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DERMATOLOGY for the CLINICIAN

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The International Academy
of Cosmetic Dermatology

The History
of Dermatology Society



The Section on Dermatology
College of Physicians of Philadelphia



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1 Draelos, Z., The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars, *Cosmetic Dermatology*, June 2008.
2 IMS Health, NDTI, December 2008. 3 Pharmacy Times, OTC Guide, June 2010.

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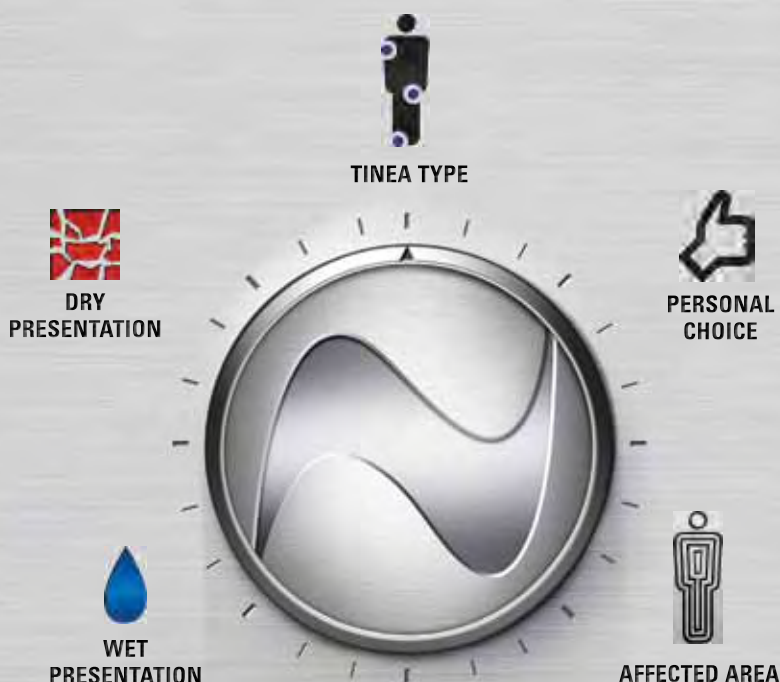
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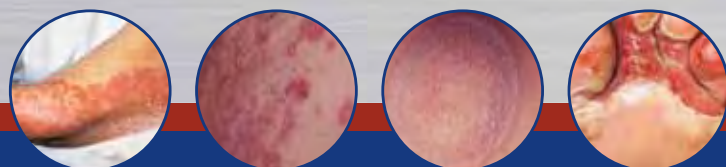


For your patients with tinea pedis, tinea cruris, and tinea corporis

Fine-tune their tinea treatment

For the fungicidal power you trust, turn to Naftin® (naftifine HCl 1%).

Designed to suit a range of patients and preferences, Naftin® delivers power against tinea pedis, cruris and corporis. Choose Naftin® Gel, Naftin® Cream, or the innovative Naftin® Cream Pump and give your patients the customized care they deserve.



Naftin® (naftifine HCl 1%) Cream and Gel are indicated for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Trichophyton tonsurans* (Gel only).

Naftin® Cream and Gel are contraindicated in individuals who have shown hypersensitivity to any of their components and are for topical use only.

During clinical trials with Naftin® Cream and Gel, the following side effects were most commonly reported: burning/stinging, dryness, erythema, itching, local irritation, skin tenderness and rash.

Please see brief summary on the following page.



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BRIEF SUMMARY
Rx ONLY
gel cream

INDICATIONS AND USAGE: Naftin® Cream, 1% is indicated for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Naftin® Gel, 1% is indicated for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans**, *Epidermophyton floccosum**. *Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS: Naftin® Cream and Gel, 1% are contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS: Naftin® Cream and Gel, 1% are for topical use only and not for ophthalmic use.

PRECAUTIONS: General: Naftin® Cream and Gel, 1%, are for external use only. If irritation or sensitivity develops with the use of Naftin® Cream or Gel, 1%, treatment should be discontinued and appropriate therapy instituted. Diagnosis of the disease should be confirmed either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Information for patients: The patient should be told to:

1. Avoid the use of occlusive dressings or wrappings unless otherwise directed by the physician.
2. Keep Naftin® Cream and Gel, 1% away from the eyes, nose, mouth and other mucous membranes.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies to evaluate the carcinogenic potential of Naftin® Cream and Gel, 1% have not been performed. *In vitro* and animal studies have not demonstrated any mutagenic effect or effect on fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits (via oral administration) at doses 150 times or more than the topical human dose and have revealed no evidence of impaired fertility or harm to the fetus due to naftifine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Naftin® Cream or Gel, 1% are administered to a nursing woman.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: During clinical trials with Naftin® Cream, 1%, the incidence of adverse reactions was as follows: burning/stinging (6%), dryness (3%) erythema (2%), itching (2%), local irritation (2%). During clinical trials with Naftin® Gel, 1%, the incidence of adverse reactions was as follows: burning/stinging (5.0%), itching (1.0%), erythema (0.5%), rash (0.5%), skin tenderness (0.5%).

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EDITORIAL

J. Graham Smith Jr, MD
(November 22, 1926–May 18, 2010)

Lawrence Charles Parish, MD, MD (Hon)

**Figure 1.** J. Graham Smith Jr, in a recent photograph.

With the passing of J. Graham Smith Jr, on May 18, 2010, following a short illness, dermatology lost one of its most distinguished envoys (Figure 1). Skee*, as he was known by his many friends, held the important offices in American dermatology for which he made many significant contributions.

BACKGROUND

Skee was born in Winston-Salem, North Carolina, on November 22, 1926. After he received his MD degree from Duke Uni-

versity School of Medicine in 1951, he interned at the Veterans Administration Hospital in Chamblee, Georgia, following which he spent his first 2 years of dermatology training under J. Lamar Callaway at Duke. He then moved to the new University of Miami School of Medicine, under Harvey Blank, for his third year. He remained at Miami and Jackson Memorial Hospital for an additional 3 years, rising to the rank of assistant professor.

From 1960–1967 he was at Duke as associate professor and then full professor. In 1967, he was invited to organize the Department of Dermatology at the Medical College of Georgia in Augusta, a post he held for the next 24 years. In 1991, he moved to Mobile, Alabama, to chair the Division of Dermatology at the University of South Alabama in Mobile from 1991–1998, then becoming professor emeritus. After retiring from his academic chores, he maintained a private practice in Mobile at the Diagnostic and Medical Clinic through December 2009.

His research interests ranged from actinic elastosis to pseudo-xanthoma elasticum. He helped to delineate the amino acid make up of elastin. His inaugural presentation at the American Dermatological Association meeting at The Homestead, Hot Springs, VA, in 1963 was on “The Dermal Elastoses” and caused the late Morris Waisman to remark:

Four years ago Dr. Smith delivered before this association the award-winning essay on the aging sebaceous gland. In this paper we have just heard, the same excellent standards of scholarship are reflected.¹

His pension for dermatopharmacology led him to publish on acne treatments from retinoids to topical tetracycline and benzyl peroxide preparations, as well as on antifungal agents and topical triamcinolone. He had worked on the initial clinical trials of griseofulvin with Harvey Blank. Skee was among the first to recognize the dangers of hepatitis B infections in dermatology, and he was an early proponent for dermatologists to wear protective gloves.²

From the Departments of Dermatology and Cutaneous Biology, Jefferson Center for International Dermatology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

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ACCOMPLISHMENTS

In our specialty, Skee held the presidency of the American Academy of Dermatology (AAD), the American Dermatological Association, and the American Board of Dermatology, serving on the board from 1974–1984. His other leadership posts included the Society for Investigative Dermatology, the Association of Professors of Dermatology, the Section of Dermatology of the Southern Medical Association, and the Section of Dermatology of the American Medical Association, making him unique in holding the highest office of the leading dermatologic societies.

Skee always had a bent for medical journalism. As the founding editor of the *Journal of the American Academy of Dermatology* in 1979, he set the high standards for which the publication has been known, serving as Editor in Chief for a decade.³ He later became Editor in Chief of the *Southern Medical Journal*, for which he wrote pithy editorials, including *Darwinian (Evolutionary) Medicine*⁴ and *Do Patients Listen?*⁵ He also served on the editorial board of the *Archives of Dermatology*, *Journal of Investigative Dermatology*, *Journal of the American Medical Association*, and *Cutis*. Skee was among the first to accept an appointment to *SKINmed*, and his comments and recommendations were always valued. He regularly attended the annual meetings of the Council of Dermatology Editors.

His many honors included the Distinguished Service Award of the Southern Medical Association in 2005 and the Gold Medal from the AAD in 2009, as well as Honorary Membership in 1997 and Master Dermatologist recognition in 2003. He was elected to Honorary Membership of the American Dermatological Association in 1996. Skee was a recipient of the Samuel J. Zakon Lectureship of the History of Dermatology Society in 1997 for his presentation “A Fifty-Year Potpourri” (Figure 2). This was actually his second Zakon presentation, for in 1981, when the late David Williams became ill, Skee read his presentation, entitled: “De mortuis nil nissi bonum.” An additional honor was the Lifetime Achievement Award of the Alabama Dermatology Society.

ANECDOTES

Skee was an ambassador par excellence. He loved to travel and lecture around the world to numerous scientific congresses. Planning for trips was not always that simple in academia. At the Medical College of Georgia, he applied for permission to participate in meetings in Cairo, Rome, and Athens. He was told by the dean's office that it was unnecessary to leave Georgia to visit these cities (LEM).

Skee and Jean Butler Smith, his wife of 60 years, often attended the annual meetings of the British Association of Dermatologists. One July, Dick and Marie Dobson joined them. The foursome boarded the train for Nottingham at St Pancras Station in London, the many pieces of luggage in tow. About an hour and a half out of London they saw that many people were preparing to debark at the next sta-



Figure 2. Skee giving the Zakon Lecture.

tion and so they joined in, only this was not Nottingham. Within minutes, a kind soul came to their rescue at Loughborough and drove the quartet some 20 miles to Nottingham (RLD).

On one of the trips in the mid-1980s to the Zagazig Conference on Dermatology and Venereology, Skee decided that this must be a Smith family reunion. Although Edgar Ben Smith, then of Albuquerque, New Mexico, and Lowell Goldsmith, then of Rochester, New York, had “Smith” in their names, they were not blood relatives (LEM).

In the early 1970s, Skee served on the General Medicine Study Section of the National Institutes of Health, along with Dick Dobson and Wilt Fisher. Because some of the grant applications needed significant revisions, the three decided to call upon several of the young investigators. After a day's work, they would have dinner, and they usually ordered a dry Beefeater martini, up. Dick asked Skee to think of a name for the drink. In a few minutes, he announced the cocktail to be a Dobson. The name spread rapidly, for Dick was on the West Coast months later and ordered his usual, which can be a mouthful, and the barmaid called out, “You mean a Dobson” (RLD).

Skee might be considered the perfect example of the type A personality. In 1975, when the AAD hired its first executive director, the officers suggested that he visit several promising candidates for future Academy leadership positions. Years later, Skee inquired who had been the first to be interviewed. When he learned that it was he, indeed, the first to receive such a visit, he remarked, “See, Claxton knew even then that I was the most important” (BWC).

As founding editor of the *Journal of the American Academy of Dermatology*, he was instrumental in the design of the publication. He chose the blue colors, for which the journal is now known, as they were the colors of Duke, his alma mater, and of whose basketball team he was an avid fan (JHE).

Matching colors was not one of his strong points. Skee was colorblind and could not choose ties, shirts, and suits that were necessarily compatible. The chore of sartorial compatibility fell to Jean (LCP). There is an apocryphal story that a resident once mixed up what Jean had organized, but no one that day noticed anything askew (LEM).

HIS LEGACY

Jean, their 3 children, 7 grandchildren, and 2 great-grandchildren, survive Skee, along with a younger brother. His legacy to dermatology will long continue.

**As an infant, J. Graham Smith Jr, was given the nickname of Skee-ball, and the name Skee stuck with him from then on.*

Acknowledgments: Bradford W. Claxton, CAE (BWC); Richard L.

Dobson, MD (RLD); John H. Epstein, MD (JHE); W. Clark Lambert, MD; Larry E. Millikan, MD (LEM); Grant B. Smith, JD; and Mickey Smith contributed to this essay.

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HISTORICAL DIAGNOSIS & TREATMENT

Diagnosis and treatments have advanced over the past century. This feature depicts conditions from a collection of stereoptic cards published in 1910 by The Stereoscopic Skin Clinic, by Dr. S. I. Rainforth.



Pityriasis Versicolor



Copyright 1910 By Dr S I Rainforth N.Y.

TREATMENT: The patient should bathe daily and scrub the affected parts with soap and warm water and then apply a 25 per cent solution of sodium hyposulphite. The spots disappear in a few days, but the treatment is to be continued for some time, as the disease is very prone to recur.

Once-daily application in the evening



VELTIN Gel

- Combines the acne-fighting properties of tretinoin and clindamycin
- Contains tretinoin, solubilized in an aqueous-based gel
- Combats inflammatory and noninflammatory acne

Important Safety Information for VELTIN Gel

- VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
- Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea occurs. Severe colitis has occurred following oral or parenteral clindamycin administration. Severe colitis may result in death
- Avoid exposure to sunlight and sunlamps when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Daily use of sunscreen products and protective apparel are recommended. Weather extremes (eg, wind and cold) also may be irritating to patients using VELTIN Gel
- Observed local treatment-related adverse reactions ($\geq 1\%$) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased
- VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component
- Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. VELTIN Gel should be used with caution in patients receiving such agents
- VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- It is not known whether either clindamycin or tretinoin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Due to possible serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug. Exercise caution if administering VELTIN Gel to a nursing woman
- The efficacy and safety have not been established in pediatric patients below the age of 12 years
- VELTIN Gel is not for oral, ophthalmic, or intravaginal use

Please see brief summary of Prescribing Information on the next page.


veltin[™]
(clindamycin phosphate and
tretinoin) Gel 1.2%/0.025%

BRIEF SUMMARY

VELTIN™ (clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

VELTIN Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

4 CONTRAINDICATIONS

VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

5 WARNINGS AND PRECAUTIONS

5.1 Colitis

Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. If significant diarrhea occurs, VELTIN 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.

5.2 Ultraviolet Light and Environmental Exposure

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

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Studies

The safety data reflect exposure to VELTIN Gel in 1,104 patients with acne vulgaris. Patients were 12 years or older and were treated once daily in the evening for 12 weeks. Observed local treatment-related adverse reactions ($\geq 1\%$) in clinical studies with VELTIN Gel were application site reactions, including dryness (6%), irritation (5%), exfoliation (5%), erythema (4%), pruritus (2%), and dermatitis (1%). Sunburn (1%) was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased.

Local skin reactions were actively assessed at baseline and at the end of 12 weeks of treatment in patients exposed to VELTIN Gel. At baseline (N=476), local skin reactions included erythema (24%), scaling (8%), dryness (11%), burning (8%), and itching (17%). At 12 weeks of treatment (N=409), local skin reactions included erythema (21%), scaling (19%), dryness (22%), burning (13%), and itching (15%). During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter.

7 DRUG INTERACTIONS

7.1 Erythromycin

VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component. *In vitro* studies have shown antagonism between these 2 antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

7.2 Neuromuscular Blocking Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women treated with VELTIN Gel. VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A limit teratology study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 2 mL/kg during gestation days 6 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and heart abnormalities were described in drug-treated groups. These abnormalities are consistent with retinoid effects and occurred at 16 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison. For purposes of comparison of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of VELTIN Gel applied daily to a 50 kg person.

Tretinoin: Oral tretinoin has been shown to be teratogenic in mice, rats, hamsters, rabbits, and primates. It was teratogenic and fetotoxic in Wistar rats when given orally at doses greater than 1 mg/kg/day (32 times the recommended clinical dose based on body surface area comparison). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, a species in which tretinoin metabolism is closer to humans than in other species examined, fetal malformations were reported at oral doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (324 times the recommended clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related teratogenic effects and increased abortion rates were reported in pigtail macaques.

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 fetus is not known.

8.3 Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of VELTIN 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 VELTIN Gel is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of VELTIN Gel in pediatric patients below the age of 12 years have not been established. Clinical trials of VELTIN Gel included 2,086 patients 12-17 years of age with acne vulgaris. [See Clinical Studies (14) of full prescribing information.]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of VELTIN Gel or the effect of VELTIN Gel on fertility. VELTIN Gel was negative for mutagenic potential when evaluated in an *in vitro* Ames *Salmonella* reversion assay. VELTIN Gel was equivocal for clastogenic potential in the absence of metabolic activation when tested in an *in vitro* chromosomal aberration assay.

Clindamycin: Once daily dermal administration of 1% clindamycin as clindamycin phosphate in the VELTIN Gel vehicle (32 mg/kg/day, 13 times the recommended clinical dose based on body surface area comparison) to mice for up to 2 years did not produce evidence of tumorigenicity.

Tretinoin: In two independent mouse studies where tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years no carcinogenicity was observed, with maximum effects of dermal amyloidosis. However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 µg (1.4 times the recommended clinical dose based on body surface area comparison) three times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenz[*a*]anthracene (DMBA).

In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoyl-phorbol 13-acetate or mezerein for up to 20 weeks. Topical application of tretinoin prior to each application of promoting agent resulted in a reduction in the number of papillomas per mouse. However, papillomas resistant to topical tretinoin suppression were at higher risk for pre-malignant progression.

Tretinoin has been shown to enhance photocarcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photocarcinogenic potential of the clindamycin tretinoin combination is unknown. Although the significance of these studies to humans is not clear, patients should avoid exposure to sun.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling.]

17.1 Instructions for Use

- At bedtime, the face should be gently washed with a mild soap and water. After patting the skin dry, apply VELTIN Gel as a thin layer over the entire affected area (excluding the eyes and lips).
- Patients should be advised not to use more than a pea sized amount to cover the face and not to apply more often than once daily (at bedtime) as this will not make for faster results and may increase irritation.
- A sunscreen should be applied every morning and reapplied over the course of the day as needed. Patients should be advised to avoid exposure to sunlight, sunlamp, ultraviolet light, and other medicines that may increase sensitivity to sunlight.
- Other topical products with a strong drying effect, such as abrasive soaps or cleansers, may cause an increase in skin irritation with VELTIN Gel.

17.2 Skin Irritation

VELTIN Gel may cause irritation such as erythema, scaling, itching, burning, or stinging.

17.3 Colitis

In the event a patient treated with VELTIN Gel experiences severe diarrhea or gastrointestinal discomfort, VELTIN Gel should be discontinued and a physician should be contacted.

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VEL:2BR5

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ORIGINAL CONTRIBUTION

Study of the Dermatoscopic Pattern of Tinea Nigra: Report of 6 Cases

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ABSTRACT

Digital dermatoscopy, a noninvasive auxiliary method that can improve the diagnosis of nearly all pigment skin lesions, was used to study 6 cases of tinea nigra, a rare dematiaceous superficial fungal infection and a potential mimicker of melanocytic nevus. Patients were first evaluated by a manual dermatoscope using a 10-fold magnification. The same patients were then reevaluated using a digital dermatoscope with 20-, 50-, and 70-fold magnifications. Direct mycologic examination and culture supported the establishment of the etiologic diagnosis. All reported cases showed a single dermatoscopic pattern. Manual and digital dermatoscopic images revealed irregularly distributed dark brown–pigmented dot lesions with filamentous aspect. The authors could not observe any melanocytic lesions. Cutaneous pigmented lesions, including superficial spreading melanoma, are the differential diagnosis. The dermatoscopic images are useful to help distinguish tinea nigra from other melanocytic diseases. (*SKINmed*. 2010;8:319–321)

Dermatoscopy is a noninvasive auxiliary method that can improve the diagnosis of nearly all pigmented skin lesions. It consists of a technique that makes it possible to obtain a better overview of the structures presented in the papillary dermis and in the epidermal-dermal junction. The manual dermatoscopes provide a 10- to 30-fold amplification, while the digital ones provide a 20- to 70-fold amplification.^{1–4}

We used digital dermatoscopy to study 6 cases of tinea nigra, a rare dematiaceous superficial fungal infection and a potential mimicker of melanocytic lesions.^{5–8} A single dermatoscopic pattern was observed in all reported cases.

MATERIALS AND METHODS

We evaluated 6 cases of suspected diagnosis of tinea nigra. Five patients were female, aged between 2 and 13 years. There was also a 5-year-old male patient. The clinical examination showed dark brown hyperpigmented maculae, with an average size of 2 centimeters and an irregular shape, located on the left palm (3 cases) (Figure 1), on the right palm (2 cases), and on the right fourth finger (1 case).

Patients were first evaluated by a manual dermatoscope (Heine mini 2000, Heine, Herrsching, Germany) with a 10-fold magnification. Subsequently, we reevaluated the patients using a

digital dermatoscope (FotoFinder Dermatoscope, TeachScreen Software, Bad Birnbach, Germany) with 20-, 50- and 70-fold magnifications (Figure 2 and Figure 3).

Between the skin and the dermatoscope, we utilized an alcohol gel immersion as the liquid medium. Direct mycologic examination, with clarification using a 20% potassium hydroxide solution, and culture on Saboraud glucose agar medium confirmed the etiologic diagnosis.

RESULTS

Manual and digital dermatoscope visualization revealed irregularly distributed dark brown–pigmented lesions, with filamentous aspect formed by dots and traces. There were no dermatoscopic melanocytic lesion features (pigmented network, globules, and streaming), as well as the characteristic parallel streaks found in melanocytic lesions located in acral skin. Direct mycologic examination confirmed the diagnosis, presenting dematiaceous septate hyphae. The culture on Saboraud glucose agar revealed growth of *Phaeoannellomyces werneckii*.

DISCUSSION

Tinea nigra is an uncommon dermatosis, first described in 1891 by Alexandre Cerqueira. It is easily treated by topical antifungals^{5,6,9} and

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Figure 1. Brown macula localized on the left palm.



Figure 2. Digital dermatoscopic image (20-fold magnification). The manual dermatoscopy displayed similar features.

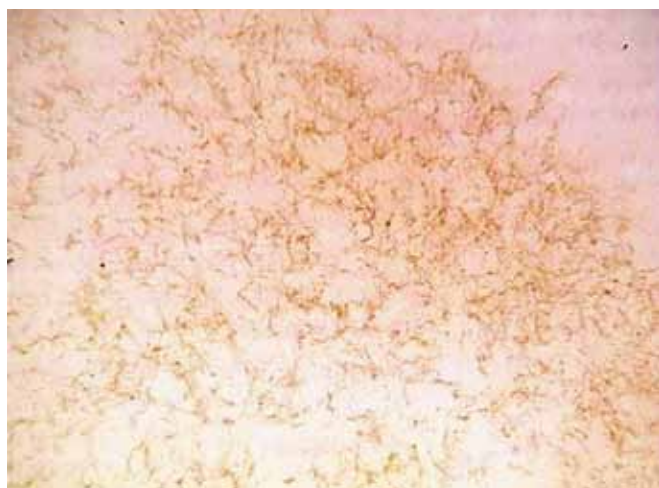


Figure 3. A 70-fold magnification showing traces and dots with a filamentous aspect.

is commonly found in tropical and subtropical areas of the world (South America, Central America, Asia, and Africa). This skin disease is clinically characterized by a small oval brown to black macula.⁵⁻⁹

Laboratory diagnosis consists in the identification of dematiaceous septate hyphae by direct examination, clarified with a 10% to 30% potassium hydroxide solution. The width of dematiaceous hyphae is 5 μ m or more. The hyphae are irregular, tortuous, and closely interlaced. Their color ranges from the yellow to yellowish brown, and melanin is the hyphae's main pigment.⁵⁻⁹

The differential diagnosis of tinea nigra includes superficial spreading melanoma, melanocytic nevi, lentigo simplex, pigmented actinic keratosis, pigmented basal cell carcinoma, post-inflammatory pigmentation, and photodermatitis.⁵⁻⁹ Dermatoscopy has proved to be very valuable in the diagnosis of these pigmented skin lesions. The analysis of images obtained by a dermatoscope allows the differentiation between melanocytic and nonmelanocytic lesions by recognizing specific structures (Table).^{3,4,10-12}

The traces and dots observed in dermatoscopic visualization of tinea nigra have a peculiar homogeneous and filamentous appearance, contrasting with the pigmented network of melanocytic nevus.

Tinea nigra is usually found on palms and the plantar surface of the feet. These regions have a specific dermatoscopic pattern for melanocytic nevus due to peculiar volar aspect (melanocytic nevus is often noted as parallel pigmented lines by dermatoscopy, corresponding to furrows of the skin markings).¹³ In tinea nigra, pigment pattern does not follow the dermatoglyphic lines of the plantar surface, suggesting pigmented cells within the stratum corneum.¹⁴

Dermatoscopic features of tinea nigra were first described in 1997 as regularly distributed pigmented spicules.¹⁵ Another article reported a homogeneous pigment pattern and emphasized that pigment did not follow dermatoglyphic lines, similar to a pseudonetwork feature.¹⁴ We could observe traces, fine lines, and dots creating a homogeneous filamentous pseudonetwork pattern.

Our results strongly suggest that it is possible to establish a preliminary dermatoscopic pattern of tinea nigra that consists of irregular dark brown filamentous structures, associated with dots of the same color, not in accordance with the dermatoglyphic lines.

CONCLUSIONS

The specialized dermatologist must be aware of this new dermatoscopic pattern and recognize (or suspect) tinea nigra in case it clinically mimics other melanocytic diseases. The usual laboratory examinations (direct examination and culture) should be recommended. We assume that the study of a larger number of cases would allow us to demonstrate a typical pattern for tinea nigra and to include this superficial fungal infection in the list of indications for dermatoscopy.

Table. Dermatoscopic Features of Melanocytic and Nonmelanocytic Lesions

MELANOCYTIC LESIONS	NONMELANOCYTIC LESIONS
Pigmented network	Homogeneous blue/gray pigmentation
Globules	Crypts
Striae	Follicular plugs
	Vacuolar pattern
	Telangiectasis

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REVIEW

Eponyms in Leprology

Khalid Al Aboud, MD

ABSTRACT

Leprology is the medical science that focuses on the study of leprosy. There are several eponymic terms that are in common use in leprology, and this paper sheds some light on these eponyms. (*SKINmed.* 2010;8:323–326)

Many eponymic terms are used in medicine, particularly leprology. Leprosy, otherwise known as Hansen disease, is a chronic disease caused by *Mycobacterium leprae*. It was extremely widespread for at least 4000 years and continues to pose a significant health problem in many parts of the world.^{1,2}

The Table shows the most common eponymic terms used in leprosy.² The name of the disease “leprosy” in itself is not used by many patients and practitioners, as it continues to carry an age-old stigma; moreover, many other conditions, including syphilis, psoriasis, and yaws, were historically mistaken as leprosy. The eponymic and emotionally neutral term *Hansen disease*, after Hansen (Figure 1), who first described the causative microbe of leprosy, is therefore often preferred.

In the 1830s, there was a significant increase in the incidence of leprosy in Norway and Iceland. Although widely considered to be of hereditary or miasmatic origin at the time, the Norwegian government invested in medical research for the treatment of the condition. In 1868, a young physician, Gerhard Henrik Armauer Hansen (1841–1912) returned to his native Bergen to assist the noted leprosy specialist D.C. Danielssen at St. Jørgen's Hospital.³

Hansen began his work logically and methodically. The first step was clinical, establishing the criteria for leprosy as a specific disease. The second stage was epidemiologic. Contrary to the main view favoring a genetic basis, the observation of patients convinced him of the infectious nature of the disease. The third stage was the search for the agent.⁴ In 1871, Hansen began to observe tiny rods in tissue specimens and considered that they could be the etiologic agents of leprosy. It was not until he gave tissue samples to the German dermatologist Albert Neisser, however, that the rods were identified as bacilli, among the first bacteria identified as causing disease in humans.

There was considerable dispute between Hansen and Neisser as to who had made the definitive discovery. Neisser, however, was reviled in his native land as “dirtying” himself by treating venereal disease (he discovered the causative microorganism of gonorrhea). Hansen, on the other hand, was a national hero. (Ironically he suffered from syphilis himself.) When Hansen died on February 12, 1912, the funeral ceremony took place in the hospital, now a museum, where his ashes are still kept.³

In 1851, the Mexican dermatologist Rafael Lucio Nájera (Figure 2) (1819–1886) published *Opúsculo sobre el real de San Lázaro o elefantíasis de los griegos*, which described diffuse lepromatosis, a form of lepromatous leprosy. The condition is characterized by a generalized diffuse infiltration of the skin but without visible nodules; complete alopecia of the eyebrows, eyelashes, and body hair; and anhydrotic and dysesthetic zones of the skin. A possible and dangerous complication of the condition is necrotic erythema, which is the ulceration of vessels, especially of the dermohypodermic union and of the hypodermis,⁵ now known as Lucio's phenomenon.

Diffuse lepromatosis was common in Mexico (23%) and in Costa Rica but very rare in other countries. It was sometimes called *lepra bonita* or *manchada*. Lucio's work was republished by the Ministry of Economic Development in 1889 for an exhibition in Paris.⁶ Because of its geographic isolation, diffuse lepromatous leprosy received little attention until it was reidentified by Fernando Latapí in 1936.⁵ Latapí (1902–1989) was a Mexican physician who for half a century was considered the dean of Mexican leprologists. Diffuse lepromatous leprosy is now known as Lucio-Latapí leprosy.

The lepromin test is useful in determining the extent of host immune reactivity to *M leprae*. Injected intradermally is 0.1 mL of lepromin, prepared from a crude extract of organisms. When

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Figure 1. Photo of Gerhard Henrik Armauer Hansen, with permission, available online at <http://www.stanford.edu/class/humbio103/ParaSites2006/Leprosy/Historical.htm>.



Figure 2. Photo of Rafael Lucio Nájera, with permission, available online at <http://redescolar.ilce.edu.mx/redescolar/efemerides/septiembre2001/conme2a.htm>.

the lepromin test results are read at 48 hours, it is known as the Fernández reaction. José Maria Fernández, born in 1902, was a trailblazing Argentinean physician.⁷ Fernández was not only a pioneer, but he participated in the creation of the first continent-wide conference on leprosy in Havana (1948), which produced the South American Classification of Leprosy.⁷

The lepromin test can also be read at 3 to 4 weeks. In this case, it is called the Mitsuda reaction, after a Japanese physician, Dr

Kensuke Mitsuda. Dr Kensuke Mitsuda (Figure 3) (1876–1964) is known as the father of Hansen disease control in Japan.⁸ He developed the lepromin test originally to test for leprosy itself, but found it useful in determining the extent of host immune reactivity to *M leprae*. Mitsuda also found that the test showed immunologic distinction between tuberculoid and lepromatous types of leprosy.^{8,9} He reported his findings in 1923 but received little attention. Ten years later, Fumio Hyashi published a definitive paper on the lepromin test, which he called the Mitsuda reaction.

Table. Selected Eponymic Terms in Leprology

EPONYM	DESCRIPTION	YEAR
Hansen disease	Name given to leprosy after Hansen, who discovered <i>Mycobacterium leprae</i>	1873
Fite stain	Special stain to detect <i>M leprae</i> in the histopathology	1962–1965
Mitsuda reaction	Introducing the lepromin test (intradermal test)	1919
Lucio leprosy and Lucio phenomenon	Special form of lepromatous leprosy and its reaction	1852
Ridley-Jopling clinical classification of leprosy	Five-group classification of leprosy according to immunity (Ridley and Jopling, 1962 and 1964)	1966

In spite of these advances, Mitsuda was a controversial figure. He advocated the sterilization of leprosy patients and their strict segregation in society. Largely due to his influence, Japan was among the last nations to legally enforce isolation.

M leprae can be better visualized in the histopathology by using Fite stain. Dr George Liddle Fite (1904–1993) (Figure 4) was arguably the most important American figure in the fight against leprosy. At first working as an academic, teaching at Johns Hopkins University School of Medicine and Northwestern University and performing research at the Rockefeller Institute, he joined the Public Health Service in 1937. His first assignment was in Hawaii, where the health service operated a major leper colony. In 1941 he was transferred to Washington, where he researched leprosy at the National Institute of Health.¹⁰

The crowning achievement of a life devoted to the treatment of leprosy was as chief pathologist of the laboratory at the United States Leprosarium in Carville, Louisiana.¹⁰

There, working side by side with his wife, Carolyn, a laboratory assistant, and the pharmacologist Sister Hilary Ross, he developed Fite's stain, a diagnostic tool in identifying the organism that causes leprosy, which remains indispensable today.¹⁰

After his retirement from the Public Health Service, the talented Fite served as senior editor of the *Journal of the American Medical Association* for 10 years.¹¹ After a lifetime of work researching leprosy, Fite then developed another elusive disease: Alzheimer's. He was moved into Oak Manor nursing home, the only establishment of its kind in the area at the time. His wife, as devoted to the illness as she had been to his work, moved into a house across the street.¹⁰ George Liddle Fite died of pneumonia at the age of 89, and was buried at Arlington National Cemetery.¹⁰

In medical nomenclature in general and leprology in particular, some names become common parlance while others who have made important discoveries remain anonymous. For instance, why is erythema nodosum leprosum not called "Murata reaction" after Mosuke Murata who described this type of reaction in 1912? And why is histoid leprosy not called "Wade's leprosy" after H. W. Wade, who described this type in 1963?

There are both advantages and disadvantages in using eponymic terms.¹² The main drawback is that in using multiple names for a single entity it may be difficult to search and index papers in the medical literature. For example, a search of PubMed on June 4, 2010, resulted in only 21,387 citations for "leprosy," vs 25,374 citations for "Hansen's disease." Leprosy remains the preferred term at both the World Health Organization and the US Center for Disease Control.



Figure 3. Photo of Kensuke Mitsuda, with permission, available online at <http://www.cscd.osaka-u.ac.jp/user/rosaldo/040220shigellal.html>.



Figure 4. Photo of George Liddle Fite, with permission.¹⁰

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REVIEW

Use of Spironolactone in Dermatology

Deepani Rathnayake, MD;¹ Rodney Sinclair, MD²

ABSTRACT

Spironolactone has been used as a potassium-sparing diuretic for more than 30 years. It is a synthetic 17-lactone steroid and primarily acts as an aldosterone antagonist. Since the accidental discovery of its antiandrogenic effects, it has been used in the treatment of many dermatologic conditions in which androgen plays a role in the pathogenesis. Antiandrogenic effects of spironolactone are exerted by reducing testosterone production and inhibiting its action on the target tissues. Spironolactone is used as a primary medical treatment for hirsutism and female pattern hair loss. Continuous treatment is required to sustain the effect. It is an effective alternative treatment for acne in women. It has the benefit of a long-term safety profile. Spironolactone should not be used in pregnancy due to its teratogenic effects and is not used in men due to the risk of feminization. (*SKINmed*. 2010;8:328–332)

Spironolactone has been used as a potassium-sparing diuretic for more than 30 years in the treatment of heart failure, ascites in patients with liver disease, low-renin hypertension, hypokalemia, secondary hyperaldosteronism (such as that which occurs with hepatic cirrhosis), and Conn's syndrome (primary hyperaldosteronism). It is a synthetic 17-lactone steroid and primarily acts as an aldosterone antagonist. Spironolactone also reduces testosterone production and inhibits androgen action on the target tissues.

The antiandrogenic effects of spironolactone were serendipitously discovered when it was used to treat hypertension in women with incidental polycystic ovary syndrome (PCOS) and hirsutism.¹ While there is no US Food and Drug Administration–approved dermatologic indication for spironolactone, it is commonly used off-label for hirsutism, female pattern hair loss (FPHL), and acne in women. Continuous treatment is required to sustain the effect.

Spironolactone should not be used in pregnancy due to potential teratogenicity and is not used in men due to the risk of loss of libido, impotence, and gynecomastia. Spironolactone is a common component in hormone therapy for male to female transsexual and transgender people.

PHARMACOLOGY OF SPIRONOLACTONE

Spironolactone is a synthetic 17-lactone steroid that acts as a competitive antagonist to aldosterone. Spironolactone inhibits the effect of aldosterone by competing for intracellular aldoste-

rone receptors in the distal convoluted tubule cells. Its primary metabolite canrenone is the active antagonist of aldosterone and contributes to the diuretic action²

Antiandrogenic actions of spironolactone are exerted by decreasing the production and blocking the effect of androgens in the target tissues. Spironolactone decreases testosterone production in the adrenal gland by depleting microsomal cytochrome p450 and by affecting cytochrome P450–dependent enzymes 17 α -hydroxylase and desmolase. Spironolactone also is a competitive inhibitor of the androgen receptor and blocks the androgen action on the target tissues.³

The drug is available in 25-mg and 100-mg tablets. Doses of 25 mg to 300 mg a day are used in dermatology practice. It is rapidly absorbed and extensively metabolized in the liver. Topical application of spironolactone has shown limited antiandrogenic effects in small case series, but this was not confirmed in large case-control studies.⁴

Menstrual irregularities, breast enlargement and tenderness, and postmenopausal bleeding are common but usually mild side effects.^{5,6} Aside from this, spironolactone is generally well tolerated and has a well-established safety profile. Postural hypotension may occur, particularly when used in conjunction with other antihypertensive medications. Hyperkalemia is a potential serious side effect but rare in the presence of normal renal functions, even at a dosage of 200 mg a day. Concurrent use of drugs that can elevate serum potassium such as angiotensin-converting enzyme

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inhibitors or indomethacin are better avoided and patients should also be advised to minimize foods with high potassium levels. Reversible impairment of renal functions may develop when used together with nonsteroidal anti-inflammatory medications. Fatigue, lethargy, and body weakness can result from the diuretic effect. These side effects are dose dependent and rarely cause discontinuation of treatment. Carcinoma of the breast has been reported in patients taking spironolactone, but a cause and effect has not been established.⁷ A past or family history of breast cancer is not a contraindication for its use.

Spironolactone is a category D drug in pregnancy. It may cause feminization of male fetuses. The risk of masculinization of the male fetus will only occur from about 6 weeks postconception onwards. Hence, if inadvertent spironolactone administration is stopped at an early stage, the risk to the male fetus is small. Small amounts of canrenone, the active metabolite of spironolactone, is excreted in breast milk and is best avoided during breast feeding.

SPIRONOLACTONE IN DERMATOLOGY

ACNE

Acne pathogenesis involves seborrhea, comedo formation, colonization of the duct with *Propionibacterium acnes*, and inflammation. Seborrhea, or greasy skin, is a result of increased sebum secretion from the active sebaceous glands and is predominantly dependent on the androgenic sex hormones.⁸ High levels of sebum production can result from either increased androgen availability or increased sensitivity of sebaceous glands to androgen. Testosterone is the main circulating androgen and it is converted to more active dihydrotestosterone (DHT) within the pilosebaceous unit by 5 α reductase enzyme. Different studies in women have found either normal levels of serum testosterone⁹ or elevated levels.¹⁰ Androgen receptor activation in sebaceous glands may be more influenced by local production and metabolism of androgens and less dependent on serum hormonal levels.¹¹ Individual follicles vary in their response to androgens and sebum excretion, explaining why some follicles are more prone to acne.¹²

Patients with hormone-related acne present with cyclic acne with premenstrual flare or late-onset adult acne. There may be associated menstrual irregularities, hirsutism, or androgenic alopecia (AGA). Investigations for underlying endocrine disorder should be considered in patients with other manifestations of virilization.

Acne patients experience embarrassment, social anxiety, lack of confidence, and reduced prospects of employment.¹³ Several topical and systemic treatments are available. Antiseptics and antibiotics with anti-inflammatory effects are considered first-line treatment and are particularly useful for papulopustular acne. Oral isotretinoin is the most effective treatment and is useful

in severe refractory acne with risk of scarring; however, the risk of teratogenicity and mucocutaneous side effects limit its use. Spironolactone is useful as a monotherapy in women with cyclic or late-onset acne. Many such women may have relapse following a course of oral retinoids. Spironolactone is also useful as an adjunctive treatment in combination with antibiotics when oral retinoids are not appropriate. While similar results may be achieved with oral contraceptive pills containing cyproterone acetate (CPA) or drospirenone, spironolactone is particularly useful for women who develop chloasma or simply prefer not to take these agents.

A randomized, placebo-controlled, double-blind study demonstrated significant improvement of acne with spironolactone 200 mg daily.¹⁴ Adult women who respond poorly to standard therapy show significant improvement with low doses of spironolactone (50–100 mg),¹⁵ and long-term administration does not seem to pose additional risk.¹⁶

HIRSUTISM

Androgen transforms fine nonpigmented vellus hair into thick pigmented coarse terminal hairs in hirsutism.¹⁷ Both excess ovarian or adrenal production or end organ hypersensitivity to androgens results in hirsutism.

Hirsutism may be idiopathic or associated with PCOS. Other causes of hirsutism such as virilizing ovarian tumors, nonclassical late-onset adrenal hyperplasia, adrenal carcinoma, endocrine disorders (Cushing's syndrome, prolactinoma, acromegaly), drugs (androgens, minoxidil, cyclosporine, phenytoin) are rare but may need to be considered.

In the presence of amenorrhea or oligomenorrhea, androgenic hair loss, deepening of voice, and clitoromegaly serum testosterone is a good screening test and imaging of the ovaries and adrenal glands should be done when the value is more than twice the normal to exclude an underlying androgen-secreting tumor.

Medical treatment of hirsutism should be accompanied by cosmetic measures and treatment of any identified underlying cause. The Cochrane database analyzed randomized controlled trials of spironolactone vs placebo and steroids; with or without the oral contraceptive pill. Spironolactone 100 mg was associated with a statistically significant subjective improvement in hair growth and a decrease in Ferriman-Galwey scores.^{18,19} Spironolactone 200 mg/d for 6 months was more effective in reducing hair density, diameter, and growth and the effect was maintained after 1 year of treatment with minimal side effects.²⁰ Similar results were achieved with combination of cyproterone acetate 50 mg and ethinylestradiol 35 μ g²¹ and with ketoconazole 400 mg/d.²² Combining spironolactone with an oral contraceptive is believed

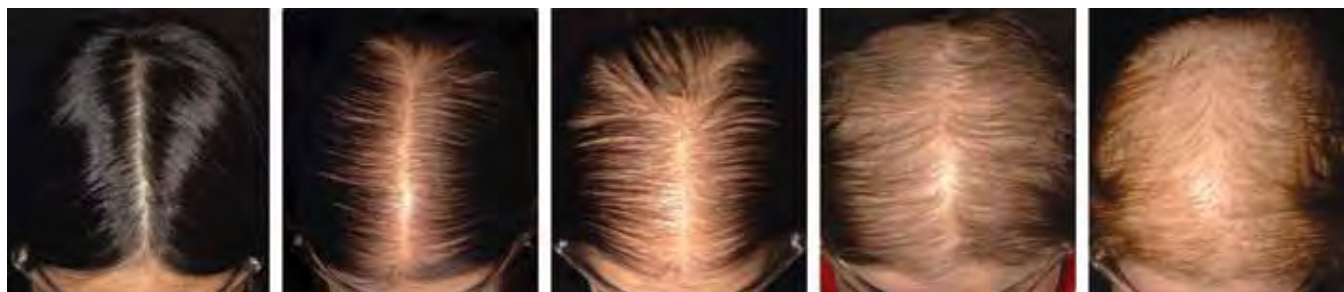


Figure 1. Five-stage clinical scale in female pattern hair loss.

to enhance efficacy while minimizing menstrual irregularity and providing contraception.²³ Spironolactone 100 mg/d was more effective than finasteride 5 mg in one small randomized trial.²⁴ CPA is approved for use in hirsutism in Europe, South America, Asia, Australia, and Canada but is not approved in the United States.

FEMALE PATTERN HAIR LOSS

FPHL is the most common cause of diffuse hair loss in women.^{25–27} Ludwig described this hair loss pattern in women in 1977 and stated it to be the female equivalent of male baldness.²⁵ A survey carried out in 2001 in an Australian population indicated that the age-adjusted prevalence of FPHL among Australian women of European descent aged 20 years and older is 32.2%. The prevalence of FPHL increases with advancing age, from approximately 12% among women aged 20 to 29 years to more than 50% of women older than 80.^{28,29}

FPHL produces a poor health-related quality of life and has a significant detrimental effect on self-esteem, psychological well-being, and body image.^{30,31} Women with early-onset FPHL have a higher incidence of hypertension and elevated aldosterone levels than their age-matched controls.³²

While FPHL is considered the female equivalent of male baldness, there are considerable differences in the pattern of hair loss in the two groups. Onset of hair loss occurs later in women than men. Only a small percentage of women show temporal regression, and the frontal hair line is usually preserved.²⁵ Women tend to have a more diffuse type of hair loss and rarely progress to total baldness. Miniaturization of hair follicles and increased number of telogen to anagen are seen in both groups, however, indicating a similar androgen-dependent pathologic process.³³

AGA is a complex polygenic condition. AGA in men is associated with polymorphism of the androgen receptor gene on the X chromosome.³⁴ This finding has been supported by several other studies,^{35,36} but the androgen-dependent nature in FPHL is not confirmed.

Investigators identified an association between FPHL and the aromatase gene (CYP19A1).³⁷ Aromatase is a key enzyme in estrogen

biosynthesis. Aromatase catalyses the conversion of testosterone to estradiol, androstenedione to estrone, and 16 α -hydroxylated dehydroepiandrosterone to estrol in the hair follicle and thereby diminishes the amount of intrafollicular testosterone available for conversion to DHT. Young women have higher levels of aromatase compared with male scalp and much higher levels in the frontal hair line.³⁸ This may explain relative sparing of the frontal hair line in FPHL. Sequence variation in the gene-encoding aromatase CYP19A1 might influence the risk of developing FPHL.

While pattern hair loss and hirsutism are seen in women with hyperandrogenism, most women with FPHL have androgen levels within the normal range.³⁹ Experts reported that the concentration of androgen receptors in women is 40% less compared with men, and women have low concentration of 5 α reductase levels.³⁸ A single case report of clinically and histologically proven FPHL in a woman with hypopituitarism and undetectable androgens raises the possibility that this pattern of hair can also be mimicked by the androgen-independent process.³⁹

The histologic hallmark of AGA is an increase in the number of miniaturized hair follicles that is best seen on horizontally sectioned scalp biopsy. The decline in the mean total follicle count, the reduction in terminal follicle counts, the increase in absolute number of vellus follicles, and terminal/vellus ratio seen histologically correlate with the clinical severity of FPHL as graded using a 5-point scale (Figure 1).⁴⁰

Widening of the midline part is used to assess the severity of the hair loss.⁴¹ A 5-point scale described by one of the authors (RDS) has been found to be helpful in assessing the progression of the disease as well as the treatment response (Figure 1).⁴²

Hand-held epiluminescent microscopy (dermatoscopy) is a valuable tool in the early diagnosis of FPHL. Dermatoscopy is able to demonstrate hair diameter diversity due to progressive miniaturization characteristic of AGA⁴³ and also demonstrate loss of terminal hair per follicular units (Figure 2). Women with associated hirsutism, acne, menstrual irregularities, or other evidence of virilization should be evaluated for PCOS or other causes of hyperandrogenism.

Without treatment, FPHL is progressive and has been estimated to progress at around 10% per year.⁴⁴ The rate of progression of hair loss was measured by the reduction in the total hair density (hairs per cm²) and meaningful hair density (nonvellus hairs per cm²) from baseline.⁴⁴ Medical management for FPHL consists of topical minoxidil, oral antiandrogens (cyproterone acetate, spironolactone, flutamide), and hair transplantation. CPA, spironolactone, flutamide, and finasteride (type II 5 α reductase inhibitor) all have been used in FPHL. There are no sufficient data on the efficacy of dutasteride, a combined 5 α reductase type I and II inhibitor in women for FPHL. Use of flutamide is limited by its potential severe liver toxicity. Finasteride is contraindicated in pregnancy due to the risk of teratogenesis, and it must be avoided or used with extreme caution in premenopausal women due to its long biological half-life. It has failed to demonstrate superiority over placebo in one study,⁴⁵ but other reports have been more promising.⁴⁶

Spironolactone is the most widely used antiandrogen for FPHL in the United States. The standard dose used is 100 to 200 mg daily.^{47,48} Dosages above 150 mg/d work best.⁴⁹ Spironolactone daily and cyproterone acetate appear to be equally effective.⁴⁸ Several small case studies have shown the beneficial effect of spironolactone in AGA.⁵⁰ Combination of spironolactone with 5% minoxidil produces additive benefit.⁵¹

CONCLUSIONS

Spironolactone has been used for more than 20 years as a treatment option for women with androgen-dependent skin disorders such as acne, hirsutism, and FPHL. In hormonal acne, spironolactone is useful as monotherapy or in combination with standard therapy. In particular it is useful in women intolerant of the oral contraceptives. In hirsutism, spironolactone is generally more effective than oral contraceptives alone. It should be used in combination with physical hair-removing methods. Spironolactone is effective in arresting the progression of hair loss and in most women produces a partial regrowth. Early treatment gives best results. Additive effects have been observed in combination with topical minoxidil.

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Figure 2. Dermatoscopic picture showing hair diameter diversity and loss of terminal hair in the follicular units.

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SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

Instructions: For each of the following numbered questions, choose the single most appropriate lettered response.

- 1) Aromatase catalyses the conversion of:
 - a. androstenedione to estrone
 - b. 16-hydroxylated dehydroepiandrosterone to estrone
 - c. testosterone to estradiol
 - d. All of the above
 - e. None of the above
- 2) Spironolactone primarily acts as a (an):
 - a. aldosterone antagonist
 - b. aldosterone agonist
 - c. testosterone antagonist
 - d. testosterone agonist
 - e. None of the above
- 3) Caurenone is:
 - a. a naturally occurring aldosterone antagonist
 - b. a naturally occurring aldosterone agonist
 - c. the primary metabolite of spironolactone
 - d. an inactive degeneration product of spironolactone
 - e. None of the above
- 4) Dihydrotestosterone is:
 - a. more active than testosterone
 - b. synthesized in the pilosebaceous unit of human skin
 - c. synthesized by the 5-alpha-reductase enzyme
 - d. All of the above
 - e. None of the above
- 5) Drugs that are better avoided when taking spironolactone include:
 - a. angiotensin-converting enzyme inhibitors
 - b. drugs that induce hypokalemia
 - c. indomethacin
 - d. a and c
 - e. a, b, and c
 - f. None of the above

ANSWERS TO SELF-TEST REVIEW QUESTIONS:

1) d, 2) a, 3) c, 4) d, 5) e

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FORMICATION

Also known as a haptic or tactile hallucination, formication represents a sensation of something happening within the body. As an example, drug users may feel something crawling within the skin, as do patients with parasitophobia.

Agents that may cause such a sensation include:

Adderall	Crystal meth	Lunestra	Wellbutrin
Alcohol	Ecstasy	Ritalin	Zyban
Cocaine	Keppra	Tridyl	

Adapted from Litt, JZ. *Curious, Odd, Rare, and Abnormal Reactions to Medications*. Fort Lee, NJ: Barricade Books; 2009:56–59.

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CORE CURRICULUM*Virendra N. Sehgal, MD, Section Editor*

Atopic Dermatitis: Current Options and Treatment Plan

Virendra N. Sehgal, MD;¹ Govind Srivastava, MD;² Sunil Dogra, MD, DNB, MNAMS³

Atopic dermatitis is a common inflammatory skin disorder of variable severity characterized by eczematous skin lesions associated with itching. This disease has an intricate immunologic basis influenced by genetic/familial predisposition and certain environmental, lifestyle, and dietary factors. Recent trends suggest a continuous rise in the prevalence of atopic dermatitis in developed nations and in countries undergoing rapid urbanization and industrialization. Pattern and morphology of skin lesions vary with different age groups, and the course of the disease is punctuated by remissions and relapses. Atopic dermatitis has a profound effect on quality of life of patients and may cause financial burden and loss of employment. Therapeutic options, although limited, are associated with risk of various side effects and are mostly appropriate when combined with education and counseling. Evolving knowledge of the pathogenesis and epidemiologic trends of the disease has led to an advent of many new therapeutic agents and treatment options. Various new methods to prevent or alleviate severity of the disease are under investigation. The authors provide a synopsis of the recent understanding of the pathogenesis, clinical features, and management of atopic dermatitis.

For nearly 2 centuries, atopic dermatitis (AD) has challenged the generation of scientists who to this date have neither found a single distinguishing clinical feature nor a diagnostic laboratory test of the universally occurring disorder with an alarming rise in prevalence.¹ The clinical phenotype that characterizes AD is the product of complex interactions among susceptibility genes, the host's environment, defects in skin barrier function, and systemic and local immunologic responses. No particular treatment modality has been found to be entirely safe and uniformly effective in all ages, tempting researchers to investigate new agents to treat this population with a minimum of side effects.²⁻⁵ In the past 30 years there has been enormous progress in our understanding of AD, including laboratory investigations, epidemiologic studies, and treatment. This article reviews AD and its treatment modalities as of now.

DEFINITION

AD is a noncontagious, intensely pruritic, inflammatory, chronic skin disorder that has a course of exacerbations and remissions that occur in infancy and childhood, run in families with a history of atopy, and is frequently associated with an elevated immunoglobulin E (IgE) levels in the serum. The diagnosis is based on clinical findings.

HISTORICAL ASPECTS

Wise and Sulzberger⁶ were the first to propose the designation of AD in 1933 to replace a host of purely descriptive, morphologic terms often recorded in the literature over a century prior to this nomenclature. These terms include neurodermatitis disseminatus (Brocq and Jacquet), prurigo diathesique (Besnier), and fruh und spat exudatives eczematoid (Rost), to name a few.^{1,7,8} The names currently in vogue are AD and atopic eczema.

EPIDEMIOLOGY

AD constitutes a major public health problem worldwide. The prevalence in children varies from 0.7%⁹ to 26%,¹⁰ while in adults it may range from 1% to 3%. Interestingly, the prevalence is much lower in developing countries when compared with industrialized nations.^{1,11} A lack of a suitable disease definition that can be uniformly used in population studies, however, may cause minor variation in the recording of prevalence and incidence of this disease. Lately, there are some suggestions that the prevalence of AD in developing countries may increase as traditional lifestyles are eroded by increasing adaptation to the living patterns of industrialized societies. This appears to be particularly true in urban areas where economic development is often polarized. The UK diagnostic cri-

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Table I. Genes Influencing Atopy, Asthma, and Eczema in Atopic Dermatitis¹³

CLASS OF GENE	REMARKS
Class I	Predisposition to atopy
FcεRIβ ¹²	Generalized immunoglobulin E (IgE) responsiveness present on chromosome 11q13. Shows close genetic linkage to atopy.
Interleukin (IL) 4 cytokine gene cluster ¹³	Present on chromosome 5q. Plays an interactive role in the final expression of atopy.
IL-4 receptor α ¹⁴	Present on chromosome 16. Is strongly associated with atopy, atopic dermatitis, and hyper-IgE syndrome.
Class II	These genes influence the specific IgE response.
T-cell receptor (TCR) ¹⁵	Genes encoding the human leucocyte antigen (HLA) proteins and genes for TCR are thought to regulate the specific IgE response. Each T cell expresses only one species of TCR, present on chromosomes 7 and 14.
HLA ¹⁶	Genes encoding HLA are present on the short arm of chromosome 6. A presumed link between HLA restriction and the development of IgE responses exists.
Class III ¹⁰	These genes influence the noninflammatory mechanisms such as bronchial hyper-responsiveness.
Class IV	These genes influence non-IgE-mediated inflammation.
Tumor necrosis factor ¹⁷	Present on chromosome 6. Has two polymorphisms within its locus that contribute to development of asthma.
Mast cell chymase gene ¹⁸	Present on chromosome 14. Is secreted by the skin mast cells as part of the dermal inflammatory response and plays a significant role in the pathogenesis of atopic dermatitis.
Abbreviation: FcεRIβ, subunit of high-affinity IgE receptor.	

teria may prove valuable in standardizing the definition of AD in epidemiologic studies and are being widely used in international studies.¹² Regarding the sex incidence, both men and women are equally effected. In children, boys show an increased incidence, while women outnumber men in adult patients.¹³ In the past 30 years, the prevalence of AD has increased 2- to 3-fold, suggesting that environmental factors are now playing a more significant role in provocation of the disease.¹⁴ The majority of recorded cases have been shown to begin in early life. The disease takes a chronic course, with a clearance rate of 60% by the age of 16.¹⁵⁻¹⁷ Severe childhood affliction, concomitant/family history of eczema, and early onset of disease indicate a worse prognosis.¹⁵

ETIOPATHOGENESIS

GENETICS

AD is a complex genetic disease and for unknown reasons shows a strong maternal influence, ie, children of mothers with atopic disease are more likely to have atopic disease than those of fathers with atopic disease.¹⁸ The inability to demonstrate a consistent pattern of inheritance in the disorder is best explained by the presence of several genes for any given atopic phenotype interacting with each other and the environment to influence disease expression.¹⁹ Relevant to AD as part of a systemic atopic disorder, candidate genes involving IgE and Th2 cytokines have been identified. Thus more complex models of inheritance are needed to elucidate this multigenic expression. A much higher disease concordance has been recorded in monozygotic twins (80%) when compared with dizygotic twins (30%).²⁰ Genes influencing the expression of AD have been briefly outlined in Table I.²¹⁻²⁷ Several genetic analyses have identified different chromosome regions with a linkage to AD features: Th2 cell cytokine genes on 5q31-33, 1q21, 3q21, 17q25, and 20p, which are closely related to some major psoriasis loci. Further genetic regions associated with AD features include gene polymorphisms activator of transcription 6; the proximal promoter of regulated upon activation, normal T cells expressed and secreted; interleukin (IL) 4; interleukin 4 Ra; and transforming growth factor β.²⁴

PATHOPHYSIOLOGY

Very complex interactions of genetic, environmental, skin barrier, pharmacologic, microbiologic, and immunologic factors contribute to the etiopathogenesis of AD. Environmental pollutions, food additives, decreasing breastfeeding habits, and change in lifestyle involving primarily indoor dwelling may be contributing to a rise in these cases.²⁸⁻³¹ The last factor in particular increases the exposure of susceptible persons to house dust mites and indoor air pollutants, such as deodorant, perfumes, tobacco, smoke, pollen-bearing house plants, and central heating. Apart from a strong hereditary background, other factors significantly contribute to the development of AD and are briefly outlined in Table II.^{1,10,32-53} The past few years have generated productive information from studies on the role of dendritic cells, keratinocytes, and neuroinflammatory elements in AD.

AD is the product of an interaction between various susceptibility genes, host and environmental factors, infectious agents, defects in skin barrier function, and immunologic responses. Activation of T lymphocytes, dendritic cells, macrophages, keratinocytes, mast cells, and eosinophils are characteristic of AD skin inflammatory responses. Recent studies have suggested an association of active AD, asthma, and allergic rhinitis with increased levels of high-affinity IgE receptor on IgE-expressing Langerhans

Table II. Etiology of Atopic Dermatitis (AD)

FACTOR(S)	REMARKS
Hereditary ^{1,10}	A positive family history is found in about 70% of patients.
Immunologic aberrations	Increasing knowledge of cell biology and cytokine mediators has revealed a complexity of immunologic aberrations.
Immunoglobulin (Ig) E, ³²⁻³⁴ IgG, and IgM ³⁵	Serum IgE levels are elevated in about 80% of adult AD patients, who also show sensitization against airborne and food allergens and/or concomitant allergic respiratory allergy. Expression of high-affinity IgE receptor (FcεRI) can be found in the epidermal skin lesions of patients with AD because of higher IgE-binding capacity of the dendritic cells in their skin and blood. They are only increased in severely affected persons. IgG can be increased when secondary bacterial infection occurs.
Lymphocytes ³⁶	Atopic state is associated with preferential activation of TH2 phenotype CD4 T cells, which produce interleukin 4, which, in turn, stimulate IgE synthesis by B cells.
Langerhans cells ³⁷	Atopic dermatosis reveals, in addition to classical Langerhans cells, certain dendritic cells without Birbeck granules, which strongly express subunit of FcεRI (FcεRIβ) resulting in its high levels.
Monocytes ^{38,39}	The monocytes in patients with AD have been shown to produce increased levels of prostaglandin E2 and an elevated activity of a phosphodiesterase isoenzyme, which, in turn, is sensitive to type 4 phosphodiesterase type 5 inhibitors. Inositol pathway of peripheral blood mononuclear cells shows evidence of chronic stimulation and hyporesponsiveness to subsequent stimulation.
Neuropeptides ⁴⁰	Atopic skin shows an increased response to injections of neuropeptides such as substance P. Vasoactive intestinal polypeptide was found to be greatly increased in skin extracts of atopic lesions. ⁴⁵
Other leukocytes ^{41,42}	The number of eosinophils and the quantity of their products show a proportioned increase with the severity of the disease. Basophils of such patients show increased spontaneous, as well as after stimulation, release of histamine.
Biochemical changes ⁴³	The aberrations in cell activities and response to cytokines produce changes in metabolism of essential fatty acids in epidermal cells and monocytes.
Intestinal permeability ⁴⁴	A nonimmunologically controlled increased permeability of the intestinal mucosa may have some bearing between food allergy and AD.
Pharmacologic/vascular abnormalities ⁴⁵	AD patients exhibit a tendency toward, for example, vasoconstriction of small blood vessels leading to pallor, low finger temperature, and white dermographism-pronounced vasoconstriction on cold exposure. A particular characteristic is delayed blanch phenomenon with acetylcholine.
Physical factors	
Dryness ⁴⁶	Keratosis pilaris and minor ichthyosis can be frequently seen in AD. The dryness is associated with reduced ceramides, lowered resistance to irritants, and increased transepidermal water loss.
Sweating ^{47,48}	A greater response of sebaceous glands to acetylcholine is seen in these patients. Sweating disturbance and aggravation of disease due to sweating may be recorded in these individuals.
Itching ⁴⁹	Atopic areas itch more readily, exhibiting their intolerance to wool. Presence of wheals may be cardinal; however, it may be difficult to define its nature (primary or secondary).
Psychological/central nervous system factors ²⁶	Atopic personality: outwardly calm, with suppressed anxieties, frustration, insecurity, aggression, egotism, and above-average intelligence is conflicting. The habit of scratching may become an automatic reflex.
Microbial pathogens ⁵⁰	Approximately 90% of patients with AD are colonized with <i>Staphylococcus aureus</i> even without clinical evidence of infection. The organisms may act as immune cell activators (superantigen), especially for IgE synthesis. It has recently been shown that the presence of antimicrobial peptides, including β-defensins 2 and 3, is significantly decreased in acute and chronic lesions of patients with AD.
Environment/climate/aeroallergens ⁵¹	A higher prevalence of the disease is seen in temperate regions, with seasonal exacerbations during spring and autumn. Environment is playing a prominent role in its increasing prevalence.
Foods ⁵²	The role of food is always suspected in aggravation and alleviation of AD. The subject of which has been exhaustively reviewed. ⁵²
Autoallergens ⁵³	The majority of sera from severe atopic dermatitis patients contain IgE antibodies directed against human proteins. ⁵³ These observations point out that although IgE immune responses are initiated by environmental allergens, the allergic inflammation can be maintained by human endogenous antigens.



Figure 1. Atopic dermatitis: excoriated erythematous eczematous plaques covered with crust and scales.

cells, relative to inactive AD, asthma, and allergic rhinitis. Patients with AD appear to have defects in innate immunity and, as a result, show increased susceptibility to bacterial or fungal infections. Polymorphisms of the TLR2 gene have been described with increased frequency in AD patients and have been associated with a severe phenotype and susceptibility to *Staphylococcus aureus*. Mutations of filaggrin occur mainly in early-onset AD and indicate a propensity toward asthma.⁵⁴ Since filaggrin mutations are identified in only 30% of European patients with AD, genetic variants of other epidermal structures, such as the stratum corneum tryptic enzyme or a new epidermal collagen, may be important.

These developments are helping to increase awareness of other important pathogenic elements, in addition to the immunologic alterations, that contribute to the inflammation that is so pertinent to AD. Complex interactions of these factors play a role in the pathogenesis of AD.⁵⁵

PATHOLOGY

The acute phase of AD, as seen in infantile form, shows features of acute or subacute eczema with spongiosis, acanthosis, edema, and infiltration of dermis with lymphocytes, histocytes, plasma cells, and eosinophils. When lichenification occurs in older age groups, however, the picture resembles that of chronic eczema, with an increasing number of Langerhans cells.⁵⁶

CLINICAL FEATURES

Symptoms of AD usually start in infancy, presenting with intense pruritus and cutaneous reactivity. Patients have a reduced threshold for pruritic erythematous papules associated with vesicles, serous exudates, and excoriation. With time, the papules become excoriated, erythematous, eczematous plaques covered with crust and scales (Figures 1, 2, and 3). In patients with chronic cases, features of lichenification and fibrotic papules may be seen.^{55–58} Typical age-related features that aid in the diagnosis of AD are illustrated in Table III.

Localized variations such as nipple eczema, eyelid eczema, cheilitis, vulval eczema, and infra-auricular and infranasal fissuring may be seen in adults and adolescents. Morphologic variants such as follicular, pityriasis alba-like, papular-lichenoid, nummular/discoid, prurigo-like, dyshidrotic, and erythrodermic can be observed in isolated cases.^{57,58} Hyperlinearity of palms and soles, Dennie-Morgan infraorbital fold, white dermographism, facial pallor, Hertoghe sign, low hairline, and keratosis pilaris can often be observed. The dermatitis can be aggravated by a variety of factors such as climate, sweating, intercurrent infections, irritants, food allergy, and psychosomatic factors. Aeroallergens such as animal dander may provoke an attack.^{57–60}

COMPLICATIONS

The prolonged course with exacerbations and remissions can often increase the chances of complications, both due to the disorder as well as therapy. The salient complications are recorded in Table IV.

DIAGNOSIS

Hanifin and Rajka⁵⁷ pioneered a systematic approach toward the standardization of the diagnosis of AD. They proposed 4 major and 23 minor criteria, of which presence of 3 major and 3 minor criteria was diagnostic. Despite certain reservation, these criteria have remained a gold standard in research and academic teaching. The UK Working Party criteria provide a validated instrument for epidemiologic studies.⁶¹ De and colleagues found statistical advantage in favor of Hanifin and Rajka's criteria (sensitivity, 96.4%; specificity, 93.75%) compared with the UK Working Party's diagnostic criteria (sensitivity, 86.14%;

specificity, 95.83%).⁶² Cultural factors may reduce its sensitivity in some areas of the world. The potential for inclusion of patients with ichthyosis and familial atopy is a concern mitigating against its use for clinical and genetic cohort studies and is considered less reliable for children younger than 1 year.

Laboratory studies are rarely required to confirm the diagnosis of AD, which is primarily based on clinical features. Estimation of serum IgE with prick tests (radioallergosorbent test) may be undertaken, which paradoxically can be negative in up to one fourth of atopic patients and may be positive in 15% of healthy patients.⁶³ Histopathology reveals acute, subacute, and chronic spongiotic dermatitis, which are not specific. Identical findings can be seen in pityriasis rosea and many other inflammatory disorders and endogenous eczemas.^{1,26}

DIFFERENTIAL DIAGNOSIS

Several disorders may be confused with AD. Scabies and infantile seborrheic dermatitis can closely mimic AD in infants, as do the immune deficiency states.⁶⁴ A brief list of the differential diagnosis is given in Table V.

CURRENT OPTIONS AND TREATMENT PLAN

Due to variations in presentation in the different age groups and severity of the disorder, therapy has to be individualized. A general approach, however, can be based on the attempt to reduce triggering factors to reduce pruritus, thus minimizing rubbing and scratching that aggravates the condition. The principles in treating AD are reducing symptoms, preventing exacerbations and recurrences, and minimizing side effects from medications. This incorporates the use of emollients, wet dressings, topical corticosteroids, antibiotics for infections, antihistamines, stress management, counseling, and avoidance of allergens or triggers. A brief guideline of management^{2,65-80} has been given in Table VI.

First-line therapy should be used as the initial management in all AD patients. Patients with mild cases may show a favorable response and undergo remission for several months or even years on the preventive regimen.^{1,26}

Bathing and emollients are often used as they keep the skin hydrated and less irritable for hours, thus preventing itching and dermatitis. Soap substitutes are preferable to harsher cleansers when bathing. Ointments and oil-based vehicles with high lipid contents are generally preferred to restore skin surface lipids. Creams and lotions, however, may be indicated in humid conditions to prevent occlusive dermatitis.

Topical corticosteroid preparations have always been a common denominator for control of moderate to severe AD. Topical 1% hydrocortisone can suffice in infants and very young children.



Figure 2. Atopic dermatitis: excoriated erythematous eczematous plaques covered with crust and scales.

More potent steroid preparations used over short periods in moderate/severe cases are useful but should be used judiciously.^{1,26}

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are highly effective and make it possible to avoid many of the local side effects associated with topical steroids that occur with long-term use. Some experts recommend them as a first-line therapy of AD after the age of 2 years. The US Food and Drug Administration, however, has warned of their injudicious use due to theoretic side effects related to immunosuppression, including cutaneous or internal malignancies.⁸¹ Tacrolimus has been found to be useful in children 2 years and older as an intermittent therapy when conventional therapy fails. A lower strength (0.03%) is generally used in children 2 to 15 years, while a higher strength (0.1%) is preferred for adult AD patients.^{76,80} Tacrolimus and pimecrolimus are safe and effective in reducing the severity of AD symptoms in children and adults.



Figure 3. Atopic dermatitis: excoriated erythematous eczematous plaques covered with crust and scales.

They have been found to be particularly useful as maintenance therapy after establishing acute control of disease flare with topical corticosteroids. Topical tacrolimus is similar to potent topical corticosteroids and may be successful for long-term use in

patients with resistant AD on sites where adverse effects from topical corticosteroids might quickly develop.

In mild to moderate cases where intermittent mild corticosteroids are effective, the more expensive calcineurin inhibitors may be avoided. The best protocol for the use of topical steroids in combination or in sequence with calcineurin inhibitors has not been adequately studied.⁸² Wet wraps⁶⁷ are useful in secondary care for inducing remission in children, but they should not be used for treatment of mild eczema or used long term. Probiotics have also been tried in AD. They are cultures of potentially beneficial bacteria that positively affect hosts with adverse reactions to certain foods, as may be the case in AD. Many interventional studies have reported variable outcomes with manipulation of diet and environment in pregnant women (primary prevention) and children with established AD (secondary prevention), but more work is required to determine the effect of such measures on the long-term outlook of patients with AD. Early treatment with microbial probiotics may be beneficial by boosting Th1 immune responses in AD.⁸³

Systemic antibiotic treatment is indicated for widespread bacterial secondary infection (primarily *S aureus*). First- or second-generation cephalosporins or semisynthetic penicillins administered for 7 to 10 days are usually effective.

Systemic corticosteroids^{1,70} in short course are useful in cases of acute flare-up.

Cyclosporine^{71,72} is effective in the treatment of both adult and childhood AD. Because of the possible side effects, particularly renal toxicity, the use of cyclosporine should be limited to patients with severe refractory disease. Oral cyclosporin can be used for inducing a remission in severe eczema.

Azathioprine⁷³ is a useful steroid-sparing agent in severe relapsing disease. The recommended dosage of azathioprine is 1 mg/kg to 3 mg/kg daily, but it should be determined based on thiopurine

Table III. Clinical Features of Atopic Dermatitis

PHASE	DURATION, Y	CLINICAL CHARACTERISTICS
Infantile	0 to 2	Onset within first 6 months Lesions begin on the face and scalp—symmetric and gradually spread to other parts Acute weeping eczematous lesions with crusting and impetiginization Runs a chronic relapsing course
Childhood	2 to 12	Frequently involved sites are flexures of the elbow/knee and wrist, ankle, and neck Subacute to chronic lichenified dermatitis is more common Aggravation by chemicals and habits/occupation modify the sites of affliction
Adolescent	12 to 18	Mainly flexural lichenified eczematous picture Clinically, both types (classic eczematous and typical lichenoid) can be observed in this age
Adult type	19+	Lichenified lesions are more common and can be seen especially on flexures and hands. Localized isolated lesions can be seen

Table IV. Complications Associated With Atopic Dermatitis^{1,26}

COMPLICATIONS	REMARKS
Retarded growth	Even before the advent of effective corticosteroid therapy, a retarded growth has been reported. This may be exacerbated by treatment with oral/topical steroids on long term basis and this should be avoided.
Bacterial infections	Secondary bacterial infections with <i>Streptococcus</i> or <i>Staphylococcus</i> are often encountered in these patients, especially those taking topical/oral corticosteroids.
Viral infections	Patients in both the active and quiescent stages can develop acute generalized herpes simplex (eczema herpeticum) and vaccinia (eczema vaccinatum). AIDS may aggravate the condition (recall atopic dermatitis).
Ocular abnormalities	Apart from Dennie-Morgan fold, eyes reveal conjunctival inflammation and keratoconjunctivitis. Keratoconus may be an infrequent accompaniment. Cataract can occur in up to 10% of severe adolescent/adult cases. Before starting steroid/psoralen-UV-A therapy, eye examination is mandatory.
Psychosocial aspects	Quality of life of the patient as well as of the family is often profoundly disturbed. It may lead to various grades of behavioral difficulties in patients.
Erythroderma	Although rare, it may occur usually due to superinfection and infrequently to withdrawal of systemic corticosteroids.

methyltransferase levels. It is a slow-acting drug, which may take about 2 to 3 months before clinical benefit is apparent.

Azathioprine can be considered for longer-term maintenance treatment. Antihistamines have therapeutic value principally due to their sedative effects, and they are useful as a short-term adjuvant to topical treatment during relapses associated with severe pruritus.

Phototherapy (narrowband UV-B, psoralen-UV-A, UV-A1)^{68,69} is helpful in chronic relapsing disease in older children (older than 12 years).^{83,84} Narrowband UV-B can be used with confidence for chronic atopic dermatitis. UV-A1 may be useful for acute eczema. There is little convincing evidence of a clinical benefit with evening primrose oil.

Additional approaches include cytokine modulation (eg, soluble IL-4 receptor, anti-IL-5 monoclonal antibody, tumor necrosis factor inhibitors), blockade of inflammatory cell recruitment (chemokine receptor antagonists, conjugated linoleic acid inhibitors), inhibition of T-cell activation (alefacept, efalizumab), and use of synthetic antimicrobial peptides.⁸⁴

PROGNOSIS

Although the outcome of the disease is difficult to predict in any given individual, it is found to be more persistent and prevalent in young children. As the child ages, the episodes of remission also become more frequent and of longer duration. A spontaneous remission after the age of 5 may be observed in 40% to 60% of patients who develop the disease in infancy. A poor prognosis is seen in individuals who have widespread disease in childhood, associated rhinitis/asthma, a positive family history, or very high serum IgE levels. Our challenge for the future will be the development of more effective and safer drugs in the treatment of

AD. Future trials should include patient-reported outcomes and longer-term aspects of disease control such as duration of remission. New advances are likely to require better definitions for the various clinical phenotypes of AD, including identification of

Table V. The Differential Diagnosis of Atopic Dermatitis^{1,26,63}

DISORDER GROUP	DISEASE
Infections/infestations	Scabies Dermatophytosis Human immunodeficiency virus
Immune deficiencies	Hyperimmunoglobulin E syndrome Wiskott-Aldrich syndrome Ommen syndrome
Genetic disorders	Netherton syndrome Familial keratosis pilaris
Immunologic disorders	Pemphigus foliaceus Graft-versus-host disease Dermatomyositis Dermatitis herpetiformis
Chronic dermatoses	Seborrheic dermatitis Contact dermatitis Psoriasis Ichthyosis Lichen simplex chronicus Nummular eczema
Metabolic disorders	Acrodermatitis enteropathica Phenylketonuria Multiple carboxylase deficiency
Malignancies	Mycosis fungoides Sezary syndrome Letterer-Siwe disease

Table VI. Treatment Modalities of Atopic Dermatitis^{26,65,66}**First-line therapy**

General advice: decrease scratching, improve family interaction, correct sleep disturbances, and avoid trigger factors

Reduction of trigger factors:

Curtail soap and detergent use

Avoid contact with wool

Use of a central or room humidifier if central heat leads to xerosis

Eliminate airborne allergens

Avoid house pets

Alleviate patient and/or family stress

Topical therapy

Bathing followed by emollients: moisturizing creams and emollients are useful and important treatment adjuncts for the daily skin care of patients with dry and inflamed skin

Initial administration of mild/mid potent topical steroids

Maintenance by ichthammol/coal tar

Systemic therapy

Oral antihistaminic therapy (hydroxyzine hydrochloride/cetirizine dihydrochloride) at bed time and antibiotics when impetigo develops

Second-line therapy

Intensive topical potent corticosteroids for short periods

Wet-wrap techniques: affected parts covered with emollient followed by a wet inner and dry outer dressing used overnight⁶⁷

If contact allergy to medications is experienced, change to different preparations or patch test to topical agents

Phototherapy

This is a useful treatment option in moderate to severe, resistant disease, which frequently needs systemic immunosuppressives. Psoralen-UV-A is recognized to be beneficial in the management of adult atopic dermatitis and children older than 12. Narrowband UV-B is preferred in pediatric populations. Limitations include visits to treatment centers and risk of premature skin aging and cutaneous malignancies.^{68,69}

Third-line therapy**Drugs**

Systemic corticosteroids^{1,70}

Cyclosporin^{71,72}

Azathioprine⁷³

Thymopentin⁷⁴

Interferon γ therapy⁷⁵

Topical calcineurin inhibitors

Tacrolimus/pimecrolimus⁷⁶⁻⁸⁰

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PERILS OF DERMATOPATHOLOGY

W. Clark Lambert, MD, PhD, Editor

Once a Biopsy, Always a Biopsy

Amit Sharma, BA;¹ Tiffany Jow, BA;¹ Amin Maghari, MD;^{1,2} W. Clark Lambert, MD, PhD^{1,2}*"You can't get there from here."*—A Popular Southern Colloquialism

An initial step in processing a specimen involves the identification of the submitted components. At most institutions, the specimen container is labeled with the patient's name, date of birth, and record number. The clinician must also identify the technique applied to procure the specimen, as well as the clinical context for the surgical procedure. When dealing with the skin, common procedures include shave biopsy, scoop biopsy, punch biopsy, and excisional biopsy. The purpose of the first three is to help to obtain a histologic diagnosis of the lesion, while the goal of the last, an excisional biopsy, is to remove the entire lesion.

A clinician may submit a skin excision and identify it as "biopsy." Some laboratories interpret "biopsy" as a punch or scoop, leading the pathologist not to identify the specimen's margins and any infiltrates that may be there; moreover, a specimen that is submitted without identification will not have its margins examined, unless it is obvious that the specimen resulted from an excision.

EXAMPLES

The first specimen (Figure 1) shows a small defect confined to the center. If it were submitted as a "biopsy," then it should not lead to problems, given the size and location of the lesion. On the other hand, the second specimen (Figure 2A–2C) illustrates a lesion that has extended beyond the excision site. If the specimen were labeled "skin excision," then all the margins, excluding the skin surface, would be painted with ink. An orienting suture, if included, would designate the "o'clock position." We recommend that a long stitch mark be the anatomically correct 12 o'clock and a shorter stitch mark 3 o'clock (toward the patient's right). The lesion would be divided into approximately 5-mm parallel slices, and the surgical margins would be cut into tangential sections (Figure 2A).¹ Taking horizontal slices of the entire specimen is another accepted method for identifying margins (Figure 2B). In both preparations, the pathologist would notice the lesion infiltrating beyond the margin at 5 o'clock. If, however, instead of "skin excision" the specimen were labeled "biopsy," the laboratory

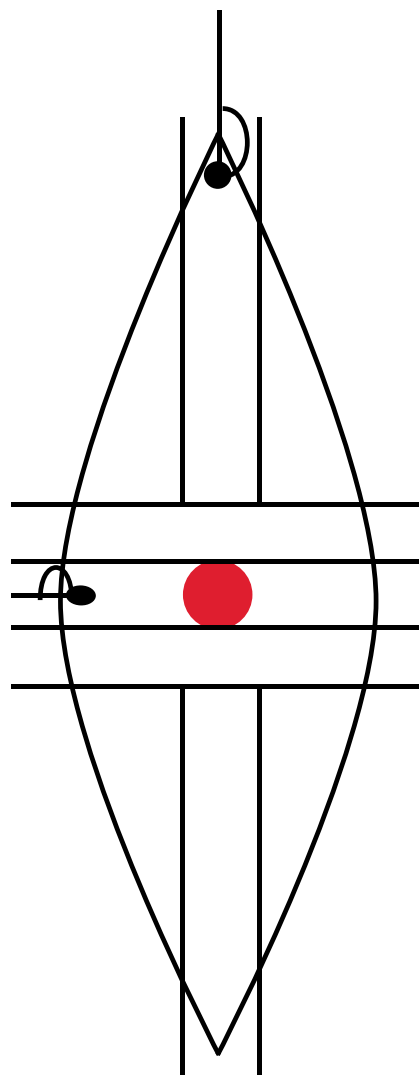


Figure 1. Specimen 1 with orienting sutures at 12 o'clock and 3 o'clock (toward the patient's right) and horizontal slices of the lesion and vertical slices at the tails. The small lesion is confined to the center.

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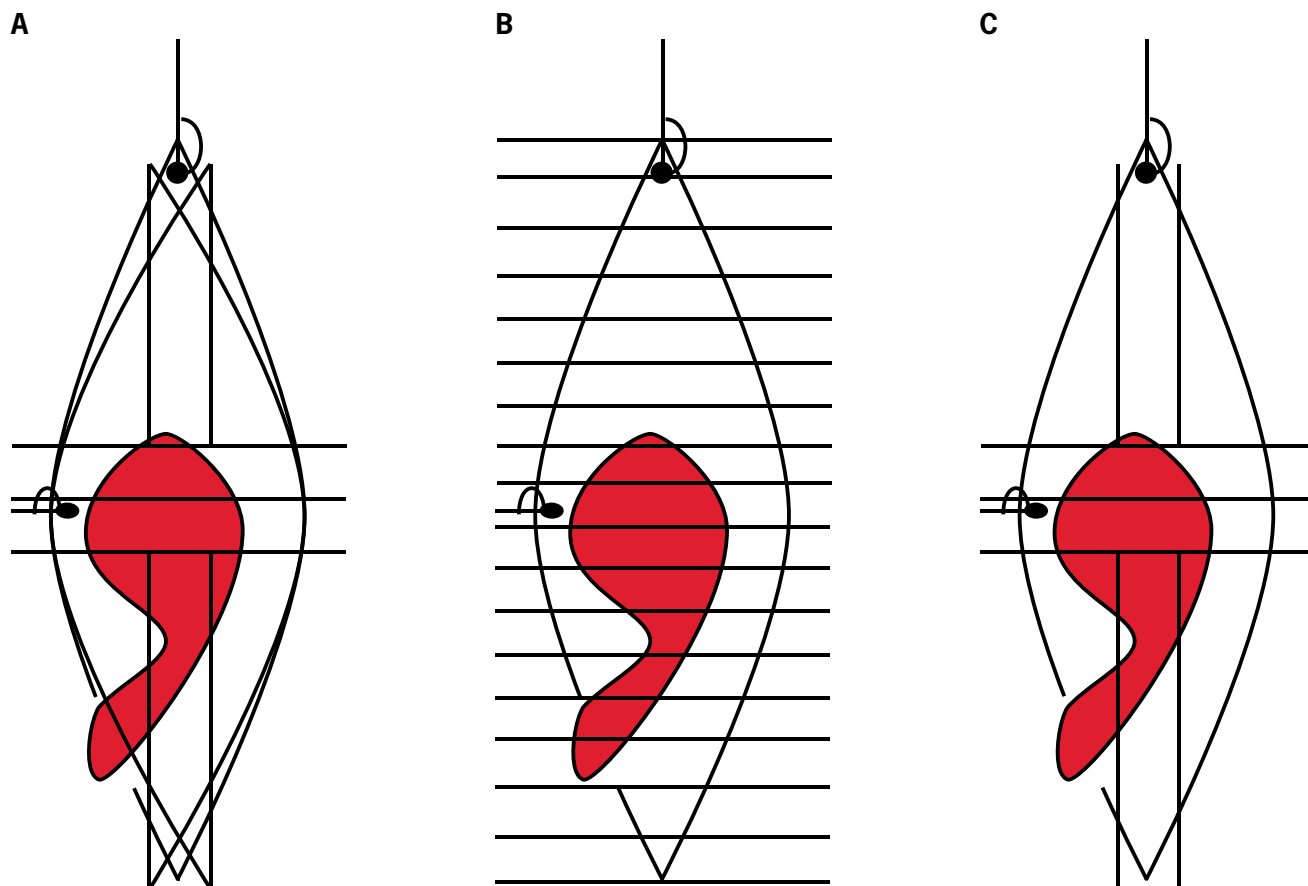


Figure 2. (A) Specimen 2 with orienting sutures and horizontal slices of the lesion and vertical slices at the tails. The tangential sections reveal that the lesion extends beyond the 5-o'clock margin. (B) Specimen 2 with orienting sutures. The horizontal slices along the entire specimen reveal that the lesion extends beyond the 5-o'clock margin. (C) Specimen 2 with orienting sutures and horizontal slices of the lesion and vertical slices at the tails. Because slices containing the margin are not taken, the extension of the lesion beyond the 5-o'clock margin is not detected.

would not routinely ink or section the margins. Thus, if only a few horizontal slices of the lesion and vertical slices of the tails were made (Figure 2C), as is standard procedure for a biopsy, the pathologist would miss the infiltrate spreading across the 5-o'clock margin. The diagnosis would be correct; however, the distribution of the defect would not be recorded. The clinician, realizing the mistake, may ask the laboratory personnel for a reading of the margins. Unfortunately, the specimen cannot be reprocessed to provide such information. Worse, the clinician may be reassured that the margins are "negative," when, in fact, the tumor has extended beyond the true margins.

CONCLUSIONS

To ensure proper processing of a specimen, clear communication

between the clinician and laboratory team is essential. Identification of the specimen provides direction to the laboratory on specimen preparation. If a specimen is labeled "skin excision," it is the laboratory's responsibility to describe how the lesion is circumscribed. If labeled "biopsy," the specimen may not have its margins read. Although histologic diagnoses may be provided in both cases, only the specimen identified as excision would, with certainty, have the margins examined. The laboratory personnel should contact the clinician, if clarification is needed, because once processed as a "biopsy," a specimen cannot be re-examined as an "excision."

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NEW TO THE CLINIC

*Noah S. Scheinfeld, MD, JD, Section Editor***Therapeutic Review 2009–2010**

Noah S. Scheinfeld, MD, JD

This contribution will review select medications with dermatologic applications approved by the US Food and Drug Administration (FDA) in 2009–2010. Most of these medications are not novel but rather variations of existing medications.

IMIQUIMOD 3.75% (ZYCLARA)

In 2004, imiquimod 5% was approved for the treatment of actinic keratoses with a dosing schedule of 2 times a week for up to 16 weeks. In 2010, imiquimod 3.75% was approved for the treatment of actinic keratoses. The clinical trial of imiquimod 3.75% involved a daily-dosing schedule with two, 2-week cycles, separated by a no-treatment interval of 2 weeks with efficacy assessed 8 weeks after the last dose. Patients treated with Zyclara had 36% complete clearance of actinic keratoses vs 6% for placebo. It is sold in units of 28 packets.

It is unclear whether the 5% or 3.75% formulations will differ in clinical utility, as no head-to-head study was done. Approval for use of 3.75% imiquimod for use in genital warts is expected in the future.^{1,2}

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (XIAFLEX)

In 2010, an injectable form of collagenase clostridium histolyticum was approved for treatment of Dupuytren's Contracture.³ A prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted in 308 patients with joint contractures of 20 degrees or up to 3 injections of collagenase clostridium histolyticum (at a dose of 0.58 mg per injection) or placebo in the contracted collagen cord at 30-day intervals. A reduction in contracture to 0 to 5 degrees of full extension 30 days after the last injection was found in 64.0% of treated patients vs 6.8% in placebo-treated patients. Cost issues aside, this could be a useful medication for the treatment of keloids, morphea, and scleroderma.

TRANSDERMAL PATCH CAPSAICIN 8% (QUTENZA, FORMERLY NGX-4010)

The approval of an 8% capsaicin transdermal patch for the management of pain due to postherpetic neuralgia was seen in 2009.⁴ Capsaicin is an agonist for the transient receptor potential vanilloid 1 receptor, which is an ion channel–receptor complex ex-

pressed on nociceptive nerve fibers in the skin. The recommended dose of transdermal patch capsaicin 8% is a single, 60-minute application of up to 4 patches. Treatment with transdermal patch capsaicin 8% may be repeated every 3 months or as warranted by the return of pain (not more frequently than every 3 months). The 8% patch is supplied with a cleansing gel, which is used to remove residual capsaicin from the skin after treatment. This patch was superior to placebo in clinical trials but it was not compared with lidocaine patches (a prescription medication) or over-the-counter versions of capsaicin, which come as creams (various concentrations) and patches of various strengths (eg, 0.025%) sold under brands such as Capzasin-P, Salonpas hot patch, and Zostrix-HP cream).⁵

GANCICLOVIR OPHTHALMIC 0.15% GEL (ZIRGAN)

In 2009, Zirgan (ganciclovir ophthalmic gel) appeared as a topical ophthalmic antiviral preparation for the treatment of acute herpetic keratitis (dendritic ulcers). It had been developed in the 1990s.⁶ In one open-label, randomized, controlled, multicenter clinical trial that enrolled 164 patients with herpetic keratitis, ganciclovir ophthalmic gel was noninferior to acyclovir in patients with dendritic ulcers. Clinical resolution (defined as percentage of healed ulcers) at day 7 was achieved in 77% (55 of 71) for ganciclovir ophthalmic gel vs 72% (48 of 67) for acyclovir. In 3 randomized, single-masked, controlled, multicenter clinical trials that enrolled 213 patients, ganciclovir ophthalmic gel was noninferior to acyclovir in patients with dendritic ulcers. Clinical resolution at day 7 was achieved in 72% (41 of 57) for ganciclovir ophthalmic gel vs 69% (34 of 49) for acyclovir. The approval of ganciclovir gel adds it to the topical antiviral armamentarium that includes acyclovir 5% ointment, trifluridine 1% solution, vidarabine 3% ointment and 1% penciclovir cream, and docosanol 10% cream. Its place in clinical dermatology has yet to be established.

ACYCLOVIR AND HYDROCORTISONE (XERESE, ORIGINALLY LIPSOVIR) TOPICAL 5%/1% CREAM

In 2009, a topical combination of hydrocortisone (an anti-inflammatory agent) and acyclovir (an antiviral agent) for the

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prevention and treatment of cold sores was approved by the FDA.⁷ This combination is approved for the early treatment of recurrent herpes labialis—cold sores—to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time. Treatment is approved for adults and children aged 12 years and older. The approval was based on data from a clinical phase 3 program showing that 42% of patients using hydrocortisone/acyclovir cream did not develop cold sores with blisters, ulcers, and crusting compared with 26% of those receiving placebo. For those patients who developed cold sores, healing time was significantly decreased, being lowered by 1.5 days in the active treatment group vs in the placebo group. The insight of combining antiviral therapy and topical corticosteroid has been reported in the past, and where this combination therapy will offer advantages over, for example, 3 days of oral valacyclovir (which is now generic) and topical clobetasol, has yet to be established.

CONCLUSIONS

Many new medications approved for use in the integument are new formulations of existing agents. While their affects are not novel, an awareness of them can enhance knowledge and patient care.

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PHOTO CAPSULES

*Ncoza C. Dlova, MBChB, FCDerm, Section Editor***Giant Molluscum in an HIV-Positive Patient**

Ncoza C. Dlova, MBChB, FCDerm

A 35-year-old man presented with a 6-month history of extensive multiple umbilicated giant lesions on the face, scalp, and groin. Extensive lesions involved the scalp, almost covering the entire scalp like a turban. The patient was otherwise asymptomatic except for the cosmetic effect. The patient is human immunodeficiency virus–positive, with a CD4 count of 200 while on highly active antiretroviral therapy.

Skin biopsy confirmed giant molluscum. Lesions were recalcitrant to the conventional treatment of molluscum. Destructive measures such as cryotherapy and electrocautery did not seem to help.



Figure 1. Coalesced plaques of molluscum contagiosum involving the groin.



Figure 2. Giant mollusca of the face.



Figure 3. Close up of lesions on scalp.

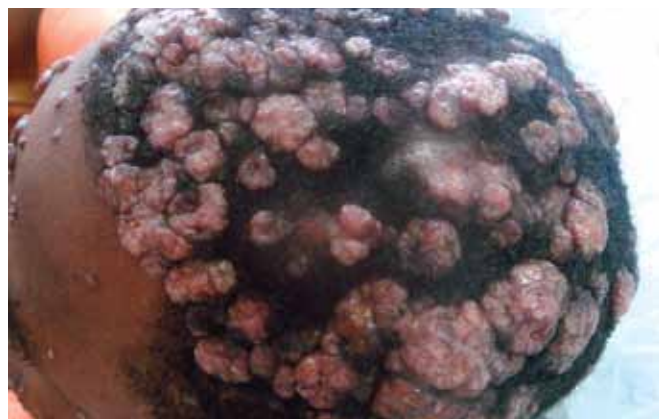


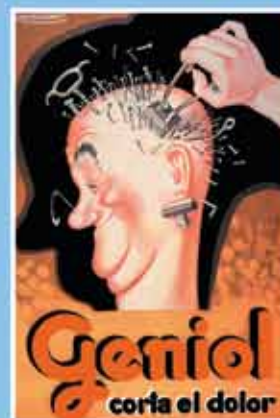
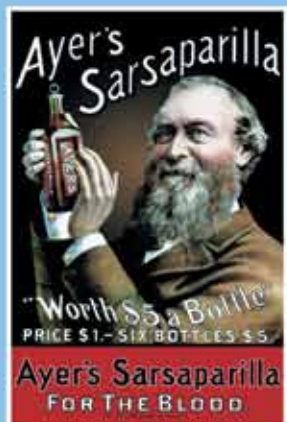
Figure 4. Giant mollusca of the scalp.

From the Department of Dermatology, Nelson R. Mandela School of Medicine, Durban, South Africa



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COMMENTARY

Consumer Groups Challenge Safety of Cosmetics

Howard A. Epstein, PhD

The Campaign for Safe Cosmetics (CFSC) and the Environmental Working Group (EWG) has funneled millions of dollars in grants to campaign a battle against the cosmetics industry claiming that many cosmetic and personal care products on the market contain toxic ingredients. The cosmetics industry, who responded through the Personal Care Products Council (PCPC), the leading national trade association representing the cosmetics industry, has countered that safety substantiation of ingredients, either by manufacturers or raw material suppliers, is based on a rigorous scientific safety process. The most recent assault on the cosmetic industry is a YouTube online video narrated by Annie Leonard that the PCPC describes as a “shockumentary.”

FACTS NOT FEARS

The video entitled “The Story of Cosmetics”¹ is severely critical of the cosmetics industry. It appears to be intended to generate consumer fear by stating that consumer products, including baby products, are loaded with toxic ingredients. The cosmetics industry is self-regulated and the video implies that the cosmetics industry is irresponsibly motivated by greed. It is claimed that the Food and Drug Administration (FDA) permits them to market products that are dangerous or contain toxins that cause cancer and other diseases. A representative of the PCPC, spokeswoman Kathleen Dezio, responded to the video stating that cosmetic companies are required by law to substantiate the safety of their products before they are marketed. Companies take this responsibility for safety substantiation very seriously.²

“Safety substantiation of ingredients, either by manufacturers or raw material suppliers, is based on a rigorous scientific safety process that includes studies of closely related substances, utilizing computer modeling to predict potential toxicity, in vitro testing, and human product safety experiences.” Under the US Food, Drug, and Cosmetic Act, it is a federal crime to market an unsafe cosmetic product in the United States. The marketing of an unsafe cosmetic product carries significant consequences. The FDA has clear and abundant legal authority to regulate the safety of cosmetic products, including authority to: ban or restrict ingredients

for safety reasons, enter and inspect manufacturing facilities, issue warning letters, seize unsafe or misbranded products, prohibit unlawful activities, and prosecute and jail violators.²

COLORADO SAFE PERSONAL CARE PRODUCTS ACT (HOUSE BILL 1248)

Colorado representative Diane Primavera and Colorado Senator Betty Boyd introduced House Bill 1248 to Colorado’s House Committee on February 3, 2010. The bill proposed to ban the sale of personal care products formulated with chemicals identified as causing cancer or reproductive toxicity. Proposed substances would include chemicals listed in the National Toxicology Report on Carcinogens as being known or reasonably anticipated to be human carcinogens; substances given an overall carcinogenicity rating of group 1, group 2A, or group 2B by the International Agency for Research on Cancer (IARC) or its successor agency (Table); substances identified by the US Environmental Protection Agency (EPA) identified as group A, group B1, or group B2 as known or probable carcinogens; substances identified by an expert panel of the National Toxicology Program’s Center for the Evaluation of Risks in Human Reproduction as having some clear evidence of adverse developmental, male reproductive, or female reproductive toxicity effects; or substances identified by the National Institute for Occupational Safety and Health, or its successor entity, as potential carcinogens. Violation of the act by a manufacturer could result in a civil penalty of \$5000 per violation per product for the first offense, increasing to \$10,000 per violation per product for a subsequent offense. The legislation would have permitted lawyers to file lawsuits against companies and collect fines and attorney fees to enforce the bill. The bill, as later amended, would provide that European Union regulations would apply to all products sold in Colorado.³

The cosmetics industry in opposition to the proposed legislation noted the bill’s numerous deficiencies. Richard Adamson, PhD, a cancer causation expert and former scientific director at the National Cancer Institute testified to the legislative committee that “no studies show any cancer risk associated with the use of cosmetics.” He further stated that links between cancer and cosmetics are

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unsubstantiated and without serious merit.”⁴ John Bailey, former director of the FDA and current executive vice president of science for the PCPC, testified that cosmetic companies substantiate safety of their products before marketing them and assess risk during their safety assessment. Dr Bailey explained that cosmetic companies go above and beyond federal and state requirements through their support of the Cosmetic Ingredient Review (CIR).⁴ Supporters of the bill, representatives of the Campaign for Safe Cosmetics, and the Colorado Women’s Lobby expressed the need for a “precautionary” approach to all chemicals and uses. In Europe, the term *precautionary* is interpreted as restricting the use of an ingredient. When challenged by a committee member to produce scientific studies showing a link between cosmetics and cancer, no example could be produced. Dr David Norris of the University of Colorado–Boulder explained that chemicals do affect organisms in the environment; however, he was also unable to demonstrate any direct link to cosmetics. Dr Norris, who is knowledgeable in his field regarding environmental toxins and endocrinology, was not well versed in cosmetics nor skin absorption and allowable dilutions. A representative of the Colorado Autism Society expressed concern not about cosmetics, but about vaccines. The Colorado House Judiciary Committee defeated the bill on March 1. Lawmakers concluded that the science doesn’t support the ban.⁴

FEDERAL LEGISLATION: THE SAFE COSMETICS ACT OF 2010 H.R. 5786

On July 21, 2010, representatives Jan Schakowsky, Tammy Baldwin, and Ed Markey introduced new federal legislation entitled The Safe Cosmetics Act of 2010. The act is intended to amend the federal Food, Drug, and Cosmetic Act to impose new requirements and restrictions on cosmetic products and ingredients. In response to this proposed legislation, the PCPC pointed out that the act as written is not based on credible and established scientific principles. This bill will place an enormous burden on the FDA and create a large new regulatory structure for cosmetics. Parts of the act would regulate cosmetics beyond food and over-the-counter drugs. Some of the measures would require hundreds of FDA scientists and millions more in funding that would ultimately not make a meaningful contribution to product safety (PCPC newsletter, August 2010). The bill is also likely to impose a large and unfair burden on small business and direct sellers. The PCPC encouraged congress to consider proposals to strengthen FDA cosmetics oversight, including FDA ingredient reviews, and encourage passage of the FDA Globalization Act of 2009, sponsored by representative John Dingell. The act includes enhanced FDA regulation of cosmetics manufacturers, increased transparency, and enhancement of existing consumer safeguards as science and technology evolve and the industry continues to grow.^{4,5}

Table. IARC Classification of Chemicals and Mixtures^a

CLASSIFICATION	DEFINITION
Group 1	Consists of chemicals that are known to be carcinogenic to humans
Group 2A	Consists of chemicals that are probably carcinogenic to humans
Group 2B	Consists of chemicals that are possibly carcinogenic to humans
Group 3	Consists of chemicals that are unclassifiable as to carcinogenicity in humans
Group 4	Consists of chemicals that are probably not carcinogenic to humans

^aThe International Agency for Research on Cancer (IARC) is an agency of the World Health Organization (WHO). The WHO compiles several databases on carcinogenic risk to humans, epidemiology, and cancer control.

CONCLUSIONS

Special interest groups clearly have an influence on legislators. The concern occurs when legislators are saturated with misinformation promulgated with faulty science. An example is the impression that the industry is deliberately adding lead to lipsticks. Lead is naturally found in certain cosmetic pigments, and the levels detected in lipsticks are lower than the amount of lead permitted in American drinking water by the EPA. The FDA regulates the amount of lead inherently found in personal care products.⁶ The PCPC notes that studies often referenced by consumer safety groups (CFSC) are based on high-dose, repeated ingestion methodology; therefore, the results do not bear any meaningful similarity to topical application via personal care products. The industry can anticipate that these debates will continue, Senator Dianne Feinstein has publicly supported H.R. 5786 and is currently working on a senate version of the bill.

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LETTER FROM THE EDITOR

Inaugural Edward L. Keyes Resident Contest for Outstanding Case Reports

Vesna Petronic-Rosic, MD, MSc, Chair, Resident Contest Committee

*To be awarded for the best case report submitted by a physician in training (resident, fellow, or registrar)
for presentation at the 8th World Congress of the International Academy of Cosmetic Dermatology in
Cancun, Mexico, January 31–February 4, 2012.*

We invite you to submit original case reports that reflect the presentation of new ideas and original observations to the academy membership and other attendees of the congress. The author whose abstract receives the highest score during the review process will be awarded a scholarship by the International Academy of Cosmetic Dermatology to present the full paper at the 8th World Congress of the International Academy of Cosmetic Dermatology in Cancun, Mexico, January 31–February 4, 2012.

Abstracts should be submitted before noon, Central Daylight Time, August 1, 2011, electronically and should be no longer than 2500 characters, including spacing. Previously published material should not be submitted; however, it is acceptable if the case report has been submitted for publication but not actually published as of August 1, 2011. Applicants should not submit abstracts that include material that has been previously presented. Applications will be graded based on the educational value of the abstract and the extent to which it presents new and significant work. The review committee strongly recommends that abstracts have an organized, coherent, well thought-out, and complete presentation.

All applicants will receive e-mail notification of the resident case report review committee's decision by October 1, 2011.

From the Department of Medicine, Section of Dermatology, University of Chicago, Chicago, IL

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VINTAGE LABELS



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Once-daily application in the evening



VELTIN Gel

- Combines the acne-fighting properties of tretinoin and clindamycin
- Contains tretinoin, solubilized in an aqueous-based gel
- Combats inflammatory and noninflammatory acne

Important Safety Information for VELTIN Gel

- VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
- Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea occurs. Severe colitis has occurred following oral or parenteral clindamycin administration. Severe colitis may result in death
- Avoid exposure to sunlight and sunlamps when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Daily use of sunscreen products and protective apparel are recommended. Weather extremes (eg, wind and cold) also may be irritating to patients using VELTIN Gel
- Observed local treatment-related adverse reactions ($\geq 1\%$) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased
- VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component
- Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. VELTIN Gel should be used with caution in patients receiving such agents
- VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- It is not known whether either clindamycin or tretinoin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Due to possible serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug. Exercise caution if administering VELTIN Gel to a nursing woman
- The efficacy and safety have not been established in pediatric patients below the age of 12 years
- VELTIN Gel is not for oral, ophthalmic, or intravaginal use

Please see brief summary of Prescribing Information on the next page.


veltin[™]
(clindamycin phosphate and
tretinoin) Gel 1.2%/0.025%

BRIEF SUMMARY

VELTIN™ (clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

VELTIN Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

4 CONTRAINDICATIONS

VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

5 WARNINGS AND PRECAUTIONS

5.1 Colitis

Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. If significant diarrhea occurs, VELTIN 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.

5.2 Ultraviolet Light and Environmental Exposure

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

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Studies

The safety data reflect exposure to VELTIN Gel in 1,104 patients with acne vulgaris. Patients were 12 years or older and were treated once daily in the evening for 12 weeks. Observed local treatment-related adverse reactions ($\geq 1\%$) in clinical studies with VELTIN Gel were application site reactions, including dryness (6%), irritation (5%), exfoliation (5%), erythema (4%), pruritus (2%), and dermatitis (1%). Sunburn (1%) was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased.

Local skin reactions were actively assessed at baseline and at the end of 12 weeks of treatment in patients exposed to VELTIN Gel. At baseline (N=476), local skin reactions included erythema (24%), scaling (8%), dryness (11%), burning (8%), and itching (17%). At 12 weeks of treatment (N=409), local skin reactions included erythema (21%), scaling (19%), dryness (22%), burning (13%), and itching (15%). During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter.

7 DRUG INTERACTIONS

7.1 Erythromycin

VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component. *In vitro* studies have shown antagonism between these 2 antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

7.2 Neuromuscular Blocking Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women treated with VELTIN Gel. VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A limit teratology study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 2 mL/kg during gestation days 6 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and heart abnormalities were described in drug-treated groups. These abnormalities are consistent with retinoid effects and occurred at 16 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison. For purposes of comparison of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of VELTIN Gel applied daily to a 50 kg person.

Tretinoin: Oral tretinoin has been shown to be teratogenic in mice, rats, hamsters, rabbits, and primates. It was teratogenic and fetotoxic in Wistar rats when given orally at doses greater than 1 mg/kg/day (32 times the recommended clinical dose based on body surface area comparison). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, a species in which tretinoin metabolism is closer to humans than in other species examined, fetal malformations were reported at oral doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (324 times the recommended clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related teratogenic effects and increased abortion rates were reported in pigtail macaques.

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 fetus is not known.

8.3 Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of VELTIN 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 VELTIN Gel is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of VELTIN Gel in pediatric patients below the age of 12 years have not been established. Clinical trials of VELTIN Gel included 2,086 patients 12-17 years of age with acne vulgaris. [See Clinical Studies (14) of full prescribing information.]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of VELTIN Gel or the effect of VELTIN Gel on fertility. VELTIN Gel was negative for mutagenic potential when evaluated in an *in vitro* Ames *Salmonella* reversion assay. VELTIN Gel was equivocal for clastogenic potential in the absence of metabolic activation when tested in an *in vitro* chromosomal aberration assay.

Clindamycin: Once daily dermal administration of 1% clindamycin as clindamycin phosphate in the VELTIN Gel vehicle (32 mg/kg/day, 13 times the recommended clinical dose based on body surface area comparison) to mice for up to 2 years did not produce evidence of tumorigenicity.

Tretinoin: In two independent mouse studies where tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years no carcinogenicity was observed, with maximum effects of dermal amyloidosis. However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 μ g (1.4 times the recommended clinical dose based on body surface area comparison) three times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenz[*a*]anthracene (DMBA).

In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoyl-phorbol 13-acetate or mezerein for up to 20 weeks. Topical application of tretinoin prior to each application of promoting agent resulted in a reduction in the number of papillomas per mouse. However, papillomas resistant to topical tretinoin suppression were at higher risk for pre-malignant progression.

Tretinoin has been shown to enhance photocarcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photocarcinogenic potential of the clindamycin tretinoin combination is unknown. Although the significance of these studies to humans is not clear, patients should avoid exposure to sun.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling.]

17.1 Instructions for Use

- At bedtime, the face should be gently washed with a mild soap and water. After patting the skin dry, apply VELTIN Gel as a thin layer over the entire affected area (excluding the eyes and lips).
- Patients should be advised not to use more than a pea sized amount to cover the face and not to apply more often than once daily (at bedtime) as this will not make for faster results and may increase irritation.
- A sunscreen should be applied every morning and reapplied over the course of the day as needed. Patients should be advised to avoid exposure to sunlight, sunlamp, ultraviolet light, and other medicines that may increase sensitivity to sunlight.
- Other topical products with a strong drying effect, such as abrasive soaps or cleansers, may cause an increase in skin irritation with VELTIN Gel.

17.2 Skin Irritation

VELTIN Gel may cause irritation such as erythema, scaling, itching, burning, or stinging.

17.3 Colitis

In the event a patient treated with VELTIN Gel experiences severe diarrhea or gastrointestinal discomfort, VELTIN Gel should be discontinued and a physician should be contacted.

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VEL:2BR5

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CASE STUDY

Vesna Petronic-Rosic, MD, MSc, Section Editor

Granular Parakeratosis: Response to Calcipotriene and Brief Review of Current Therapeutic Options

Aman Samrao, MD;¹ Marit Reis, MD;² George Niedt, MD;³ Donald Rudikoff, MD⁴

A 34-year-old Hispanic woman presented with an 18-month history of an intermittent, asymptomatic eruption that began on her left axilla after using a depilatory cream containing corn starch and thioglycolate (Figure 1A). The eruption then spread to her right axilla and lower abdomen (Figure 1B). She reported worsening with deodorant use, but had been using the same deodorant for many years and had continued using it twice a day. Treatment with topical corticosteroids had not helped. The patient coincidentally had been started on isotretinoin 5 months previously for acne, but it had no effect on her axillary or abdominal lesions. Physical examination revealed multiple dark brown and black papules with a “stuck-on” appearance in both axillae and on the lower right abdomen. A biopsy of the left axilla revealed a thickened parakeratotic stratum corneum with retention of keratohyalin granules within the parakeratotic cells, which is considered diagnostic of granular parakeratosis (Figure 2). The patient was prescribed calcipotriene cream twice daily. After 2 weeks, she had complete resolution of the axillary lesions, but the abdominal lesions persisted. She has since had mild recurrences while using calcipotriene.

Axillary granular parakeratosis is a benign acquired keratotic dermatitis first described by Northcutt and colleagues in 1991.¹ The terms *intertriginous granular parakeratosis* and *granular parakeratosis* have since been proposed because the entity can occur on multiple sites including the face, abdomen, inframammary regions, groin, and perianal area.²⁻⁴

Granular parakeratosis typically presents over days to months as keratotic brownish red papules that coalesce into well-demarcated plaques, with varying degrees of maceration. Although it typically affects middle-aged or older women, an infantile form exists and has been reported in patients as young as 9 months.⁵ The infantile form clinically presents as two variants: bilateral plaques in the inguinal folds and erythematous geometric plaques underlying pressure points from diapers. Both infantile patterns have a characteristic thick, flake-like scale.⁵⁻⁷

Pruritus is a common symptom of granular parakeratosis although the lesions can be asymptomatic. They are unilateral or bilateral, solitary or disseminated, and can flare in warm months. Resolution is possible, but recurrence is common and can persist for more than 20 years.⁸

Although the exact incidence of granular parakeratosis is unknown, there have been more than 50 case reports in the literature to date. This likely underestimates the true incidence since it is often misdiagnosed as other more common conditions such as acanthosis nigricans, contact dermatitis, and intertrigo and can mimic less common entities such as pemphigus vegetans, Darier disease, Hailey-Hailey disease, and confluent and reticulate papillomatosis of Gougerot and Carteaud. Pathologic examination shows a hyperplastic epidermis with a parakeratotic stratum corneum and retention of keratohyalin granules within the parakeratotic cells.

There is no apparent correlation of the disease to other medical conditions such as obesity, diabetes, malignancy, or nutritional deficiencies, nor has any common chemical irritant been found. Although there have been multiple case reports of granular parakeratosis, the etiology remains elusive. Although once considered to be caused by contact dermatitis, there have been many case reports in which granular parakeratosis did not resolve with discontinuation of the suspected agent. A number of reports showed negative patch test results to aluminum chlorohydrate, various cosmetics, and toiletries and the absence of spongiosis on histopathology.⁹

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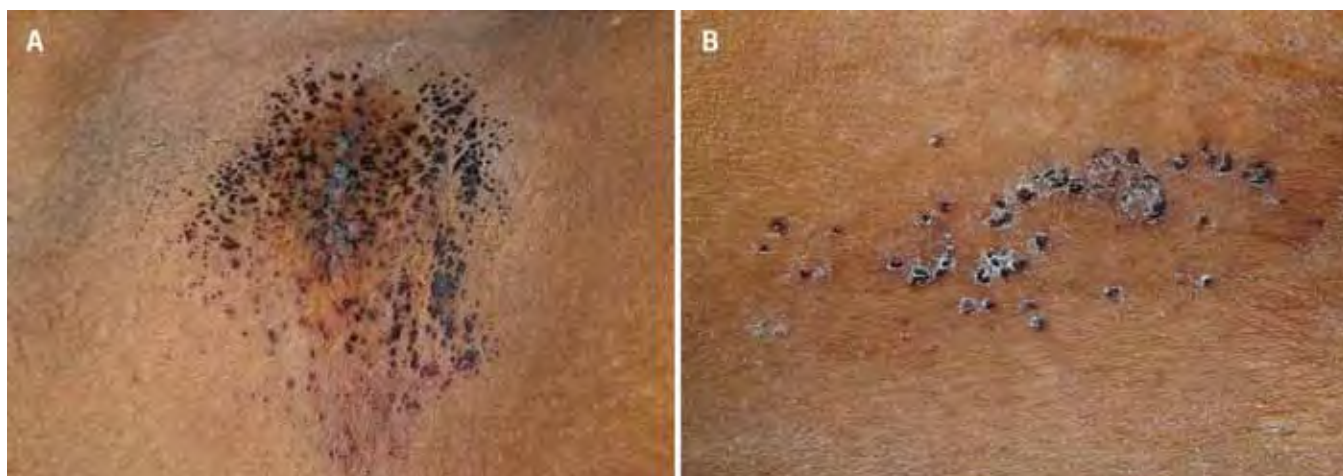


Figure 1. (A) Keratotic dark brown to black papules with surrounding hyperpigmentation involving the axilla. (B) Dark keratotic papules on the abdomen.

Some authors have proposed that granular parakeratosis represents a reaction pattern rather than a distinct disease *sui generis*. One hypothesis is that it is a protective mechanism in humid intertriginous regions exposed to mechanical irritation.² It is thought that mechanical/chemical irritation may cause denaturation of keratins, removal of surface lipids, alteration of cell membranes, and/or direct cytotoxic effects on keratinocytes.¹⁰ This reaction pattern hypothesis is supported by recent incidental findings of granular parakeratosis within other skin lesions such as molluscum contagiosum, dermatomyositis, and a variety of epidermal neoplasms including basal cell and squamous cell carcinomas.^{11–14}

The primary defect in granular parakeratosis is thought to be in the processing of profilaggrin to filaggrin. Profilaggrin is a component of keratohyalin granules, which undergoes proteolysis to release filaggrin thereby promoting aggregation and cross-linking of keratin filaments

in the stratum corneum. Ultrastructural analyses by Metze and Rutten showed that the parakeratotic cells in granular parakeratosis expressed filaggrin in keratohyalin granules but not in the cytoplasm, indicating a defect in profilaggrin processing. Evidence to support the theory of defective processing of profilaggrin to filaggrin includes the following: (1) the effectiveness of glucocorticoids in some cases since the latter have been shown in vitro to affect the processing of profilaggrin to filaggrin; (2) the effectiveness of retinoids in some cases since retinoids can increase expression of filaggrin; and (3) the effectiveness of vitamin D analogs, which are known to promote terminal differentiation of keratinocytes in the stratum corneum.^{9,15,16}

The largest compilation and review of cases to date in 2003 reported a variety of treatments to be effective in the treatment of granular parakeratosis. These include discontinuation of the offending agent, cool climate, and cryotherapy.^{1,4} Topical steroids,⁹ topical and oral antifungals,^{2,4} topical and oral retinoids,^{15,17} topical antibiotics,¹⁸ tacalcitol,⁴ and keratolytics^{3,16} have also proven to be effective in some cases. Since 2003, however, a number of other therapeutic options have also been reported in the literature, including calcipotriene,¹⁶ topical pimecrolimus,⁷ botulinum toxin,¹⁹ and most recently laser treatment¹⁰ (Table). Thus, review of the literature indicates that there is as yet no definitive therapy for granular parakeratosis, and treatment may entail trial and error in a given patient to bring about resolution of the lesions.

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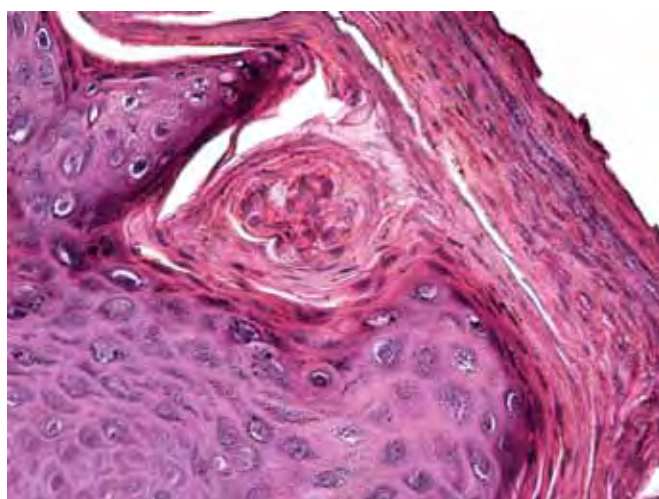


Figure 2. Biopsy specimen from axilla showing fine granules within the parakeratotic stratum corneum.

Table. Treatment Options for Granular Parakeratosis Since 2003

REPORT	SEX/AGE, Y	LOCATION OF LESIONS	TREATMENT	OUTCOME
Contreras et al ¹⁶	M/70	Bilateral axillae	Right axilla: calcipotriene ×1 mo Left axilla: ammonium lactate 12% ×2 mo	Complete resolution
Chang et al ⁵	F/18 mo	Diaper region	Pimecrolimus 1% BID ×2 wk	Complete resolution
Ravitskiy et al ¹⁹	F/44	Bilateral axillae	Botox 50 units/axilla ×1 treatment	Complete resolution
Laimer et al ¹⁰	M/45	Left axilla and groin	Localized yttrium-aluminum-garnet laser (pulsed, 2500 mJ, 10 Hz) ×1 session to one area (instant resolution) and then carbon dioxide laser (continuous wave, 12 W) to other lesions ×1 session	Complete resolution

Abbreviations: BID, twice a day; F, female; M, male.

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WAX MOULAGE



Lues connata. Moulage No 468 made by Lotte Volger in the Dermatology Clinic in Zurich in 1918. Museum of Wax Moulages Zurich, www.moulagen.ch

Courtesy of Michael Geiges, MD

See also page 361

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COMMENTARY

Parakeratosis: What It Is and What It Is Not

Naili Ma, MD;¹ Amin Maghari, MD;^{1,2} Navér Sarkissian, MD, PhD;^{1,2,3} W. Clark Lambert, MD, PhD^{1,2,3}

The epidermis is a unique tissue in a number of respects. Separated from the circulation by a basement membrane, it functions based mainly on anaerobic metabolism,¹ expressing unique proteins and forms of DNA very different from the classical helical “B-DNA” of the Watson-Crick model.² It also undergoes denudeation associated with keratinization, occurring in at least two types, epidermal and trichilemmal, the former with a stratum granulosum in which granular cells are visible, lining the epidermis and the superficial part of hair follicles, and the latter with direct keratinization of epithelial cells, lining the deeper part of hair follicles. In “combined cysts,” both forms are present (Figure 1).

APOPTOSIS

These forms of keratinization have provided dermatopathologists with unequivocal evidence, every time they peered through

their microscopes, of programmed cell death for many decades before it was “discovered” using complex quantitative radio-tracer techniques and named “apoptosis.” Apoptosis was just too obvious and too easy to see and therefore remained unnoticed. Johann Wolfgang von Goethe, German poet and philosopher (1749–1832), said: “What is the most difficult thing of all to see? It is that which is directly in front of you.”

PARAKERATOSIS

A vast number of cellular aberrations can interfere with this maturation process. These can cause keratinocytes to be immature or dysmature and consequently retain their nucleus throughout the keratinization process, a phenomenon known as parakeratosis by dermatopathologists (Figure 2).

Parakeratosis, used in this way, is actually a misnomer because the term means a process like but different from (“para-”) keratinization

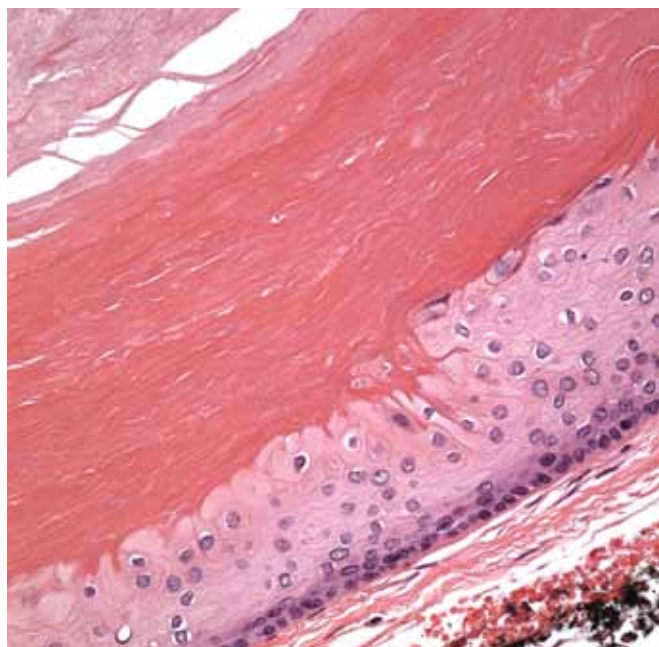


Figure 1. Wall of combined cyst showing trichilemmal keratinization, without a stratum granulosum (left) and epithelioid keratinization, with a faint stratum granulosum (right) (hematoxylin and eosin, $\times 340$).

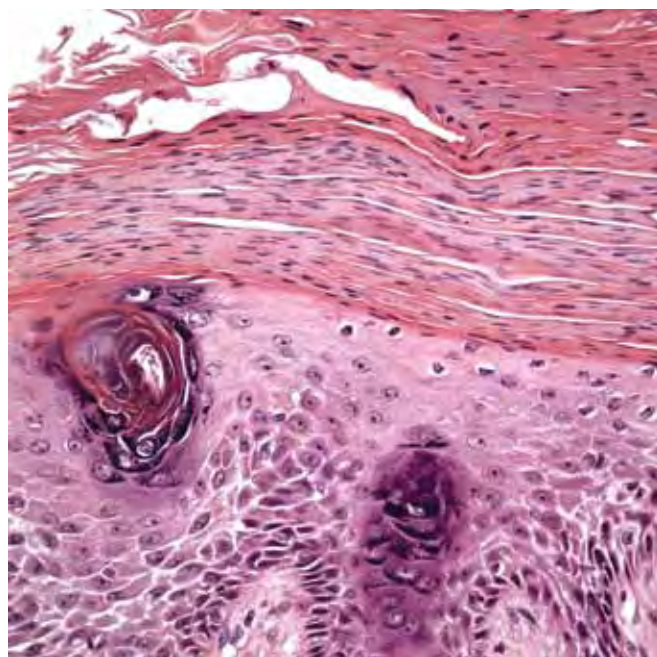


Figure 2. Psoriasis vulgaris, with parakeratosis (retained nuclei in the stratum corneum) (hematoxylin and eosin, $\times 340$).

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("keratosis"). This dysmaturation is simply recognized by dermatopathologists based on the retention of nuclei by cells in the stratum corneum. Parakeratosis may, therefore, be used as a clinical term (referring to abnormal keratinization, with or without retention of nuclei by keratinocytes in the stratum corneum), although it is rare in common usage. Alternatively, it may be used in the name of a diagnosis based on histopathologic changes associated with a particular entity, as in the accompanying paper on granular parakeratosis.³

CONCLUSIONS

Whatever the way the term is used and whatever the cause, the histopathologic phenomenon parakeratosis (ie, retention of nuclei by cells in the stratum corneum) itself causes profound metabolic changes in the epidermis, with, for example, loss of a large quantity of nucleotides that otherwise would be available for

recycling. These alterations are potential targets for therapeutic intervention, and therefore the entire process needs to be further investigated and better understood.

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See also page 357

VINTAGE LABEL

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Average adult laxative dose: 1 tablespoonful dissolved in $\frac{1}{2}$ glass warm water. Follow with glass of cold water. Not recommended for small children.

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CASE STUDY

Pseudo-Blue Lunula and Beyond: A Normal Variant

Yusra Siddiqui, BA; Rashid M. Rashid, MD, PhD

A 12-hour-old newborn was noted by his parents and primary care team to have distinctive blue nail color changes. The blue color extended from the proximal nail bed to the mid-nail bed region. This did not resolve over the next 2 days, and dermatology was consulted. The child was born full term, and he and his mother had no medical history. He had an Apgar score of 9, and regular pulse oximeter showed >97% saturation. No signs of cyanosis were noted on full skin and mucosa examination. Complete blood cell count and basic metabolic panel results were unremarkable. The blue discoloration (Figure) was not blanchable and did not resolve with warming of the hands. Physical examination was otherwise unremarkable and no murmur was appreciated. Due to the lack of physical or laboratory alterations, observation was recommended as the best approach. On discharge, the blue discoloration continued and was still noted by the pediatrician on day 7. The parents eventually noted clearance at 2 weeks.

The lunula is a part of the nail matrix that develops in the 14th week of gestation. Its physical description is varied and can range from a pale blue-gray region to a white half-moon. The more prominent blue lunula, also known as azure lunula, is a darker discoloration and is not associated with any one etiology. It generally involves the matrix area¹ and nail bed² but is probably unrelated to deep connective tissue and vascular differences,³ as these are not related to the normal lunular coloration. Blue lunulae are more common in the fingernails than the toenails⁴ and are most common in the thumbnails.⁵

LITERATURE REVIEW

The literature and research on the lunula is limited. Lunular pathology, and studies distinguishing isolated from secondary lunula changes in relation to the nail bed changes, is even less studied. A literature search on PubMed and in a library catalog was performed using the words “blue lunula,” “azure lunula,” “lunula pigmentation,” “blue nail bed,” and “nail and lunula.” The “blue” and “azure lunula” searches gave no results in the library, but several nail books with limited and overlapping information were found. The articles and books that were relevant led to further searches for “neonatal cyanosis” and “Wilson disease.”

COMMENT

The different parts of the nail vary in their vascularity and thickness. A reduction in epithelial thickness transitioning from nail matrix to the nail bed marks the free edge of the lunula.⁶ The nail bed vascularity depends on the collaterals arising from the distal phalanx. The networks formed by the vessels coincide with the

vascularity of the skin but are also affected by the histology of the nail. The pseudopapillary network consists of vessels parallel to and found in the germinal matrix of the proximal nail bed and is normally responsible for the color of the lunula.⁷

ASSOCIATIONS

The origins of blue lunula can stem from a variety of origins.⁸ The following offers a brief review of some associations with blue lunula presentation.

ORAL INTAKE

Argyria, blue or gray discoloration, which may follow silver poisoning has commonly been associated with blue lunula,⁹ as has the presentation of cutaneous pigmentation.¹⁰ In this condition, silver is thought to be deposited in the region, and further photoaggravation may play a role.² Many drugs have also been linked to blue lunula, such as antimalarials,¹¹ which may complex with melanin and localize in the nail bed and matrix.² Other drugs with unknown mechanisms have also been associated with blue lunula, including 5-fluorouracil, zidovudine,⁹ phenolphthalein as in laxatives, heavy metals, and chemotherapeutics in general.^{9,12–14}

DISEASE STATES

In Wilson disease, copper metabolism problems caused by a deficiency in ceruloplasmin production and subsequently impaired copper excretion are associated with blue lunulae,^{9,15,16} but the specific pathogenesis leading to the blue discoloration is unclear. For unknown reasons, the phenolphthalein-associated blue lunula is darker in comparison to that associated with Wilson

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Figure. Blue lunula in a newborn. Reproduced with permission from the Morzak Center Nail, Hair and Skin division.

disease.¹⁴ When associated with Wilson disease, the discoloration can fade proximally and remain darker in the remaining distal region, but is not affected by changes in pressure.^{5,17} Blue lunula has also been associated with hemoglobin M disease.⁹ In this case there is a cyanosis of the lunula due to the presence of abnormal hemoglobin.¹⁷ In the instance of neonatal cyanosis, studies show that in various presentations of cyanosis on the body, the most reliable site in relation to arterial oxygen saturation is the lips. The nail bed was one of the sites of highest false-positives. No specific mention of the lunula was made in these studies.¹⁸

Imaging studies on the matrix in the lunula region are also possible. In the literature, features reported were obtained with high-resolution sagittal images that described the subnail plate lunula region and its association with the matrix and submatrix region. To obtain the images, a high-resolution surface gradient coil specially designed for skin imaging was used on a 1.5-T magnetic resonance unit. This study showed an oval area in the dermis beneath the nail matrix that gives a particular signal. This subnail matrix area displayed a significantly longer T2 relaxation time and a higher enhancement ratio, after injection of contrast, than did the nail bed dermis. The length of the subnail matrix area distal to the free edge of the proximal nail fold was highly correlated with the length of the lunula. The total length of the subnail matrix area was nearly correlated with the nail thickness. The histology and microvascularization of the subungual tissue showed that this subnail matrix area had specific features of loose connective tissue without bundles, and the reticular and subdermal vascular networks had large regular meshes in this oval area; thus, the lunula was shown to be linked to a well-defined area in

the dermis with a specific histology and microvascularization for which future studies on alterations and pathologic presentations may be based on and compared with.¹⁹

No effective treatment is currently available and the prognosis has not been reported in this potential normal variant in newborns. A search of the literature did not reveal other reports on newborn blue lunula. Close follow-up for resolution is recommended, and more extensive tests may be warranted in certain situations. A notable deficit in peer-reviewed works on this subject emphasizes the need for more research in the field of nail disease and normal variant presentations.

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CASE STUDY

Cutaneous and Subcutaneous Phaeohyphomycosis

Juan Pedro Russo, MD;^{1,2} Rocío Raffaeli, MD;^{1,3} Stella Maris Ingratta, MD;¹Patricia Rafti, MD;¹ Silvana Mestroni, MD⁴

Case 1: A 17-year-old male rural worker from Bolivia living in La Plata (Argentina) for the past year had a lesion on the flexor side of his right forearm (6×4 cm). The lesion was formed by several confluent nodular areas, wine-red in color, some fistulized, with hemopurulent drainage. The area was hot and painless (Figure 1). On physical examination, no regional adenomegalies were reported. The following analyses were requested and results reported. Soft tissue ultrasound: material of solid consistency with layered liquid areas, located in the subcutaneous cellular tissue, with fistulous tract, connecting through superficial planes. Evidence of peripheral edema. Bacteriologic analysis (puncture aspiration): methicillin-sensitive *Staphylococcus aureus*. Mycologic analysis (puncture aspiration): negative; laboratory results: eosinophilia; and human immunodeficiency virus: nonreactive. Histopathologic examination: lesions of necrosis with granulomatous inflammatory reaction. Fungi techniques (periodic acid-Schiff, Grocott stains): negative. Bacilos acid-alcohol resistentes (acid-alcohol resistant bacillus) (BAAR) techniques (Kinyoun, Ziehl-Neelsen): negative. Foreign body examination tested with polarized light: negative. Mycologic and bacteriologic examinations were repeated, including a search for mycobacterium species using material obtained from the biopsy performed on the cutaneous lesion. Macromorphology: the colony was initially black and of creamy consistency, to later become velvety. Micromorphology: dark blastoconidia, then cylindrical phialides with elliptical conidia (Figure 2). Identification: *Exophiala dermatitidis* infection. On the basis of these characteristics, the diagnosis is phaeohyphomycosis due to *E dermatitidis*. The patient is treated with antimycotic therapy, with oral itraconazole (400 mg/d), plus indication of surgical procedure to remove the lesion. The patient's condition evolves favorably with no recidivant episodes after the sixth month post-treatment (Figure 3). During the first year, controls were scheduled every 2 months. Case 2: A 72-year-old diabetic man had a painful chronic varicose ulcer on the side of his left foot, with black friable exudate, 2×3 cm in diameter after 1 year. Every time the black material was removed, it would quickly grow back again. No response was obtained with different therapies applied to seal the lesion (Figure 4). Routine laboratory results included the following. Glucemy: 1.82 g/dL. Histopathology: filamentous septate fungal elements with positive Grocott stain (Figure 5 and Figure 6). Mycologic examination and culture: direct: fungal elements in dematiaceous group. Culture: positive for *Curvularia lunata* (Figure 7). The treatment selected was oral itraconazole (400 mg/d) for 12 months, with periodic laboratory controls, plus application of wet pads on the ulcer containing sodium borate and ketoconazole cream. At the fourth month, the ulcer had completely closed (Figure 8).

Phaeohyphomycosis is an uncommon infection caused by a group of fungi called dematiaceous, or darkly pigmented fungi. These are usually found in temperate climates, and adult men from rural areas are most likely affected.¹

The disease can occur at superficial, cutaneous, subcutaneous, or systemic levels. Lesions usually appear on exposed areas of the human body, such as the arms and legs, and less frequently on the buttocks, neck, and face.

Patients with subcutaneous phaeohyphomycosis usually recall local minor trauma or presence of foreign bodies (sometimes unnoticed), and often present with subcutaneous cystic or nodular lesions without systemic symptoms or swelling of soft tissue. The lesions grow slowly and are frequently mistaken for granulomas

caused by foreign bodies or epidermic or ganglion cysts.² Bones and joints can occasionally be affected, which could require more extensive surgery and/or prolonged antifungal therapy.

The diagnosis of cutaneous and subcutaneous phaeohyphomycosis rests on histopathologic examination of clinical specimens and extensive microscopic examination and identification of cultures obtained through biopsy material.³

The presence of levaduriform dematiaceous cells, plus pseudohyphae or hyphal elements, are vitally important.

One of the most frequent etiologic agents of subcutaneous phaeohyphomycosis is *Exophiala dermatitidis*, formerly *Wangiella dermatitidis*, a widely spread dematiaceous fungus commonly present in soil, wild animals, wood, and debris.⁴

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The main manner of inoculation appears to be skin trauma; less frequent is through inhalation of spores. This is in agreement with the fact that it usually colonizes the sputum of patients with cystic fibrosis or causes pneumonia (pulmonary phaeohyphomycosis) in those with chronic lung disease.⁵ It can also cause disseminated phaeohyphomycosis and fungemia.

Direct examination allows the detection of a dark-colored tabicated hyphae, or initially to a lesser extent, levaduriform cells forming moniliform chains in varied lengths.

To achieve a definitive diagnosis it is essential to develop sample cultures in Sabouraud agar at room temperature or 30°C and obtain several isolates of the same species on repeat cultures. The isolates must be observed during 3 to 4 weeks, since the growth is slow.

Exophiala colonies are initially small, but after 7 to 14 days, the size increases and typically become olivaceous to dark brown. *Exophiala dermatitidis* is the only species that can grow in temperatures >40°C with negative nitrate assimilation.⁶ It presents melanin in the cell wall, therefore conferring the typical dark brown to black color to the hyphae and conidia, tested by a positive Fontana-Masson staining protocol.

The melanin pigment may offer protection through different mechanisms—it might scavenge free radicals and hypochlorite that are produced by phagocytic cells in their oxidative burst and that would normally kill most organisms.⁷

The correct functioning of the immune system is vital, especially cell-mediated immunity, for the positive prospects of the disease.

Curvularia is a dematiaceous filamentous fungus. Most species are facultative pathogens of soil, plants, and cereals in tropical or subtropical areas, while the remaining few are found in temperate zones. *Curvularia lunata* is one of the most commonly found species. While the infections may develop in patients with an intact immune system, the pathogen has recently emerged as an opportunistic microorganism that infects immunocompromised hosts as well.^{8–10}

Macroscopically, *Curvularia* produces rapidly growing, woolly colonies whose color changes from pinkish gray to olive brown or black when mature. Regarding its microscopic features, septate, brown hyphae, brown conidiophores, and conidia are visualized. Conidiophores are simple or branched and are bent at the points where the conidia originate. The septa are transverse and divide each conidium into multiple cells.

Differentiation of *Curvularia* species is based primarily on microscopic features (eg, number of the septa in the conidia, the shape and color of the conidia, existence of dark median septum).

Curvularia was not documented as a human pathogen until 1959, when it was isolated from a mycetoma.¹¹ *Curvularia* has been



Figure 1. Tumoral lesion.

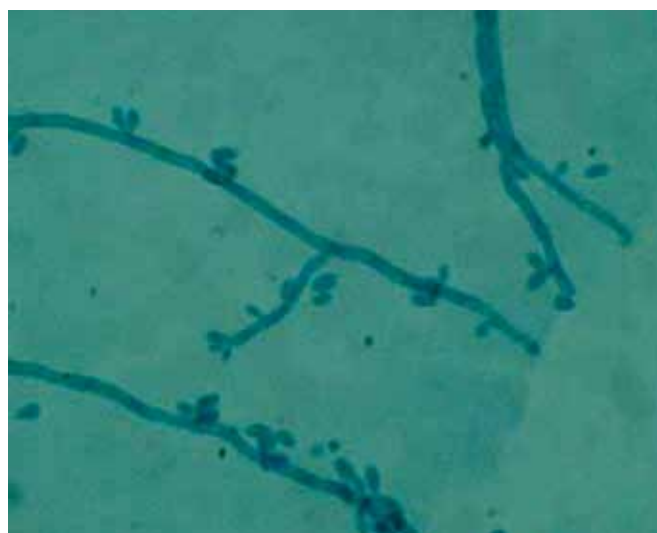


Figure 2. Culture with dark blastoconidia, cylindrical phialides with elliptical conidia.



Figure 3. Fourth month post-treatment.



Figure 4. Varicose ulcer with black exudate.

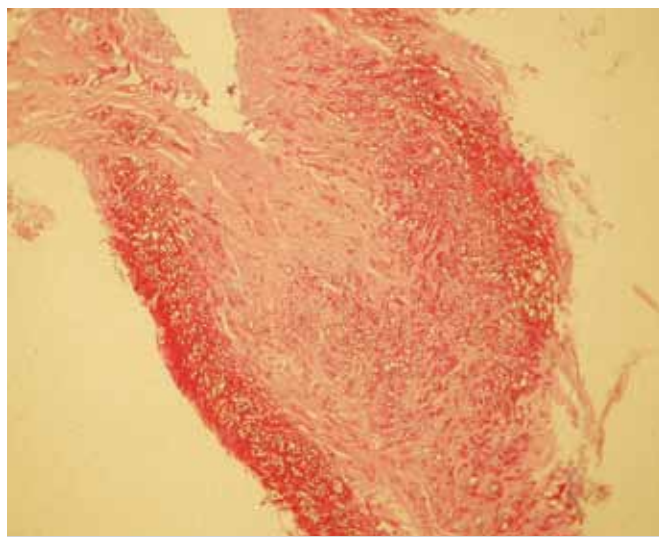


Figure 5. Histopathologic examination.

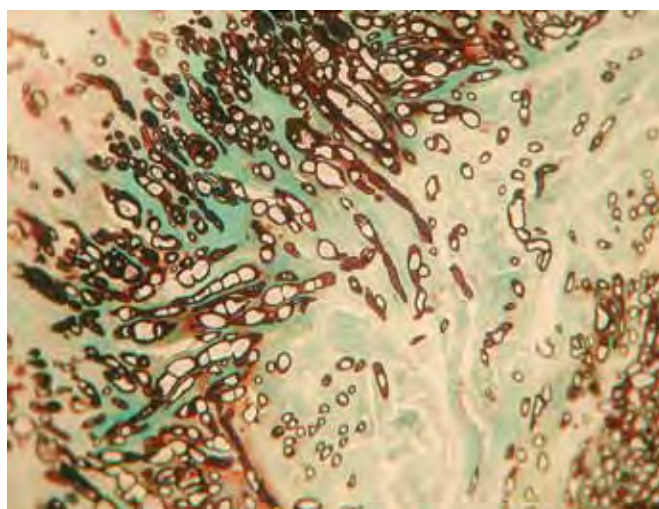


Figure 6. Grocott stain, positive.

reported as a cause of disease in the upper and lower respiratory tracts, cutaneous and subcutaneous tissue, endocardium, and central nervous system. Wound infections, mycetoma, onychomycosis, keratitis, allergic sinusitis, cerebral abscess, pneumonia, allergic bronchopulmonary disease, endocarditis, dialysis-associated peritonitis, and disseminated infections may develop due to *Curvularia*.

Similar to other syndromes that implicate dematiaceous fungi, there is no standard therapy for infections caused by this group. Most published cases describe a combination of surgical procedures and azolic antifungal agents as suggested therapy. At the moment, surgery on subcutaneous nodules added to systemic treatment with oral itraconazole was recommended for the patient in case 1 and only local and oral therapy for the patient in case 2.

Regarding azole therapy, most in vitro studies conclude that itraconazole has the most consistent activity against dematiaceous fungi. This is generally attributed to its low minimum inhibitory concentration. Ketoconazole is not entirely recommended due to its several adverse side effects, although it presents a good response against these pathogens.¹

Investigators determined in vitro sensitivity of 52 isolates of dematiaceous filamentous fungi against 10 antifungal agents and found a high fluconazole resistance (96%).

Terbinafine shows an excellent in vitro activity against *Exophiala*; however, it is metabolized very fast in mice and therefore concentration in blood levels would not be enough for treatment of serious systemic fungal infections. It would only be recommendable in combination with itraconazole against resistant strains, when both drugs act synergically.

Although Amphotericin B presents good in vitro activity against dematiaceous fungi, it could exhibit resistance to some strains of *Exophiala* species, besides being nephrotoxic in its standard form.

Despite the fact that several authors agree that surgical practices added to oral itraconazole therapy is the best established therapeutic approach, there is no standard dose or length of antifungal treatment.

In our case, we decided to stop the drug therapy after 6 months for both patients, with a favorable outcome until the present.

CONCLUSIONS

Two clinical cases of phaeohyphomycosis are presented. The first one favorably responded to a therapy that combined surgery and oral itraconazole to treat a subcutaneous phaeohyphomycosis. The second one, a cutaneous phaeohyphomycosis, presented an uncommon secondary contamination caused by the application of sugar on a varicose ulcer, a situation that required the consideration of several differential diagnoses. In this last case, the patient was completely healed after treatment with only oral itraconazole.



Figure 7. Culture *Curvularia lunata*.



Figure 8. Closed ulcer (4 months after treatment).

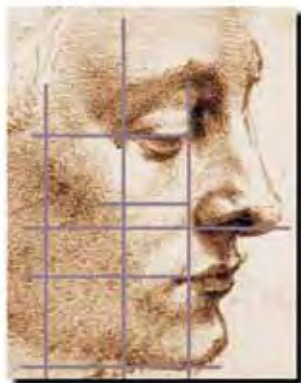
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CASE STUDY

Harlequin Ichthyosis

Nadia Akhdari, MD;¹ Mohamed Ouladsiad, MD;² Abdelmounaim Aboussad, MD;³ Said Amal, MD¹

A 2-hour-old newborn boy hospitalized in the neonatal intensive care unit was examined for unusual cutaneous lesions. He had firm plaques covering his body, with fissures especially in flexural areas. Other remarkable findings included edematous hands and feet, ectropion, eclabium, and contractures (Figure). Topical emollients and etretinate were advised, but the newborn died a few hours later. The parents were first-degree relatives. There was no family history of similar lesions. On the basis of clinical features, the diagnosis of harlequin ichthyosis was made.

Harlequin ichthyosis is an extremely rare ichthyosis with an incidence of 1 in 300,000 births.¹ Nearly all cases have an autosomal recessive inheritance, but some cases may present new dominant mutations. Defects in keratin expression and epidermal lipid deposition have been reported.^{2,3} Severe causative mutations have been identified, including a mutation in the ABCA12 gene.⁴ ABCA12 is a member of the adenosine triphosphate-binding cassette (ABC) superfamily of active transporters; it works as a keratinocyte lipid transporter

associated with lamellar granule formation and lipid transport on the surface of keratinocytes.

Clinical features include hyperkeratotic, yellow-brown, firmly adherent plaques covering the entire body surface. Facial features are distorted due to ectropion, conjunctival edema, and eclabium. Most affected infants die within the first few days of life due to causes from infection, dehydration, respiratory compromise, and hypothermia. Until now, few children have survived. Intensive neonatal care including



Figure. Hyperkeratotic scales, ectropion, eclabium, contractures, and fissures in a newborn.

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replacement in a humidified incubator, temperature regulation, nutrition and fluid replacement, infection control, skin and eye care, and early administration of systemic retinoids may be responsible for their survival.⁵ Severe nonbullous ichthyosiform erythroderma is the essential outcome. Genetic counseling is required for affected families. Prenatal diagnosis testing is available in select centers; it includes amniocentesis at 17 weeks' gestation, fetal skin biopsy, and ultrasonography.

CONCLUSIONS

Harlequin fetus is the most severe form of congenital ichthyosis, inherited as an autosomal recessive trait and usually considered to be fatal. Treatment combines neonatal intensive care, skin treatment, and administration of systemic retinoids.

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VINTAGE LABEL



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BRIEF SUMMARY

INDICATIONS AND USAGE

Locoid Lipocream is a topical corticosteroid indicated for: relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults and the treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age.

WARNINGS AND PRECAUTIONS

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid.

Systemic effects of topical corticosteroids may also include manifestations of Cushing's syndrome, hyperglycemia, and glucosuria.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios.

Initiate appropriate therapy if concomitant skin infections develop.

Discontinue use if irritation develops.

ADVERSE REACTIONS

The most common adverse reactions (>1%) are HPA axis suppression and application site reactions.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, Locoid Lipocream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please refer to full prescribing information for detailed information regarding systemic embryofetal development studies.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Locoid Lipocream is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below 3 months of age have not been established.

Because of higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (three times daily) in this HPA axis study were different from the subject population (mild to moderate atopic dermatitis) and the dosing regimen (two times daily) for which Locoid Lipocream is indicated. Five of the 82 evaluable subjects (6.1%) demonstrated laboratory evidence of suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Suppressed subjects ranged in age from 5 months to 16 years and, at the time of enrollment, had 25% to 95% BSA involvement. These subjects did not develop any other signs or symptoms of HPA axis suppression. At the first follow up visit, approximately one month after the conclusion of treatment, cosyntropin stimulation results of all subjects had returned to normal, with the exception of one subject. This last subject recovered adrenal function by the second post treatment visit, 65 days post-treatment.

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

Geriatric Use

Clinical studies of Locoid Lipocream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies were conducted to determine the photocarcinogenic or dermal carcinogenic potential of Locoid Lipocream.

Hydrocortisone butyrate revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames test and L5178Y/TK⁺ mouse lymphoma assay) and one in vivo genotoxicity test (mouse micronucleus assay).

No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to and including 1.8 mg/kg/day (0.7X maximum topical human dose [MTHD]). Mild effects on maternal animals, such as reduced food consumption and a subsequent reduction in body weight gain, were seen at doses ≥ 0.6 mg/kg/day (0.2X MTHD).

PATIENT COUNSELING INFORMATION

Patients using Locoid Lipocream should receive the following information and instructions:

Apply a thin layer to the affected skin two or three times daily for corticosteroid-responsive dermatoses in adults. Consult with your physician to determine if treatment is needed beyond 2 weeks. Apply a thin film to the affected skin areas two times daily for atopic dermatitis in patients 3 months of age and older. Safety of Locoid Lipocream in pediatric patients has not been established beyond 4 weeks of use.

Rub in gently.

Avoid contact with the eyes.

Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician.

Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may constitute occlusive dressings.

Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician.

If no improvement is seen within 2 weeks, contact your physician.

Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from freezing. Keep out of the reach of children.



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By: Ferndale Laboratories, Inc.
Ferndale MI 48220

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**Now younger eczema
patients have something
to smile about**

**Now approved for use in children
down to 3 months of age**



Locoid Lipocream®
(hydrocortisone butyrate 0.1%) Cream

The power of an ointment with the elegance of a cream

Locoid Lipocream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, including the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Safety and effectiveness in pediatric patients below 3 months of age have not been established.

Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing's syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.

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