacks. There are three primary areas of focus that can be implicated in triggering an attack:

1. Any hyperactivity of the sympathetic nervous system, which leads to an increased release of catecholamines, stimulating the constriction of vascular smooth muscle.
2. Increase in muscle tension to the soft tissues of the neck and upper back region, which can cause constriction of the blood supply to the bilateral arms; 3) narrowing of the thoracic outlet, which can compromise blood flow distally and often disrupt the nerve endings as well.

The neck is composed of three cervical fascia: superficial colli fascia, middle colli fascia, and deep colli fascia. These fascia envelop important bony and neurovascular structures. The middle colli fascia is continuous with the subclavius muscle, which is situated between the clavicle and first rib, passing upward and laterally to a groove on the undersurface of the middle third of the clavicle. Any spasm, adhesion, or fibrosis can lead to compression of the thoracic inlet, bringing the clavicle closer to the first rib and thus causing decreased blood flow to the periphery, causing the ischemic changes that occur with Raynaud’s phenomenon. The deep colli fascia consists of well-defined fibrous sheets. The subclavian artery and brachial nerves run behind the clavicles as the axillary sheet of the deep colli fascia. Any tension to this fascia will compress this vital neurovascular supply to the extremity.

The scalene muscles of the neck are crucial gateways to the blood supply to the upper extremities. The subclavian artery runs between the anterior and middle scalene on its route to the shoulder, where it will become the axillary artery and then subsequently the brachial artery with further divisions in the arm. Any compression of the anterior and middle scalene can therefore compromise the blood supply to the arm, putting patients at further risk of developing a Raynaud’s attack. This is one of the several key areas that can lead to thoracic-outlet syndrome.

Thoracic-outlet syndrome can also occur between the clavicles and first rib, with an abnormal insertion of the pectoralis minor muscle, or due to the presence of a cervical rib. The Adson’s, Wright’s, and costoclavicular tests assess the blood supply to the radial artery, helping to further evaluate the presence of thoracic-outlet syndrome. Patients with this syndrome are at increased risk of developing primary Raynaud’s phenomenon.

Lastly, it is crucial to address the cervical and upper thoracic spine in an individual with Raynaud’s phenomenon. The sympathetic trunk emerges from the thoracic spine, and its ganglia are located in front of the heads of the ribs. These ganglia, specifically at the levels of T2 through T8, supply the upper extremity with sympathetic fibers. The postganglionic sympathetic fibers, which join the spinal nerves, are vasoconstrictors of blood vessels in the arm. Therefore, osteopathic treatment should focus on thoracic segments 2 through 8. Additionally, the stellate ganglion, C7, has vascular branches extending from it as well as the thoracic sympathetic nerves that supply the subclavian arteries.

There are several techniques that can address these restrictions. First, cervical soft-tissue and thoracic soft-tissue are two osteopathic manipulative treatments (OMT) that can help ease pressure on the cervical fascia (Figures 1 and 2). Soft-tissue is a direct technique, which involves lateral and linear stretching and deep pressure, with separation of muscle origin and insertion, while monitoring tissue response and motion changes by palpation. These techniques provide a gentle but firm stretching of the fascia as well as the muscles of the neck and upper back to increase range of motion and improve blood supply to the periphery.

Myofascial release is another form of OMT, first described by the father of osteopathy, Andrew Taylor Still. This technique can be used to free the clavicle and open up the thoracic inlet by engaging the restrictive barrier or through an indirect treatment by engaging the tissues in the direction of freer motion (Figures 3 and 4). Through continual palpatory feedback, an inherent release of the involved tissues is achieved. In respect to the clavicles, they can be gently translated laterally and held until release is felt. These maneuvers eliminate any tension on the subclavian artery on its path underneath the clavicle.

The first rib is another important player in the cause of Raynaud’s phenomenon. Using the direct technique, high-velocity/low-amplitude (HVLA), the malpositioning of the first rib can be eliminated, opening up the thoracic inlet and allowing the neurovascular supply to run smoothly from the neck down the arms (Figure 5). This is the most aggressive OMT technique, involving engagement of the restrictive barrier and then application of a directional force to correct the
dysfunctional rib. Proper positioning is crucial to a therapeutic effect. Similarly, HVLA can be applied to the thoracic region to address the hyperactivity of the sympathetic nervous system contributing to the catecholamine surge and vasoconstriction of the peripheral digits. There are several other HVLA techniques that can be used depending on the physician’s comfort level, such as the supine thoracic double arm thrust (“Kirksville Crunch”), knee-in-the back, and epigastric thrust.

Potentially, a clinical trial involving OMT in patients with Raynaud’s phenomenon could be done using the five OMT techniques in the following order to minimize the necessity of patients’ positional adjustments and increase treatment efficiency: 1) prone thoracic soft-tissue techniques; 2) supine cervical soft-tissue techniques; 3) supine direct myofascial release clavicular spread technique; 4) supine direct and indirect myofascial release of the thoracic inlet technique; 5) sitting high-velocity/low-amplitude treatment of the first rib. In a previous study, this protocol demonstrated OMT as a viable therapeutic intervention in affecting the autonomic nervous system. The treatment of the thoracic and the cervicothoracic regions should duplicate this change to sympathetic nervous system activity and benefit patients with Raynaud’s phenomenon, but a formal clinical trial would be necessary to confirm.

By combining the medical and osteopathic approach, we can successfully treat our patients suffering from Raynaud’s phenomenon. This will enable us to address the various structural and functional changes in the chemical and hormonal modulators, receptor activation, and muscle and tissue strain and stress that can trigger this potentially devastating disease.

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Dermatophytosis. We provide a literature review of tinea faciei’s potential presentations, differential diagnosis, work-up, and treatment.

Tinea faciei has the most variable clinical presentation of all the dermatophytoses. Treatment is often delayed due to missed diagnosis on initial clinical evaluation.

Abstract

Tinea faciei has the most variable clinical presentation of all the dermatophytoses. Treatment is often delayed due to missed diagnosis on initial clinical evaluation. The following case demonstrates an example of tinea faciei’s clinical variability, presenting seemingly as common perioral dermatitis with further workup revealing dermatophytosis. We provide a literature review of tinea faciei’s potential presentations, differential diagnosis, work-up, and treatment.

Introduction

Facial dermatophyte infections may present in multiple configurations, often deviating from the typical ringed, erythematous, scaling pathognomonic picture. Termed “tinea incognito,” initial misdiagnosis and application of steroids or other anti-inflammatory agents may alter these lesions, potentially further delaying diagnosis. Depending on which site on the face it affects as well as its potential variable morphology, tinea faciei may mimic other erythematous facial rashes such as acne, rosacea, perioral dermatitis, lupus erythematosus, seborrheic dermatitis, and contact dermatitis. The following case exemplifies tinea faciei’s clinical variability. It presented as common perioral dermatitis, but further workup revealed dermatophytosis, which responded excellently to an oral antifungal agent.

Case Presentation

A 72-year-old woman presented to the clinic with a history of an increasingly painful, erythematous rash of 10 days duration in a perioral distribution. Assuming this was an irritant or allergic dermatitis related to cosmetics, her primary physician prescribed the patient a topical steroid. She used the steroid from days 2 to 4 after onset, with further worsening of symptoms. Her medical history was significant for hypertension, hypercholesterolemia, depression, and bilateral knee replacements. From a dermatologic standpoint, she had a history of a facial basal-cell carcinoma treated with Moh’s surgery, hyaluronic-acid filler injections many years prior, and about 15 years of toenail onychomycosis. She had no recent changes in medications and had been on the same antidepressant, antihypertensive, and lipid-lowering agent for years.

On exam, the patient was anxious and distressed, complaining of severe burning. Groups of many single and confluent pink papules on a mildly swollen, erythematous base were noted surrounding her mouth with extension to her chin, sparing the vermillion border of the upper lip (Figure 1). Of note, no scale was present in the area of the patient’s rash.

She denied photosensitivity; exposure to new products, grooming habits, animals, supplements, or travel; and previous use of topical corticosteroids besides those recently prescribed to her. There were no other lesions elsewhere. An initial diagnosis of perioral dermatitis was made with consideration for possible rosacea, and the patient was instructed to immediately discontinue topical steroids. She was placed on a course of oral doxycycline and topical metronidazole gel. A biopsy was taken at this time for confirmation of the diagnosis. At her one-week follow-up appointment, her perioral rash and discomfort persisted. Biopsy results showed hyperkeratosis with parakeratotic scale, and PAS stain demonstrated many fungal hyphal elements consistent with dermatophyte infection (Figure 2).

Doxycycline and topical metronidazole were discontinued, and the patient was started on oral terbinafine at a dose of 250 mg per day. At her follow-up visit, the patient showed marked clinical improvement, with full resolution of lesions and symptoms at four weeks (Figure 3).

She continued this regimen for a total of three months for treatment of her concomitant onychomycosis of the lower-extremity nails, without recurrence of any perioral lesions.

Discussion

Tinea faciei accounts for 3% to 4% of all cases of tinea corporis, with causative agent varying according to geography and potential reservoirs. The dermatophytes Trichophyton tonsurans, Trichophyton rubrum, and Microsporum canis are the most common causative species, particularly in the United States. One characteristic of a dermatophyte is an acquired ability to metabolize and subsist upon keratin, a protein resistant to most other organisms, allowing the fungi to invade where keratin is the major structural protein.6

Classified as a dermatophyte infection involving non-bearded areas of the face, tinea faciei affects females more frequently than males, likely because dermatophyte infections on the bearded areas of males are often diagnosed as tinea barbae. It may present in both children and adults, and is more prevalent in those who are in regular contact with animals (both domestic and livestock), have histories of recent travel, and live in tropical, humid climates.

Unfortunately for patients, it has been reported...
that in 70 percent of cases of tinea faciei, other dermatoses are considered first, and many lesions persist for more than six months -- and even up to 2 years -- before a correct diagnosis is made. Tinea faciei is thought to have the most variable presentation of the dermatophytes, likely due to the complex structure of the face and a large range of depth and extent of invasion manifesting as many different lesions. A typical presentation may consist of single or multiple erythematous patches with an annular configuration and an active scaly border; however, this may be modified with lesions that may or not be raised and may or may not consist of papules, vesicles, or crusts. There may be itching, burning, or no symptoms at all. If the lesions surround a particular facial structure, such as the oral cavity, as with our patient, certain differential diagnoses must be considered.

**Differential Diagnosis**

Acne vulgaris can sometimes present similarly to an inflamed tinea faciei, with lesions consisting of pustules, papules, nodules, or comedones. Treatment with topical agents may cause irritation and erythema, further confounding the similar clinical appearance.

Tinea faciei presenting as rosacea has been described in the literature, as well. Usually affecting the central face, rosacea is characterized by persistent erythema, papules, papules, and telangectasias. Other features of rosacea include oculaar involvement, flushing, and discomfort at the site of involvement.

Another differential diagnosis is perioral dermatitis, a papulopustular inflammation of the skin surrounding the mouth, usually sparing the vermilion border. Chronicity is common. It is mostly seen in decades three to five in women; however, the incidence is increasing in men due to changes in grooming habits. Skin lesions occur as grouped follicular erythematous papules, and vesicles with possible confluence. Burning may accompany lesions, but rarely itching. Use of topical corticosteroids may cause perioral dermatitis, either as a direct effect from prolonged use or in a rebound effect.

There have been case reports of lesions of tinea faciei mimicking cutaneous lupus erythematosus. Since lesions of cutaneous lupus are largely photodistributed, facial lesions when annular, erythematous, and scaly, with or without scarring, deserve its diagnosis as a consideration.

The two main groups of contact dermatitis, allergic and irritant, have similar clinical facial inflammatory presentations. Over time, an allergic contact dermatitis may develop to cosmetics or other skin care products via a delayed-hypersensitivity reaction. Usually, patient history is telling, as are the distribution of lesions, as irritants will usually cause an eczematous reaction in the area of application. Acute zinc deficiency from malnutrition can also present as dermatitis, notably in a perioral distribution. Zinc deficiency may also involve other areas of the body in a periorificial distribution, in contrast to tinea faciei, which is confined to the face.

Commonly seen in highly sebaceous areas of the face and body, seborrheic dermatitis can involve the nasolabial fold and glabella. The typical presentation is erythematous patches with yellow-white scale and crust. When confined to the face and flared, this may present with a clinical picture similar to tinea faciei.

Sarcoidosis is also a great masquerader and can be included in the differential for papular lesions on the face that appear erythematous-to-violaceous.

**Diagnosis and Treatment**

Laboratory testing to confirm the presence of a dermatophyte infection include KOH preparation, fungal culture, tissue biopsy and PCR. The clinically representative area should be sampled, usually from an active area with scale. Potassium hydroxide (KOH) solution in 10 percent to 15 percent is applied to the specimen, and numerous hyphae with septa are present in a positive sample. Fungal culture is obtained with a swab and grown on Sabouraud's dextrose agar or dermatophyte test medium. However, growth in culture medium may occur in as few as 20% of specimens, due to low dermatophyte count or previous antifungal treatment. Polymerase chain reaction (PCR) is not yet widely available, but new assays are in development for identification of dermatophytes. Special stains, either PAS or GMS, are needed because dermatophytes are not visualized well with H&E. The histopathologic features are variable, ranging from hyperkeratosis with patchy parakeratosis to marked spongiosis and perivascular lymphocytic infiltrate. Fungal elements must be present on biopsy to confirm the diagnosis.

Tinea faciei is generally curable, with treatment options including topical and systemic antifungal agents, in addition to avoidance of risk factors. Topicals such as clotrimazole, ketoconazole, and miconazole applied daily or twice daily for approximately three to four weeks, and an additional one week after resolution of lesions, may be used in most cases of superficial tinea faciei. Topical terbinafine may be effective as well, possibly with a shorter treatment time. Recurrent and persistent infections may be associated with combination antifungal and corticosteroid topical preparations, which are widely used by non-dermatologists. In cases of inflammatory, persistent, or extensive dermatophyte infection, a systemic agent such as oral fluconazole, griseofulvin or terbinafine may be used. Systemic terbinafine, dosed at 250 mg daily for two weeks, can be used for superficial tinea infections. Liver function testing should be done at baseline and during sustained treatment, as in the 12-week course of terbinafine for onychomycosis. Other systemic therapies include pulse dosing of fluconazole 150 mg weekly for two to four weeks or griseofulvin 500 mg daily for two to four weeks. In our case, the patient showed marked clinical improvement after a four-week course of terbinafine. Also, avoidance of direct contact with infected animals or other persons should be recommended.

**Conclusion**

Tinea faciei, although relatively simple to treat, may at times be an elusive diagnosis. Patients frequently suffer weeks to months after initial presentation to a physician's office before the diagnosis is made. With its broad spectrum of presenting morphology, it may clinically mimic other causes of erythematous facial eruptions. Particularly in patients who do not respond to therapy, a dermatophyte infection of the face is an important diagnosis to consider.

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A Case of Cutaneous Pili Migrants: A Creeping Eruption Mimicking Larva Migrans

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Abstract

Cutaneous pili migrants is a cutaneous condition caused by an embedded hair shaft producing a migratory, creeping eruption that may closely mimic cutaneous larval migrans. We present a case of a 3-year-old female with pili migrants of the left foot that likely resulted from penetration of a foreign hair shaft from the family bathroom where her father frequently cut his hair. Migration of the hair due to walking and muscular contraction caused a presentation that was easily mistaken for the parasitic creeping eruption of cutaneous larva migrans.

Introduction

Creeping eruption is a clinical symptom describing a linear or serpiginous, erythematous, cutaneous track that is mobile.1 It is most often associated with cutaneous larva migrans, a larval parasitic infestation, but may also be caused by an embedded hair shaft in the condition cutaneous pili migrants. We present a case of pili migrants in a child initially mistaken for larva migrans.

Case Report

A 3-year-old Hispanic female from southern Florida presented with a seven-day history of a cutaneous track that is mobile.

In February 2009, the patient’s pediatrician diagnosed her with cutaneous larva migrans and prescribed topical thiabendazole ointment to be applied three times a day. The patient’s mother reported no improvement in pain with very mild surrounding erythema (Figure 1). Pathologic examination of the hair was consistent with a normal human hair shaft. A diagnosis of cutaneous pili migrants was made. On follow-up, the patient’s mother reported immediate and complete relief of symptoms following extraction of the hair and no difficulty with wound healing.

On further questioning, the patient’s mother revealed that her husband regularly cut his own hair in their bathroom, where the patient frequently walked barefoot.

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Figure 1

A small incision was made to the leading edge of the mark using a #11 scalpel, and dark brown hair was easily extracted using a forceps (Figures 2 and 3).
Discussion
Cutaneous pili migrans is a condition in which a hair shaft migrates below the surface of the skin and can closely mimic the creeping eruption of cutaneous larva migrans. Pili migrans presents as a painful, linear, migratory eruption with a hair shaft often visible at the advancing edge. Similarly, cutaneous larva migrans is a creeping eruption; however, it is caused by the penetration of the skin by the larva of non-human-specific nematodes and is usually contracted in sandy areas of the Caribbean, the central and southeastern United States, Africa, southeast Asia and South America. In contrast to pili migrans, the migratory tracks of larva migrans are usually serpiginous and intensely pruritic, and the organism cannot be visualized.1

Pili migrans was first described by Yaffee in 1957 in a report of a 19-year-old female with a two-week history of migratory hair shaft in the skin of the ankle.3 It has since been reported in more than 21 cases in the literature as reviewed by Kim and Silverman and by Luo et al., and it may occur as result of either an ingrown hair or penetration of a foreign hair.2,4 Kim and Silverman note that the majority of cases have been reported in Japan (14 out of 21) and hypothesize that this may be due to the large cross-sectional diameter and high tensile strength of Asian hair.2,6 Locations involved included the ankle, sole, toe, breast, cheek, and neck.2,4 Luo et al. note in their review that pili migrans of the abdomen, cheek or neck is more commonly due to ingrown hair but may also occur as a result of penetration of foreign hair.4 In sites where there is no hair growth, such as the sole, it is likely that the source of the hair is exogenous. The proposed mechanism of migration is body motion and muscular contraction while walking.

We reported on a 3-year-old Hispanic female with pili migrans mistakenly diagnosed as cutaneous larva migrans. It has been noted that this is a common misdiagnosis at first examination in patients with pili migrans.6 In our case, both history (exposure to sandy environment in the southeastern U.S.) and physical symptoms (subsequent development of a migratory eruption on the sole of the foot) lead to this initial misdiagnosis. However, complaint of pain, lack of pruritus, and physical examination showing a visible hair shaft at the leading edge of the migratory eruption can be valuable clues to the diagnosis of cutaneous pili migrans. In this case, exposure of the wet, pliable skin of a child’s sole to cut hair shafts on the bathroom floor may have been the etiology of the eruption.

References

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**Vicks VapoRub® May Have Nailed It as a Safe First-Line Treatment for Uncomplicated Onychomycosis**

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Abstract

Many dermatologists have been recommending Vicks VapoRub® (Proctor & Gamble Co., Cincinnati, OH) for the treatment of onychomycosis. Because of this, we set upon a literature quest to see if there is logic in this recommendation. We have concluded that there is logic in this recommendation.

Objective

To determine if Vicks VapoRub® topical cream is a safe and effective alternative to oral systemic therapy in the treatment of onychomycosis.

Background

It is estimated that the human body harbors more than 10 microorganisms that colonize the human skin. The mixture of organisms found at any particular site is termed “indigenous microbiota,” or normal flora, and typically does not harm healthy individuals. Non-indigenous flora simultaneously coexists in a constant battle to colonize the skin but is usually eliminated by the skin’s defense system. Trichophyton rubrum (T. rubrum) is a species of fungus that has adapted certain mechanisms that allow it to survive on the human surface, including the ability to suppress the human immune response to the invading fungus, as well as the ability to breach the anatomic barrier, thus causing long-term chronic infection. T. rubrum invades damaged and even healthy tissue and begins to proliferate in the stratum corneum layer of the skin, where it is better protected against the body’s suppressor T-cells. The fungal pathogen has become so specialized that among a recent retrospective study examining 4,046 patients, T. rubrum accounted for 87% of subungual Onychomycosis, followed by Trichophyton mentagrophytes and Candida albicans (yeast).

Onychomycosis has shown a rapidly growing prevalence in the United States. It now accounts for an average of 8% of physician visits, ranging 4% to 18% depending on age and population studied. Those with weakened immunity or with poor circulation are at the highest risk for the infection, and males older than 60 years old and 70 years old have the higher prevalence of 20% and 30%, respectively. The organism causes a thickened and discolored nail that is susceptible to brittle breakage, and over time, it spread to local nails often occurs. Patients with the condition may not suffer from physical pain, but often experience significant psychosocial problems that can alter self-image.

Introduction

Commonly used medications used to treat onychomycosis have their limitations. Topical agents have generally been shown to be minimally effective, while oral agents are associated with higher effective cure rates but are associated with treatment failure, recurrence and toxic side effects. Vicks VapoRub® topical cream has been shown to be an effective treatment for Onychomycosis.

Results from Trials

Trial 1: The studies evaluating mentholated creams as a treatment for onychomycosis are small, but have demonstrated positive results and suggest the need for larger trials to better compare VapoRub® with more established regimens for onychomycosis. A 2010 trial was performed by U.S. Air Force 375th Medical Group Family Medicine Program with 18 patients who applied VapoRub® once daily to the nail bed. Of the 18, 83% showed positive improvement at the end of a 48-week study, 27.8% resulted in complete mycological cure rates, 55.6% had partial cure, and 16.7% showed no change. The group was then given a 5-point Likert scale satisfaction questionnaire and reported a strong satisfaction rating average of 9 out of 10, or “very satisfied.” The study showed the best results for individuals who cultured Candida parapsilosis and T. mentagrophytes, with 100% cure rate in these individuals. Those with T. rubrum and other dermatophytes had partial cure rates, suggesting VapoRub® may be more effective when used synergistically for these pathogens.

Trial 2: Researchers from the Dept. of Horticulture and the Dept. of Food Safety and Toxicology studied the antifungal effects of the ingredients in VapoRub® against fungal pathogens responsible for onychomycosis. The study reported a clinical observation that 32 out of 85 (38%) patients showed clinical clearance in patients who applied VapoRub® once daily for five to 16 months; 21 (25%) had no record of change but also no record of compliance; 19 (22%) had only one follow-up visit documented; 9 (11%) of the patients reported not following...
through with the treatment; and 4 (5%) never had a follow-up visit. Factoring out patients who had only one or no return visits and those who were poorly compliant with the treatment, we narrowed the applicable patients down to 53. The efficacy of the treatment then became much stronger, showing a 60.37% effective cure rate. For a medication used sparingly with once-a-day external application and negligible side effects, the results are impressive.

VapoRub® has not been definitively proven to be more effective than oral antifungal medications, which include terbinafine, itraconazole, griseofulvin, and fluconazole. The University of Toronto's Medical Dermatology Division compiled the treatment results of these four systemic medications in a cumulative meta-analysis of 36 trials from 1966-2002. The chart below reflects the mycological cure rates in controlled randomized trials as compiled by the study, as well as documented adverse effects for each medication.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effectiveness</th>
<th>Major Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td>76 ±3%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>(18 studies, 933 patients)</td>
<td>CNS: headache (13%)</td>
<td>CNS: fever (7% granules)</td>
</tr>
<tr>
<td></td>
<td>1-10%</td>
<td>Dermatologic: rash (6%), pruritus (3%)</td>
</tr>
<tr>
<td></td>
<td>CNS: fever (7% granules)</td>
<td>Gastrointestinal: diarrhea (6%), dyspepsia (3%), taste disturbance (3%), abdominal pain (2%), nausea (granules 2%), toothache (granules 1%)</td>
</tr>
<tr>
<td></td>
<td>CNS: fever (7% granules)</td>
<td>Hepatic: liver enzyme abnormalities (3%)</td>
</tr>
<tr>
<td></td>
<td>CNS: fever (7% granules)</td>
<td>Respiratory: nasopharyngitis (granules 10%), cough (granules 6%), pharyngeal pain (granules 2%), rhinorrhea (granules 2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: fever (7% granules)</td>
<td>Miscellaneous: influenza (granules 2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: fever (7% granules)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>CNS: fever (7% granules)</td>
<td>Too numerous to list; see citation 9.</td>
</tr>
<tr>
<td>Itraconazole (pulse and continuous therapy)</td>
<td>Pulse: 63 ±7% (6 studies, 318 patients)</td>
<td>CNS: headache (3-11%), diarrhea (3-11%)</td>
</tr>
<tr>
<td></td>
<td>Continuous: 59 ±5% (7 studies, 1,134 patients)</td>
<td>1-10%</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Cardiovascular: edema (4%), HTN (3%), chest pain (3%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Dermatologic: rash (3-9%), pruritus (≤5%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Endocrine/Metabolic: hypertriglycericidemia (≤3%), hypokalemia (≤2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Hepatic: LFTs abnormal (≤4%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Neuromuscular &amp; skeletal: bursitis (3%), myalgia (53%), tremor (2%), weakness (≤2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Renal: cystitis (3%), UTI (3%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Respiratory: rhinitis (5-9%), URI (8%), sinusitis (2-7%), cough (4%), dyspnea (2%), pharyngitis (≤2%), pneumonia (2%), increased sputum (2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Miscellaneous: increased diaphoresis (3%), herpes zoster (2%)</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>&lt;2%</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (4-10%), fever (2-7%), dizziness (2-4%), anxiety (3%), depression (2-3%), pain (2-3%), malaise (1-3%), abnormal dreams (2%)</td>
<td>Too numerous to list; see citation 10.</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>60 ±6 percent (3 studies, 167 patients)</td>
<td>CNS: dizziness, fatigue, headache, insomnia, mental confusion</td>
</tr>
<tr>
<td></td>
<td>Dermatologic: angioneurotic edema, erythema multiforme-like drug reaction, photosensitivity, rash, urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: diarrhea, epigastric distress, GI bleeding, nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genitourinary: menstrual irregularities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematologic: granulocytopenia, leucopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic: hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuromuscular &amp; skeletal: paraplegia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal: nephrosis, proteinuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous: drug-induced lupus-like syndrome, oral thrush</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>48 ±5 percent (3 studies, 131 patients)</td>
<td>Cardiovascular: angioedema</td>
</tr>
<tr>
<td></td>
<td>CNS: headache (2-13%), dizziness (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermatologic: rash (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: nausea (2-7%), abdominal pain (2-6%), vomiting (2-5%), diarrhea (2-3%), dysgeusia (1%), dyspepsia (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic: alkaline phosphatase increase, elevated ALT/AST, hepatic failure, hepatitis, jaundice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous: anaphylactic reactions</td>
<td></td>
</tr>
<tr>
<td>VapoRub®</td>
<td>27.8%</td>
<td>dermal irritation</td>
</tr>
<tr>
<td>(1 study, 18 patients)</td>
<td>allergic reaction</td>
<td></td>
</tr>
</tbody>
</table>
The outcome of this study demonstrates that more traditional systemic oral antifungals show consistently effective results, but with significant broad-spectrum adverse reaction profiles. Additionally, oral antifungal medications may require baseline and continued lab monitoring for hepatotoxicity. Frequent medical follow-up visits, lab monitoring and medication costs can be expensive for patients. By comparison, VapoRub® has documented adverse effects of dermal irritation and allergic contact dermatitis, and the expected one-year costs of the treatment are low, averaging $30.1

Uncomplicated vs. Complicated Onychomycosis

The question arises as to when it may be appropriate to treat onychomycosis with statistically proven methods of oral treatment versus with mentholated topical ointment. It is important to establish when the complications of onychomycosis outweigh the risks of the medication side effects of the traditional oral treatments. Patients who may develop serious complications due to onychomycosis are considered to have a complicated form of the infection. These types of patients are typically immunocompromised with diseases such as diabetes or COPD and/or have cardiovascular diseases such as chronic heart failure, peripheral vascular disease and chronic venous insufficiency. Onychomycosis has proven to be a significant risk factor for acute bacterial cellulitis in patients who suffer these common diseases, and patients with these conditions should be considered as higher priority for the use of proven oral systemic treatments.1

Conclusion

T. rubrum and other common fungal pathogens have become so effective at skin invasion that they have overcome both innate and cell-mediated immunity to permanently colonize the human tissue in a significant portion of the population. Traditional oral treatment regimens for the past several decades have been costly and have on rare occasions had harmful effects on patients. A limited yet potentially promising evaluation of small trials using VapoRub® as a treatment reveals very positive results. While not definitive, the clinical observations and studies mentioned above pull together a growing body of evidence that suggests VapoRub® may be a notably effective treatment. Treatment with this over-the-counter medicated cream is cost-effective, devoid of major clinical side effects and does not require lab monitoring. More rigorous clinical trials with more participants should be conducted to determine more precisely the substance’s efficacy against onychomycosis. In our practice, we have recommended application to affected nail(s) twice daily to reduce opportunity for medication resistance and increase concentration, with a total therapy time of at least 12 months.14 Our evaluation supports Vicks VapoRub® as a logical choice for a first-line treatment against uncomplicated onychomycosis.6,7

References

Basal Cell Nevus Syndrome in an African-American Female: A Case Report and Review of the Literature

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**Fourth-year Medical Student, Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, Florida
***Program Director, Palm Beach Centre for Graduate Medical Education, West Palm Beach, Florida

Abstract
Basal cell nevus syndrome (BCNS) is an autosomal-dominant, multisystem disorder caused by a germline-inactivating mutation in the PATCHED gene. The three most characteristic manifestations of this syndrome include multiple basal cell carcinomas manifesting at a young age, palmoplantar pits, and odontogenic keratocysts. We present a case of a 30-year-old African American female who presented to the clinic with the chief complaint of a non-healing, growing axillary lesion. The pathogenesis, clinical manifestations, diagnostic evaluation, and treatments of BCNS are discussed.

Case Report
A 30-year-old African American female presented to the outpatient dermatology clinic with a chief complaint of a left axillary lesion that had been growing in size over the past several months. Dermoscopic evaluation of the lesion demonstrated a pearly papule with irregular, pigmented globules and superficial telangiectasias, clinically consistent with a pigmented BCC. A full skin exam was then performed due to the atypical axillary location of the lesion. Bilateral palmar/plantar pits (Figure 1), frontal bossing, hypertelorism, and marked pectus deformity were noted.

Upon further questioning, the patient revealed she had previously been diagnosed with several facial BCCs that were surgically removed in her early twenties. She also disclosed a history of “multiple cysts” that she had to have surgically removed when she was 15 years of age. Gorlin syndrome was diagnosed; she is currently awaiting an MRI of the brain for chronic headaches.

Discussion
Basal cell nevus syndrome, also known as Gorlin-Goltz syndrome and nevoid basal cell carcinoma syndrome, was first reported in 1894, but the clinical manifestations were more clearly defined in 1960 by Gorlin and Goltz.1 It is a rare, autosomal-dominant, multisystem disorder caused by mutations in the human PATCHED gene that affects the skin with multiple basal cell carcinomas (BCCs) in childhood or adolescence and continues throughout life.2 Up to 50% of BCNS cases represent new mutations without a significant family history.2 Patients may present with multiple developmental anomalies such as frontal bossing and skeletal anomalies at birth, and jaw cysts along with palmar/plantar pits in childhood. BCNS affects approximately 1:60,000 people, males and females equally, with a high degree of penetrance but variable expressivity.3 Age at first diagnosis of BCNS ranges from 3 to 53 years, with an average age of 20 to 21.4 Race also plays an important role in the expression of cutaneous BCCs in patients with BCNS. This syndrome can affect all races but occurs mostly in Caucasians, with a low frequency in Asian and black populations. Of all BCNS case reports, only 5% involve black patients.5 Furthermore, dark-skinned individuals as well as Asians have a lower frequency of expressing BCCs with Gorlin syndrome. About 40% of black persons with BCNS have BCCs (and fewer than 15% have more than two BCCs), whereas 80% of Caucasians with BCNS have BCCs.6,6 The cause of BCNS is a germline inactivating mutation in the PTCH1 (PATCHED1) gene on chromosome 9q22.3-q31, the human homolog of the Drosophila patched gene.7 PTCH1 is a tumor suppressor gene that functions as a receptor for the hedgehog (HH) protein. This HH protein along with the PTCH1 receptor are components of the sonic hedgehog (SHH) signaling pathway, which is significant for controlling cell fate, patterning, and growth in various structures within the developing embryo.8 Experimental models with abnormalities of the hedgehog signaling pathway were shown to exhibit significant developmental anomalies in mice and flies.9 PTCH1 regulates and represses a transmembrane protein, smoothened (SMO), which limits the effect of the SHH signaling. When HH binds to its receptor, PTCH1, the repression of SMO is removed, causing signals to be transduced via the Gli1 and Gli2 transcription factors to the nucleus. In basal cell nevus syndrome, the PTCH1 mutation simulates hedgehog binding and results in constitutive overexpression of transcription factors Gli1 and/or Gli2, which has been implicated in the development of BCC and other tumors.10 An activating mutation in SMO also results in constitutive signaling and has been identified in approximately 10% of basal cell carcinomas.11 Similar to the retinoblastoma gene, two somatic “hits” in the same cell appear to be required for sporadic cases, while one somatic “hit” plus the inheritance of one defective allele underlies familial cases of BCNS.12

Patients with BCNS may present with multiple abnormalities, none of which are exclusive to this syndrome. The three most characteristic abnormalities include BCCs, pits of the palms and soles, and cysts of the jaw (odontogenic keratocysts).9 The distinguishing trait of BCNS compared to sporadic cases of BCC is the appearance of BCCs in large numbers starting at an early age. Histologically, BCNS cannot be differentiated from sporadic cases of BCC. In BCNS, BCCs may resemble angiomas, skin tags, or melanocytic nevi.2 The BCCs that occur in children are often small, banal-appearing, smooth, dome-shaped papules that are acrochordon-like.8 Nodular BCCs occur primarily on the face, while superficial BCCs are usually found on the torso.2 They can appear on any part of the body but are more frequently found on sun-exposed areas, with the first tumor occurring at a mean age of 23 years.7 The second most common
finding, palmpplanter pits, present as depressed lesions in the stratum corneum, usually 1-3-mm in size, sharply margined, and erythematous, and they rarely develop into BCCs (Figure 1). Up to 87% of patients with BCNS have pits. Odontogenic keratocysts are often the first abnormality detected and can cause pain, swelling, drainage, and an increase in molar and premolar areas in the maxilla.

Other key features of BCNS include anomalies of multiple organ systems. Abnormalities in the musculoskeletal system include macrocephaly, frontal bossing, bifid ribs, vertebral fusion, and kyphoscoliosis. Patients may manifest with a larger body size than that of other family members or present with long limbs due to tissue overgrowth, a feature of the SHH signaling pathway activation. CNS manifestations may include ectopic calcification with lamellar calcification of the falx cerebri, agensis of the corpus callosum, medulloblastomas at an early age, meningiomas, and even mental retardation. Genitourinary features include ovarian fibromas and fibrosarcomas. Patients also may present with hypertelorism, congenital blindness, cataracts, colobomas, and strabismus. Multiple skin tags in a child can be a clue to diagnosing BCNS, and a biopsy should be performed. It is important to note that variation in severity of BCCs can be attributed to environmental factors such as exposure to UV light and ionizing radiation.

Differential diagnoses include Bazex-Dupré-Christodoul syndrome, Rombo syndrome, melanocytic nevi, and xeroderma pigmentosum. Initial evaluation for diagnosing BCNS includes evaluating for a family history of BCNS and whether the patient is taller or heavier than his/her relatives. Yearly panoramic radiographs of the jaw are recommended, with complete removal of identified odontogenic keratocysts as they can be extremely aggressive and lead to resorption of the jaws. Radiological evaluation should be performed to check for calcification of the falx cerebri and abnormalities of the ribs, vertebrae, and phalanges. Other workup modalities include MRI of the brain, echocardiogram for cardiac fibromas, and transvaginal/transabdominal ultrasound for pelvic masses. An MRI of the entire neurological axis may be warranted due to the wide range of skeletal anomalies present in BCNS.

Diagnostic guidelines have been proposed by Kimonis and colleagues. The presence of two major, or one major and two minor criteria supports the diagnosis of BCNS (see Table 1).

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than two BCCs, or one BCC before the age of 20 years</td>
<td>Macrocephaly (determined after adjustment for height)</td>
</tr>
<tr>
<td>Odontogenic keratocysts of the jaw (proven by histology)</td>
<td>Congenital malformations: cleft lip or palate; frontal bossing; &quot;coarse face&quot;; moderate or severe hypertelorism</td>
</tr>
<tr>
<td>Three or more palmar or plantar pits</td>
<td>Other skeletal abnormalities: Sprengel deformity (unilateral elevation of smaller-sized scapula); marked pectus deformity; marked syndactyly of the digits</td>
</tr>
<tr>
<td>Bilamellar calcification of the falx cerebri</td>
<td>Radiologic abnormalities: bridging of the sella turcica; vertebral anomalies such as hemivertebrae and fusion or elongation of the vertebral bodies; modeling defects of the hands and feet; flame-shaped lucencies of the hands or feet</td>
</tr>
<tr>
<td>Bifid, fused or markedly splayed ribs</td>
<td>Bilateral ovarian fibroma</td>
</tr>
<tr>
<td>First-degree relative with NBCC syndrome</td>
<td>Medulloblastoma</td>
</tr>
</tbody>
</table>

in decreasing the tumor burden and shrinking the size of the tumors, but a high rate of side effects will likely prevent its long-term use in patients with lifelong basal cell nevus syndrome.

References
14. Winstead ER. For People with Rare Skin Cancer Syndrome, Drug brings Relief and Hope.
Pyogenic Granuloma-like Kaposi’s Sarcoma: An Atypical Histologic Variant

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Abstract

Kaposi sarcoma (KS) is a vascular neoplasm associated with human herpesvirus-8 (HHV-8). The histologic appearance of KS is broad and varies with the stage of the disease. Pyogenic granuloma-like Kaposi sarcoma (PG-like KS) is a rare clinicopathologic variant of Kaposi sarcoma (KS) and can be challenging to diagnose due to clinical and histologic overlap between PG-like KS and pyogenic granuloma (PG). The only definitive distinguishing feature is the presence or absence HHV-8 latent nuclear antigen-1 (LNA-1) staining, which is a specific marker for KS. We report a case of PG-like KS in an elderly man.

Introduction

KS is a vascular neoplasm associated with HHV-8. HHV-8 has been detected in other conditions, such as multi-centric Castleman’s disease and primary effusion lymphoma, but has not been found to be associated with other vascular tumors.1 PG-like KS is a rare clinical and histologic variant of KS that has been infrequently reported in medical literature.2,3 We report a case of PG-like KS on the foot of an elderly man with negative HIV status.

Case Report

A 91-year-old black male presented to an outpatient clinic with a several-month history of a mildly tender polypoid mass on the left lateral heel. He denied any memorable trauma to the area. Except for occasional bleeding, the lesion was otherwise asymptomatic. Medical history was unremarkable. The patient had never received any blood transfusions or had any memorable recent history of sick contacts, viral syndromes, or travel outside of the U.S. There was no significant family history for malignancy or blood dyscrasias. The patient denied smoking, drinking, and any history of drug abuse.

Physical exam revealed a 3 cm x 2 cm, non-tender, exophytic, friable nodule on the left lateral heel (Figure A). The provisional diagnosis was pyogenic granuloma versus traumatized poroma versus angiosarcoma versus melanoma, given the clinical presentation. A 4 mm punch biopsy was performed and placed in 10% formalin for hematoxylin and eosin (H&E) staining.

Histologic exam at low power showed a well-circumscribed, exophytic proliferation of well-formed capillaries arranged in lobules and contained within an epidermal collarette consistent with a pyogenic granuloma (Figure B). At higher power, a dermal spindle-cell proliferation with irregular vascular spaces and hemorrhage, more consistent with Kaposi sarcoma, was noted (Figure C and D). Based on these architectural features, immunohistochemical stain with HHV-8 LNA-1 was performed, which was strongly positive for human herpesvirus-8 (Figure E).

After the diagnosis of PG-like KS, the patient was screened for immunodeficiency states including human immunodeficiency virus and hepatitis; both were negative. The patient was offered conservative treatment with monitoring, as there was only one lesion. The patient opted for surgical excision of the lesion as it was tender and bleeding. At his six-month follow-up, there was no evidence of reoccurrence.
Discussion

KS is a low-grade spindle-cell vascular neoplasm caused by human herpesvirus-8, which is transmitted by saliva and blood and has been contracted from organ transplantation as well. The cutaneous presentation of KS can vary greatly from pink patches to dark-violet plaques, nodules or polyps, depending on clinical variant or stage. There are four principal clinical settings in which KS presents:

Classic KS is an indolent variant typically presenting with lesions on the lower extremities of older males of Jewish or Mediterranean decent. Early lesions may regress while others evolve, which leads to simultaneous presence of different-staged lesions.

Endemic (African) KS can be classified into four subgroups, including indolent nodular, more aggressive florid, infiltrative, and lymphadenopathic types. The lymphadenopathic type of endemic KS predominately affects children and is fatal.

AIDS-related (epidemic) KS affects HIV patients with a CD4+ count <500 cells per cubic millimeter. The presentation is extremely variable, but it is typically a more aggressive type with lesions involving skin and viscera.

Immunosuppression-associated KS occurs in patient receiving T-cell inhibitors such as cyclosporine after organ transplant. The presentation is very similar to classic KS and may resolve if immunosuppressant therapy is stopped. However, with prolonged high-dose immunosuppressant use, this variant may become more aggressive, causing death if there is internal involvement.

The histopathology of KS is essentially identical in all four of the different clinical KS types. Three main pathological stages have been described in the progression of the lesions of KS from patch to plaque and eventually to nodular. The early patch-stage KS is characterized by ectatic vessels lined by thin endothelial cells dissecting the dermis. Normal adnexal structures and preexisting blood vessels often protrude into newly formed blood vessels, which is referred to as the promontory sign. This sign is not pathognomonic for KS as it has also been described in other vascular lesions, including benign vascular tumors and angiosarcoma. The early histologic changes of plaque stage may be inconspicuous and easily missed on biopsy. The plaque-stage KS lesions are characterized by a proliferation of spindle cells and vessels. It extends through most of the dermis and tends to displace collagen. The spindle cells form cleft-like spaces filled with red blood cells. The overall picture is that of a hemorrhagic spindle-cell proliferation in the dermis. In the tumor or nodular stage of KS, there is a well-defined nodule in the dermis composed of vascular spaces and spindle cells, typically more tightly arranged than in the plaque stage, that replace the collagen completely.

Histologically, the differential diagnosis for the typical presentation of KS varies depending on stage of the lesion, but includes inflammatory dermatosis, bacillary angiomatosis, angiodermatitis, pseudo-Kaposi's, pyogenic granuloma, bullous KS, and arteriovenous malformation. While KS can clinically mimic PG, the distinction can usually be made easily histologically. However, the recent finding of the PG-like KS variant makes the histologic distinction unreliable.

In recent decades, numerous histologic variants of KS have been described outside of this typical continuum. At this time, the clinical significance of these variants remains largely unknown. As suggested by Grayson et al., the wide variety of histologic presentations of KS can be divided into four large groups:

Usual KS lesions. These are the typical histologic lesions associated with disease progression (patch, plaque and nodular stage).

Variants reported in the older literature. This includes anaplastic and telangiectatic KS, as well as several lymphematosus KS variants including lymphematosus, lymphangiomma-like, lymphangiectatic, and bullous.

Contemporary variants. These are the lesions that have most recently been described in the literature, including hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, and intravascular KS. Most of these lesions are atypical presentations of one of the "usual KS lesions."

Variants related to therapy. This includes KS that flares as a result of immunotherapy used to treat either KS or the underlying immunodeficiency, making the patient susceptible to KS.

In this discussion, we will focus on PG-like KS, which falls into the contemporary variant. PG-like KS occurs when a very superficially located nodular lesion of KS protrudes from the skin, eliciting the formation of a collarette. These lesions typically become traumatized due to their superficial location in the skin, ulcerate, and become inflamed, and they present clinically and histologically identical to PG. Histologically, cellularity, lobulation, extravasation of red blood cells, infiltration of neutrophils and ulceration are consistent features in both. Endothelial differentiation markers such as CD31, CD34, and factor VIII-related antigen are used for identifying tumors of vascular origin, but do not distinguish one vascular tumor from another.

Usually, immunohistochemical analysis with antibodies to smooth-muscle cells and factor VIII only seen in PG pericytes and mature endothelial cells can distinguish between PG and typical KS. However, in PG-like KS, these stains may also be positive and are no help in differentiating. Several studies have examined the expression of HHV-8 LNA-1 in a broad spectrum of vascular tumors and found expression to be limited to KS.

LNA-1 is a gene product made by the DNA virus when the virus is in its latent form in the spindle cells of the KS lesions. All viruses of the human herpesvirus family have an active and latent period, and HHV-8 is no exception. In fact, most cells of KS lesions contain HHV-8 in its latent state. During the latent period, the HHV-8 gene product LNA-1 contributes to the oncogenic potential of HHV-8 by down-regulating the retinoblastoma protein transcriptional regulatory pathway and allowing HHV-8 to elude the immune system during its latent phase. However, HHV-8 does not cause KS unless there is already a defect in the host's cellular immunity. Once the virus evades the immune system, HHV-8 contributes to the uncontrolled cellular proliferation by stimulating pro-inflammatory interlukin-6, which up-regulates vascular endothelial growth factor and lymphatic vessel endothelial receptor. HHV-8 also prevents apoptosis of cells by viral interferon and inhibiting tumor suppressor genes.

Therefore, HHV-8 LNA-1 stain is the only stain that can definitively distinguish PG from PG-like KS.

Treatment goals of KS, regardless of histologic or clinical presentation, are centered around symptom control, cosmetic improvement, and prevention of progression, organ compromise and psychological stress. At this time, there is no cure for KS. One option for localized KS is surgical excision. Typically, this is used to address cosmetically disturbing KS lesions, alleviate discomfort, or control local tumor growth. Other local therapies used include external beam radiation, laser therapy, cryotherapy, photodynamic therapy, topical alitretinoin gel, and intraslesional vinblastine. Systemic chemotheraphy typically includes anthracyclines and taxanes. Systemic therapy is indicated if there is widespread skin involvement, extensive oral KS, marked symptomatic edema, rapidly progressive disease, symptomatic visceral KS, and KS flare. HHV-8 is susceptible to antiviral medications such as ganciclovir, but only in the active phase. Most cells in KS contain HHV-8 in its latent phase. The only clinical variants that are treated differently are AIDS-related and immunosuppression-associated KS, which are treated with reconstitution of the immune system. In AIDS-related KS, optimal control of HIV infection, using antiretroviral therapy, is a key component in the treatment. In immunosuppression-associated KS, changing the immunosuppression medication or decreasing the dose has been associated with improvement of lesions. The use of sirolimus in place of cyclosporine for post-transplant immunosuppression has been shown to decrease vascular endothelial growth factor as well as interleukins 6 and 10, which are key factors in the pathogenesis of KS.
Case Report
A 32-year-old G3P2 female, six months pregnant, presented to the clinic. She had noticed new-onset, painful nodules that first appeared on the trunk and then the extremities, increasing in both size and color over the past five months. On examination, she had multiple fleshy, hyperpigmented nodules, several of which demonstrated the classic "button hole sign." They were present on the back, chest and abdomen, with a few nodules on the upper and lower extremities. She had nine café-au-lait macules which were >1.5 cm (Figure 2). There was also freckling of the axilla bilaterally, also known as "Crowe's sign" (Figure 1). The patient stated the café-au-lait macules and freckling of the axilla had been present for as long as she could remember, but the painful nodules were all new. The patient had never been diagnosed with neurofibromatosis.

Two nodules were biopsied, and on pathology demonstrated a non-encapsulated intradermal nodule of mildly cellular spindle cells. The spindle cells had indistinct cytoplasm and spindled nuclei with tapering ends that mixed with fine, wavy collagen matrix consistent with neurofibromas.

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References

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Neurofibromatosis in Pregnancy: A Case Report and Discussion
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Abstract:
Neurofibromatosis type I has an incidence of approximately 1 in 3,000 persons, with half of the cases inherited and the remainder by new mutations. Neurofibromatosis in pregnancy is underreported, with only a limited number of studies to date. We report a case of a 32-year-old female in her third pregnancy who met the criteria but was previously undiagnosed with NFI, indicating new-onset neurofibromas during pregnancy. We also review the current understanding of cutaneous changes associated with neurofibromatosis and pregnancy.

Case Report
A 32-year-old G3P2 female, six months pregnant, presented to the clinic. She had noticed new-onset, painful nodules that first appeared on the trunk and then the extremities, increasing in both size and color over the past five months. On examination, she had multiple fleshy, hyperpigmented nodules, several of which demonstrated the classic “button hole sign.” They were present on the back, chest and abdomen, with a few nodules on the upper and lower extremities.

The patient was referred to ophthalmology, and no Lisch nodules or optic gliomas were found. She reported no physical findings of neurofibromatosis in her two children. Other than the development of neurofibromas, she...
had not had any complications with her current pregnancy. Genetic counseling was offered, which the patient declined.

**Discussion**

Neurofibromatosis type I is inherited in an autosomal-dominant fashion, although new mutations account for approximately 50 percent of new cases. NF1 plays a role as a tumor suppressor gene, and most NF1 mutations result in reduced intracellular levels of neurofibromin, which is found in a variety of cell types including neurons, oligodendrocytes and nonmyelinating Schwann cells. As observed in other autosomal-dominant genodermatoses, a somatic mutation inactivating the remaining allele of the gene can be found within skin lesions of NF1. Biallelic NF1 inactivation has been identified in Schwann cells from neurofibromas as well as in melanocytes from café-au-lait macules in patients with NF1.1,2 This appears to be sufficient to cause most of the clinical manifestations of the disease.

As established at the National Institutes of Health Consensus Development Conference in 1987, two or more of the following are required for diagnosis of NF1: six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and over 15 mm in postpubertal individuals; two or more neurofibromas of any type or one plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; two or more iris Lisch nodules; a distinctive osseous lesion such as sphenoid dysplasia or thinning of long-bone cortex with or without pseudoarthrosis; and a first-degree relative with NF-1 by the above criteria.3,4

There are a limited number of studies on pregnancy and neurofibromatosis to date. In 1976, Ansara and Nagamani demonstrated growth of neurofibromas with regression in size after pregnancy.5 Another study (n=105) reported new-onset neurofibromas in 60% of their pregnant patients; four patients received their diagnosis for the first time during the study.6 Exploring a hormonal link, Geller et al. demonstrated progesterone-receptor positivity via routine immunohistochemistry in 19 out of 25 neurofibromas collected from both men and women, with no statistically significant difference in expression between sexes.7

**Conclusion**

Although neurofibromas have been reported to occur and increase in size during pregnancy, our case is unique in that our patient did not develop neurofibromas until her third pregnancy. She elected to have several painful neurofibromas removed and is being closely monitored, with no complications in her pregnancy so far.

**References**


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The antigens act as skin-selective receptors. The that acquire specific antigens on their cell surfaces.

CD4+ T cells are then antigens to CD4+ T cells found in peripheral lymph nodes. The CD4+ T cells are then converted to cutaneous T-cell lymphoma cells that acquire specific antigens on their cell surfaces. The antigens act as skin-selective receptors. The T cells are then able to adhere to dermal blood vessels and therefore infiltrate the epidermis. This process describes epidermotropism and is very characteristic of early stage CTCL and variations of CTCL, such as pagetoid reticulosis.

Pagetoid reticulosis was first named for its similarity to the intraepidermal adenocarcinomatous cells found in Paget’s disease of the nipple. The disease has currently been classified into two variants: The benign localized variant commonly found on the extremities is known as Woringer-Kolopp (WK) and presents with hyperkeratotic inflammatory plaques; the disseminated type is known as Ketron-Goodman (KG) and carries with it an unfavorable prognosis. While the two have no significant differences in morphology or histology, they vary significantly in their clinical course as the disseminated Ketron-Goodman type can run an aggressive and fatal course.

The clinical differential diagnosis of Woringer-Kolopp is broad due to the nonspecific morphology of a solitary, indolent plaque. With Ketron-Goodman, there are multiple plaques, with a differential diagnosis that includes fungal infections (blastomycosis and chromomycosis), porokeratosis of Mibelli, atrophic dermatofibroma, psoriasis, nummular dermatitis, and mycosis fungoides. With resolving hypopigmented macules, the differential diagnosis includes post-inflammatory and post-traumatic hypopigmentation and dermatophyte infection.

### Case Report

In July 2012, a G2P1, 20-year-old female who was 19 weeks pregnant presented with a one-year history of at least 18 pruritic, raised, hypopigmented lesions. On physical exam, lesions were found on the dorsal aspect of both hands, bilateral legs, and the left foot (Figures 1 and 2). The lesions were primarily localized to the distal extremities. The patient denied any history of dermatological diseases, and her personal history was unremarkable for any previous medical problems.

A skin biopsy from a lesion on the left foot showed hyperkeratosis and mild epidermal hyperplasia. Variable attenuation of the granular cell layer was also seen. The primary pathologic finding in the specimen was the presence of striking epidermotropism of atypical lymphocytes with abundant, pale-to-clear cytoplasm (Figure 3). They were present predominantly along the lower half of the epidermis and along the dermoeidermal junction in a pagetoid distribution.

The pattern was also seen in small aggregates within the epidermis. The dermis contained a mild perivascular infiltrate, and atypia of the dermal component was minimal. A PAS stain was performed with the appropriate reactive controls. Immunoperoxidase stains were also performed with appropriate reactive controls in order to further characterize the lymphoid infiltrate. The lymphocytes comprised nearly entirely CD3-positive T-cells with rare scattered CD20-positive B-cells within the dermis. The intraepidermal lymphocytes comprised predominantly CD8-positive cells with only scattered CD4-positive cells in a ratio of approximately 5:1. There was mild, patchy reduction in immunoreactivity for CD5 and a striking loss of immunoreactivity for CD7 within the intraepidermal component. Occasionally, intraepidermal lymphocytes were positive for CD30 cells. The sample was also sent for T-cell receptor (TCR) gene rearrangement, which was positive.

The clinical presentation of multiple plaques on distal extremities and histological examination with immunohistochemistry led to the diagnosis of pagetoid reticulosis. Our patient’s presentation of more than 18 plaques on bilateral legs, hands and left foot caused it to be difficult to classify as either KG or WK. Previous cases have been...
described in the literature of WK presenting with multiple plaques on distal extremities. KG is known for its disseminated plaques and can be found on proximal extremities or the trunk. It is difficult to classify as the classification is one made clinically. Having presented with multiple plaques on all four extremities, with extension up the legs, the decision was made to treat the lesions. Due to the patient's current pregnancy, the patient was limited to treatments that could be administered immediately. She was recommended that she undergo light therapy with UVB and began treatment.

The patient presented to our office with a referral from her OBGYN. With the exception of her unremarkable prenatal labs, she did not have any prior workup. At the initial visit to our office, a biopsy was completed. When the clinicopathologic diagnosis of pagetoid reticulosis was made, we referred the patient to oncology. CBC, CMP, and LDH were normal, and monoclonal gammapathy was negative. No imaging has been completed. Oncology recommended continuing UVB therapy, but any additional treatments, including topical nitrogen mustard, are on hold at the present time. Her case remains ongoing.

Discussion

Pagetoid reticulosis is a rare form of disseminated T-cell lymphoma with striking epidermotropism. KG typically presents as multiple, diffuse, hyperkeratotic plaques; however, the diagnosis is one made by pathology. Biopsy will show intraepidermal, highly activated, proliferating T cells with variable loss of pan-T-cell antigens, contrasting with non-activated dermal reactive T cells. The atypical lymphocytes are typically surrounded by clear halos in the epidermis, creating the typical pagetoid appearance.

Some argue today that KG should no longer be classified under pagetoid reticulosis due to its difference in clinical behavior and clinical similarity to mycosis fungoides (MF). However, KG has been the topic of much debate concerning its association with MF and whether it is a variant of the latter based on their clinical and histopathologic similarities. Haghigi et al. demonstrated a few significant differences between the two. First, KG typically only has tumor cells found in the epidermis, while MF presents with tumor cells found in both the dermis and epidermis. Another key difference is found in the composition of the dermal infiltrate. KG typically consists of reactive lymphocytes and histiocytes, while eosinophils are not typically present; mycosis fungoides contains a polymorphous infiltrate consisting of reactive lymphocytes, histiocytes, plasma cells and eosinophils. A third difference can be found in the T-cell subtype of KG, which includes a heterogeneous immunophenotype of multiple possibilities, most commonly including CD4+/CD8+ T helper cells, CD8+ T-cytotoxic/suppressor cells or CD4/CD8 double-negative cells; MF characteristically has an immunophenotype of only CD4+ cells.

As stated, KG has been characterized as a number of different heterogeneous phenotypes including most commonly CD4+/CD8+, CD4+/CD8−, or CD4−/CD8+. Immunophenotypic evidence has been studied in great detail to try and understand the origin of KG and classify the disease; however, while common immunophenotypic trends have been found as stated above, some researchers report that the differences exceed the similarities in more than 50% of the reported cases. This was the case with our patient, who did not present with one of the typical immunophenotypes but was found to have CD3+, CD8+/CD4+ in a ratio of 5:1. Nakada described a patient with a similar immunophenotype who was treated with chlorambucil for one month followed by PUVA for eight weeks. He reported disappearance of the lesion but recurrence after four years. No standard treatment currently exists for KG, and many different treatment options have been tried in the past. Treatments have included UVB, PUVA, steroids, chlorambucil, topical N2 mustard, chemotherapy agents and, most commonly, combined modality therapy, all reported to have widely variable efficacy. Our patient presented with a significant challenge due to the rarity of her disease and her coexisting pregnancy. Phototherapy with UVB was selected due to its ability to resolve lesions temporarily and its safety for use in pregnant patients. UVB can be an effective treatment of immediate lesions in KG by altering the environment of the surface of the skin, creating an inhospitable environment for the cancer cells. However, long-term remission is uncommon. Regardless of treatment choice, long-term follow-up is necessary due to common recurrences, which have been reported anywhere from several weeks to 10 years after the disappearance of lesions. Our patient had variable success with UVB treatment, with multiple lesions that faded while new lesions appeared. However, due to the third trimester of the patient's pregnancy, the patient was noncompliant with a consistent treatment regimen and frequently missed scheduled treatments.

In summary, the case presented here is interesting in that to our knowledge, this is the first known case of pagetoid reticulosis in a pregnant patient. The case also presented a rare immunophenotype of CD4+/CD8+. The diagnosis of pagetoid reticulosis is often delayed for several years because Woringer-Kolopp disease is an uncommon condition that is rarely suspected. This rare condition typically presents as a solitary plaque located on the extremities, with an indolent clinical course in the case of Woringer-Kolopp disease or, in Keton-Goodman patients, a more generalized presentation with diffuse cutaneous involvement and a more aggressive clinical course. The fact that our patient presented while pregnant served as a distractor and had no bearing on diagnosis once a biopsy was completed. It did, however, limit our treatment options. Pagetoid reticulosis is a diagnosis that will rarely be at the top of a clinician's differential diagnosis. This case study hopes to raise awareness regarding the disease. Given the impact disseminated pagetoid reticulosis may pose to the long-term health of a patient, it should be at least considered when dealing with solitary or disseminated hyperkeratotic plaques on the trunk and proximal extremities. In our case, further follow-up will be conducted after the pregnancy is complete and may include more aggressive treatments, such as chemotherapy with other combined treatment modalities.

References


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Painful, Erosive and Exudative Plaque on the Scalp of an Elderly Male

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Abstract

Erosive pustular dermatosis of the scalp (EPDS) is a rare disorder affecting the scalp of elderly individuals, distinguished by persistent sterile pustules, crusted erosions, and subsequent scarring alopecia. We present a case of an 83-year-old Caucasian male with EPDS, discuss the clinical and histopathologic findings characterizing the disease, and review therapeutic options.

Case Report

An 83-year-old Caucasian male presented to our clinic complaining of a bleeding, non-healing, painful lesion on his left frontal scalp. He reported that the lesion occurred one year previously, after a sunburn to the area, but would only temporarily heal, and that it demonstrated associated hair loss. His past medical history was significant for type II diabetes, treated with metformin. The patient did not report any prior personal history of skin cancer, nor was there any significant family history of skin cancer. A review of systems was negative for preceding illness, recent weight loss, or constitutional symptoms.

Physical examination revealed an elevated, 6.0 cm x 4.0 cm, moist, erythematous, amoeboid plaque with pinpoint erosions and the appearance of granulation tissue on the left frontal scalp (Figure 1). A neoplasm was initially suspected, and a 3-mm punch biopsy of the scalp was obtained, as well as bacterial, viral, and fungal cultures.

Microscopic Findings and Clinical Course

Three biopsies were performed over a 15-month period. Histopathologic analyses of two specimens revealed pale edematous stroma with increased numbers of capillaries and a mixed inflammatory cell infiltrate consistent with granulation tissue. A third biopsy was consistent with a scar. Bacterial and fungal cultures on several different examinations showed growth of *Staphylococcus aureus*, *Serratia marcescens*, *Achromobacter xylosoxidans* and *Candida parapsilosis*. Viral cultures were negative for HSV and VZV.

The patient was treated initially with appropriate antibiotics without any clinical improvement. Treatment with silver-nitrate destruction and intralesional steroids was also unsuccessful. The patient received the most benefit from the use of topical dapsone 5% gel, used twice daily, with near complete resolution (Figure 2). The lack of any primary infectious presence, the absence of a tumor, the non-specific histological finding, and the clinical presentation all pointed toward a diagnosis of EPDS.

Discussion

Erosive pustular dermatosis of the scalp (EPDS) was first described by Rye et al. in 1979. Clinically, EPDS has a slow and progressive course, beginning as localized pustules that later evolve into eroded areas covered by superficial crusts. Pustules are painful, and can begin as discrete lesions, but after months to years enlarge into confluent plaques with erosions and scarring.

With the exception of inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein and hypergammaglobulinemia, laboratory tests are typically normal. Associations with rheumatoid arthritis, Hashimoto’s thyroiditis, autoimmune hepatitis and Takayasu’s arteritis have all been described in patients with EPDS, but no direct relationship has been proven as the majority of patients lack autoimmune disease.1

EPDS is a diagnosis of exclusion, and therefore all infectious and neoplastic processes must be ruled out. Secondary colonization with bacteria and yeast may occur, as in our patient, but is not suspected to contribute to pathogenesis. *Staphylococcus aureus* and *Candida albicans* are amongst the most commonly isolated agents; *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, coliforms, diphtheroids, *Candida parapsilosis* and *Aspergillus ochraceus* have been described as well.1

Mastroianni et al. hypothesize that physical damage to the scalp skin could induce production of autoantibodies against epidermal and dermal structures, leading to a secondary inflammatory response. Our patient did report sunburn prior to the development of the lesion. Trauma previously reported in association with EPDS includes scalp surgery such as craniotomies, skin grafting, synthetic hair fiber implantation, cryotherapy, 5% fluorouracil cream, photodynamic therapy and accidental injury.3–6 In addition, long-standing damage by ultraviolet radiation may contribute to the development of EPDS.

The differential diagnosis is extensive and includes basal cell, Merkel cell or squamous cell carcinoma, cutaneous metastatic disease, bacterial folliculitis, tinea, herpes infections, discoid lupus erythematosus, bullous disease and temporal arteritis.1 For these reasons, all patients with suspected EPDS should have bacterial, fungal, and viral cultures, as well as biopsies.

Histopathologic findings are non-specific and differ according to the site of biopsy.1 Biopsies can show parakeratosis, hyperkeratosis, and epidermal atrophy or erosion. Occasionally, subcorneal pustules are seen in the epidermis.4 Inflammatory infiltrates with lymphocytes and plasma cells can be found in the dermis, particularly surrounding hair follicles and sebaceous glands. Foreign-body giant cells and fibrosis can be found near remnants of destroyed pilosebaceous units.3,6 However, none of the aforementioned changes are diagnostic.

Patients are often recalcitrant to treatment. Both topical and oral antibiotics have little efficacy. Other treatment options with variable results include steroids (topical, oral and intralesional), photodynamic therapy, and calcipotriol cream.1

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A Case of Subcutaneous Fat Necrosis of the Newborn

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Abstract

Subcutaneous fat necrosis of the newborn (ScFN) is an uncommon, usually self-limited disease affecting full-term newborns in the first few weeks of life. It can often follow perinatal complications such as hypothermia, meconium aspiration, forceps delivery, or maternal complications such as high blood pressure or gestational diabetes. It is often characterized by sharply demarcated, firm plaques typically affecting the upper back and sparing the anterior trunk. Prognosis is often excellent, with hypercalcemia as a rare association. Infants should be followed for several months with serial calcium-level evaluation.

Case Report

A 25-day-old female born full-term via normal spontaneous vaginal delivery presented to the pediatric dermatology office with a three-week history of “hardening” of her skin. The mother reported that the child was hospitalized in the neonatal intensive care unit following delivery for five days secondary to “fluid in her lungs” from presumed meconium aspiration. While in the hospital, she was found to be hypocalcemic, which subsequently resolved, and her pulmonary function also improved. She was discharged home after hospital day five and was being breast-fed. Her family history was non-contributory.

On physical examination, the infant appeared alert and comfortable. She had non-tender, pink-to-erythematous, indurated plaques on the upper back and shoulders, sparing the anterior trunk (Figures 1a,b). The remainder of her skin examination was within normal limits. Based on her history and presentation, a diagnosis of subcutaneous fat necrosis of the newborn was made.

Discussion

Subcutaneous fat necrosis of the newborn (ScFN) is an uncommon, self-limited panniculitis that appears in full-term or post-term neonates often in the first two to three weeks of life.1,2 The frequency of this disorder is unknown as it is quite rare, and no racial or sexual predilection exists.

The etiology and pathogenesis remains largely unknown; however, it is believed that a systemic and/or local hypoxia-hypoperfusion episode during the peri-natal period, leading to certain cold- or stress-induced injury to fetal fat, results in the development of solidification and/or necrosis.1,2 Fetal fat has a high ratio of saturated (stearic and palmitic acids) to unsaturated fatty acids. These fetal saturated fatty acids have a higher melting point, and states of hyperthermia can result in crystallization of the fat, leading to necrosis, injury to adipocytes, and granulomatous inflammation.3,5 The macrophages in the area of infiltration lead to increased 1,25-dihydroxyvitamin D3, which leads to increased non-renal intestinal absorption of calcium and ultimately gives rise to subsequent complications of hypercalcemia.4

Factors thought to induce such stress to fetal adipocytes include perinatal complications such as asphyxia, hypothermia, meconium aspiration, newborn failure to thrive, forceps use, and smoking; however, this association remains unclear.1,2 Hogeling et al. reported three neonates with hypoxic ischemic encephalopathy who were treated with therapeutic hypothermia and developed extensive ScFN as a result.1

References


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ScFN is characterized by firm, sharply demarcated nodules and plaques that appear on the upper trunk, arms and buttocks, often in a symmetrical distribution. Lesions may appear up to several weeks after delivery. Often, these begin as edematous plaques that progress to become firm and indurated. Lesions can later become fluctuant and drain necrotic fat as they resolve.

Although the diagnosis can be made clinically, definitive diagnosis is made histologically. Histologic examination often reveals necrosis of fat lobules with crystallization of fat, radial crystals in lipocytes and granulomatous inflammation (Figure 2).

Hypercalcemia is the most common and most serious complication that has been associated with ScFN. This may develop in the fourth to sixth weeks of life and even up to six months after the onset of skin lesions. Morbidity associated with hypercalcemia includes anorexia, irritability, hypotonia, seizures, renal failure and cardiac arrhythmias. Hypocalcemia has been described in one case report, similar to our patient’s, although it is rare. Other complications of ScFN can include thrombocytopenia. Although the mechanism is unclear, it is believed to be due to local sequestration of platelets in the subcutaneous tissue. The thrombocytopenia can last up to several weeks and usually resolves spontaneously.

The differential diagnosis of ScFN includes sclerema neonatorum (SN), characterized by a diffuse, wax-like hardening of the subcutaneous tissue. SN generally affects premature, debilitated infants, usually during the first week of life, and portends a poor prognosis.

ScFN resolves spontaneously, and treatment is mainly supportive. Treatments for severe hypercalcemia include fluid loading followed by loop diuretics such as furosemide, corticosteroids, and bisphosphonates to reduce bone resorption of calcium. Infants should be fed a low-calcium, low-vitamin D diet. Although plaques usually resolve without sequelae, some areas may develop deposits of calcium and drain spontaneously, which may heal with scarring. Most plaques, however, undergo resolution within several weeks to months. Serial monitoring of calcium levels is advised, as hypercalcemia can be delayed.

**Conclusion**

Subcutaneous fat necrosis of the newborn is usually self-limited, benign panniculitic process, with most cases resolving spontaneously. Although rare, hypercalcemia and other metabolic abnormalities can occur, warranting monitoring in the months following disease onset and even after resolution of lesions.

**References**


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Use of Acitretin in a Patient with Epidermolytic Hyperkeratosis: A Case Report and Literature Review

Abstract

Epidermolytic hyperkeratosis (EHK) is a rare, inherited skin disorder that presents in childhood with blistering and erythema, eventually progressing to hyperkeratosis with scaling. The cause is attributed to an autosomal-dominant mutation in the genes encoding keratins that affect the integrity of intermediate filaments in suprabasal keratinocytes. To date, six phenotypes and one recessive form of the disorder have been reported. The standard treatment involves systemic retinoids. We report the case of a 14-year-old Hispanic male with lifelong multiple linear hyperkeratotic lesions with no history of childhood blisters. At the time of presentation, the patient had previously been diagnosed in Mexico with epidermodysplasia verruciformis (EV), an autosomal-recessive condition spread by the human papilloma virus. EV presents with flat, wart-like lesions and hypo- and hyperpigmented macular lesions. The patient was prescribed topical steroids and reported no improvement in his condition. He therefore sought additional care, and we initiated treatment with acitretin.

Introduction

Discovered in 1970 by Albert Bernard Ackerman, EHK was originally considered a minor pathologic reaction pattern in skin due to its appearance coinciding with multiple skin conditions. With time, EHK was found to present independently as widespread blistering at or soon after birth with eventual ichthyotic erythroderma that persisted into adulthood. This genodermatosis displays an autosomal-dominant inheritance pattern, with mutations of keratins K1 and K10, specifically found in their helix boundary motifs. Clinical EHK is subdivided into six phenotypes based on the presence or absence of involvement of the palms and soles (Table 1). Individuals who display severe sole and palm hyperkeratosis are known to harbor a KRT1 mutation, while those with KRT10 mutations lack sole and palm hyperkeratosis.

Case Report

A 14-year-old Hispanic adolescent presented with chronic skin lesions. He complained of dry, cracking, thick, raised skin lesions. The patient was accompanied by family members who stated the lesions have been present since he was 3 months old and have occurred in a stable, persistent pattern. The family denied any history of childhood blisters. He was biopsied in Mexico and was diagnosed with epidermodysplasia verruciformis. He was given topical steroid creams that resulted in no improvement in his lesions. Physical exam revealed hyperkeratotic, hyperpigmented and hypopigmented, whorled plaques on his back, chest, neck, and extremities (Fig. 1-2). There were no blisters, odor or palpable involvement. At this time, a diagnosis of epidermolytic hyperkeratosis was suspected.

Table 1. Characteristics of EHK subtypes

<table>
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<tr>
<th>Trait</th>
<th>NPS types (without severe palmoplantar hyperkeratosis)</th>
<th>PS types (with severe palmoplantar hyperkeratosis)</th>
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<tbody>
<tr>
<td></td>
<td>NPS-1</td>
<td>NPS-2</td>
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<tr>
<td>Palmoplantar hyperkeratosis</td>
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<td>Scale</td>
<td>Hystrix</td>
<td>Brown</td>
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<td>Generalized</td>
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<td>Absent</td>
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<td>Blistering</td>
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<td>Present</td>
</tr>
<tr>
<td>Other features</td>
<td>Relative sparing of face and scalp</td>
<td>Scalp severely involved</td>
</tr>
</tbody>
</table>
A biopsy was performed, which revealed orthokeratosis with hypergranulosis and epidermolytic changes within the epidermis consistent with EHK (Fig. 3-4).

Discussion

Treatment of both ichthyosis hystrix and EHK includes topical and oral retinoids, with topical therapies reported as less effective and more likely to cause local irritation. Retinoids inhibit cell growth by their effect on transcription factors in skin cell lines, and induce cell apoptosis. Their success in hyperkeratosis-related conditions may be due to their effect on keratins, with an upregulation of K4, K6, K13, and K19 and a down-regulation of K2e, K1 and K10.

Acitretin is a treatment option for both EHK and ichthyosis hystrix. Studies have shown substantial improvement in keratinization disorders treated with acitretin, with one study reporting 23 of 28 cases cured in patients receiving an average dose of 0.86mg/kg/day over two months to 36 months. The most frequent side effects discussed included chelitis (46.3%) and skin fragility (35.7%), with no effect on growth or bone. However, in a study involving patients aged 45, 60, and 69 who received 0.5-0.75mg/kg/day for 14, 22, and 28 years, respectively, clinical condition improved but reports of spinal hyperostosis occurred. Further review of literature reveals fewer significant systemic events when shorter periods of acitretin are prescribed, even at higher dosages.

Variability in response to retinoid treatment has been reported. In a study comparing patients with K1 and K10 mutations, good responders included patients with K10 mutations who experienced an upregulation of K4 when treated with retinoids. Patients with K1 mutations exhibited a lower tolerability to retinoid treatment. A down-regulation of K2e was discovered in these patients following treatment, and this may serve as one mechanism of variability in clinical improvement.

This patient discussed herein presented a diagnostic challenge. He was initially diagnosed with epidermolytic verruciformis in Mexico, but this diagnosis was questioned based on clinical exam findings. Two additional biopsies were performed, and a diagnosis of EHK was made based on the histological findings. This diagnosis, however, was also in question due to the patient’s negative history of skin blistering and negative family history of the disease, but incomplete penetrance and variable expressivity of EHK were considered as possibilities. However, taking into account the full clinical history in addition to histological evidence, ichthyosis hystrix is currently believed to be the most likely diagnosis.

Conclusion

It is imperative to consider all clinical and histological information when making a diagnosis in order to properly treat and counsel patients. Ichthyosis hystrix can have a similar clinical appearance to EHK, and approximately 16% of cases have the histologic subtype of epidermolytic hyperkeratosis. The patient was started on acitretin and showed improvement of his lesions after one month of treatment with minimal side effects. Although he declined genetic testing at this time, it was still encouraged due to the possibility of full-blown EHK in his offspring.

References

Case Report: Follicular Mucinosis in an Adolescent

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Abstract

Follicular mucinosis, also known as alopecia mucinosa, is a rare disorder characterized by follicular papules and indurated plaques that affects both adolescents and adults. In adolescents, it is usually confined to the head and neck region and runs a benign course that resolves within months to years. In adults presenting with a widespread distribution of lesions, it runs a more malignant course and is usually associated with lymphoma, specifically with mycosis fungoides (MF). We report the case of a 9-year-old male with a past medical history of acute myelogenous leukemia (AML) presenting with grouped follicular papules within hypopigmented patches of alopecia diffusely on his body. The clinical presentation, histology, and treatment will be discussed in this case report.

Introduction

Follicular mucinosis (FM) is a rare, chronic cutaneous disease of the outer root sheath of the hair follicle and sebaceous gland. The dermatologic eruptions present with follicular papules with or without indurated plaques. The accumulation of mucinous material in the damaged hair follicles and sebaceous glands causes an inflammatory condition and subsequent degeneration. The face, neck, and scalp are the most commonly affected areas, although lesions may appear anywhere. We present the case of 9-year-old male with a history of acute myelogenous leukemia (AML) who was diagnosed with biopsy-proven follicular mucinosis that was treated with clobetasol and narrowband ultraviolet B light (UVB) therapy.

Case Report

A 9-year-old male presented with a two-month history of “white spots” spreading diffusely over his body (Figures 1 and 2). The patient’s mother reported that a few spots grew on his arm over a period of weeks, and others began to crop up thereafter. The patient’s medical past included a two-year history of AML, which was in complete remission four months prior to onset of the “white spots.”

On physical examination, the lesions presented as grouped follicular papules within hypopigmented patches of alopecia scattered diffusely all over his body but predominantly located on the bilateral upper extremities. No palpable lymph nodes were appreciated. The patient denied pruritus, pain, or any other symptoms associated with the lesions. A deep shave biopsy was performed, and histopathology revealed mucin deposits within the hair follicles, confirming the diagnosis of follicular mucinosis (Figures 3 and 4). T-Cell receptor rearrangement studies were negative. Clobetasol ointment was initially tried over a four-week period with no improvement. More lesions began to appear during that time. Narrowband UVB is currently being used with significant improvement, and the patient’s treatment is ongoing at the time of this paper’s publication.

Discussion

Follicular mucinosis is a rare, chronic, histopathologic cutaneous disease presenting with mucin deposits and edema in the outer root sheath of hair follicles and sebaceous glands. Clinically, it presents with shiny papules or sharply demarcated, infiltrated, erythematous scaling plaques on the head and neck, the most frequent sites, as well as the trunk and extremities. The accumulation of mucinous material in the outer root sheath of the hair follicle and sebaceous glands causes damage and creates an inflammatory condition that eventually breaks down the follicle and gland. When follicular mucinosis occurs in hair-bearing areas of the body, it is named alopecia mucinosa. Alopecia mucinosa was first reported by Pinkus in 1957. The same year, Braun-Falco noted a relationship between alopecia mucinosa and mycosis fungoides and Sézary syndrome. This type is more widespread and chronic, affecting adults over 40 years of age. Ten years later, in 1969, Emmerson and Coskey re-categorized the disease into three distinct entities. The first type has an acute presentation and is called benign primary follicular mucinosis (PFM). PFM is an idiopathic, benign condition presenting as pink papules or plaques confined to the head and neck region with perinatal polyclonal infiltrates of lymphocytes. PFM affects children and young adults and tends to spontaneously regress in a few months to a year. The second type, known as cutaneous lymphoma-associated follicular mucinosis, is characterized by cutaneous manifestations of lymphoma such as mycosis fungoides and Sézary syndrome. This type is more widespread and chronic, affecting adults over 40 years of age.
age with no signs of systemic disease.\textsuperscript{3,4} The third type is associated with a more generalized distribution of larger plaques, more elderly patients, and an underlying systemic, malignant lymphoproliferative disorder.\textsuperscript{6} The most common malignant associations are leukemias such as Hodgkin's disease, renal carcinoma, cutaneous B-cell lymphoma, and lymphosarcoma.\textsuperscript{6}

The etiology of follicular mucinosis is unknown; however, cell-mediated immunity is believed to play a role in the pathogenesis. The majority of the lymphocytes in follicular mucinosis are T-helper cells (CD4).\textsuperscript{7} It has been suggested that cytokines released from the T-lymphocytes stimulate the follicular keratinocytes to secrete mucin.\textsuperscript{8} Clonal T-cell receptor (TCR) gene rearrangement is present in some cases of primary follicular mucinosis.\textsuperscript{9}

Clonal TCR gene rearrangement in FM was found to be associated with CTCL in some studies; however, other studies have debunked this theory, and as of now TCR gene rearrangement studies are equivocal as a diagnostic tool. It has been shown that lesions confined to the head and neck region usually run a more benign course, while diffuse lesions are associated with a higher predilection for malignancy. Alikhan et al. reported a retrospective study of 33 patients with FM, where lesions confined to the head and neck had no incidence of CTCL. However, patients with diffuse lesions had an increased association with CTCL.\textsuperscript{9}

On histology, mucin within the follicular epithelium, acanthosis, mild follicular spongiosis, CD4 predominant lymphocytic inflammation, and CD2, CD3 and CD5 (+) perifollicular T-cell infiltrate with partial loss of CD7 are seen. Follicular mucin can be confirmed by positive colloidal iron staining.\textsuperscript{9}

**Treatment**

There is no standard effective treatment for primary FM, and a wide variety of therapies have been described, such as topical and oral antibiotics, topical retinoids, isotretinoin, steroids (topical, intralesional, oral), dapsone, methotrexate, immunosuppressive drugs, nitrogen mustard, ultraviolet A light (UVA) therapy, and psoralen with UVA (PUVA) treatment. The treatment of secondary follicular mucinosis is aimed at curing the underlying malignancy.\textsuperscript{10} Case reports have shown the success of photodynamic therapy (PDT), imiquimod, and minocycline.\textsuperscript{4,11,12}

**Conclusion**

Follicular mucinosis in a younger population usually follows a benign and non-progressive course, while in an older population, it is usually associated with cutaneous T-cell lymphoma. However, in cases of benign FM, long-term follow-up with repeated biopsies is still recommended, and a minimum period of five years has been suggested.\textsuperscript{10} In addition, molecular genetics studies are recommended in every suspected patient. It is also important to note the distribution of the disease. Lesions confined to the head and neck region are generally thought to run a benign course, and lesions with a widespread distribution are associated with a higher rate of malignancy.

Our patient did have diffuse involvement; however, the initial biopsy did not reveal CTCL. The patient is doing well and seeing improvement with narrowband UVB. Per the current recommendations, follow-up biopsies will be performed in order to monitor for any malignant transformation.

**References**


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Abstract
Gianotti-Crosti syndrome is a disease occurring mainly in children, presents with an abrupt onset of symmetrically distributed papules or plaques localized to the extremities, face, and buttocks. It is thought to be a self-limited disease with an infectious etiology, often preceded by an upper respiratory infection. We present a case of an 11-year-old boy with an acute eruption of edematous monomorphic papules followed by complete resolution within six weeks, illustrating the classic presentation of this disease entity.

Case Presentation
An 11-year-old male presented to our office with an abrupt onset of “bumps” on his bilateral extremities. He reported that one week prior, he’d developed a single lesion on his right knee, followed the next day with numerous similar lesions on his bilateral extremities. They continued to increase in number. He denied pruritus or pain and reported they were completely asymptomatic. His mother stated that one week prior to the onset of the lesions he had complained of a sore throat and had developed a fever but required no medication as it quickly resolved on its own. They denied similar lesions in other family members. The patient was current on all vaccinations including hepatitis B, and was taking no medications.

Physical examination revealed a well-nourished patient with multiple skin-colored to pink, edematous papules symmetrically distributed on the patient’s elbows, knees and ankles with sparing of the face and trunk. Lymphadenopathy was noted in the patient’s axillae.

The diagnosis of Gianotti-Crosti was discussed with the patient and his mother. Due to the benign nature of the disease and the patient’s asymptomatic presentation, an observation-only approach was decided upon, as most lesions generally resolve in three to four weeks. The patient was seen back in the clinic six weeks later with full resolution of the lesions noted.

Discussion
Gianotti-Crosti syndrome is an eruption primarily seen in children between the ages of six months and 14 years, with a mean age of 2 years, although it has been seen in adults. The typical presentation is an abrupt eruption of flesh-colored or pink-red monomorphic papules or papulovesicles that are symmetrically distributed on the extensor surface of the extremities, face, and buttocks. The trunk and mucus membranes are spared, but the presence of a few truncal lesions does not exclude diagnosis. Although commonly asymptomatic, some patients may report pruritus or low-grade fever or present with axillary or inguinal lymphadenopathy. When associated with HBV infection, patients may also demonstrate hepatomegaly.

The mechanism whereby the GCS eruption develops is not completely understood. Patients may report a preceding upper respiratory infection with mild constitutional symptoms. There are multiple case reports describing an association with a host of different viruses, vaccinations, and bacteria (Table 1).
Table 1. Viruses, Vaccinations, and Bacteria Reported to be Associated with Gianotti-Crosti Syndrome3-6

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Vaccinations</th>
<th>Bacteria</th>
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<tbody>
<tr>
<td>Hepatitis A</td>
<td>Hepatitis A</td>
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</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B</td>
<td>Mycoplasma pneumonia</td>
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<td>Influenza</td>
<td>B-hemolytic streptococci</td>
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<tr>
<td>Poxvirus</td>
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<tr>
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</table>

Worldwide, HBV and EBV are the most commonly associated viruses.3 With widespread HBV vaccination in developed countries, EBV has become the most commonly recognized associated virus. Ricci et al described an increased incidence of GCS in patients with a history of atopy, suggesting that preexisting immune dysregulation may play a factor in developing GCS following a viral infection or immunization.4 Despite a possible association between certain vaccines and GCS, a history of GCS should not serve as a contraindication to receiving future vaccinations.3 Despite many potential causative agents, no significant clinical or histological difference has been identified regardless of the suspected causative agent.1,5

The histopathological findings in GCS are relatively non-specific but may include acanthosis accompanied by diffuse spongiosis and vesicles. Langerhans cells are the dominant cell appearing in the vesicle. There is a non-vesicular eruption, lichen planus, scabies, papular urticaria, and molluscum contagiosum. The clinician should conduct a thorough history to narrow the differential and screen for risk factors of serious viral disease such as HBV. If clinically indicated, laboratory tests for hepatitis or specific viral agents may be obtained.7 With a benign physical exam and the absence of serious risk factors, an asymptomatic patient does not require laboratory workup or treatment, as was the case with our patient. For most patients and their parents, reassurance is all that is needed. If the patient complains of pruritus, supportive treatment in the form of oral antihistamines and topical antipruritics may be used, although these will not shorten the duration of the eruption.1 Topical corticosteroids are often of little benefit. In one case of particularly disabling and long-lasting GCS, spontaneous resolution was observed after the initiation of ribavirin therapy.8

In summary, GCS is a benign, self-limited eruption of uncertain pathogenesis that is commonly associated with a preceding viral infection or immunization. It is most commonly observed in the pediatric population, and although its appearance may alarm parents, no treatment is usually required.

References

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Pyoderma Gangrenosum: A Case Report and Proposed Evidence-based Guidelines for Working-up the Condition

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Abstract

Pyoderma gangrenosum (PG) is a relatively uncommon inflammatory skin disease. General incidence has been estimated at between 3 and 10 persons per million per year. It can initially present to any medical specialty and have many clinical variations that make a timely diagnosis very difficult for the non-dermatologist. A delay in diagnosis can lead to severe scars, disfigurement, increased morbidity and mortality. Most cases are associated with an underlying systemic condition, such as inflammatory bowel disease (IBD), arthritis, and hematological malignancies. A skin biopsy is needed to exclude other skin conditions. First-line therapy is long-term immunosuppression, usually with high-dose prednisone. Evidence-based work-up guidelines are lacking in the current literature. This article discusses an interesting case presentation of pyoderma gangrenosum, briefly reviews the condition, and proposes evidence-based guidelines in the work-up of PG.

Case Report

A 44-year-old African American male presented to the dermatology clinic with a complaint of a “painful leg ulcer” present for several months. He stated the ulcer began as several small, red bumps that progressively grew larger over several days. The patient had a past medical history of ulcerative colitis, status post partial colectomy and colostomy in 2001, and had skin graft surgery over his right lateral leg in 2008. Physical examination was significant for a 6 cm by 4 cm erythematous, friable ulceration with rolled edges located over his right lateral leg (Figure 1).

A 5 mm punch biopsy was obtained, and the pathology results confirmed the diagnosis of PG, showing mixed cellular inflammation with predominant neutrophils in the superficial and deep dermis, vascular necrosis, and erythrocyte extravasation (Figure 2).

The patient was started on a slow prednisone taper beginning at 60 mg daily. Local wound care instructions were given along with esomeprazole 40 mg daily for gastrointestinal prophylaxis. The patient was subsequently referred to gastroenterology to rule out recurrence of ulcerative colitis. He did extremely well over the next four months of follow-up, with near-complete clearing of the ulceration (see Figures 3-5). Soon after, the patient was lost to follow-up.

Pyoderma Gangrenosum

Although the etiology of PG remains unclear, the current literature suggests there is a dysregulation of the immune system that leads to altered neutrophil chemotaxis. Fifty percent of affected patients have an associated systemic condition, most commonly inflammatory bowel disease (IBD), followed by arthritis, hematologic malignancy, and paraproteinemia. It classically presents as an acute, painful ulceration with distinct rolled edges, typically on the lower extremities, in adults 40 to 60 years old. Both genders are affected; however, there is a slight female predominance. Many lesions begin at the sites of previous trauma (pathergy). Patients often complain of concomitant systemic symptoms such as fever, malaise, arthralgia, and myalgia.

PG can be subdivided into four distinct types: classic (ulcerative), pustular, bullous, and...
vegetative. The ulcerative and pustular types are usually more associated with IBD, while the bullous types are more suggestive (up to 70% of cases) of an underlying hematologic malignancy. The differential diagnosis includes Sweet’s syndrome, traumatic ulceration, squamous cell carcinoma, and Wegener’s granulomatosis. A diagnosis of PG is generally made based on clinical and histopathologic findings. Histology will show massive dermal edema with epidermal neutrophilic abscesses at the violaceous undermined border. Other findings include: mixed cellular infiltrates with predominant neutrophils in the superficial and deep dermis; leukocytoclastic vasculitis; vascular necrosis; and erythrocyte extravasation.

Management of PG depends on the severity of disease and the underlying cause. First-line therapy for PG is systemic treatment with high-dose corticosteroids alone or high-dose corticosteroids with cyclosporine. Alternative therapeutic options include infliximab, mycophenolate mofetil, tacrolimus, thalidomide, ustekinumab, dapsona and plasmapheresis. Patients usually respond well to high-dose systemic corticosteroids with up to 50% improvement in size of lesions within one month of treatment. When managing a patient with an established history of PG, it is important to discuss and avoid any unnecessary surgical manipulation to help prevent new lesions from developing. The prognosis of PG is generally favorable. However, the disease may recur, and residual scarring is common.

Discussion

Pyoderma gangrenosum is an interesting skin disease due to its known association with IBD and its propensity to develop at a site of skin trauma. Although the patient described in this case report meets the textbook description of PG, it is important to note that this may not always be the case. Besides IBD, PG has many other systemic associations, and while less common, they are equally important to rule out. Some of those associations include leukemia, myeloma, monoclonal gammopathy, polycythemia, polyarteritis nodosa, subcutaneous pustular dermatosis, cryoglobulinemia and hepatitis C infection. Unfortunately, there is a lack of consensus in the current literature to the approach of working up PG, especially when there is no clear underlying cause. This may lead to an incorrect or untimely diagnosis and increase morbidity and mortality. A proposed solution is the development of evidence-based work-up guidelines. Currently, authors recommend numerous laboratory investigations to aid in identifying any possible associated underlying diseases as well as to rule out other conditions that mimick PG. These laboratory studies include: complete blood count, erythrocyte sedimentation rate, blood chemistry, coagulation profile (including antiphospholipid-antibody), antineutrophil cytoplasmic antibodies, cryoglobulins, protein electrophoresis, chest radiography, colonoscopy, and venous and arterial-hematological malignancies. Rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR) would be useful in establishing seropositive/seronegative arthritis. Although there are other systemic conditions associated with the classic subtype, they are extremely rare and are mentioned sporadically in the current literature; therefore they should not be initially addressed.

The pustular form of PG is the rarest subtype, usually presenting on the trunk or extensor surfaces of limbs. Since most of the pustular cases are associated with active IBD (specifically ulcerative colitis), initial work-up should include a CBC and colonoscopy. The bullous subtype of PG is also a relatively rare subtype, and it has the worst prognosis. This is most often associated with hematologic malignancies, especially when the upper limbs or face is affected. Therefore, the initial work-up is simply a CBC.

The vegetative subtype, a superficial variant of the disease, seems to be the least-aggressive form of PG. This type is usually not associated with any underlying conditions, and patients are otherwise healthy. These patients do not need an initial work-up, and the lesions can be treated with local therapeutics. If systemic symptoms (fever, arthralgias, and weight loss) are present, then an initial work-up is warranted.

Conclusion

PG remains an intriguing inflammatory dermatosis. Our proposed guidelines are intended to help the medical professional in the initial work-up of PG. The algorithm was developed based on established associations between specific subtypes of PG and their respective conditions. Abnormalities in the initial work-up will prompt further studies and consultations. More research is needed to validate and perfect our algorithm.

References


A Basal Cell Carcinoma Simulator: Case Report and Review of the Clinical, Dermoscopic and Reflectance Confocal Microscopy Features of Sebaceous Hyperplasia

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Abstract

Sebaceous hyperplasia is a common mimicker of basal-cell carcinoma, particularly when it occurs on uncommon locations of the body. Dermoscopy and reflectance confocal microscopy (RCM) help to differentiate between these different entities.

Case Report

A 52-year-old Caucasian male with a past medical history of non-melanomatous skin cancer presented for a routine skin cancer screening. He was otherwise healthy and took no medications regularly. On full-body skin examination, he was found to have a 2 mm, skin-colored papule on his left mid flank (Figure 1). The patient was unaware of this lesion and denied any symptomatology.

On dermoscopy, the lesion lacked a pigmented network and displayed blue globules centrally as well as arborizing blood vessels suggestive of basal cell carcinoma. Conversely, there also was an area of faint yellow coloration suggestive of sebaceous differentiation. Clinical examination and dermoscopy did not yield a definitive diagnosis, and therefore reflectance confocal microscopy was performed.

Reflectance confocal microscopy (RCM) allows for the in vivo evaluation of skin lesions. RCM was performed using the Lucid VivaScope 1500.
This unit utilizes a diode laser, which emits a wavelength of 830 nm, allowing the visualization of structures beneath the skin surface to approximately 200 μm in depth. In sebaceous-gland hyperplasia, key features normally found on RCM include: 1) a dilated central follicular infundibulum; 2) clusters of round cells with bright speckled cytoplasm and dark round nuclei corresponding to sebaceous lobules; and 3) vessels around the periphery of the lobular structures, which correlate with crown vessels described in dermoscopic features of sebaceous hyperplasia.1,3

In comparison, the RCM features seen in pigmented basal cell carcinoma include: 1) tumor islands or silhouettes; 2) clefting around tumor islands; 3) presence of dendritic cells suggestive of melanocytes; 4) presence of bright round cells suggestive of melanophages; and 5) canalicular or linear vessels.8,9

Based upon our findings clinically, dermoscopically and on reflectance confocal microscopy, our final diagnosis was sebaceous-gland hyperplasia.

A deep shave biopsy was performed for definitive diagnosis. Histopathology showed a collection of sebaceous lobules with normal morphology within the papillary dermis. No basaloid proliferation was identified, thereby confirming the diagnosis of sebaceous hyperplasia.

**Discussion**

Sebaceous hyperplasia is a common, benign enlargement of sebaceous glands surrounding a follicular infundibulum. These lesions clinically present as asymptomatic, yellowish, occasionally telangiectatic papules with a central depression and are most often found on the face. There have been few reported cases of solitary tumors of sebaceous hyperplasia occurring on the areola, genitals, and chest.6,7 Additionally, multiple tumors with sebaceous hyperplasia can be seen in transplant patients on immunosuppressive therapy with cyclosporine, as well as in certain genodermatoses such as Muir-Torre syndrome and pachydermoperiostosis.8

Sebaceous glands are found throughout all surfaces of the skin except for the palms and soles. The largest number of sebaceous glands is found on the face, chest and back. Sebaceous glands exhibit holocrine secretion and exist as a portion of the pilosebaceous unit surrounding a follicular infundibulum. Sebaceous glands can less frequently open directly to the skin surface, particularly in areas with modified skin such as Fordyce spots on the lips and buccal mucosa, Montgomery glands within the areolae, Meibomian glands within the eyelids, and Tyson glands in the clitoris and glans penis.

The number of sebaceous glands remains relatively stable throughout life. Their size and activity can be altered by androgenic influence and age. High levels of circulating androgens are present during puberty, resulting in increased sebaceous-gland activity and size. With increasing age, androgen levels begin to decline, leading to decreased holocrine secretion of sebocytes. Sebaceous-gland hyperplasia occurs as a result of decreased sebocyte turnover and therefore an enlargement of the sebaceous-gland subunit with decreased sebum secretion.

**Conclusion**

There have been no reported cases of solitary sebaceous hyperplasia of the back in the literature to date. When an isolated lesion of sebaceous hyperplasia occurs outside of the face, it can easily be mistaken for basal-cell carcinoma, prompting biopsy. With the use of dermatoscopy and reflectance confocal microscopy, diagnostic accuracy may be improved.

**References**


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Hypopigmented Mycosis Fungoides: Case Report and Review

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Abstract
Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL). It is characterized by a malignant clone of CD4+ helper T-cells that homes to the skin. Several variants of MF have been described, including a hypopigmented subtype. Herein, we describe a case of hypopigmented MF in a 13-year-old Hispanic boy and review the current literature on the disease. We discuss some of the important challenges in diagnosis of the disease, with a focus on histopathologic findings and their clinical correlations.

Introduction
Mycosis fungoides (MF) is a cutaneous T-cell lymphoma (CTCL) involving a malignant clone of CD4+ helper T-cells that homes to the skin. The majority of cases presents in the classical form, referred to as Alibert-Bazin disease, which evolves clinically through three stages: patch, plaque and tumor.1 MF has been described to present in several other forms as well, including hypopigmented, hyperpigmented, erythrodermic, ichthyosiform, pityriasis lichenoides-like, granulomatous, folliculotropic, bullous, palmoplantar, pagetoid reticulosis, and granulomatous slack skin.2 This paper will specifically review hypopigmented mycosis fungoides and discuss some of the challenges surrounding diagnosis of the disease.

Case
A 13-year-old Hispanic male presented to our office complaining of itchy white spots all over his body for seven years. He had previously been treated with several topical steroids and antifungal agents and completed a course of griseofulvin with no improvement. Review of systems was positive for pruritus only. The patient’s past medical history included asthma, controlled with an albuterol inhaler, and seizure disorder, stable without medication. His family and social histories were non-contributory. He was born in the United States, had no history of recent travel, and had no pets.

Physical examination revealed widespread, hypopigmented, reticular patches with slight scale affecting >75% of his body surface area (Figures 1a,b,c). Sensation in the affected areas was intact. No lymphadenopathy or hepatosplenomegaly was appreciated. A 4 mm punch biopsy was obtained from the right posterior shoulder. On histological examination, the dermis contained a dense lichenoid and superficial perivascular infiltrate of lymphocytes with mild nuclear atypia, and foci of exocytosis into the epidermis. Pigment incontinence was also seen, supporting the diagnosis of hypopigmented mycosis fungoides (Figures 2a [10x], 2b [40x]). Laboratory studies were performed, including a complete blood count with differential, chemistry panel, and liver function tests, all of which were within normal range. Treatment with narrow-band ultraviolet light therapy has resulted in significant clearing.

Epidemiology
Mycosis fungoides is the most common type of CTCL, representing nearly 50% of all primary cutaneous lymphomas, and has an incidence rate of 4.5 per 1 million persons.1,3 It occurs most commonly in adults aged 50 to 60 years old, but can also be seen in children and young adults.2 The male-to-female ratio is approximately 2:1.2 Hypopigmented mycosis fungoides (HMF) was first described by Ryan et al. in 1973.4 It is an uncommon disease, but it may be under-reported due to the frequent delay in diagnosis and lack of recognition. It has a predilection for dark-skinned children of African American, West-Indian, and Asian origin, but has also been reported in Caucasians.5 The average age of onset of HMF is 29 years old, in comparison to...
ultimately expand, escape the surveillance of the activated, producing a dominant clone that may
CTCLs have the potential to become chronically
Early MF expresses a predominantly TH1
cytokine profile evidenced by an increase in interferon-gamma and interleukins 2 and 12 in the skin. Histopathologically, both CD4+ and CD8+ T-cells are present. In contrast, late MF has been shown to have more of a TH2 response with an increase in interleukins 4, 5, 10, and 13 and an increased number of CD4+ T-cells. It has been suggested that the progression of MF may be due in part to the loss of the CD8+ T-cells, which are known to mount an anti-tumor response. Interleukins 15 and 16 and TH17 cytokines such as interleukins 17A, 21, and 22 may also be expressed in MF. While classic MF is characterized as having mostly CD4+ T-cells, hypopigmented MF has an immunophenotype consisting of mostly CD8+ T-cells. The predominantly CD8+ T-cell immunophenotype in HMF may offer an important anti-tumor response and possibly contribute to its indolent course.

There are several mechanisms speculated to be involved in the pathogenesis of hypomelanosis in HMF. Three mechanisms include atypical mycosis cells causing abnormal melanogenesis, defects in melanosome transfer to keratinocytes, and non-specific inflammation causing damage to melanocytes from cytotoxic CD8+ T-cells. One other mechanism that may be involved in the hypomelanosis of HMF is the cytotoxic effect of CD8+ T-cells on the CD117 receptor. CD117 is a receptor on melanocytes that binds with stem-cell factor to maintain melanocytes within the epidermis. Studies have found that there is a decrease of CD117 in both vitiligo and HMF.

Etiology and Pathogenesis
The etiology of MF is unknown. Persistent antigenic stimulation has been proposed as an initial event in the disease, as MF has been observed to be a disease of mature CD4+ memory cells, but no specific antigen has been identified. Infectious agents have been implicated, including human T-cell lymphotropic virus (HTLV)-1, Epstein-Barr virus, and HIV; however, evidence is lacking to support such associations. MF may be viewed as a disease of immune deregulation, since tumor progression is associated with decreased antigen-specific T-cell responses and impaired cell-mediated cytotoxicity.

The pathogenesis of MF is not completely understood but is believed to initially involve the presentation of an antigen to Langerhans cells in the skin. Langerhans cells carry the antigen to peripheral lymph nodes, where it is presented to CD4+ helper T-cells. This presentation converts the helper T-cells into cutaneous T-cell lymphoma cells (CTCLs). These cells express cutaneous lymphoid antigen (CLA) on their surface, which binds to E-selectin (CD62E) located on vascular endothelial cells in skin. Chemokines involved in the homing of CTCLs to skin include CCR4, CCR3, CCR4, and CCR10. Once in the epidermis and dermis, CTCLs have the potential to become chronically activated, producing a dominant clone that may ultimately expand, escape the surveillance of the immune system, and progress beyond the skin.

Early MF expresses a predominantly TH1

Clinical Manifestations
HMF typically presents with asymptomatic, hypopigmented macules, patches, and/or plaques distributed on the trunk and extremities, similar to the areas of classic MF. It can occur as a sole manifestation or in combination with classic MF lesions such as erythematous patches, plaques, or tumors. HMF may evolve to include the peripheral lymph nodes, and internal organs. A differential diagnosis to consider in HMF patients includes atopic dermatitis, pityriasis alba, tinea versicolor, vitiligo, post-inflammatory hypopigmentation, progressive macular hypomelanosis, lichen sclerosis et atrophicus, pityriasis lichenoides chronica, morphea, sarcoidosis, syphilis, leprosy, and onychocoriasis.

Chronic inflammatory diseases resistant to treatment should be suspicious for MF, and several reports of chronic inflammatory diseases that have transformed into CTCL are reported. Some reports suggest an increased risk of CTCL in patients with atopic dermatitis and psoriasis. Several cases have also been described in which chronic inflammatory lesions, including those from contact dermatitis, inoculation injury, rhus dermatitis, and a chronic draining hemotoma, eventuated into MF.

Diagnosis
Diagnosis of early MF can be quite challenging.
lesions have evolved into the plaque stage, a denser infiltrate with more atypical lymphocytes can be found. Other T-cell markers include markers that may be found in benign inflammatory disorders, not sensitive or specific for MF, as it has also been demonstrated in benign inflammatory disorders and in the dermis. The clones can also be found where in later stages the clone is only located in the epidermis. Immunophenotypic studies of early MF show CD8+ and CD4+ T-cells; however, in later stages of MF, there seems to be a loss of the CD8 marker, leaving a CD4+ predominance phenotype. HMF, on the other hand, typically shows a predominance of CD8+ T-cells, although patients with CD8-/CD4-, equal ratios of CD4+/CD8+, and predominantly CD4+ T-cells have also been found. T-cell markers in MF include CD2, CD3, CD5, CD7, and CD26, which are usually lost with progression of disease. Loss of these markers may be found in benign inflammatory diseases as well. Other T-cell markers include CD45R0, CD25, CD56, TIA1, and CD30 and oligoclonal T-cell repertoire. Early biopsies of HMF may suggest a T-cell dyscrasia but will evolve into MF with time.

Staging/Prognosis

The staging of MF is based on a Tumor, Node, Metastasis (TNM) approach and uses a revised classification scheme from the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC). Stages IA, IB, and IIA are considered limited-stage disease, while stages IIB – IVB are advanced stages. HMF appears to have a slow progression and an excellent prognosis, with a 20-year overall and disease-specific survival of 98.6%. Progression to tumor stage or systemic involvement is rare. Wain et al. reviewed 30 cases of HMF, 85% of which (2830) did not progress beyond stage IB disease. Because it is possible for patients to progress to systemic disease and develop secondary malignancies, it is advised to monitor patients throughout their lifetime.

Treatment

Pсорalen UV-A (PUVA), UV-B radiation, total skin electron irradiation, topical nitrogen mustard, carbustine, and corticosteroid creams have all shown a good response in adults and children with HMF, with PUVA being the most commonly described. There is no widely accepted protocol pertaining to the treatment of HMF in children, so they are managed in the same way as adults. Topical class 1 steroids have been shown to be effective in HMF. PUVA was found to be more effective than narrowband-UVB (NB-UVB), with lower rates of relapse; however, NB-UVB has the benefit of re-pigmentation and lacks the side effects and carcinogenicity of psoraleen. The long-term effects of phototherapy and radiotherapy in children should be considered.

Conclusion

Hypopigmented mycosis fungoides is an uncommon variant of MF that can present a number of diagnostic challenges. The disease can resemble many other inflammatory conditions, and no studies are entirely sensitive or specific. Diagnostic algorithms used for classic MF, such as the revised ISCL algorithm, cannot be applied to variants such as HMF. When the diagnostic criteria for MF cannot be met, a diagnosis of T-cell dyscrasia might be considered. More explicit guidelines and/or specific disease markers for MF would greatly aid in diagnosis, especially during the early stages of the disease.

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Scalp Psoriasis Treated with Excimer Laser, Clobetasol Propionate Spray, and Calcitriol Ointment: A Case Report

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Abstract

Psoriasis is a chronic dermatologic disease affecting 2% to 3% of the general population. The disease can remain stable over a person’s lifetime or gradually become more widespread. Given that there is currently no cure available, patients with psoriasis need long-term treatment. Scalp psoriasis presents a unique challenge since treatment may be limited, cumbersome, or ineffective. We present a case that demonstrates how combination therapy consisting of excimer laser therapy and topical therapy (clobetasol propionate spray and calcitriol ointment) can be a highly efficacious method of treating scalp psoriasis.

Introduction

Psoriasis is a chronic dermatologic disease affecting 2% to 3% of the general population. The disease can remain stable over a person’s lifetime or gradually become more widespread. Given that there is currently no cure available, patients with psoriasis need long-term treatment. Psoriasis can affect any area of the body. Scalp psoriasis presents a unique challenge since treatment may be limited, cumbersome, or ineffective. There is no universal guideline for the treatment of scalp psoriasis. First-line therapy in treating scalp psoriasis includes topical treatment, such as medicated shampoos, steroids, salicylic acid, tars, calcipotriene/calcitriol, tazarotene, and anthralin. For those patients with more severe scalp disease or who need a faster response, treatment can include combination therapy (i.e. simultaneous use of a steroid agent and non-steroid agent), more occlusive formulations, keratolytics, and superpotent corticosteroids. If topical agents are not able to adequately treat the scalp psoriasis, the patient may benefit from systemic therapy, ultraviolet phototherapy or excimer laser therapy. Of these three therapies, excimer laser therapy may present clear advantages over the others. The risk of side effects from systemic medication is usually a deterrent for patients with isolated scalp disease. Though light therapy is a well-established therapeutic option for psoriasis, hair often prevents penetration of light to the psoriatic plaque. Since traditional phototherapy is administered in a nonspecific fashion and may reach uninvolved skin, the therapeutic capacity is limited by the minimal erythema dose (MED). For these reasons, traditional phototherapy is often impractical and/or ineffective for treating scalp psoriasis.

For excimer therapy, the patient was started at energy of 600 millijoules per square centimeter (mJ/cm²). The dose was increased 25% on each subsequent visit to a maximum tolerable dose of 1551 mJ/cm². The maximum dose was determined by examination of blistering at the treatment site. After three weeks of combination therapy with excimer laser and clobetasol spray, the patient demonstrated marked improvement on the entirety of his scalp and body, all similar to that seen in Figure 2. The head PASI score decreased to 0.6, less than one quarter the score at the baseline visit three weeks prior. With continued treatment, the patient noted further improvement, with total clearance of his scalp psoriasis (PASI 0) by the end of the treatment (week 12).

Discussion

Most algorithms for the treatment of scalp psoriasis rely on topical therapy. One strategy, coined the “yin-yang” technique, uses sequential clobetasol spray and calcipotriene ointment. This strategy is based on treating two types of psoriatic inflammation that a patient may experience: 1) acute and highly inflamed, and 2) chronic and indolent. During the highly inflamed phase, treatment with clobetasol spray is used. In a placebo-controlled study of scalp psoriasis,
85% (35/41) of patients treated with clobetasol spray were “cleared” or “almost clear” at week 4, compared to 13% (5/40) of patients in the placebo group. During the chronic and indolent phase, the yin-yang strategy uses calcitriol ointment. In one open-label study of patients cleared with four weeks of clobetasol spray, 92% and almost 80% of patients maintained clearance at week 8 and week 12, respectively, with two months using calcitriol ointment. 

Wong et al. proposed an updated algorithm for the treatment of scalp psoriasis, introducing the excimer laser as a viable option if the psoriasis is resistant to topical therapies or scalp involvement is severe. Targeted ultraviolet B (UVB) 308 nm excimer laser is at the cutting-edge of dermatologic therapies and may potentially change the use of phototherapy for scalp psoriasis. In contrast to traditional phototherapy, UVB excimer laser delivers targeted transmission through a handheld device with a spot diameter of 14 mm to 30 mm. Since psoriatic plaques can tolerate much higher doses of light when compared to noninvolved skin, a much higher dose of energy can be delivered directly to the plaques than through traditional UVB phototherapy. The resulting dose of energy is many times greater than the MED, thus delivering a supra-erythemogenic dose. As a result, the psoriasis can be treated in fewer treatments with a faster clearance compared to traditional phototherapy. In addition, excimer laser therapy results in a long duration of remission. Two studies showed that a single dose of excimer laser at least eight times MED is sufficient to clear individual psoriatic plaques. One of the studies reported that patients were still completely clear in the treated area four months after the single treatment. Though there is concern that hair can inhibit the penetration of the excimer laser to psoriatic plaques, a hair-parting device can be used to minimize interference. Such devices were used in two separate studies of excimer laser for scalp psoriasis. In one prospective study, the modified PASI score decreased from 4 to 2.6 after 15 weeks of twice-weekly excimer scalp therapy using a hair-blowing device. In a retrospective study using manual separation of the hair to increase scalp exposure, almost half of the patients achieved complete clearance. A case of a woman with a 20-year history of refractory scalp psoriasis had 90% improvement in PASI score after 11 weeks of treatment. The area that was treated with excimer laser continued to be clear 10 weeks post-cessation of treatments. 

Clobetasol propionate spray and excimer laser work by very different mechanisms, so combination therapy is likely to result in an additive therapeutic effect. Therefore, clobetasol propionate spray is a worthwhile addition for excimer laser. Clobetasol propionate spray also provides the additional benefit of decreasing the risk of phototoxic reaction from the excimer laser. 

**Conclusion**

Like most psoriasis types, topical therapy is the mainstay for treatment of scalp psoriasis. In recalcitrant cases, the addition of other therapeutic modalities such as excimer laser may be useful. This case demonstrates that combination therapy consisting of excimer laser therapy and topical therapy (clobetasol propionate spray and calcitriol ointment) can be a highly-efficacious method of treating scalp psoriasis. The external approach of both excimer laser therapy and topical therapy minimize the risk of systemic side effects. Larger studies are needed to substantiate these findings, optimize the dosimetry of excimer laser therapy, and evaluate for proper therapeutic technique in treating scalp psoriasis.

**References:**

Abstract
Ichthyoses represent a large heterogeneous group of disorders of cornification. Lamellar ichthyosis affects approximately 1:200,000–300,000 in the United States. The majority of lamellar ichthyosis cases are of autosomal recessive inheritance caused by transglutaminase-1 deficiency resulting from mutations in both copies of the gene on chromosome 14. Transglutaminase-1 is necessary for the structural formation of the stratum corneum. When the skin barrier is ineffective, it stimulates epidermal hyperplasia and hyperkeratosis. This explains the classic phenotype of diffuse, large, brown, polygonal scales over the entire body. In more severe cases, ectropions, eclabium, scarring alopecia, palmoplantar keratoderma with hyperlinearity, dystrophic nails, and crumpled ears can be seen. We present a case report of two brothers with lamellar ichthyosis and then discuss lamellar ichthyosis in further detail.

Introduction
Ichthyoses represent a large heterogeneous group of disorders of cornification. Classification schemes have been sought not only to aid in diagnosis and treatment options, but also to help further research. The classification consensus began in 2007 at the First World Conference on Ichthyosis in Germany. At the First Ichthyosis Consensus Conference in France in 2009, the proposed term “autosomal recessive congenital ichthyosis” was accepted as an umbrella term for the following subtypes: Harlequin ichthyosis, lamellar ichthyosis, and congenital ichthyosiform erythroderma.

Case Report
Two brothers, ages 18 and 19 years, were referred to our dermatology clinic for evaluation and treatment of their skin condition. The boys were born in Dominican Republic and then moved to the United States with their grandmother when they were 6 months old for medical care. They were diagnosed clinically with lamellar ichthyosis at ages 3 and 4, respectively, per their history. The two brothers are the only children of non-consanguineous parents. They were born full-term. There was no recollection of any family members with ichthyosis or any other skin conditions. Their grandmother described the classic presentation of a collodion membrane at birth in both boys. The grandmother stated that the layer peeled away within a week, and then the boys had very thick pale skin with deep red fissures. After several weeks, they began to develop the classic dark brown scales covering their entire bodies. The grandmother stated that both boys had a very difficult time with feeding and growing with subsequent hospitalizations.

Upon social history, the brothers admitted to past depression, but denied any current depressive symptoms. They both denied any current or history of suicidal ideation. The elder brother left high school, is pursuing his GED, and is working as a mechanic. The younger brother is two years behind in school, currently a sophomore in high school. They have been living with their grandmother since 6 months of age. Their parents still reside in Dominican Republic.

Physical examination revealed a generalized distribution of large, dark brown, polygonal, adherent scales without apparent underlying erythema (Figure 1). The flexural regions had prominent skin markings. The palms and soles demonstrated hyperkeratosis and hyperlinearity. Facial skin was taut with significant scales. Bilateral lower congenital ectropions were present in both brothers. Their nails showed exaggerated curvature. Their hair, teeth, and auricular cartilage appeared normal. Other extracutaneous systems were normal. Intellectual and physical development was also normal.

Diffuse, large, brown, polygonal scales noted in two brothers with lamellar ichthyosis at initial visit (a=Brother 1; b=Brother 2).

After a thorough history and physical and blood work, the patients were started on acitretin 25mg daily for one month. At their follow-up visit, the acitretin dose was increased to 50mg daily and they continue to improve at this dose with no changes noted in their blood work (Figure 2). They also have been prescribed Drisdol 50,000 units once weekly to correct their low vitamin D levels with noted improvement in their levels at subsequent follow-up visits. Furthermore, they have been applying Lac-Hydrin 12% lotion once to twice daily for keratolytic purposes. Of note, the patients noted that lotions and creams adhere to the scales and leave their skin with white residue. Ointments or gels would be the more preferred vehicles if possible, based on availability, insurance coverage, and cost.

Improvement in appearance with significant reduction of scale noted at three-month follow-up with acitretin treatment (a=Brother 1; b=Brother 2).

Epidemiology
According to the Foundation for Ichthyosis and Related Skin Types, autosomal recessive congenital ichthyosis-lamellar ichthyosis type affects approximately 1:200,000 in the United States. The most frequently reported prevalence is 1:200,000-300,000. Consanguinity of parents is present in about 8% of cases. Premature birth occurs in 25% of individuals and 51% of siblings are affected. Lamellar ichthyosis is most commonly inherited as an autosomal recessive
Genetics
As previously mentioned, lamellar ichthyosis is most commonly inherited in an autosomal-recessive manner. The parents of the affected individual must carry a mutant allele. A sibling has a 25% chance of being affected, a 25% chance of being unaffected, and a 50% chance of being a carrier. The offspring of an affected individual is a carrier, unless the partner is also a carrier, in which case the offspring has a 50% chance of being a carrier or a 50% chance of being affected.

Pathogenesis
The majority of cases of lamellar ichthyosis are caused by transglutaminase-1 deficiency resulting from mutations in both copies of the gene on chromosome 14. Transglutaminase-1 is expressed in the upper layers of the epidermis, facilitating the formation of the stratum corneum through cross-linking structural proteins and attaching the lipid envelope. This ineffective barrier, in a means to correct itself, stimulates epidermal hyperplasia and hyperkeratosis. Hence, the clinical phenotype of lamellar ichthyosis is a reflection of the underlying physiologic cascade in the epidermis in an attempt to normalize barrier function.

Clinical Findings
Neonates with lamellar ichthyosis typically present with a collodion membrane at birth. The membrane dries and peels away within the first few days to weeks of life. The skin then develops diffuse, large, brown, polygonal scales over the entire body. The skin manifestations are unremitting and persist throughout life. Ectropion, eclabium, scarring alopecia, palmoplantar keratoderma with hyperlinearity, dystrophic nails, and crumpled ears can be seen in severe cases. Erythroderma is mild if at all present. Hypohidrosis is not uncommon and temperature regulation/monitoring is critical. During the neonatal period, they can have significant transepidermal water loss, fluid and electrolyte disturbances, and are at an increased risk for infection and sepsis.

Ophthalmologic involvement is a significant comorbidity among lamellar ichthyosis individuals. Ocular manifestations can include exposure keratitis secondary to ectropion, unilateral megalocornea, enlarged corneal nerve, blepharitis, absent Meibomian gland, trichiasis, madarosis, and absence of lacrimal puncta. Corneal ulcerations can occur. With prolonged excessive dryness, patients can develop bilateral cicatricial ectropions with subsequent contractures. Late presentation can lead to severe, sight-threatening complications.

Hypovitaminosis D in individuals with ichthyosis and other disorders of keratinization have been reported, which is consistent with the case we present, and is most likely due to the impaired synthesis in the skin. Vitamin D is essential for a healthy skeleton. Deficiency can lead to rickets in children and osteoporosis in adults. Vitamin D has also been shown to be a potent antiproliferative and prodifferentiation mediator. One study involving children with ichthyosis showed improvement of skin with topical application of calcipotriene, a vitamin D analog. Their systemic vitamin D deficiencies, however, did not improve. Similarly, systemic medication that resolved vitamin D deficiencies did not improve skin findings. Measurement of 25-hydroxyvitamin D in individuals with ichthyosis would allow for identification and treatment of those at risk for vitamin D deficiency, preventing development of rickets, osteoporosis, or other conditions that may develop or worsen due to low vitamin D levels.

Diagnosis
The diagnosis of lamellar ichthyosis can be established by a thorough history and physical examination. Skin biopsy is not necessary to establish the diagnosis. Histologic findings in lamellar ichthyosis are nonspecific with massive compact hyperkeratosis covering an underlying acanthotic epidermis. The Ichthyosis Consensus Conference stated, “Diagnosis is based on dermatologic evaluation, careful family and medical history, and can be strongly supported by directed morphologic examinations and other special analyses. If available, molecular analyses are suggested to confirm diagnosis, and allow for testing of family members and prenatal diagnosis.”

Management
Bathing is recommended at least once daily. Exfoliation should be done after soaking with sponge, microfiber cloth, or pumice stone. Propylene glycol, vitamin E, and glycerol are emollients that should be reapplied throughout the course of the day. Pure sodium bicarbonate has been successfully used as a bath additive to mechanically remove scale. During the neonatal period, temperature, fluids, and electrolytes need to be regulated. Risk of infection needs to be closely monitored. Environment needs to provide humidity/moisture. Urea cream is commonly avoided in neonates. Dexpanthenol 5% is an alternative to urea that is safe to use during infancy. Salicylic acid is contraindicated in neonates or infants.

In children and adults, keratolytic agents such as urea, lactic acid, salicylic acid, and alpha-hydroxy acid may help thin the stratum corneum and induce peeling. Topical or oral retinoid therapy is recommended for those with severe skin involvement. Acitretin is efficacious, especially in lamellar ichthyosis and congenital ichthyosiform erythroderma. Isotretinoin may be preferred in female patients due to shorter duration of teratogenicity risk after taking the medication.

For individuals with ectropion, prevention of corneal dessication is through use of lubrication with artificial tears or prescription ophthalmic ointments.

An up and coming treatment is the new class of retinoic acid metabolism-blocking agents, otherwise known as RABAs. This class of medications inhibits catabolism of endogenous all-trans-retinoic acid. The pharmacokinetic profile is promising as the effects of retinoic acid on epidermal growth and differentiation are indirectly achieved and with better
tissue specificity. Therefore, the retinoic acid metabolism-blocking agents offer the possibility of reduced side effects and reduced potential for teratogenicity when compared with synthetic retinoids. 10 A recent phase II/III, randomized, double-blind, controlled study indicated that liarozole at a daily dose of 150mg is equally effective as treatment with acitretin. In a study involving a patient with lamellar ichthyosis treated with liarozole 150mg daily, significant reduction in scale was noted. Liarozole has been granted orphan drug status for the treatment of congenital ichthyosis by the European Medicines Agency and the US FDA. 9 Such drugs as liarozole may become the treatment of choice for cases of ichthyosis that warrant systemic therapy.

Another medication of interest is the compounded combination of topical 10% N-acetylcysteine and 5% urea emulsion. A report of five children with lamellar ichthyosis being treated with this medication describes marked overall improvement in the appearance of their skin with noteworthy reduction of scale. N-acetylcysteine has been shown to inhibit the proliferation of keratinocytes, and when combined with a commonly used keratolytic such as urea, significant benefit was noted with effectiveness that was greater than that seen with each entity separately. The emulsion was applied twice daily for 6 weeks and then continued once daily. The drug was well tolerated, efficacious, and safe. 11

Genetic counseling should be offered to affected individuals and their families. The comprehension of their condition is a central part of their care and should be a standard in the management of such conditions. Genetic testing and counseling enables patients to seek answers to their many questions regarding the nature of the disorder, inheritance pattern, and probability of affected family members or offspring. 4 Further information can be found at the Gene Tests Clinic Directory website, www.ncbi.nlm.nih.gov/sites/GeneTests/clinic. 3 The Gene Tests Clinic Directory is a voluntary list of United States and international genetics clinics.

Additional Concerns and Patient Resources

Social and psychological support for the management of such chronic skin diseases is a crucial entity of care. The negative impact on the quality of life is immense. The burden of daily skin care alone is significantly cumbersome and laborious. Patients commonly spend hours caring for their skin, with little to no visible improvement. Furthermore, patients commonly suffer from severe psychological stress and depression. In many cases, parents are hesitant or fearful to touch their children, depriving them of the need for human touch and emotional connection. Later in life, affected individuals experience constant ridicule and mockery. They have difficulty finding a life partner. 10 This social stigmatization is endless and only deepens their insecurity and prevents their acceptance of themselves. In certain areas of the world, families believe socialization of their affected child will result in severe castigation for the whole family. Affected individuals are treated as outcasts and marriage is not acceptable due to poor genetics. A case report of two sisters with lamellar ichthyosis from sub-Saharan Africa discusses the isolation that individuals with such conditions endure. The girls in this report were removed from society, denied an education, and medical treatment was withheld. 11

Affected individuals and their families should be guided to educational and supportive groups such as FIRST, Foundation for Ichthyosis and Related Skin Types. The FIRST Skin Foundation states, “Our mission is to educate, inspire, and connect those touched by ichthyosis and related disorders through emotional support, information, advocacy, and research funding for better treatments and eventual cures. Governed by a Board of Directors and guided by a Medical & Scientific Advisory Board, FIRST provides accurate and timely information to meet the medical, social, and educational needs of our community.” Patients should also be encouraged to review and enroll in the National Registry for Ichthyosis and Related Disorders. This source was created to encourage research into the diagnosis and treatment of the ichthyosis and remains a resource for investigators. Information regarding the FIRST Skin Foundation and the National Registry for Ichthyosis and Related Disorders can be found at http://www.firstskinfoundation.org.

Conclusion

Classic lamellar ichthyosis is most notably due to mutations in the transglutaminase-1 gene. This is most likely the situation in this case we report. TGM1 is crucial for the formation of the cornified cell envelope, which provides the barrier function of the skin. Current treatment is symptomatic and is largely directed towards improving the appearance of the skin by reducing scaling. This, however, defeats the body’s natural protective compensatory for a defective stratum corneum. Furthermore, due to the dysfunctional barrier, there is an increased risk for systemic absorption and toxicity, especially during infancy. Significant research of the underlying genetic and biochemical mechanisms has lead to a greater understanding of this disease, furthering the progress and development of more targeted therapies. 12

The website www.clinicaltrials.gov is a database of registries and results of publicly and privately supported clinical studies. This service is provided by the U.S. National Institutes of Health. This can provide access to information on clinical studies and trials for this particular disorder.

References


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

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

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

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

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

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

1. According to IMS NPATM (National Prescription Audit) July 2010-August 2013

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For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravaginal Use
Rx only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
FINACEA® Gel is indicated for topical treatment of the 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.

5 WARNINGS AND PRECAUTIONS
5.1 Skin Reactions
Skin irritation (i.e., pruritus, burning or stinging) may occur during use of FINACEA Gel, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and persists, discontinue treatment and institute appropriate therapy. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, monitor these patients for early signs of hypopigmentation.

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two vehicle-controlled and one active-controlled U.S. clinical trials, treatment safety was monitored in 788 subjects who used twice-daily FINACEA Gel for 12 weeks (N=333) or 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks. In all three trials, the most common treatment-related adverse events were: burning/stinging/tingling (39%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). In the active-controlled trial, overall adverse reactions (including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness) were 19.4% (24/124) for FINACEA Gel compared to 7.1% (9/127) for the active comparator gel at 15 weeks.

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

<table>
<thead>
<tr>
<th></th>
<th>FINACEA Gel, 15%</th>
<th>Vehicle Gel, 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=457 (100%)</td>
<td>N=331 (100%)</td>
</tr>
<tr>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Burning/ stinging/ tingling</td>
<td>n=99 (22%)</td>
<td>n=61 (13%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>71 (16%)</td>
<td>42 (9%)</td>
</tr>
<tr>
<td>Scaling/ dry skin/ xerosis</td>
<td>29 (6%)</td>
<td>18 (4%)</td>
</tr>
<tr>
<td>Erythema/ irritation</td>
<td>21 (5%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>6 (1%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Edema</td>
<td>5 (&lt;1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Eyes: iridocyclitis upon accidental exposure of the eyes to FINACEA Gel

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. Therefore, FINACEA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15% gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose (MRHD) based on body surface area (BSA)); rabbits given 150 or 500 mg/kg/day (19 or 65 times the MRHD based on BSA) and cynomolgus monkeys given 500 mg/kg/day (65 times the MRHD based on BSA) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys. An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose of 2500 mg/kg/day (162 times the MRHD based on BSA) that generated some maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual maturation of the fetuses were noted in this study.

8.3 Nursing Mothers
It is not known whether azelaic acid is excreted in human milk. However, in vitro studies using equilibrium dialysis were conducted to assess the potential for human milk partitioning. The studies demonstrated that, at an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0. These data indicate that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of 20% azelaic acid cream 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. Nevertheless, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

17 PATIENT COUNSELING INFORMATION
Inform patients using FINACEA Gel of the following information and instructions:

Use only as directed by your physician.

• For external use only.
• Before applying FINACEA Gel, cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel.
• Avoid use of alcoholics cleansers, tinctures and astringents, abrasives and peeling agents.
• Avoid contact with the eyes, mouth and other mucous membranes. If FINACEA Gel does come in contact with the eyes, wash the eyes with large amounts of water and consult your physician if eye irritation persists.
• Wash hands immediately following application of FINACEA Gel.
• Cosmetics may be applied after the application of FINACEA Gel has dried.
• Avoid the use of occlusive dressings or wrappings.
• Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, usually during the first few weeks of treatment. If irritation is excessive or persists, discontinue use and consult your physician.
• Report abnormal changes in skin color to your physician.
• To help manage rosacea, avoid any triggers that may provoke erythema, flushing, and blotching. These triggers can include spicy and thermally hot food and drinks such as hot coffee, tea, or alcoholic beverages.

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