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DIFFERIN® (adapalene) LOTION, 0.1%—
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PRESCRIBE DIFFERIN® LOTION, 0.1% TODAY!

*A 12-week, multicenter, randomized, double-blind, parallel-group study of patients 12 to 18 years of age with acne vulgaris (N=1075).
†The most frequent adverse event reported was dryness. Erythema, stinging/burning, and scaling may also occur.1

Important Safety Information
Differin® Lotion, 0.1% is indicated for the topical treatment of acne vulgaris in patients 12 years and older. A thin film of Differin® Lotion, 0.1% should be applied once per day to the face and other areas of the skin affected by acne. In clinical trials, the most common adverse event (>1%) reported with use of Differin® Lotion, 0.1% was mild to moderate skin dryness. Erythema, scaling, stinging and burning may also occur. Excessive exposure to sunlight and sunlamps should be avoided during treatment, and use of sunscreen products and protective clothing is recommended. Concomitant use of drying or irritating topical products (like products containing resorcinol, salicylic acid or sulfur) should be used with caution. Instruct patients to avoid the eyes, lips and mucous membranes when applying Differin® Lotion, 0.1%, and not to apply to areas that have been depilated with wax products. Differin® Lotion, 0.1% has not been tested in pregnant or nursing women, or with the elderly. Pregnancy Category C.

www.differin.com/HCP

Please see Brief Summary of Prescribing Information on adjacent page.
DIFFERIN® (adapalene) Lotion 0.1%

For Topical Use Only
Not For Oral, Ophthalmic, or Intravaginal Use.

BRIEF SUMMARY

INDICATIONS AND USAGE

DIFFERIN Lotion is a retinoid product indicated for the topical treatment of acne vulgaris in patients 12 years and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. Erythema, scaling, dryness, and stinging/burning may occur with use of DIFFERIN Lotion.

ADVERSE REACTIONS

Dry skin of mild to moderate severity was the most frequently reported (≥ 1%) treatment related adverse event. Erythema, scaling, dryness, burning/stinging were also seen during treatment.

DRUG INTERACTIONS

Concomitant use of topical products with a strong drying effect can increase skin irritation. Use with caution, especially in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Lotion. Wax depliation should not be performed on treated skin.

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with DIFFERIN Lotion. Therefore, DIFFERIN Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of human response.

Human Data

In clinical trials involving DIFFERIN Lotion, 0.1% in the treatment of acne vulgaris, women of childbearing potential initiated treatment only after a negative pregnancy test. Two women became pregnant while using DIFFERIN Lotion, 0.1%. One patient delivered a healthy full term baby and the other patient electively terminated her pregnancy.

Animal Data

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of DIFFERIN Lotion. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 times the MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m²) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Systemic exposure (AUC 0-24h) to adapalene at topical doses (6.0 mg/kg/day) in rats represented 101 times the exposure to adapalene in patients with acne treated with DIFFERIN Lotion applied to the face, chest and back (2 grams applied to 1000 cm² of acne-involved skin).

Nursing Mothers

It is not known whether adapalene is excreted in human milk following use of DIFFERIN Lotion. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Lotion is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of DIFFERIN Lotion in pediatric patients under the age of 12 have not been established.

Geriatric Use

Clinical studies of DIFFERIN Lotion 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 carcinogenicity, mutagenicity and impairment of fertility studies were conducted with DIFFERIN Lotion.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of DIFFERIN Lotion.

In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g. retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test).

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F₁ males and females, or growth, development and reproductive function of F₂ offspring.

PATIENT COUNSELING INFORMATION

• Apply a thin film of DIFFERIN Lotion to the affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. DIFFERIN Lotion may cause irritation such as erythema, scaling, dryness, stinging or burning.

• Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply DIFFERIN Lotion to the entire face or other acne affected areas as a thin layer, avoiding the eyes, lips and mucous membranes.

• Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis and eye irritation.

• Patients should be advised not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.

• Avoid patients to minimize exposure to sunlight including sunlamps. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.

• Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.

• This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.

• Wax depliation should not be performed on treated skin due to the potential for skin erosions.

• This product is for external use only.

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PS1503-0
Revised: March 2010

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With the influx of new diagnoses, even a disease with a long dossier may create problems for the International Classification of Diseases (ICD). Let’s visit with fictitious patient encounters:

Mr Doe, you have interleukin (IL)-12/23 psoriasiform disease. This is the new way insurance companies want us to call your condition so that it will be properly coded. A few years ago, you and I would have called it psoriasis, but now we know that there are several dermatoses that look like psoriasis but, at a molecular level, differ enough to make it of practical value to give them more specific names.

Other patients with skin lesions that look like yours suffer from IL-17–driven psoriasiform disease, which we also used to call psoriasis. There are a few other types of psoriasiform diseases whose names depend on the molecule that drives the development of psoriasis-looking lesions. The one you have will not get well enough with etanercept, adalimumab, or infliximab, which work great on another type of psoriasiform disease, driven by a different protein called tumor necrosis factor alpha (TNF-α), made by some cells of the immune system. For you, ustekinumab and briakinumab are the right choice. I can assure you of this because the test we performed showed that you have a mutation of the gene modulating IL-12/23 production.

A cardiologist across the hall might be saying: “You don’t have garden-variety coronary artery disease (CAD), you have TMEM43 CAD, which is associated with sudden cardiac death at a young age, and because you also have a mutant CYP2C19 gene, your disease is resistant to therapy with clopidogrel, so we may have to use low-dose warfarin to prevent your premature demise.”

A rheumatologist at the office above may be telling his patient: “This joint swelling is due to an excess of IL-1. I’m placing you not just on indomethacin, but also on anakinra, a biologic drug that blocks the action of such proinflammatory molecule. Even if I’m wrong, and what you have is gout, you should notice improvement in a few days.”

**COMMENT**

The above scenarios are likely to happen before the 10th revision of ICD (ICD-10) is implemented. Even though about 138,000 diseases are expected to be added to the nearly 17,000 in the ICD-9, the speed at which we are learning about genetic and other pathogenic mechanisms will lead to the outpacing of any fixed catalog based on clinical grounds. ICD-10 is mandated for implementation on October 1, 2013, after many years of delay. Estimations for the cost of doing this are as high as $8 billion, which translates to an expenditure of $84,000 for each small physician practice.

Coding systems should be flexible enough to incorporate new diseases as they become accepted by the medical community, and exact enough to identify a diagnosis. ICD-10 is neither. So, from the realization of this, ICD-11 is already in advanced stages of development. The incompetence of the currently used ICD-9 is, by the way, one of the many reasons making it practically impossible to properly implement electronic health records at this time. But we digress.

Case in point, the auto-inflammatory syndromes, such as the periodic fevers, which include Muckle-Wells syndrome and the Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) syndrome, are now known to be due to cytokine activation of inflammatory pathways. These conditions are increasingly being recognized. They arise from single gene mutations and are not to be confused with autoimmune diseases mediated through the adaptive immune system and antibody aberrant recognition of self. With the skin being involved in many of these conditions, it is inevitable that the scope of dermatology alone will expand. The last time we checked, there were some 25 ILs, a couple of tumor necrosis factors, and 3 interferons that you...
may need to memorize. And we can’t forget the receptors (such as toll-like [at least 9]), which are likely to be targeted for therapeutic reasons in the near future. We may also be giving targeted therapies for spider bites, staphylococcal infections, viral rashes, melanomas, and epithelial cancers, each with a unique set of cytokines to inactivate. Our ability to identify what cytokine must be blocked by what antibody or other biologic product for successful therapy will be required beyond a board test and will further separate those who went through medical school from some usurpers of dermatology, those who think that by learning through repetition they can become as qualified to deliver skin care as dermatologists. But we digress.

CONCLUSIONS
The above exemplifies how any insufficiently flexible and open disease coding system will, in real-time, become obsolete, as we predict will happen with ICD-10. We may as well consider skipping it. Otherwise, you may be left with a year or two to relax, retire, or put your physician assistant or nurse practitioner to good use making them learn a barrage of new, yet transient, ICD-10 codes, or to prepare.

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.

ROSAECA
SYNONYMS: Acne rosacea; Gutta rosea; Telangiectasis faciei.

DIAGNOSIS: Erythematous eczema burns and itches, causes early infiltration of the skin and scaling but no vascular dilatation, and does not remain confined to the rosacea region. The eczema, however, may complicate rosacea. Lupus erythematosus occurs in the same location but the lesions are sharply circumscribed and scaling and cause cicatrization. The distribution of tubercular syphilids is never so symmetrical; their grouping is usually serpiginous and they ulcerate. Telangiectases are absent.

TREATMENT: The disease is obstinate but mild cases can be cured and the others favorably influenced. Attention must first be directed toward the regulation or removal of all the conditions which tend to aggravate the disease. The acne should receive appropriate treatment. The lotion containing three per cent each of zinc sulphate and potassium sulphid, used in acne is beneficial also in rosacea. Or the more powerful liquor calcis sulphuratae may be used. It should be diluted at first with five parts of water and applied twice a day. The dilution is to be lessened by degrees. The object is to produce a mild desquamation. When this is accomplished the treatment should be suspended until the irritation has subsided. The larger venules are best destroyed by electrolysis. The needle attached to the negative pole should be inserted into the lumen of the vessel and a current of two milliamperes employed. Hypertrophic protuberances can be removed only by ablation with the scalpel.
COMMENTARY

What Is Kindler Syndrome?

Joey E. Lai-Cheong, MBBS, PhD, MRCP; John A. McGrath, MD, PhD, FRCP

In 1954, Dr Theresa Kindler, a pediatrician working in London, England, published a case report in the British Journal of Dermatology of a 14-year-old white girl with trauma-induced blistering, poikiloderma, and skin atrophy.1 The girl had features of both dystrophic epidermolysis bullosa (EB) and a congenital poikiloderma syndrome. In 2003, the molecular basis of Kindler syndrome (KS; OMIM 173650), named after the original author, was elucidated with the discovery of pathogenic mutations in the KIND1 (also known as FERMT1) gene, which encodes kindlin-1 (or fermitin family homolog 1).2,3 KS is an autosomal recessive genodermatosis, with approximately 100 cases reported to date. In 2008, KS was added to the classification of EB,4 but unlike the other forms of EB, which are caused by defects in the hemidesmosome-anchoring filament complex, KS results from a primary defect in an actin cytoskeleton-related protein that also impacts the underlying extracellular matrix.3

CLINICAL FEATURES OF KS

The cutaneous features of KS consist of acral trauma-induced blistering and skin atrophy, progressive poikiloderma, and varying degrees of photosensitivity (Figure).6 Both the blistering and the photosensitivity tend to diminish with age. Pseudosyndactyly, nail dystrophy, and finger webbing have also been reported. The noncutaneous features comprise desquamative gingivitis, severe periodontitis with loss of teeth,7 gastrointestinal involvement due to colonic inflammation resembling ulcerative colitis,8 ectropion, and stenosis of the esophagus, anus, vagina, and urethra.9 In addition, there is also an increased risk of mucocutaneous squamous cell carcinoma.

PATHOPHYSIOLOGY OF KS

KS results from pathogenic mutations in the KIND1/FERMT1 gene located on chromosome 20.2,3 The gene encodes kindlin-1/fermitin family homolog 1, an actin cytoskeleton-related protein that localizes at integrin-rich sites, termed focal adhesions, where it participates in integrin activation,10 an important process that mediates cell adhesion, cell migration, and cell-extracellular matrix interactions. Deficiency of the protein in KS, which is normally mainly expressed in basal keratinocytes, leads to reduced keratinocyte adhesion, loss of cell polarity, abnormal deposition of extracellular matrix such as laminin-332, and reduced proliferation of keratinocytes.10,11 In KS skin, kindlin-1/fermitin family homolog 1 is typically undetectable, and there is a major disorganization of the cutaneous basement membrane, with focal interruptions and reduplication at the dermal-epidermal junction.10

INVESTIGATION AND DIAGNOSIS OF KS

The diagnosis of KS can be difficult due to its clinical overlap with other mechanobullous and poikiloderma syndromes. The differential diagnoses include dystrophic EB (due to COL7A1 gene mutations)12 with which it is often confused, particularly in infancy; EB simplex with mottled pigmentation (resulting from KRT5 gene mutations)13; and Rothmund-Thomson syndrome (due to mutations in the RECQL4 gene).14 A clinical diagnosis of KS can be made on the basis of features such as acral blistering, poikiloderma, and skin atrophy, although skin biopsy and gene sequencing are helpful. Transmission electron microscopy of KS skin often shows extensive reduplication of the lamina densa, focal widening of the lamina lucida, and multiple planes of cleavage (intra-epidermal, within the lamina lucida and sublamina densa).15 Immunofluorescence microscopy labeling of KS skin can reveal abnormal labeling patterns for several basement membrane proteins, including 66β4 integrin, type XVII collagen, laminin-332, and types IV and VII collagens, reflecting the basement membrane disruption.10 A marked reduction or complete absence of immunostaining with antibodies to kindlin-1/fermitin family homolog 1 can also be useful diagnostically, although the availability of robust and reliable antibodies to the protein is currently limited.

To confirm the diagnosis of KS, KIND1/FERMT1 gene sequencing is helpful, but this test currently is restricted to a few diagnostic centers. To date, 44 different pathogenic FERMT1 mutations (including nonsense, frameshift, splice site, and large internal deletions) have been reported in individuals with KS.16

MANAGEMENT OF KS

Neonates with KS should be handled with care because of the fragile skin resembling dystrophic EB. During childhood, however, the blistering tendency diminishes in most cases of KS and may cease...
completely. The skin can be xerotic, and regular use of an emollient is advocated. Sun protection is recommended due to photosensitivity and the increased risk of early-onset squamous cell carcinoma. In some individuals, dysphagia can be a presenting symptom of esophageal stenosis. Radiographic imaging should be performed to determine the location and extent of the stricture. Esophageal dilatation may be required to relieve the stenosis. In men with KS, difficulty in micturition and urine retention can indicate urethral stenosis. In pregnant women, elective cesarian sections should be considered, because vaginal stenosis is not an uncommon feature of KS. Dental care, such as scaling and root planing and careful regular hygiene attention, are important due to aggressive periodontitis and gingivitis.18

CONCLUSIONS

KS is the first inherited disease resulting from pathogenic mutations in a gene that encodes an actin cytoskeleton-related and focal adhesion protein. Recent studies in the field of integrin biology and the clinical features of KS have highlighted the importance of kindlin-1/fermitin family homolog 1 in skin homeostasis; nevertheless, more work is required to further our understanding of the pathophysiology of this interesting genodermatosis. This may also generate new data about mechanisms underlying more common acquired skin pathologies, including skin aging and nonmelanoma skin cancer.

REFERENCES

VELTIN Gel—A Topical Treatment for Patients 12 Years or Older With Acne Vulgaris

Once-daily application in the evening

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 (≥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 actively assessed local 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

Please see brief summary of Prescribing Information on the next page.
**INDICATIONS AND USAGE**

VELTIN™ (clindamycin phosphate and tretinoin) Gel 1.2%/0.025% is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Colitis**

Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, blood, 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.

**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 require exposure to possible ultraviolet 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.

**ADVERSE REACTIONS**

**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 (≥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.

**DRUG INTERACTIONS**

**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.

**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.

**USE IN SPECIFIC POPULATIONS**

**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 teratogenicity study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 2.5 mg/kg during gestation days 6 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and Sprague-Harland 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.

**Transplacental**

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 species make it difficult to compare the embryotoxicology noted in these species with the 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 (32 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.

**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.

**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 2,986 patients 12-17 years of age with acne vulgaris. [See Clinical Studies (14) of full prescribing information.]

**NONCLINICAL TOXICOLOGY**

**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 not mutagenic for mutagenic potential when evaluated in a 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 photoco-carcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photoco-carcinogenic 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.

**PATIENT COUNSELING INFORMATION**

[See FDA-approved Patient Labeling in full prescribing information.]

**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 not 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.

**Skin Irritation**

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

**Colitis**

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

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Primary Anetoderma
Zain Husain, BS; W. Clark Lambert, MD, PhD

A netoderma is a dermatologic condition marked by localized laxity of the skin resulting from elastolysis, first described by Jadassohn in 1892. Clinically, lesions manifest on the upper trunk, arms, and thighs as round, well-circumscribed patches or papules of slack skin. They may appear atrophied or flaccid and demonstrate inward herniation. Histopathology often demonstrates deep or perivascular lymphocytic infiltrates. Elastic fiber stains generally show decreased or absent elastic fibers in the upper and middle dermis.

CLASSIFICATION
Anetoderma can be classified as primary or secondary based on etiology. Secondary anetoderma arises from an abnormal reparative mechanism of skin lesions, whereas the pathologic mechanism underlyign primary anetoderma (PA) has not been elucidated. Several theories have been proposed. PA may be caused by immunologic targeting of elastic fibers due to cross-reaction between related epitopes of elastic fibers and phospholipids. It may be due to disequilibrium of metalloproteinases and their inhibitors as a result of tissue ischemia. There may be increased release or activation of elastase by inflammatory cells. Loss of elastic fibers due to phagocytosis by macrophages and reduced production of elastic fibers have also been proposed.

PA may signify the presence of other disease processes. A relationship between PA and immunologic diseases has been well documented, especially with systemic lupus erythematosus (SLE). Other systemic associations include discoid lupus erythematosus, lupus profundus, systemic sclerosis, vitiligo, alopecia areata, thyroiditis, multiple sclerosis, and Addison’s disease. The association between PA and antiphospholipid syndrome was first described in 1991. Subsequent studies have shown antiphospholipid antibodies to be commonly associated with PA. Antiphospholipid syndrome (APS) is a disorder of hypercoagulation caused by specific autoantibodies against membrane phospholipids. Antibodies against B2GP1 (apolipoprotein H) cause a disturbance in the coagulation cascade, giving rise to hypercoagulation and thrombosis. The close relationship between PA and APS should be investigated further to determine whether the antiphospholipid antibodies develop in response to the pathologic mechanism giving rise to PA, or in contrast, the cutaneous findings are a result of antibody action.

ANTIPHOSPHOLIPID ANTIBODIES
The accompanying paper suggests that PA may be an early cutaneous manifestation of antiphospholipid antibodies. The authors have shown evidence from various serologic studies that strongly support this. The antibodies likely trigger the pathologic mechanism underlying PA. As a result, the diagnosis of PA can be helpful in the identification of other undiagnosed immunologic diseases. Physicians should be encouraged to test patients with PA for antiphospholipid antibodies and other autoimmune disorders such as SLE. If the diagnosis of APS is established early, measures can be taken to prevent thrombotic events induced by antiphospholipid antibodies. These patients can be given aspirin and preventive anticoagulant therapy to decrease their risk; furthermore, physicians can recommend lifestyle changes to minimize risk such as increasing exercise, quitting smoking, and avoiding oral contraceptives.

REFERENCES

See also page 168
Dengue (dengue hereafter) has shown a significant re-emergence in the world and particularly in the western hemisphere. Current statistics indicate that Venezuela alone had 100,000 cases in 2010; however, because dengue is not compulsorily reported, the true number likely exceeds this estimate. The disease is characterized by high fever (up to 40°C), profound malaise, headache, and pain within the orbits and in the bones and joints. The term dengue is taught to mean “breakbone fever.” The etymology is complex and has recently been well summarized by researchers. Yet, breakbone fever is a true and graphic description of the disease, wherein patients require rest but find difficulty in being comfortable while lying down. After a week or so, there may be a respite in discomfort and then another bout of fever and malaise returns (this is called the “saddle seat febrile curve”). A morbilliform eruption often appears and is associated with extreme itchiness and burning. The cheeks and trunk appear red, but the dorsa of the hands are usually not affected. There is no gross visible desquamation (Figure 1).

Fever is reduced by lysis, but there is a period of several weeks in which patients experience extreme weakness, depression, and fatigue. Patients often complain of feeling dull and uninterested in their usual tasks. Intellectual performance has been shown to decline during this period, but eventual recovery is complete.

In about 5% of cases, patients show petechiae and ecchymoses (“hemorrhagic dengue”), after temporary defervescence as described above. There may be bleeding in the gums, nose, or elsewhere in the body (Figure 2). Symptoms and signs depend on the sites affected by bleeding, which may include the kidneys and brain. In untreated and treated patients, shock and even death may occur as a result of increased permeability of capillaries. Survivors have an evolution similar to what is described above, but the period of weakness is longer and sequelae may occur, particularly in the nervous system.

**ETIOLOGY**

Dengue is caused by a flavivirus transmitted by the bite of arthropods. It is argued that the current re-emergence of the disease is the result of the predominance of aggressive vectors, namely *Aedes aegypti*, which also transmits yellow fever. Historically, there have been other vectors and the disease was found in rural areas, but this noiseless slow-flying, white-banded *Aedes* is a city-dweller. It deposits its eggs in small amounts of clear water. They can be found in houses or near them, flower pots, bonsai, or puddles. The mosquito is very mobile and insecticides have proven to be ineffective, except for residual compounds that are now inexistent since the banning of DDT.

There are four known serotypes of the virus. While infection elicits immunity, this is seemingly effective only against the causing genotype and leaves the host susceptible to infection by other vectors. It is unclear whether even isologous immunity is all encompassing or only temporary.

**PATHOGENESIS**

Damage caused by viremia is not completely understood in any viral disease. It is clear, however, that most effects are caused not by the microorganism itself but by immune or inflammatory mechanisms set in motion by the virus. Whether pathways of individuals who have no or very mild clinical disease and those who have severe conditions are qualitatively or merely quantitatively different, is something that has to be determined. Hemorrhagic dengue causes a fall in platelet number below a critical level. It is taught that this clinical form occurs when successive infections are caused by different serotypes, as if partial immunity is conducive to immune damage. This is congruent with known data, but it is not satisfying from a conceptual point of view: We do not fully believe this notion, although we have no valid alternative explanation.

**DIAGNOSIS, FOLLOW-UP, AND TREATMENT**

Suspicion of dengue is based on clinical features and presence of the disease in the community. Standard blood tests show leucopenia with neutropenia and a progressive lowering of platelet numbers. In typical cases, this does not reach critical levels (ie, <30,000/μL).

There are serologic tests to confirm the diagnosis, usually enzyme-linked immunosorbent assay, which show positive results after the first week, but earlier testing may serve to rule out preexisting antibodies. The typical patient needs only rest, an abundance of fluids with electrolytes, and acetaminophen. Aspirin is formally contraindicated. Dermatitis and pruritus may be difficult to manage. Antihistamines may prove ineffective (although desloratadine seems to work...
better). The same can be said of the usual antipruritic lotions, suspensions, and emulsions. In fact, some patients complain that hydroalcoholic shake lotions produce increased burning. Some patients benefit markedly from gabapentin 400 mg at bedtime or twice daily. Signs of concern include the following: age younger than 5 years or older than 65 years, presence of preexisting chronic diseases (diabetes, asthma, chronic renal ailments, and systemic autoimmune diseases), spontaneous bleeding in skin or other organs (Figure 2), and the presence of a positive Rumpel-Leede test. In these patients, there should be special attention to diuresis, hematocrit to detect hemoconcentration, and levels of transaminases, since the liver may be affected.

Patients with severe cases should be hospitalized to provide adequate anti-shock treatment10 and, in some instances, platelet transfusions.

PREVENTION

There is no current vaccine against dengue nor specific antiviral treatment that prevents transmission. Mosquito nets, including those treated with insecticides, are of theoretical use and not widely available or easy to employ. Fumigations with available insecticides are often performed, mainly for political reasons, but they are ineffective. DDT was useful but is not currently employed except in some areas of Africa. We know of no modern nontoxic residual insecticide on the market. Mosquito-fighting measures and public education to avoid stagnant water in homes and to cover containers look good on posters, brochures, and television ads, but they are ludicrous. Anyone who has lived in a country where dengue is endemic, with torrential rain, pot holes, and obstructed drains in the streets, knows that such posters and educational measures are futile.

Studies on the pathogenesis of the disease and of its immunology, including vaccines, are urgently needed. It is true that only a fraction of individuals exposed to Aedes under epidemic conditions develop the disease, but the mechanism of transmission of dengue parallels that of yellow fever. The latter is much more lethal but provides clear postinfection immunity and effective vaccines against it. Neither dengue nor yellow fever are exclusive diseases of the tropics. Outbreaks of dengue, including hemorrhagic forms, in temperate areas have been reported.7 Yellow fever has been historically present as far north as Philadelphia.

**Disclosure:** This contribution does not necessarily represent the opinion of the Vargas School of Medicine, Central University of Venezuela.

**REFERENCES**


Sulfur mustard (mustard gas) is an alkylating agent with mutagenic effects\(^1\) that was used extensively as a chemical warfare against Iranian civilians and veterans in the Iran-Iraq conflict (1983–1988).\(^2\) Sulfur mustard produces severe chemical injuries in primarily 3 major organs: skin, eyes, and lungs.\(^3\) Skin, due to its high surface area, plays an important role as a port of entry for liquid or vapor sulfur mustard. Sulfur mustard penetrates human skin at a rate of 1 mg/cm\(^2\)/min to 4 mg/cm\(^2\)/min.\(^4\) Skin involvement by mustard gas can be divided into acute and chronic effects. Chronic skin complications of sulfur mustard have been previously reported.\(^4–7\) Pruritus, the most common cutaneous complication in the chronic phase, occurs in 70% to 90% of patients exposed to sulfur mustard. Other late complications of sulfur mustard include blistering, necrotic wounds, and hyperpigmentation or hypopigmentation.\(^8\) Treatment in this phase is mainly symptomatic and includes topical corticosteroids, systemic antihistamines, and local emollients to reduce itching and improve skin dryness. The chronic nature of the lesions and their resistance to treatment require long-term application of these drugs.\(^9,10\) Long-term application of topical corticosteroids, however, can produce adverse effects such as skin atrophy, striae, rosacea, and acne.\(^11,12\)

Doxepin is a tricyclic compound with potent antihistaminic, antimuscarinic (by inhibition of H1 and H2 receptors), and antiserotonergic actions and is commonly used in pruritic conditions such as atopic eczema and chronic idiopathic urticaria.\(^13–15\) Topical doxepin acts by increasing norepinephrine and serotonin concentrations in central nervous system synapses and preventing their removal. Although the efficacy and safety of topical doxepin has been reported in atopic dermatitis associated with severe pruritus,\(^16\) its efficacy to control chronic skin lesions caused by sulfur mustard has not been evaluated. In the present study, the effect of topical doxepin 5% cream compared with betamethasone for the treatment of pruritus was investigated. Knowing that pruritus may affect patient’s quality of life (QOL) and daily activities,\(^17–19\) the Dermatology Life Quality Index (DLQI) was evaluated before and after treatment.\(^20,21\)

**ABSTRACT**

Oral doxepin was shown to reduce chronic pruritus due to sulfur mustard. The present study compared the effects of topical doxepin 5% with betamethasone 1% for the treatment of pruritus in veterans exposed to sulfur mustard. This investigator-blinded, randomized, clinical trial was conducted in an outpatient dermatology clinic. Seventy-five men who were exposed to sulfur mustard 23 to 28 years ago during the Iran-Iraq war who complained of pruritus were randomized to receive doxepin cream 5% (n=40) or betamethasone cream 0.1% (n=35) twice a day for 6 weeks. Pruritus severity and Dermatology Life Quality Index (DLQI) were evaluated before and after each treatment. Both groups showed significant improvement regarding pruritus (\(P<.05\)), burning sensation, skin dryness (\(P<.001\)), and skin scaling (\(P<.05\)). The lesions of all regions significantly reduced after treatments (\(P<.05\)), except those on the head, face, and genitalia. Pruritus, visual analog scores, and DLQI significantly decreased (\(P<.01\), \(P<.01\), and \(P<.001\), respectively) in doxepin- and betamethasone-treated groups, and there was no difference between groups. All DLQI subscores decreased after both type of treatments (\(P<.01\)). Equal efficacy of doxepin cream and betamethasone suggest that doxepin is a potential alternative to control pruritus caused by sulfur mustard in exposed veterans. (SKINmed. 2011;9:152–158)
T reatment of Chronic Skin Lesions With Topical Doxepin

included itching caused by systemic or cutaneous nonchemical diseases and history of topical treatments within 1 month before the study. The present study was approved by the ethics committee of Baqiyatallah Medical Sciences University, and all patients signed written informed consent before enrollment.

A total of 75 patients were randomly entered into two groups (A and B) based on a randomization protocol made by computer-generated random numbers, sequenced blocks AB and BA. Group A (n=40) received doxepin cream 5% (Zonalon, DPT Laboratories, Ltd, San Antonio, TX) and group B (n=35) received betamethasone cream 0.1% (Aburaihan Pharmaceutical Co, Tehran, Iran) twice daily for 6 weeks. To determine effective drug quantity, we applied the fingertip unit (FTU), which was equal to 0.47 g in men, so that 1 FTU was enough to cover both sides of a hand from rest to finger tips. The first session of treatment was held in the outpatient clinic to determine any hypersensitivity reactions.

Patients could not be blinded to treatment, because there were obvious differences in the color, smell, and consistency of the two studied medications. To ensure that the dermatologist remained blinded to treatment allocation throughout the study, however, he/she was not permitted to see the medications. Patients were visited twice (before and after the treatment), at which times physical examination and assessment of pruritus severity were performed by the dermatologist.

Pruritus severity was assessed by both pruritic score questionnaire and visual analog scale (VAS). The VAS is designed as a 100-mm horizontal line without scaling (0 = no pruritus to 100 = unbearable pruritus). Patients were then instructed to place a vertical mark reflecting their feeling of pruritus severity. A pruritic score was also calculated before and after the treatment course for each patient. The severity, distribution, and frequency of pruritus and pruritus-related sleep disturbance were monitored (Table I). Pruritus score has ranged from 0 to 48, where the higher score indicated severe pruritus. The severity of pruritus was graded to three categories as mild (1–16 points), moderate (17–32 points), and severe (33–48 points).

The DLQI, which includes 10 items and covers 6 domains, was used for evaluation of health-related QOL (HRQOL). The 6 domains of DLQI are symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The severity of itching during the previous week is assessed by the first question of the DLQI questionnaire. Patients were asked to score 0, 1, 2, and 3 categories of “not at all,” “a little,” “a lot,” and “very

Table I. Calculation of Total Pruritus Score From Detailed-Related Variables

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Slight itching sensation without necessity of scratching</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Slight itching sensation with necessity to scratch, but without excoriations</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Scratching accompanied by excoriation</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Pruritus causing total restlessness</td>
<td>5</td>
</tr>
<tr>
<td>Distribution</td>
<td>For each region (arms, trunk, or legs)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Generalized itching</td>
<td>5</td>
</tr>
<tr>
<td>Frequency</td>
<td>Two periods of less than 10 minutes</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>For each period more than 10 minutes</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Maximally</td>
<td>5</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Each scratching episode leading to excoriation during the night. Maximum=5.</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Each episode of waking up due to itching. Maximum=10.</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>For each time, morning, evening, and night with itching, 1 point was added to the score. Maximum=1+1+3.</td>
<td>3</td>
</tr>
<tr>
<td>Total score</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

‘For example, in patients who showed maximal frequency both in the morning and the afternoon, their score for frequency calculated as the following: 5+5=10. *For example, if a patient had experienced itching through the morning and evening that affected sleep, 2 points were added to the total score.

The score of severity, distribution, and frequency of pruritus was recorded separately for the morning and the afternoon, so that a maximum of 30 points could be achieved.^[15+15=30]"
much” responses as how much their skin problem has affected their life during the past week; moreover, “not relevant” and unanswered responses were scored “0.” The total score equals the sum of the scores of all the items, with a range between a maximum score of 30 and a minimum score of 0. In this type of evaluation, the higher scores indicate a lower QOL for patients.

STATISTICAL ANALYSIS

Difference of pruritus severity according to VAS and pruritic score was tested by the independent sample t test. Comparison of changes in these two measures before and after the treatment period was tested by paired sample t test. Chi-square test was used to compare presentation of other skin lesions between the two studied groups. Comparison of changes in DLQI and sub-scores before and after the treatment period was tested by Wilcoxon signed-rank test. Mann–Whitney nonparametric test was used to compare DLQI or subscores between the two groups. Data are presented as frequency, percentage, mean (standard deviation [SD]), and median, and P<.05 was selected as the significance level. All analyses were performed using SPSS software version 14.0 (SPSS Inc, Chicago, IL).

RESULTS

All patients were men who had been exposed to sulfur mustard about 20 to 25 years ago. The mean (SD) age of patients in the doxepin and betamethasone groups was 44.3 (5.2) and 46.16 years, respectively (P=0.2, data not shown). All patients completed the study.

Distribution of skin complications before and after treatment in each group is presented in Table II. Both groups showed a significant change in pruritus (P<.05), burning sensation, and skin dryness (P<.001) and scaling (P<.05). No significant difference was observed, however, between the two groups regarding each of these complications at baseline or after treatment.

Table III presents itching and eczema locations before and after treatment. Doxepin and betamethasone effectively reduced lesions on the thorax (P<.01 and P<.001, respectively), back (P<.01 and P<.001, respectively), upper and lower extremities (P<.001 and P<.01, respectively), and the armpit region (P<.01). Doxepin, not betamethasone, reduced the itching area in the groin region (P<.01). Between-group comparisons showed that the effects of doxepin on the groin region was significantly more than that seen with betamethasone (P<.05), while the differences were not significant with other regions.

According to pruritus score, severe pruritus was more frequent in both groups. A total of 23 patients (57.5%) in the doxepin group and 21 patients (60%) in the betamethasone group had severe pruritus. After treatment, 67.5% in the doxepin group and the majority of patients (30 cases, 94.2%) in the betamethasone group had moderate pruritus (P<.05). The levels of severity of pruritus (mild, moderate, and severe) in both groups before and after treatment are shown in Table IV.

Pruritus mean score was significantly decreased (P<.01) from 32.4±11.3 and 33.6±7.2 to 21.7±8.4 and 20.8±4.0 in the doxepin- and betamethasone-treated groups, respectively (Table V). Similarly, VAS mean score was decreased from 40.5±20.7 and 49.9±15.3 to 28.4±12.8 and 34.6±11.4 in the doxepin- and betamethasone-treated groups, respectively (Table V). There was no significant difference between the two groups in pruritic score or VAS.

The first question of the DLQI questionnaire (Q1) is about the patient’s skin itchiness during the past week. Analysis of first question results showed that at baseline, 24 patients (57.5%) in the doxepin group and 28 patients (80%) in the betametha-

### Table II. Distribution of Skin Complications in Both Groups Before and After Treatment

<table>
<thead>
<tr>
<th>Skin Complication</th>
<th>Treatment Status</th>
<th>Doxepin</th>
<th>Betamethasone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Before</td>
<td>100</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>45.2a</td>
<td>37.5b</td>
<td>.3</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>Before</td>
<td>61.3</td>
<td>68.8</td>
<td>.5</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>25.8a</td>
<td>28.1b</td>
<td>.8</td>
</tr>
<tr>
<td>Skin dryness</td>
<td>Before</td>
<td>58.1</td>
<td>71.9</td>
<td>.2</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>16.1a</td>
<td>25.0b</td>
<td>.3</td>
</tr>
<tr>
<td>Scaling</td>
<td>Before</td>
<td>71.0</td>
<td>65.6</td>
<td>.6</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>35.5a</td>
<td>31.3b</td>
<td>.7</td>
</tr>
</tbody>
</table>

All data are expressed as percentage. *P<.05 and bP<.01 show the significance between before and after treatment values of the same group. P values for comparison between groups are in the right column of this table.
sone group had very itchy skin during the previous week, which significantly decreased \( (P<.01) \) to 7 (17.5%) and 13 (37.5%) after treatment, respectively (Table VI). The same results were obtained for total DLQI \( (P<.001) \) and DLQI-Q1 \( (P<.001) \) in the doxepin- or betamethasone-treated patients (Table VII). Between-group comparisons showed no significant difference before treatment \( (Q_1, P=.29; \text{DLQI}, P=.12; \text{DLQI-Q1}, P=.09) \) or after treatment \( (Q_1, P=.12; \text{DLQI}, P=.09; \text{DLQI-Q1}, P=.08) \).

All evaluated subscores, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment significantly decreased with doxepin or betamethasone \( (P<.01) \), and there was no significant difference between the two types of treatment in DLQI subscores (Table VIII).

**DISCUSSION**

Treatment of chronic skin complications caused by sulfur mustard exposure is limited to oral antihistamines and topical corticosteroids. After exposure to sulfur mustard, 10% of the agent is absorbed and fixed to the skin for years\(^{24,25}\) which requires long-term application of topical medications to relieve pruritus and control other symptoms. The mean DLQI in the present study was 18.6 and 25 for the doxepin and betamethasone groups, respectively, at the beginning of the study. Comparison of these results with other skin diseases such vitiligo, psoriasis, and atopic dermatitis (DLQI=7, 14, and 18, respectively)\(^{26,27}\) shows that HRQOL of chemically injured veterans is greatly affected by dermal complications.\(^{28}\)

Some clinical trials have been designed to evaluate the efficacy and safety of treatments that can be administered over a long period instead of short-term treatment with corticosteroids.\(^{28,29}\) In a recent study in our center, it was revealed that pimecrolimus cream 1% was well tolerated and as effective as topical betamethasone 0.1% in the treatment of chronic skin lesions and pruritus caused by sulfur mustard.\(^{29}\) In another study, we showed that a combination of phenol 1% and menthol 1% had significant therapeutic effects on pruritus and other chronic skin lesions compared with placebo and decreased the prevalence of pruritus from 100% to 85%.\(^{30}\) In the present study, topical treatment with doxepin potentially reduced pruritus (from 100% to 45.2%) that was similar

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**Table III. Distribution of the Involved Region Before and After Treatment in Both Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Status</th>
<th>Doxepin</th>
<th>Betamethasone</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>Before</td>
<td>19.4</td>
<td>15.6</td>
<td>.4</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>19.4</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>Before</td>
<td>29.0</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>19.7</td>
<td>13.1</td>
<td>.2</td>
</tr>
<tr>
<td>Thorax</td>
<td>Before</td>
<td>48.4</td>
<td>56.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>23.3(^a)</td>
<td>18.8(^b)</td>
<td>.2</td>
</tr>
<tr>
<td>Back</td>
<td>Before</td>
<td>41.9</td>
<td>46.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>25.8(^a)</td>
<td>9.4(^b)</td>
<td>.08</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>Before</td>
<td>58.1</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>16.1(^b)</td>
<td>10.0(^b)</td>
<td>.1</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Before</td>
<td>77.4</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>41.9(^a)</td>
<td>25.0(^b)</td>
<td>.1</td>
</tr>
<tr>
<td>Groin</td>
<td>Before</td>
<td>67.7</td>
<td>62.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>21.6(^a)</td>
<td>50.0</td>
<td>.05</td>
</tr>
<tr>
<td>Armpit</td>
<td>Before</td>
<td>29.0</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>6.5(^a)</td>
<td>4.3(^b)</td>
<td>.1</td>
</tr>
<tr>
<td>Genitals and perinea</td>
<td>Before</td>
<td>19.4</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>16.1</td>
<td>19.4</td>
<td>.4</td>
</tr>
</tbody>
</table>

All data are expressed as percentage. \(^{a}P<.01\) and \(^{b}P<.001\) show the significance between before and after treatment values of the same group. \( P \) values for comparison between groups are in the right column of this table.
to the effect of betamethasone (from 100% to 37.5%). In addition, a significant decrease after treatment was observed regarding burning sensation, scaling, and skin dryness in both doxepin- and betamethasone-treated groups (Table II). These findings confirm the results of a 2007 study that compared the safety and efficacy of doxepin (oral consumption, 10 mg/d) for the treatment of chronic pruritus and showed that it decreased the severity of pruritus in 75% of patients.31 Another study also confirmed the role of oral doxepin in decreasing chronic pruritus as a result of sulfur mustard.32 It seems, however, that the effects of local treatment with doxepin are comparable with oral consumption, while patients can tolerate the topical treatment better than the oral treatment.33 Doxepin can affect different types of receptors13–15; therefore, oral doxepin can produce systemic side effects that are absent when doxepin is applied topically.

Doxepin cream 5% showed equal efficacy compared with betamethasone cream 0.1% in decreasing pruritus, scaling, burning sensation, and skin dryness caused by sulfur mustard. One of the advantages of topical doxepin compared with systemic doxepin is a lack of severe side effects, which can make it intolerable for patients. Although no significant improvement was observed in

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Doxepin</th>
<th>Betamethasone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5 (12.5)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (30)</td>
<td>14 (40)</td>
<td>0.3</td>
</tr>
<tr>
<td>Severe</td>
<td>23 (57.5)</td>
<td>21 (60)</td>
<td>0.9</td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9 (22.5)</td>
<td>1 (2.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (67.5)</td>
<td>33 (94.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (10)</td>
<td>1 (2.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>P value</td>
<td>0.05</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

All data are expressed as frequency (percentage).

<table>
<thead>
<tr>
<th>Assessment Time</th>
<th>Doxepin</th>
<th>Betamethasone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritic score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>32.4±11.3</td>
<td>33.6±7.2</td>
<td>.6</td>
</tr>
<tr>
<td>After</td>
<td>21.7±8.4</td>
<td>20.8±4.0</td>
<td>.5</td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td>0.01</td>
<td>–</td>
</tr>
<tr>
<td>VAS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>40.5±20.7</td>
<td>49.9±15.3</td>
<td>.4</td>
</tr>
<tr>
<td>After</td>
<td>28.4±12.8</td>
<td>34.6±11.4</td>
<td>.4</td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td>0.01</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviation: VAS, visual analog scale. Data are expressed as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Q1 of DLQI Before and After Treatment</th>
<th>Doxepin</th>
<th>Betamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little</td>
<td>3 (7.5)</td>
<td>0</td>
</tr>
<tr>
<td>A lot</td>
<td>14 (35)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Very much</td>
<td>23 (57.5)</td>
<td>28 (80)</td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: DLQI, Dermatology Life Quality Index; Q1, question 1. Data are shown as number (percentage) of patients for each group.
lesions of the head and face, both medications reduced lesions on the thorax, back, upper and lower extremities, and axillae. One of the reasons for failure of treatment to improve lesions on the head can be attributed to the presence of hair, which decreases its absorption. The effect of doxepin treatment in reducing groin lesions was more significant than with betamethasone; however, the effect on the genitals and perinea was similar. In a 2007 survey, 68% of chemically injured veterans experienced pruritus on their inguinal area; itching in this area within the company of others is an extremely uncomfortable experience. In the present study, the effects of both treatments on DLQI subscores of work and school activities and personal relationships were significant.

Pruritus was the most common symptom in the current study (reported in 100% of patients), and its severity according to VAS and pruritic score decreased significantly in doxepin- or betamethasone-treated patients. In our opinion, this is the most valuable finding to date, because decreased pruritic and VAS scores accompanied by reduction in itchy skin was revealed in the first question of the DLQI questionnaire (Table VI). Due to long-term application of topical corticosteroids in patients exposed to sulfur mustard, the skin becomes sensitive as a result of scratching behavior caused by the pruritus, which is believed to play an important role in initiating cutaneous infections and inflammatory responses; therefore, reducing the pruritus severity is considered more valuable.

Other DLQI subscores were also significantly affected by doxepin and showed decreased DLQI scores.

**CONCLUSIONS**

Doxepin cream 5% reduced pruritus, VAS, and DLQI scores effectively, and these results suggest that it can be applied in the clinic without producing betamethasone-related adverse effects. Further studies to evaluate the effects of topical and oral doxepin may highlight the beneficial effects of topical doxepin in the treatment of chronic skin lesions caused by sulfur mustard.

**Disclosure:** All financial aid for this study was funded by Baqiyatalab Medical Sciences University, Tehran, Iran.
REFERENCES


**Important Safety Information for DUAC Topical Gel**

- DUAC Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin.
- DUAC Topical Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.
- Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus.
- For dermatologic use only; not for ophthalmic use.
- Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.
- The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.
- Clindamycin- and erythromycin-containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known.
- DUAC Topical Gel may bleach hair and colored fabrics.
- Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.
- DUAC Topical Gel should be given to a pregnant woman only if clearly needed.
- It is not known whether DUAC Topical Gel is secreted into human milk after topical application. 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.
- Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.
- Adverse reactions may include erythema, peeling, burning, and dryness.
- Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with DUAC Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**PLEASE NOTE:**
The soap-free cleanser is no longer included in the package. Please prescribe DUAC Topical Gel 45 g.

**DUAC Topical Gel**

**Delivers on efficacy…**

**Handles Patients With Care**

**DUAC Topical Gel** is indicated for the topical treatment of inflammatory acne vulgaris.

**DUAC Topical Gel** has not been demonstrated to have any additional benefit when compared with benzoyl peroxide alone in the same vehicle when used for the treatment of noninflammatory acne.

**DUAC Topical Gel is the once-daily clindamycin/benzoyl peroxide combination with a patented formula containing both glycerin and dimethicone.**

The contribution to efficacy by individual components of the vehicle has not been established.

- No therapeutically equivalent generic substitute
- More than 6 million prescriptions of DUAC Topical Gel dispensed since launch

**References:**
**PRECAUTIONS**

**General:** For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. The use of antibiotic agents may be associated with the overgrowth of nonresistant organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures. Avoid contact with eyes and mucous membranes. Clindamycin and erythromycin containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known.

**Information for Patients:** Patients using DUAC Topical Gel should receive the following information and instructions:

1. DUAC Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.

4. Patients should report any signs of local adverse reactions to their physician. Patients who develop allergic symptoms such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.

5. DUAC Topical Gel may bleach hair or colored fabric.

6. DUAC Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.

7. Before applying DUAC Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.

8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

**ADVERSE REACTIONS**

During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

<table>
<thead>
<tr>
<th>Local reactions with use of DUAC Topical Gel</th>
<th>% of patients using DUAC Topical Gel with symptom present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combined results from 5 studies (n = 397)</td>
</tr>
<tr>
<td></td>
<td>Before Treatment (Baseline)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Erythema</td>
<td>28%</td>
</tr>
<tr>
<td>Peeling</td>
<td>6%</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Percentages derived by # subjects with symptom score/# enrolled DUAC Topical Gel subjects, n = 397). Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in post-marketing use with DUAC Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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A pattern of seborrhoeic dermatitis characterized by follicular prominence in truncal lesions has been recognized by textbook authors for more than a century. Because it is somewhat uncommon, and shares a number of features with *Malassezia* folliculitis it is not consistently diagnosed by all physicians. I will describe a typical case, summarize other cases seen in my practice, and review the history and differential diagnosis of this disorder.

CASE REPORT

A 62-year-old man was seen on referral from his primary care physician because of persistent dermatitis involving his scalp, neck, and torso. He stated that the problem had been present for more than 10 years but had only been present on the neck for about 5 years. He reported that the condition had been partially controlled with fluocinolone cream applied every 2 to 3 days. He washed his hair daily with a zinc pyrithione shampoo. He also previously had used oral ketoconazole and ketoconazole shampoo with some success. He noted that the areas of involvement seemed to be enlarging gradually.

Skin examination revealed elongated oval patches of erythematous skin parallel to the skin folds on the anterolateral neck, with trace scaling and without follicular accentuation. There were large, poorly circumscribed areas of faint erythema on the back (Figure 1), more prominent on the left side, studded with 1- to 2-mm pink-to-red follicular papules with no visible scale. Similar patches of clustered small papules were prominent on the lower chest and upper abdominal skin (Figure 2).

The diagnosis of seborrhoeic dermatitis, follicular variant, was made, and the patient was treated with ketoconazole foam for the torso and ketoconazole shampoo for the scalp. Five weeks later, his neck and back lesions had resolved and the chest lesions had been reduced to very subtle faint pink papules.

DISCUSSION OF CASES

Seven patients were men, and one was a woman (Table I). Only one patient was younger than 25 years, and he had concomitant acne. All patients had involvement of the skin of the back, with some patients having chest and neck involvement as well, and one patient had similar follicular lesions on his legs. In all cases, the involved areas occupied a geographic pattern (Figure 3) of somewhat circumscribed areas of follicular macules, small papules, and variable erythema and fine scaling. These areas were usually asymmetric in distribution and were not limited to the presternal or interscapular areas as is seen in classic petaloid seborrhoeic dermatitis of the torso. No patients were noted to have associated keratosis pilaris, none had Down syndrome, and none complained of pruritus.

Only two patients underwent biopsy. One biopsy showed follicular enlargement and perifollicular lymphocytic inflammation, with a negative fungal stain. The other patient had a follicular pustule, but unfortunately the fungal stain, which showed scant surface yeast forms, did not include any follicular structures to examine.

Some patients had experienced temporary improvement after the use of ketoconazole or topical steroids, but case 2 showed no clinical response after 4 weeks of weekly ketoconazole orally at a dose of 400 mg per week.
Four of the patients were treated with oral isotretinoin. In two of these patients, total clearing was achieved by the end of 3 months of therapy. The dermatitis returned within 2 months of completing treatment in one of these men; the other was lost to follow-up. One patient failed to improve after 4 weeks and was then lost to follow-up. The fourth patient discontinued isotretinoin after 2 weeks because of intolerance of the resulting retinoid cheilitis.

HISTORICAL REVIEW

While Paul Gerson Unna is often given credit for the best early description of seborrheic dermatitis in 1887,1 the disorder is recognizable in the writings of earlier authors, under such names as “eczema squamous,” and Ferdinand von Hebra devoted several pages to the manifestations of seborrhea on the scalp, face, and external genitalia2 in 1860. Before Unna’s classic paper, Philadelphia dermatologist Louis A. Duhring had clearly described involvement of the torso under the name of “seborrhea corporis.”3 He pointed out that the chest and back may be simultaneously involved, but “owing to the difference in the anatomical structure of the skin, the lesions are somewhat unlike.” He describes the chest lesions as smaller and better circumscribed. The back lesions are said to be “as large as a silver dollar. They may exist separately, but they more often coalesce, forming one continuous, irregularly-shaped patch.”

“They are pinkish or reddish in color, but being partially covered with yellowish or grayish scales often have a pale look. The scales are rarely in any quantity; they are usually loose, and are in many cases altogether wanting, having been detached and rubbed away by the friction of the clothing. The mouths of the follicles are observed to be open and sluggishly discharging their secretion.” He further alludes to the follicular prominence by pointing out that “acne papules and pustules are occasionally seen here and there about the borders of the disease.” Subsequent Philadelphia textbooks by John Shoemaker4 and Henry Stelwagon5 reiterate these descriptions.

The English dermatologist Henry Radcliffe Crocker described the typical midchest and interscapular eruption of seborrheic dermatitis familiar to most dermatologists, labeling it “seborrhœa papulosa seu lichenoides” and equating it with Duhring’s seborrhea corporis. He mentions the presence of pinhead-sized papules, but only occurring as individual early lesions, or located at the margins of enlarging patches.6 This localization of papules at the margins of enlarging patches continues to be mentioned in textbooks up until the present day, but was not uniformly seen in the patients described in this article.

Richard Sutton’s dermatology text of 19167 discusses the common presternal and interscapular presentations of seborrheic dermatitis, but makes no reference to follicular involvement. Andrews refers to the follicular variant briefly in his standard textbook.8 Writing in 1939, he states “the affection has a predilection for the sternal and interscapular areas, the axillae, groins, navel, and gluteal crease. In these areas symmetrical macular yellowish patches with more or less greasy scaling are characteristic, but less frequently the lesions are circinate patches or follicular papules.” Early editions of Arthur Rook’s textbook also mention follicular lesions in truncal seborrheic dermatitis. Emphasizing the presence of follicular lesions in the development of petaloid forms of the disease, it is stated,9 “The initial lesion is a small, red-brown follicular papule covered by a greasy scale; some patients have a widespread eruption of lesions which do not progress beyond this stage. More often, extension and confluence of the follicular papules have given rise to a figured eruption consisting of multiple circinate patches with fine, branny scaling in their centres and with dark red papules with larger greasy scales at their...
advancing margins.” In a subsequent edition, while retaining the same clinical description, the morphologic variants of seborrheic dermatitis are enumerated, including a follicular (“acneiform”) pattern, which is said to be seen predominantly on the back, but also occasionally elsewhere on the body.10

The authors discuss *Pityrosporum* folliculitis a few pages later, and list it as synonymous with “seborrheic folliculitis.” The same categorization is used in the 2004 edition of Rook’s textbook.11

In reading the clinical description of *Pityrosporum* folliculitis in this section, one begins to wonder whether the authors are including follicular seborrheic dermatitis under this label, without providing conclusive evidence that the two conditions are identical. They write on page 17.15, “The condition most commonly affects adult males, and is associated with a tendency to seborrhoeic dermatitis or severe dandruff. It has been reported in 12 of 42 patients with Down’s syndrome. The dermatitis is dimorphic, with erythematous follicular papules and follicular pustules. Lesions occur mainly on the upper trunk and shoulders, and are usually pruritic.”

Further potential for confusion can be found elsewhere in the same textbook,11 where on page 31.14, Hay and Moore describe *Malassezia* folliculitis in the Mycology section as comprising “itchy papules and pustules, which are often diffusely scattered on the shoulders and back,” consistent with my concept of this disorder. In contrast, on pages 43.33, Simpson and Cunliffe11 discuss *Pityrosporum* folliculitis in the differential diagnosis of acne and characterize it as presenting “on the upper trunk as moderately ill-defined superficial plaques, among which are scattered many papules or pustules” and illustrate the disorder with a photograph of a patient with a large patch of apparently eczematous skin, well-margined and studded with papules, that appears to me to be a typical example of follicular seborrheic dermatitis.

An excellent example of the type of patient I am describing is illustrated with a photograph in *Fitzpatrick’s Dermatology in General Medicine*, 7th edition, labeled as “seborrheic dermatitis of the upper back.”12

Two articles describe lesions similar to my cases in individuals with Down syndrome. In the earliest of these,13 the eruption was seen in 42% of 110 men, predominantly in those aged 20 to 40 years, and was rare in women. Two cases underwent biopsy, showing parafollicular inflammation, but without mention of yeast forms. The authors concluded that the condition was likely a follicular variety of seborrheic dermatitis.

The second article by Kavanaugh and colleagues14 (mentioned above in the Rook citation) described a nonpruritic folliculitis in 45% of 22 men with Down syndrome and 10% of 20 women. A biopsy was not performed, but cultures were attempted in 12 cases, with 4 growing *Malassezia furfur*. A good clinical response to oral itraconazole led the authors to conclude that their patients had *Malassezia* folliculitis. I believe the clinical description of the patients in both of these papers is more consistent with follicular seborrheic dermatitis than with *Malassezia* folliculitis, but the authors of the Rook section on *Malassezia* folliculitis apparently accept the conclusion of the Kavanaugh presentation that these are examples of *Malassezia* folliculitis.

**DIFFERENTIAL DIAGNOSIS**

Several entities can be considered here. Keratosis pilaris shares some features, but it is most often found on the posterior aspect of the arms, which is almost never the case with seborrheic dermatitis. The follicular lesions of keratosis pilaris can at times consist solely of discrete dark red circular macules, which are similar in appearance to some cases of follicular seborrheic dermatitis. Lichen spinulosus shares the presence of multiple red follicular papules grouped in geographic patterns but is not associated with superficial scaling of the interfollicular skin and is not predisposed to be limited to the sebaceous areas of the trunk. *Tinea versicolor* manifests as patterned areas of scaly erythema on the sebaceous areas of the torso, but it lacks follicular papules...
and has a characteristic preponderance of filamentous forms of *Malassezia* on potassium hydroxide preparations from the scales. Petaloid seborrhoeic dermatitis can overlap or coexist with this pattern, but it is usually symmetrically centered about the midline of the chest and/or back and often lacks the follicular accentuation seen in these patients.

*Malassezia* folliculitis is the most important alternate diagnosis to consider, and if the Rook textbook is to be believed, there may be no difference. This is not an unreasonable position, considering the fact that the disorders under discussion are both follicular, both are predominantly seen on areas of abundant sebaceous glands, and both involve the *Malassezia* species of yeast in their pathogenesis. There are stereotypical differences in the clinical presentations, however, that are troublesome if they are to be considered synonymous.

**MALASEZZIA (PITYROSPORUM) FOLLICULITIS**

*Malassezia* folliculitis was first described as a complication of antibiotic administration by Weary in 1969 and in 7 additional cases by Potter in 1973. The lesions may be acute or chronic, erythematous, pruritic follicular papules and pustules, usually encountered on the back and chest, and occasionally on the neck, shoulders, arms, and face. The causative organism is part of the normal endogenous cutaneous microflora, with a recent study from Japan demonstrating *Malassezia globosa* and *Malassezia sympodialis* in lesion cultures. It is said to have a 1.5:1 female to male ratio. A recent case series from France, however, included 22 men and only 4 women, with 70% of patients complaining of itching. Affected patients are often in the 13- to 45-year age range and are often treated unsuccessfully for acne. A series from Sweden stated that “the typical patient is a young woman complaining of itching…” In contrast, the Rook description of *Pityrosporum* folliculitis states that most patients are men, and many have seborrhoeic dermatitis. Is it possible that these authors are discussing two distinct but overlapping disorders?

### Table I. Additional Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age, y</th>
<th>Distribution</th>
<th>Associated Disorders</th>
<th>Biopsy/KOH</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Female/38</td>
<td>Neck, upper part of back</td>
<td>None</td>
<td>Superficial follicular pustule with perifollicular lymphocytic infiltrates. Inconclusive periodic acid-Schiff results</td>
<td>Topical steroids, oral ketoconazole, sulfur/sulfacetamide lotion, isotretinoin</td>
</tr>
<tr>
<td>3</td>
<td>Male/15</td>
<td>Chest and back</td>
<td>Acne vulgaris, bacterial folliculitis on legs</td>
<td>None</td>
<td>Desoximetasone cream</td>
</tr>
<tr>
<td>4</td>
<td>Male/27</td>
<td>Back</td>
<td>Contact dermatitis of axillae</td>
<td>None</td>
<td>Ketoconazole shampoo scrubs, isotretinoin</td>
</tr>
<tr>
<td>5</td>
<td>Male/52</td>
<td>Lower midback</td>
<td>Psoriasis, rosacea</td>
<td>None</td>
<td>Desoximetasone cream</td>
</tr>
<tr>
<td>6</td>
<td>Male/40</td>
<td>Chest, back</td>
<td>None</td>
<td>Slightly widened follicular infundibulum with hyperkeratosis, perifollicular spongiosis, and lymphocytic exocytosis, negative fungal stains</td>
<td>Cephalexin, isotretinoin</td>
</tr>
<tr>
<td>7</td>
<td>Male/42</td>
<td>Back, chest, abdomen, thighs</td>
<td>None</td>
<td>Negative KOH scraping</td>
<td>Isotretinoin</td>
</tr>
<tr>
<td>8</td>
<td>Male/36</td>
<td>Chest, back</td>
<td>Atopic dermatitis and rhinitis, steroid rosacea</td>
<td>Negative KOH scraping</td>
<td>Tacrolimus ointment, doxycycline</td>
</tr>
</tbody>
</table>

Abbreviation: KOH, potassium hydroxide.
It is likely that some patients may experience a combination of *Pityrosporum* folliculitis and seborrheic dermatitis, but this highlights the question of whether all patients with follicular papules on the back that respond to antifungal therapy have *Malassezia* folliculitis, or do some of them actually have a distinct disorder, namely follicular seborrheic dermatitis?

Skin biopsy in *Malassezia* folliculitis shows follicular dilation, keratin plugging, and an inflammatory infiltrate including lymphocytes, histiocytes, and neutrophils. *Malassezia* yeasts are abundant in the ostium, as well as in the central and deep portions of the follicle.18

While most patients with *Malassezia* folliculitis are treated successfully with antifungal therapy, both successes and failures have previously been reported with the use of isotretinoin. One case of unsuccessful treatment occurred in a man with an eruption similar to the cases reported here but with a biopsy demonstrating yeast elements in a follicle.21

In contrast to the 8 cases reported in this contribution, patients that I have recognized in my practice as having *Malassezia* folliculitis have had lesions that are more acute and edematous in appearance, resembling acne, that are more symmetrically located across the upper torso (Figure 4), and that lack grouping into geographic patterns. Patients are more likely to have pruritus and more often are women than men.

**TO LUMP OR TO SPLIT?**

Are patients fitting the description of follicular seborrheic dermatitis best categorized as *Malassezia* folliculitis, as portions of the Rook text and the Kavanaugh articles suggest, or should they continue to merit a separate designation in the absence of biopsy proof of intrafollicular *Malassezia*? Faergemann and associates22 extensively studied the inflammatory mediators and inflammatory cells present in 15 cases of seborrheic dermatitis and 8 cases of *Pityrosporum* folliculitis, but the issue of clinical overlap was not addressed in those patients. The fact that little has been written regarding this issue suggests that the distinction is probably not a very important one. It is a question worth asking, however, because seborrheic dermatitis, including the follicular variant, is by definition a chronic and relapsing disorder not amenable to permanent cure, whereas some cases of yeast folliculitis, especially those provoked by external factors such as antibiotic administration, may clear completely and permanently.

**Table II. Distinctions Between Follicular Seborrheic Dermatitis and *Malassezia* Folliculitis**

<table>
<thead>
<tr>
<th></th>
<th><strong>FOLLICULAR SEBORRHEIC DERMATITIS</strong></th>
<th><strong>MALASEZIA FOLLCULITIS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex predominance</td>
<td>Male</td>
<td>Female?</td>
</tr>
<tr>
<td>Lesion morphology</td>
<td>Monomorphous papules and macules with some scaling</td>
<td>Acneiform, succulent papules, and pustules</td>
</tr>
<tr>
<td>Interfollicular skin</td>
<td>Variable redness and scale</td>
<td>Normal</td>
</tr>
<tr>
<td>Grouping</td>
<td>Geographic clustering with sharp margination, sometimes asymmetrical</td>
<td>Diffuse and symmetrical</td>
</tr>
<tr>
<td>Location</td>
<td>Back and chest</td>
<td>Back, chest, and neck</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Usually absent</td>
<td>Usually prominent</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Yeast sparse or absent in follicle</td>
<td>Abundant intrafollicular yeast</td>
</tr>
</tbody>
</table>
It is possible that patients, resembling those described here, do indeed have *Malassezia* folliculitis superimposed on seborrheic dermatitis, but, to verify this, more cases will need to be examined with skin biopsy to demonstrate abundant follicular yeast forms. Since both seborrheic dermatitis and *Malassezia* folliculitis typically respond to antifungal agents such as ketoconazole or itraconazole, response to such therapy cannot be regarded as a distinguishing feature. In the few previous case series of patients resembling mine, few if any skin biopsies have been performed. If future cases prove on skin biopsy to be devoid of yeast, such as my case 6, that would argue for a continued separation of these two diagnoses.

Pending further reports with biopsies, I propose the two disorders be considered separate, with distinguishing features as summarized in Table II.

**Disclosure:** There are no conflicts of interest.

**REFERENCES**

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A netoderma is an elastolytic skin process clinically characterized by circumscribed, rounded areas of slack skin. Two forms are usually recognized: primary and secondary anetoderma.

Secondary anetoderma is due to an abnormal repairing mechanism of previous skin lesions. Acne and varicella are the most frequent causes.

In the primary form, the lesions appear de novo on previously healthy skin. Primary anetoderma (PA) has been related to a variety of pathologies, mainly autoimmune diseases; however, a strong link between PA and the presence of antiphospholipid antibodies was recently established.

Clinically, PA lesions are characterized by circumscribed, round or oval areas of atrophic skin with reduced consistency on palpation that occasionally adopt a protruding saccular appearance (Figure 1 and Figure 2). Most frequently, the lesions are localized on the trunk, neck, and arms, but other sites can be affected. No previous dermatosis precedes them on the location where they develop. Patients with PA may be totally asymptomatic or may develop pruritus, redness, or other signs of inflammation at any time.

Histologically, a superficial, and usually deep, perivascular lymphocytic infiltrate is identified with hematoxylin and eosin (Figure 3). Although lymphocytes dominate, other inflammatory cells may be found. No epidermal or subcutaneous cell tissue alterations are observed. Occasionally, giant cells may be found in the dermis, including granuloma formation. In a minority of patients, microthrombi in the dermal vessels has been described. This phenomenon is likely related to the exact period when the biopsy was performed.

Diagnosis of anetoderma is made by finding elastolysis and elastorrhexis via elastic fiber stains. These changes affect mainly the papillary dermis, but the reticular dermis is also frequently involved. In addition, some fibers may adopt a characteristic tortuous and thinned aspect (Figure 4 and Figure 5).

The role of direct immunofluorescence in the study of PA is not clear. Case series and isolated reports show variable results, and immune deposits may or may not be found. Morphology of the deposits may be granular or linear. Several combinations of immunoglobulins (Ig) (mainly IgM and IgG, and occasionally IgA) and complement fractions (especially C3 and C1q) are possible. They may be found in the dermoeidermal junction area, in the vascular walls, or along dermal elastic fibers.

PA has been related to multiple diseases. Its association with autoimmune pathologies, mainly lupus erythematosus (LES) and antiphospholipid syndrome (APS), has been highlighted. PA has also been related to other diseases such as cutaneous LES, thyroiditis, Addison disease, scleroderma, hemolytic anemia, and autoimmune thrombocytopenia. Likewise, PA has been associated with antinuclear antibodies, rheumatoid factor, antithyroid antibodies, and other serologic markers. Recently, some cases of PA have been found in patients with the human immunodeficiency virus (HIV).

In recent years, many publications have shown, nevertheless, that the strongest and most constant associated finding of PA is the presence of antiphospholipid antibodies. Although these antibodies may arise as an isolated phenomenon, they usually appear related to autoimmune diseases or infections, and this may, in fact, justify the heterogeneity of

Primary anetoderma is a rare idiopathic disease of the skin characterized by circumscribed areas of slack skin and loss of elastic fibers found on histopathologic examination. It has been related to systemic lupus erythematosus and other immune diseases. In recent years, however, its association with antiphospholipid antibodies has been highlighted, and it should be considered a clinical manifestation of these antibodies. (SKINmed. 2011;9:168–171)
conditions linked to PA in the past. As an example, among LES patients, PA is only found in those with antiphospholipid antibodies.5,19,20

**LINK BETWEEN PA AND ANTIPHOSPHOLIPID ANTIBODIES**

In reviewing the literature, it is noteworthy that several old publications report cases of PA associated with positive serologic tests for syphilis, but without cutaneous manifestations of syphilis.2 In one of the largest series of PA, it was determined that in 14 patients, the Venereal Disease Research Laboratory test (VDRL) (which has low sensitivity and specificity as an antiphospholipid antibody detection method) found only one false-positive case.2 Researchers performed VDRL and lupus anticoagulant on 6 patients, but only one was positive for the latter and no one was reactive for VDRL.7

By introducing anticardiolipin (aCL) IgG and IgM antibodies in the screening of PA patients, however, the sensitivity of antiphospholipid antibody detection has increased. In one study, 4 of 5 patients with anetoderma and LES were positive for lupus anticoagulant and 3 for aCL antibody isotype IgG, IgM, and/or IgA. In spite of that, in a later survey, the same author studied retrospectively the presence of lupus anticoagulant and aCL antibody isotypes IgG and IgM in 14 patients with PA (one of them with LES), but found only one case with antiphospholipid antibodies.21

As the search of antibodies is performed with higher sensitivity and specificity methods, the association of cases of PA-antiphospholipid antibodies increases. In this regard, the strongest data are shown by publications that supplement the analysis with the anti-β2-glycoprotein I antibodies (anti-β2-GPI) search.22 In one report, antiphospholipid antibodies were found in all patients studied with anetoderma.16 A later investigation described the same findings in 8 of 9 cases.23 Recently, we have reported two cases of PA, finding anti-β2-GPI and aCL antibodies in both patients. None of them fulfilled criteria for systemic lupus erythematosus or APS; however, one patient had glomerulonephritis (possibly of lupus etiology) and the other had tumid lupus lesions.8

Where in addition to IgG and IgM isotypes, IgA isotypes of aCL and anti-β2-GPI antibodies are investigated, the results are even more conclusive. Thus, yet another study detected presence of antiphospholipid antibodies in each of 9 patients with PA analyzed. None of them had a diagnosis of LES.15

PA is currently recognized as a possible manifestation of the presence of antiphospholipid antibodies.15,24,25 These antibodies may arise as an isolated laboratory disturbance, they can be found related to autoimmune diseases and infections, or they can specifically be part of an APS.25-27 Noteworthy, almost half of patients studied in the most recent case series may be included in the cases with APS, since in addition to the presence of the antiphospholipid antibodies, these patients also showed thrombotic events or obstetric complications.15,16,25 In some of them,
these alterations took place years after the development of anetodermic lesions, which had constituted the first clinical sign of the syndrome.15

**POSSIBLE PATHOGENIC MECHANISMS**

Pathogenesis of PA is unknown. Many theories try to explain the elastolytic phenomenon. A possible mechanism may be the immunologic attack of elastic fibers, as a consequence of cross-reaction between β₂-glycoprotein I and epitopes of those fibers. This would be supported by the presence of immune deposits surrounding elastic fibers, as is found in some patients.7,12 The current tendency considers the problem as a metalloproteinases and their inhibitors disequilibrium. The antiphospholipid antibodies may trigger tissue ischemia and/or an inflammatory response, thus increasing the expression of gelatinase and reducing the expression of their inhibitors, causing elastolysis.20 The presence of dermal vessel microthrombosis would suggest that ischemia may trigger the phenomenon.5,21 On the other hand, perivascular immune deposits would support inflammation as a main cause.7,12,13

**CONCLUSIONS**

PA should be considered a cutaneous lesion highly suggestive of antiphospholipid antibodies presence, with or without APS. In every patient with PA, therefore, those antibodies should be investigated thoroughly, in addition to ruling out autoimmune diseases (especially LES) and HIV infection. In patients with moderate-high titers of antiphospholipid antibodies and without a history of thrombotic events, treatment with low doses of aspirin is recommended and primary preventive anticoagulant therapy is justified in surgeries requiring immobilization.30 It is also important to prevent other prothrombotic factors such as obesity, smoking, and use of oral contraceptives. Because PA may be an early sign of diverse autoimmune diseases, especially APS, long-term follow-up of this group of patients is mandatory.

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Fabry disease (FD) is an X-linked lysosomal disorder caused by the deficient activity of the enzyme α-galactosidase A, which leads to multi-systemic storage of globotriaosylceramide in visceral tissues and vascular endothelium. FD manifests primarily in affected hemizygous men, with a wide range of clinical signs in heterozygous women. Acroparesthesias, angiokeratomas, pain crisis, and cornea verticillata are early manifestations of FD. With age, severe complications involving the kidneys, heart, and brain cause considerable morbidity and premature death. Although the clinical onset of FD occurs in childhood, diagnosis is often delayed or missed. In men, the diagnosis must be confirmed biochemically by demonstration of decreased levels of α-galactosidase A activity. In women, the disease is diagnosed by identification of a mutation in the α-galactosidase A gene. Until a few years ago, the existing treatment for FD was based on clinical manifestations, but the advent of enzyme replacement therapy should stimulate the identification of the signs and symptoms suggestive of this disorder to allow earlier diagnosis and treatment. (SKINmed. 2011;9:173–177)

Epidemiology and Pathophysiology

FD, after Gaucher disease, is the second most prevalent lipid storage disease, with an incidence estimated to be 1:117,000 of live births and 1:40,000 of men.12

FD is an X-linked recessive inherited disease; therefore, sons who inherit the gene are affected by the disease and daughters are carriers but may also be variably affected by random inactivation of the X chromosome. Parents with the disease do not transmit the defective gene to their sons, but they do transmit it to their daughters.1

The gene for α-galactosidase A is located on the X chromosome at q22.1, and more than 370 mutations have been identified, where the missense mutations account for more than half. The mutations are usually “private,” restricted to a single or few families.13

A deficient activity of α-galactosidase A results in impaired biodegradation of glycosphingolipids and progressive accumulation of globotriaosylceramide (Gb3) in epithelial cells of the kidney, myocardial cells, valvular fibrocytes, neuronal cells, and endothelial, perithelial, and smooth muscle cells of blood vessels.1

Clinical Manifestations

FD is a slowly progressive disease. Clinical manifestations begin in childhood or adolescence and change as the patient ages (Table). The main causes of death are renal failure, heart disease, or stroke around the age of 50 years for hemizygous men14 and 70 years for obligate carrier women.15

Although clinical onset occurs in childhood, the appearance of the disease may be subtle or attributed to other disorders; therefore, there is often a long delay between the onset of the symptoms and the correct diagnosis of FD.12–16

Cutaneous lesions appear in childhood, and their number increases with the age. The simplest recognizable clinical...
characteristics are AKs and telangiectasias. Although not pathognomonic of this disease, they are part of the cutaneous manifestations of “Fabry disease rash” according to some authors.14–17

AKs are red-to-violaceous papular lesions that do not disappear on pressure, generally in the buttock, umbilical, thigh, and genital areas (typical bathing suit distribution), and may extend to the lips, fingers, chest, and arms (Figure 1, Figure 2, Figure 3). In men, AKs tend to join by regions, and in women are usually smaller, more disseminated and more frequent on the chest, periumbilical area, and fingers.18,19 Histopathology of AK consists of dilated blood filler vessels in the upper dermis lying beneath a thinned epidermis. Hyperkeratosis is especially severe in AK on the hands, feet, legs, or older lesions, but it may be absent in scrotum or early lesions (Figure 4). Ultrastructural tests reveal lipid-containing intracytoplasmic vacuoles in endothelial cells, fibroblasts, and pericytes (“zebra bodies”). Such inclusions, however, are not pathognomonic for FD, because they are also found with other lysosomal storage diseases.20

AKs have to be differentiated from hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease), solitary AK, AK of Mibelli, AK of Fordyce, eruptive angioma, pyogenic granuloma, petechiae of meningococcal meningitis, fucosidosis, and sialidosis.17–21

Telangiectasias are present mostly in men on the face, lips, oral mucosa, and conjunctivae. Hypohidrosis and, more rarely, anhidrosis, are reported frequently in men. Impairment of sweating ability in these patients produces xeroderma with intolerance to heat and exercise, nausea, dyspnea, headache, or loss of consciousness.18,19

Leg edema and lymphedema, in the absence of cardiac or renal disease, appear more commonly in patients with FD than in the general population.19 Fifty percent of patients may also have reduced production of tears and saliva.17

Neuropathic pain typically occurs during childhood in 80% of patients and declines as patients age. It may be chronic on the soles and palms or episodic “crisis” acroparesthesia may occur on the hands and feet. Recurrent painful episodes are most frequently triggered by cold, heat, fever, exercise, stress, or fatigue. A burning sensation in the palms and soles often radiating to the proximal extremities and occasionally to the abdomen is common.22

Central nervous system symptoms include tinnitus, disturbance of concentration, dizziness, headaches, and learning difficulties, and personality changes, cognitive deficits, and dementia have also been reported. Transient ischemic attacks or stroke affect 15% to 20% of FD patients.23 More frequent misdiagnosis of pain and neurological symptoms comprise rheumatoid arthritis, rheumatic fever, arthritis, Raynaud’s syndrome, “growing pains,” multiple sclerosis, or simulation, among others.16–21

The eyes are affected in most patients, and cornea verticillata is a distinctive sign found in more than 80% of men and 60% of women. Posterior cataracts, vascular lesions (blood vessels showing varying degrees of tortuosity) in the retina, and conjunctiva are seen in both men and women.21 High-frequency sensorial hearing loss is common.24

Most FD patients develop proteinuria in late adolescence, which progresses to isosthenuria and produces tubule function alterations. Renal complications announce the terminal stage of the disease and progression to renal failure is the primary cause of death in homozygous patients.14–25

Cardiac involvement is variable and includes left ventricular hypertrophy, an enlarged left atrium, heart valve abnormalities, atrial arrhythmia, and conduction disturbance.26 Cardiac involvement may be the only symptom in some hemizygous men, with hypertrophic cardiomyopathy (“cardiac variant of FD”).27

Gastrointestinal manifestations may occur as abdominal pain, diarrhea, nausea, vomiting, postprandial feeling of fullness, early satiation, and weight loss.25–28

Obstructive airway disease is common in FD, and is more pronounced in older patients. Smokers with FD exacerbate pulmonary impairment and may produce recurrent respiratory tract infections than would be expected from smoking alone.29
DIAGNOSIS

The diagnosis of FD in hemizygous men begins with a comprehensive history taking of the chronologic development of pain, AKs, hypohidrosis, palpitations, and gastrointestinal symptoms and with a complete clinical examination. A family history may reveal relatives of patients who have died from kidney or heart disease at an early age.

In a series of reported cases, there are positive correlations between the presence of AK and other early signs and symptoms of FD, such as acroparesthesias, cornea verticillata, and proteinuria,18,19–22 which emphasizes that early recognition of cutaneous manifestations increases the chances of a timely diagnosis.

In men, the diagnosis must be confirmed biochemically by demonstration of α-galactosidase A activity in plasma or peripheral leukocytes, tears, tissue biopsies, or culture skin fibroblasts. In contrast, women can have normal to very low α-galactosidase A activity; therefore, demonstration of a genetic alteration is necessary to confirm the diagnosis. Prenatal diagnosis is possible by measurement of α-galactosidase A activity in fetal cells obtained by amniocentesis of chorionic villus sampling.16

TREATMENT

Until a few years ago, treatment was nonspecific, symptomatic, and supportive.

Standard doses of nonsteroidal anti-inflammatory drugs, phenytoin, carbamazepine, or gabapentin often at a low dose, and minimization of activities that trigger painful episodes (emotional stress, exercise, temperature changes) may treat or prevent painful crises and acroparaesthesias.16

AKs have been treated with excision surgery, electrocoagulation, freezing with liquid nitrogen or carbon dioxide ice, and laser systems.17

Prophylactic anticoagulants and antiplatelet agents are recommended for patients who are susceptible to stroke, while coronary artery and bypass grafting and heart transplant have been successfully conducted in a few patients.

Antihypertensive drugs are crucial for management of renal impairment. Angiotensin-converting-enzyme inhibitors are recommended for proteinuria. Dialysis or renal transplant could extend life, but, although the transplanted kidneys remained free from the disease, damage to other systems continue to progress, especially in the brain and the cardiovascular system.16

In mid-2001, two groups of investigators published randomized placebo-controlled studies evidencing that in FD, enzymatic replacement may revert to the main pathological consequences: agalsidase α, manufactured using a new genetic engineering procedure from a human fibroblast cell line; and agalsidase β, from genetically modified ovarian cells from Chinese hamsters. Agalsidase α is infused at a dose of 0.2 mg/kg intravenously every 2 weeks for 40 minutes, and agalsidase β at a dose of 1 mg/kg intravenously every 2 weeks for 3 or 4 hours.30,31

Patients treated with agalsidase α exhibit a significant reduction in pain and increase in quality of life, compared with patients treated with placebo. There is a normalization of the structure of renal glomeruli, a normalization of cerebral perfusion, and improvement in cardiac function. In addition, agalsidase α therapy leads to improvements in auditory function, cardiomyopathy, sweat secretion, gastrointestinal problems, and neuropathy. The studies that led to the approval of agalsidase β show statistically significant reduction in urine and plasma Gb3 content and improvement in renal histopathology, and lysosomal inclusions in liver, heart, and skin decreased. Agalsidase β has shown a benefit
relative to placebo in delaying progression to a renal, cardiac or cerebrovascular event, or death in patients with mild to moderate kidney disease.32

The safety of enzyme replacement therapy in children has been demonstrated recently. Treatment is generally well tolerated, and the most common adverse events reported are infusion reactions in the form of rigor and fever. Immunoglobulin G antibody formation has been reported with both preparations in 50% of patients, but there is no clear evidence of any impact on clinical efficacy of treatment.32

Another approach to the treatment of FD is substrate deprivation, based on the inhibition of an earlier step in the synthesis of the accumulating glycosphingolipid.33

An emerging strategy for the treatment of lysosomal storage diseases is pharmacologic chaperone therapy, based on the use of chaperone molecules that assist the folding of mutated enzymes and improve their stability and lysosomal trafficking, increasing the level of residual enzyme activity.34 Future research should be directed toward the development of treatment protocols based on the combination of different therapies to improve the clinical outcome of FD patients.

Gene therapy offers hope that, one day, there will be a cure for FD and other lysosomal storage diseases. A possible approach would involve gene transfer to hematopoietic cells.35

CONCLUSIONS

FD is a rare X-linked inherited multisystemic disorder, often underdiagnosed, with early onset, progressive organ damage, and premature mortality. With the advent of enzyme replacement therapy, it is important that physicians recognize the signs and symptoms of this disease so that effective treatment can be given. The early presence of dermatologic manifestations stand out; therefore, just like the initial description by dermatologists, the analysis of cutaneous signs emphasize the role that dermatology plays in the early diagnosis of this disease.

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References:

*In vitro activity does not necessarily correlate to in vivo activity.

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A novel two-compound scalp formulation (topical suspension) containing calcipotriol (50 µg/g) and betamethasone (0.5 mg/g, as dipropionate) (Xamiol, Taclonex Scalp, LEO Pharma Inc, Parsippany, NJ) (aka calcipotriene 0.005% and betamethasone dipropionate 0.064% combination topical suspension) has been shown to be an effective and safe treatment for scalp psoriasis. Betamethasone is a class 2 topical corticosteroid and must be distinguished from augmented betamethasone, which is a class 1 topical corticosteroid. Studies have shown that Taclonex Scalp (1) has superior efficacy when compared with either of its components alone at 8 weeks; (2) has a rapid onset of action with significant clinical affect in 1 week; (3) improves patient quality of life; and (4) has few side effects. Taclonex Scalp topical suspension joins the combination of calcipotriol (50 µg/g) and betamethasone ointment in being approved for treatment of limited stable plaque psoriasis. In some markets, this combination in a gel preparation is also available.

Taclonex Ointment (calcipotriene 0.005% and betamethasone dipropionate 0.064%) is approved for use on the skin to treat psoriasis vulgaris (plaque psoriasis) in adults aged 18 years and older and should be applied to affected areas once daily for up to 4 weeks. Taclonex Scalp Topical Suspension (calcipotriene 0.005% and betamethasone dipropionate 0.064%) is approved for treating moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and older and should be applied to affected areas on the scalp once a day for 2 weeks until cleared. If the affected area is not cleared, Taclonex Scalp may be continued for up to 8 weeks. Do not exceed the recommended weekly dosage of 100 g. Neither product is recommended for use in children.

A new $0 copay program for both Taclonex Ointment and Taclonex Scalp has been put in place in the first quarter of 2011. The program is offered through health care providers and online at www.taclonex.com. Patients who have been prescribed Taclonex Ointment or Taclonex Scalp can obtain a patient savings card from their health care providers or visit the Web site to download the card. The site generates a personalized card that can be presented at the pharmacy along with a prescription. The card entitles the patient copay assistance for up to 6 prescriptions, with a maximum benefit of $200 off per prescription. There is no activation required, and the card is valid until December 31, 2012. This card, as is true with all cards, is not valid with Medicare or Medicaid patients.

PHASE III DATA

The approval of Taclonex Scalp Topical Suspension rests on several phase III studies. One 8-week, multicenter, double-blind, parallel-group study randomized adult patients with scalp psoriasis involving >10% of the scalp to the two-compound scalp formulation (n=568), betamethasone dipropionate 0.5 mg/g (n=563) or calcipotriol 50 µg/g (n=286). The primary efficacy measure was the proportion of patients with “absence of disease” or “very mild disease” according to investigators’ assessments at week 8. The proportion of patients with “absence of disease” or “very mild disease” at week 8 was significantly higher in the two-compound scalp formulation group (68.4%) than the betamethasone dipropionate (61.0%) or calcipotriol (43.4%) groups. The proportion of patients rating their scalp psoriasis as “clear” or “almost clear” was significantly higher in the two-compound scalp formulation (69.6%) than for betamethasone dipropionate (59.9%) or calcipotriol (44.7%). The incidence of lesional/perilesional adverse events was lower in the two-compound formulation (69.6%) than for betamethasone dipropionate (59.9%) or calcipotriol (44.7%). The incidence of lesional/perilesional adverse events was lower in the two-compound and betamethasone dipropionate groups than the calcipotriol group.

Another phase III study found similar efficacy for the two-compound scalp formulation and betamethasone dipropionate,
slightly lower efficacy for calcipotriol, and a noninsubstantial positive placebo effect. In this second 8-week, multicenter, randomized, double-blind study, patients with scalp psoriasis were randomized to treatment with the two-compound scalp formulation (calcipotriene 50 μg/g plus betamethasone 0.5 mg/g, as dipropionate) (n=541), betamethasone 0.5 mg/g (as dipropionate) in the same vehicle (n=556), calcipotriene 50 μg/g in the same vehicle (n=272), or vehicle alone (n=136). More patients achieved “absent” or “very mild” disease at week 8 with the two-compound scalp formulation (71.2%) compared with betamethasone dipropionate in the same vehicle (64.0%), calcipotriene in the same vehicle (36.8%), or the vehicle (22.8%).

ONE-WEEK EFFICACY DATA
Calcipotriene 0.005% and betamethasone dipropionate 0.064% combination topical suspension works quickly. Analysis of pooled data from two large pivotal phase III trials with 2920 patients receiving once-daily treatment for up to 8 weeks with either the two-compound scalp formulation (n=1108), betamethasone dipropionate (n=1118), calcipotriol (n=558), or the vehicle (n=136) assessed the progress that patients had after 1 week of medication use. The percentage of patients who had “absent” or “very mild” disease according to Investigator’s Global Assessment after 1 week of treatment was significantly higher with the two-compound scalp formulation (30.6%) compared with betamethasone (24.1%), calcipotriol (10.0%), or vehicle (6.9%).

POSITIVE EFFECTS ON QUALITY OF LIFE
Taclonex Scalp has positive effects on patients’ quality of life. This 8-week, randomized, investigator-blind study, compared the once-daily, two-compound scalp formulation (calcipotriol 50 μg/g plus betamethasone 0.5 mg/g) with twice-daily calcipotriol scalp solution (50 μg/mL) in patients with scalp psoriasis of at least moderate severity covering ≥10% of the scalp. Quality of life was assessed (weeks 0, 2, 4, and 8) using the 36-item Short-Form Health Survey (version 2; SF-36v2) and Skindex-16. Treatment with the two-compound scalp formulation (n=207) resulted in significant improvements from baseline on the SF-36v2 (Physical Component Summary week 8; Mental Component Summary, weeks 2, 4, and 8). A significant change from baseline in the calcipotriol scalp solution group (n=105) was seen only on the Mental Component Summary (P=.04, week 8). Change from baseline in Skindex-16 was significantly in favor of the two-compound scalp formulation. Change was significant on both total score and individual scales.

CONCLUSIONS
Calcipotriol (50 μg/g) and betamethasone (0.5mg/g, as dipropionate) combination scalp solution (Taclonex Scalp) is a useful preparation that treats scalp psoriasis. A Scottish study found a two-compound formulation calcipotriol and betamethasone dipropionate gel for the treatment of scalp psoriasis cost-effective. No cases of atrophy, striae, or steroid purpura were noted in two 52-week studies of combinations of these agents in a gel form. How this combination product compares in effectiveness and side effects with augmented betamethasone dipropionate scalp solution or clobetasol propionate gel, solution, or foam or class 1 steroids has yet to be determined. The patient assistance cards should make this preparation widely available to appropriate patients.

REFERENCES
The Food and Drug Administration (FDA) has proposed new rules for sunscreen products. The proposed final monograph includes a new UV-A rating system for products with sun protection factor (SPF) claims. It sets standards for formulating, testing, and labeling over-the-counter sunscreen drug products with UV-A and UV-B protection. In the United States, very few sunscreens are currently available that provide adequate UV-A protection. Under the new monograph, only sunscreens that demonstrate both UV-A and UV-B protection may claim “broad-spectrum” coverage. What remains unclear is the nature of UV-A–induced mechanisms of skin injury and how adequate UV-A filters provide protection from UV-A exposure. Under the existing sunscreen monograph, few approved UV-A sunscreens are available for use. In the absence of such filters, what additional approaches are available to minimize UV-A damage to skin? What does adequate UV-A protection really mean in the context of our ability to measure it?

SPF values have been used to indicate the level of UV-B protection for more than 30 years. The deleterious effect of UV-A (320–400 nm) for human skin was not well appreciated at that time. The proposed final sunscreen monograph will provide ratings derived from two tests that the FDA proposes for assessing the effectiveness of sunscreens in providing protection against UV-A light. The first test measures a product’s ability to reduce the amount of UV-A radiation that passes through it, and the second test measures a product’s ability to prevent tanning. This test is nearly identical to the SPF test used to determine the effectiveness of UV-B sunscreen products.

The proposed regulation creates a consumer-friendly rating system for UV-A products designed to help consumers identify the level of UV-A protection offered by a product. The FDA proposal provides a rating system for UV-A sunscreen products on a scale of 1 to 4 stars. One star would represent low UV-A protection, 2 stars would represent medium protection, 3 stars would represent high protection, and 4 stars would represent the highest UV-A protection available in an over-the-counter sunscreen product.

If a sunscreen product does not provide at least a low level (1 star) of protection, the FDA is proposing to require that the product bear a “no UVA protection” marking on the front label near the SPF value.

CUTANEOUS PIGMENTATION

The synthesis of melanin by melanocytes and the transfer of melanosomes containing melanin to the surrounding keratinocytes results in cutaneous pigmentation. Once in the keratinocytes, melanin granules accumulate above the nuclei and absorb harmful UV radiation, minimizing DNA damage. UV-A (320–400 nm) passes through most glass (auto, office, and windows) and penetrates deep into the dermal layer of skin. It is estimated that about 19% to 50% of solar UV-A light can reach the depth of melanocytes, while only about 9% to 14% of solar UV-B light reaches the same cells. UV-A stimulates tanning that is transient and less protective against UV-induced injury compared with tans generated after UV-B exposure. It is hypothesized that UV-A reacts with endogenous photosensitizers, flavins, porphyrins, and melanins, generating reactive oxygen species, which, in turn, generate DNA single-strand breaks or photoadducts.

Other studies have shown that use of narrow-band UV-B, about 311 nm) is more preferable for phototherapy than psoralen and UV-A therapy, which can cause undesirable side effects, including cutaneous cancers. UV-A causes immediate tanning after exposure, which begins to fade within 3 hours and may be based on photodestruction of preexisting melanin, melanin precursors, and possibly other epidermal constituents. It is known that UV-A produces harmful oxygen species including singlet oxygen, hydroxyl radicals, and superoxide and melanin interacts with them to protect from further skin damage.

ANTIOXIDANTS AND SOLAR EXPOSURE

Biopsies from patients with histologically confirmed solar elastosis and biopsies taken from non–UV-exposed sites of age-matched controls and young volunteers were analyzed. Levels of antioxidant enzymes catalase, copper-zinc superoxide dismutase,
and manganese superoxide dismutase were investigated using immunohistochemistry. In photoaged skin, a significant depletion of antioxidant enzyme expression was observed in the stratum corneum and epidermis. An accumulation of modified proteins was found within the upper part of the dermis of photoaged skin. Acute UV exposure of healthy persons was associated with depleted catalase expression and increased protein oxidation. Exposure of keratinocytes and fibroblasts to UV-B and UV-A and hydrogen peroxide led to dose-dependent protein oxidation. The investigators concluded that the observed protein oxidation alterations may be linked with photodamaged skin. These observations, in the opinion of the investigators, provide a rationale for antioxidant strategies to prevent photoaging and acute photodamage in skin.

**UV-A–INDUCED PHOTOCARCINOGENESIS**

Both UV-B and UV-A exposure are involved in photocarcinogenesis. UV-A exposure generates dipyridimidine photoproducts, which are poorly repaired and isomerizes into Dewar products that are highly mutagenic compared with UV-B produced photoproducts. UV-A induction of singlet oxygen production is involved in signal transcription factor–mediated gene expression and observed in UV-A–damaged skin. Formation of thymine-thymine–type cyclobutane pyrimidine dimers in UV-A–induced damage is associated with a greater tendency of UV-A radiation to induce DNA genotoxicity, promoting malignancy. UV-A exposure has been shown to mediate transcription factor–induced expression of cell adhesion molecules. The upregulation of matrix metalloproteinases promotes invasiveness of the tumor and expression of cell adhesion molecules (ICAM-1), permitting tumor anchorage and vascular invasion, which are involved in tumor metastases.

**UV-INDUCED OXIDATIVE STRESS AND PHOTOIMMUNOSUPPRESSION**

Wavelengths in the UV-A region may be equally effective as UV-B in activating immune suppression. Solar-simulated UV radiation was found to suppress delayed-type hypersensitivity to recall antigens. UV radiation also suppressed contact allergy in individuals presensitized to nickel, indicating that solar UV-A radiation plays a role in activating immune responses.

**CONCLUSIONS**

Protection against erythema and sunburn is provided primarily by UV-B filters. UV-B filters do not provide equal immune protection when the immunologic end point is used. In addition to UV-B sunscreens, there is a need for sunscreens and other topical agents to provide UV-A protection as well.

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The use of epinephrine in areas of terminal circulation in the body has generally been contraindicated. It is standard practice in dermatologic surgery to use anesthetics without epinephrine, when working with the fingers, toes, nose, ears, or penis. This is a principle commonly accepted among practitioners, as we are instilled with the notion that epinephrine used in these regions can lead to ischemia and necrosis. Medical textbooks and postgraduate training courses continue to forewarn us about the dangers of epinephrine; yet, it seems the validity of this longstanding dogma is questionable. The belief that epinephrine should never be used in areas of end circulation has recently been challenged and may, in fact, be inaccurate.

Epinephrine is an α- and β-receptor agonist. It is considered a potent vasoconstrictor, because it activates the α receptors of blood vessels. Epinephrine is used in conjunction with anesthetic agents to prolong the duration of analgesia and to minimize complications of bleeding. Historically, it has long been established that epinephrine injected into the digits, tip of nose, outer ear, or genitals leads to hypoxia or necrosis, and thus should not be used in these areas. A review was conducted of Index Medicus from 1880–1966 and a National Library of Medicine search from 1966–2000 for reported cases of digital gangrene and necrosis caused by local anesthetics with epinephrine. After thorough analysis of the resulting 48 cases, it was established that the data were not sound or complete enough to conclude with certainty that epinephrine use resulted in necrosis of the fingers. Many of the historic reports had confounding factors such as the use of older anesthetics, postoperative hot soaks, inappropriate tourniquets, excess anesthetic agent, nonstandardized epinephrine concentrations, or the presence of concurrent site infections. These findings were corroborated by a review which determined, after careful investigation, that epinephrine was not the sole cause of necrosis in the previously reported cases. Also, only 4 of 21 cases that used epinephrine for digital anesthesia actually reported the concentration, making it difficult to support a generalized warning against its use. Furthermore, an in-depth literary analysis reinforced the notion that the established doctrine, regarding the dangers of epinephrine used specifically in the fingers, is invalid.

DISCUSSION

Historical reports of the consequences of epinephrine use in areas of terminal circulation are unfounded in the claims made. It is fair to say that after retrospective analysis, the standard practice of not using this agent in the fingers, toes, nose, ears, or penis is based on unsubstantiated reasoning. Many investigators have conducted prospective studies to determine the effects of epinephrine use, with appropriate concentrations and technique, on the development of ischemia and necrosis. Investigators performed 121 digital blocks using 1% lidocaine with 1:200,000 epinephrine in a 30-gauge needle, and none had complications of finger gangrene; furthermore, the use of buffered 0.5% lidocaine with 1:200,000 epinephrine was determined to be safe after local tumor infiltration of the hands and feet in 63 patients undergoing Mohs surgery. A multicenter prospective study of 3110 cases demonstrated no incidence of digital tissue damage in the hand after elective injection of concentrations of ≤1:100,000 epinephrine. In 59 described cases, necrosis of the fingers did not occur even after injection of high-dose 1:1,000 epinephrine, and only 27 of these cases received any form of treatment. Examination of Doppler flow imaging after digital block anesthesia revealed a return to normal blood flow after 60 to 90 minutes and deemed the use of a vasoconstrictive agent safe in patients undergoing surgical procedures of the hands or feet. Many investigations have focused on the use of epinephrine in the fingers or toes. A clinical study in Germany of 10,201 procedures involving the outer ear or nose also resulted in no problems due to the use of 1:1,000,000 epinephrine. On this basis, recent high-quality investigations into the safety of epinephrine usage in areas with end-arterioles have failed to support the longstanding principle.

There is concern that using epinephrine in regions of the body with terminal blood vessels in patients with comorbid conditions may
be dangerous; however, patients with pheochromocytomas, hyper-
thyroidism, hypertension, heart disease, or peripheral vascular dis-
Ease were included in the study of epinephrine effects on cutaneous 
ear and nose surgeries.\textsuperscript{10} No complications of ischemia or necrosis 
were noted to occur in this subset of patients. When considering the 
conditions of hypertension, diabetes, and circulatory or thrombotic 
disorders and patients taking anticoagulation therapy, there was no 
change in the findings of the safety of epinephrine use in the hands 
or feet.\textsuperscript{1} Despite these comorbidities, injections of epinephrine did 
not cause tissue damage in areas with end circulation.

CONCLUSIONS

The longstanding practice of avoiding the use of vasoconstrictive 
agents in the fingers, toes, nose, outer ear, or penis is anecdotal and 
unsubstantiated. Contrary to this established clinical principle, there 
is substantial evidence to support the use of local anesthetics with 
epinephrine in these areas of the body. As long as proper technique 
is used, with a small-caliber needle, appropriate anesthetic volume, 
and correct epinephrine concentration, there is minimal to no risk of 
ischemia or necrosis.\textsuperscript{3,4} In fact, when compared with lidocaine alone, 
lidocaine plus epinephrine 1:100,000 was found to decrease patient-
experienced pain significantly 1 hour after injection and increased the 
total time of analgesia by 2.2 hours.\textsuperscript{11} Not only is epinephrine use not 
dangerous, but it also can be beneficial as a result of enhanced pain 
control, reduced bleeding, and the need for less total anesthesia.\textsuperscript{12}

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Pachydermoperiostosis (PDP), or primary hypertrophic osteoarthropathy (PHO), is a rare, genetic disease that affects both the skin and bones. In 1868, Friedreich observed PHO in two brothers and defined it as “hyperostosis of the entire skeleton.” In 1935, PDP was identified by Touraine, Solente, and Gole as the primary form of hypertrophic osteoarthropathy, distinct from the more common form, secondary hypertrophic osteoarthropathy (SHO), which always has an underlying cause (eg, pulmonary or cardiac disease, occasionally neoplastic).

PDP predominantly occurs in men (with a male to female ratio of 7:1), who usually show a more severe phenotype. Disease onset is often at puberty, with progressive thickening and furrowing of the skin on the face and the scalp (pachydermia), enlargement of the fingertips (digital clubbing), swelling of periarticular tissue, and shaggy, periosteal, new-bone formation in the long bones (periostosis). The major complication is in the joints, in the form of arthralgia, arthritis, and hydrarthrosis/hemarthrosis. Other cutaneous features include seborrhea, blepharoptosis, acne, hyperhidrosis of palms and soles, cutis verticis gyrata, erythematous lesions over the joints, pole-like lower legs, and warmth or burning sensation in the hands and feet. Radiologically, acro-osteolysis, periosteal changes of the short and flat bones, and ossification of ligaments and interosseous membranes have also been reported. Additional features include myelofibrosis and gastrointestinal abnormalities (ie, peptic ulcer, chronic gastritis, gastric carcinoma, Menetrier’s disease, and Crohn’s disease). Other findings such as compressive neuropathy, corneal leukemia, hypoplastic internal genitalia, gynecomastia, and periodontal and alveolar bone abnormalities have been reported in single patients.

**A 25-year-old man presented with Touraine-Solente-Golé syndrome (primary pachydermoperiostosis), with an area of inflammatory dermatosis (12-month evolution) of the scalp at the cranial vertex. The patient presented with arthropathy, clubbing of the digits, diffuse periostosis, pachydermia of the hands and feet, and periosteal hyperostosis of the knee. Facial seborrhea and sebaceous gland hyperplasia were evident (Figure 1A and 1B and Figure 2A and 2B). Examination of the scalp revealed an erythematous pruritic plaque with erosions, crusts, and pustules, on which multiple tufts of 10 to 20 normal-looking hairs emerged from single follicular openings (Figure 3A). Slight pressure on the perifollicular areas resulted in the discharge of purulent material through the dilated follicular openings. Cervical and occipital lymph nodes were not enlarged, and the patient was in generally good health. Routine laboratory findings were normal. Immunologic studies, including a screening for antinuclear antibody, complement, and immunoglobulins, were normal. Both potassium hydroxide staining and fungal culture were negative. Bacteriologic culture of purulent material taken from the affected area was positive for *Staphylococcus aureus.* Videodermoscopy of the lesion showed rarefied interfollicular twisted red loops centered around actively affected follicles and white dots with absence of normal vascular pattern (Figure 3B). These dermoscopy patterns are markers for folliculitis decalvans, of which tufted hair folliculitis (THF) is a clinical variant. Histologic examination showed hair plugging, a dense perifollicular infiltrate of plasma cells, lymphocytes, neutrophils, and large areas of scarring and fibrosis, which would confirm suspected THF. THF was diagnosed on the grounds of clinical, microbiologic, histologic, and videodermoscopy data. The patient was treated with amoxicillin 875 mg plus clavulanic acid 125 mg twice daily and topical nadifloxacin 1% twice daily for 20 days, achieving substantial clinical improvement. One month after antimicrobial therapy, a single area of cicatricial alopecia with a few hair tufts emerging from single orifices was observed, and no new lesions or symptoms had appeared.

**Tufted Hair Folliculitis in a Patient Affected by Pachydermoperiostosis: Case Report and Videodermoscopic Features**

Adone Baroni, MD, PhD; Francesca Romano, MD
Both PHO and SHO share the same poorly understood pathogenesis. A neurologic basis is posited. More recently, abnormalities in fibroblast functionality have been implicated, along with an increase in collagen fiber synthesis. The involvement of platelets, with their potent growth factors, has also been suspected. In certain cases, alcohol intake aggravates the process. PDP is diagnosed on the basis of 3 major criteria: pachydermia, periostosis, and digital clubbing. Other minor criteria that assist in the diagnosis include seborrhea with sebaceous gland hyperplasia, acne, hyperhidrosis, and cutis verticis gyrata.

THF is a recurrent and progressive folliculitis of the scalp, developing irregular areas of scarring alopecia with numerous hair tufts emerging from dilated follicular openings. It is considered a peculiar form of folliculitis decalvans and is characterized by multiple hair tufts scattered within the patches of scarring alopecia that give the scalp its typical “dolly hair” appearance.

THF occurs in adults of both sexes. The etiology remains unclear. Staphylococcus aureus may often breed within the pustules. The chronic/relapsing course of THF could be the result of an inadequate immune response to the pathogen “noxa.” In fact, hair tufting can occur in several inflammatory disorders of the scalp, such as folliculitis decalvans, acne keloidalis nuchae, dissecting cellulitis of the scalp, kerion celsi, and follicular lichen planus.

CONCLUSIONS
The association of PDP with certain dermatologic disorders, such as papular mucinosis, atopic dermatitis, acanthosis nigricans,
vitiligo, pyoderma gangrenosum, squamous cell carcinoma, palmoplantar keratoderma, and cutis verticis gyrata, has already been reported. PDP associated with folliculitis decalvans, such as THF in our patient’s case, has never previously been described.

Disclosures: Drs Adone Baroni and Francesca Romano had full access to all of the data in the study and take responsibility for the reliability of data and the accuracy of data analysis. Study concept and design: Baroni and Romano. Acquisition of data: Baroni and Romano. Analysis and interpretation of data: Baroni and Romano. Drafting of the manuscript: Baroni and Romano. Critical revision of the manuscript for important intellectual content: Baroni and Romano. Statistical analysis: None. Obtained funding: Baroni and Romano. Administrative, technical, and material support: Baroni and Romano. Study supervision: None.

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Figure 3. Tufted hair folliculitis. Erythematous plaque with erosions, crusts, and pustules, on which multiple tufts of normal-looking hairs emerge from single follicular openings (A). Videodermoscopy pattern of folliculitis decalvans: interfollicular twisted red loops and white dots (B).
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Pustular psoriasis is an uncommon form of psoriasis in children. Annular pustular psoriasis is the most common form of pustular psoriasis in children. It has a chronic recurrent course and usually a good prognosis. Familial juvenile generalized pustular psoriasis is extremely rare.

Our patients had skin lesions characteristic of generalized pustular psoriasis. The onset of the current episode in the sister was probably idiopathic or due to sudden withdrawal of potent topical steroids. In the brother, it seems to have been precipitated by hypocalcemia. These children were born as a result of consanguineous marriage. Apart from these two siblings, family history of chronic plaque psoriasis was also present in their paternal grandmother.

The options available for the treatment of generalized pustular psoriasis in children are mainly systemic retinoids and methotrexate. Usually, high doses of retinoids are required to achieve control of the disease. It may be associated with significant side effects, especially in children. For this reason, we decided to treat these siblings with methotrexate, which has been used successfully in the past for the treatment of juvenile generalized pustular psoriasis. Juvenile generalized pustular psoriasis has a better prognosis than generalized pustular psoriasis in adults. The cases highlight one of the rarest entities of psoriasis, i.e., familial juvenile pustular psoriasis (generalized form).

Management of such a condition remains a challenge in children. The response of our patients to methotrexate further strengthens the role and safety of methotrexate in childhood psoriasis.

**CONCLUSIONS**

Retinoids, although the drug of choice for pustular psoriasis, are associated with significant side effects, especially in...
children, thus limiting their use in children. On the other hand, methotrexate is a relatively safer option with a more convenient dosing schedule.

Methotrexate can serve as a more cost-effective drug for juvenile generalized pustular psoriasis vis-à-vis retinoids.

REFERENCES


Figure 2. Histopathology of the pustular lesion (hematoxylin-eosin stain, original magnification ×100).

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Vitiligo, an idiopathic depigmentation of the skin, is a well-known entity that is characterized by chalky/ivory white macule(s). It is of autoimmune origin. Its association with various autoimmune disorders, including alopecia areata and subclinical/clinical hypothyroidism, has been well documented. Vitiligo is an acquired, idiopathic depigmentation of the skin. The presentation of vitiligo is often exclusive. It may coexist occasionally with other cutaneous and/or systemic disorders (Table II).

Vitiligo and hypothyroidism may coexist and, therefore, should be considered in patients with either condition. The current case, along with the other 4 case reports of vitiligo and hypothyroidism, should focus attention on vitiligo as a skin marker of hypothyroidism. This may also be true in other coexisting disorders. It is, therefore, useful to measure T3 and T4 values, since they control metabolism of almost all cells in the body. TSH, on the other hand, is secreted from the pituitary gland and augments thyroid gland hormone production. Primary hypothyroidism is frequently accompanied by depressed T3 and T4 values and an elevated serum TSH level. Hashimoto’s thyroiditis, a result of the autoimmune process, may destroy the thyroid gland and bring about systemic or cutaneous changes. These are imperative to define, along with a history of fatigue, constipation, depression, sensitivity to cold, weight gain, muscle weakness and cramps, increased menstrual flow (menorrhagia), and increased risk of miscarriage, as has been illustrated presently.
Significant symptoms of vitiligo and hypothyroidism include dry, coarse, cold, and pale skin; puffy, boggy/edematous discoloration; carotenemia ichthyosis; palmoplantar hyperkeratosis; and capillary fragility. In addition, thin, brittle, striated, and slow-growing onycholysis of the nails are common findings. Other salient features include dull, coarse, brittle, and slow-growing hair, with an increase in telogen/resting hair and madarosis. In addition to T3, T4, and TSH values, thyroid microsomal peroxidase antibodies (thyroid microsomal antibody and thyroid peroxidase) and antithyroglobulin antibodies are important to investigate, despite their speculative significance in the diagnosis of vitiligo. It may prove useful to unfold hypothyroidism of autoimmune origin, in children and adolescents in particular. Vitiligo and the associated systemic disorder should be treated simultaneously to ensure positive results.

### Table I. Vitiligo: A Skin Marker of Clinical/Subclinical Hypothyroidism—Clinical Features

<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>AGE/SEX</th>
<th>CLINICAL VARIANTS</th>
<th>THYROID PROFILE*</th>
<th>DURATION OF HYPOTHYROIDISM</th>
<th>DURATION OF VITILIGO</th>
</tr>
</thead>
</table>
| 1        | 64 y/female | Nonsegmental vitiligo (acrofacialis) | T3=1.68 (0.6–3.0) ng/mL  
 T4=14.6 (4.0–12) ng/dL  
 TSH=0.36 (0.3–6.0) μIU/mL | 21 y (since 1984) | 1.5 mo after diagnosis of hypothyroidism |
| 2        | 37 y/male | Nonsegmental vitiligo (acrofacialis) | T3=2.44 (2.30–4.20) pg/mL  
 T4=0.73 (0.89–1.80) ng/dL  
 TSH=39.66 (0.35–5.50) μIU/mL | 5 y (since 2000) | 3 mo |
| 3        | 52 y/female | Nonsegmental vitiligo (acrofacialis) | T3=102.0 (86–186) ng/mL  
 T4=7.9 (4.5–12.5) ng/dL  
 TSH=5.0 (0.2–5.0) μIU/mL | 9 y (since 1996) | 38 y (1967) |
| 4        | 11 y/female | Segmental (zosteriformis) | T3=0.2 (0.2–1.8) ng/mL  
 T4=1.8 (2–11) ng/dL  
 TSH=9.3 (0.2–6.30) μIU/mL | 5 y (since 2005) | 5 y (2005) |

Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone. *Variation in values was a result of different techniques used.

### Table II. Vitiligo, Alopecia Areata, and Hypothyroidism: Association and Coexisting Disorders

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>YEAR</th>
<th>CUTANEOUS AND/OR SYSTEMIC DISORDERS</th>
</tr>
</thead>
</table>
| Chojnacki et al⁴ | 1973 | Vitiligo  
 Diabetes  
 Hypothyroidism |
| Midel et al⁵   | 1983 | Chronic urticaria  
 Vitiligo  
 Thyroiditis |
| Jaggarao et al⁵ | 1989 | Vogt-Koyanagi-Harada syndrome  
 Hypothyroidism  
 Diabetes mellitus |
| Madden et al⁶  | 1989 | IgA nephropathy  
 Vitiligo  
 Primary hypothyroidism |
| Curti et al⁷   | 1992 | Vitiligo  
 Acrochaxy |
| Saban et al⁸   | 1991 | Vitiligo  
 Autoimmune hypothyroidism  
 Alopecia universalis |
| Dervis et al⁹  | 2004 | Vitiligo  
 Morphea  
 Hashimoto's thyroiditis |
| Aghaei et al¹⁰ | 2004 | Vitiligo  
 Hypothyroidism  
 Diabetes mellitus |

Abbreviation: IgA, immunoglobulin A.

Figure 1. Vitiligo subclinical/clinical hypothyroidism: ivory/chalky white macules and white hair (leukotrichia) located on the temporoparietal region of the head.
CONCLUSIONS

Occurrence of alopecia areata is an additional association, a few reports of which are found in the literature.² ⁷ ⁸ ¹⁴

REFERENCES


Figure 2. Vitiligo, alopecia areata, and subclinical/clinical hypothyroidism, depicting segmental vitiligo (zosteriformis) of the neck (A), and alopecia areata affecting the temporoparietal region of the scalp (B).
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Sterile pustular eruptions have been reported with ulcerative colitis (UC) but rarely with Crohn’s disease.¹⁻⁴ In 1978, investigators described a diffuse pustular eruption with UC as “an unusual variant of pyoderma gangrenosum” (PG).⁵ This impression has persisted, perhaps incorrectly. The term pustular PG has been used to describe one of the 4 classic clinical variants of PG, the other 3 include ulcerative, bullous, and vegetative.⁶ Pustular PG is at best a forme fruste or an abortive form of PG.⁷ The confusion may occur because of the pustules that develop in the evolution of the classic Brunsting type of PG.⁸ Classic or ulcerative PG starts as a tender red nodule that becomes pustular, then dusky and necrotic, and finally produces an enlarging ulceration with violaceous undermined borders.⁹ The pustular subtype does not ulcerate, undermine, or rapidly expand.

The pustular eruption associated with our patient’s Crohn’s disease flare was characterized by a sudden onset of pustules

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**CASE STUDY**

**An Unusual Cutaneous Manifestation of Crohn’s Disease**

Jessica A. Weiser, MD;¹ David M. Markowitz, MD;² Sameera Husain, MD;¹,³ Marc E. Grossman, MD¹,⁴

A 61-year-old man with a 12-year history of quiescent Crohn’s disease on mesalamine presented to his gastroenterologist in April 2009, complaining of abdominal cramping, diarrhea, and a 25-lb weight loss over 6 weeks. He did not respond to prednisone 50 mg and 6-mercaptopurine 100 mg daily. Abdominal computed tomography findings revealed diffuse submucosal edema consistent with extensive colitis. Colonoscopy demonstrated diffuse inflammation with erythema, friability, and shallow ulcerations in the rectum and colon. Biopsies were consistent with Crohn’s colitis. He was admitted for infliximab infusion for his unremitting diarrhea. Five days before admission, the patient noted mild swelling and redness of the left lower eyelid, which progressed to involve the right lower eyelid with frank pus draining from both eyes. He had no visual impairment or eye pain. Two days before admission, an ophthalmologist prescribed a steroid eyedrop with no relief. He also complained of seropurulent painful skin lesions on his face and scalp, which spread to involve his upper trunk and proximal arms. On admission to the hospital, dermatology, ophthalmology, and infectious disease consults were obtained to rule out disseminated infection before initiation of infliximab therapy. The patient was afebrile and hemodynamically stable. His oral mucosa was normal. He had prominent bilateral lower eyelid edema, erythema, and superficial erosions with hemorrhagic crusting and frank green purulent drainage from both eyes, with crusting along the lower lash line and bilateral sclera injection (Figure 1). On his scalp, face, trunk, and proximal extremities, he had 25 to 30 erythematous, 4- to 8-mm papulopustules with narrow red halos, some with central necrosis and crusts (Figure 2). Cultures from the purulent ocular drainage and pustules on the trunk and arms were all negative for bacteria, virus, and fungi. Gram stain from the eye drainage showed polymorphonuclear leukocytes without organisms. Tissue cultures were negative for bacterial, fungal, and mycobacterial infection. Skin biopsy taken from the central upper back demonstrated subcorneal pustules with areas of eroded epidermis and collections of neutrophils in the superficial dermis (Figure 3). Special stains were negative for organisms. He received infliximab infusion 5 mg/kg for a total dose of 420 mg over 2 hours. Within 48 hours of infusion, there was notable decrease in size of lesions, in addition to reduction of purulent drainage from both eyes. The patient was discharged home following infliximab infusion. His skin lesions resolved during a period of 2 weeks, leaving small pink atrophic scars. He received his second infusion of infliximab 2 weeks after discharge with continued improvement in his gastrointestinal symptoms.

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**Figure 1.** Ocular examination demonstrating prominent bilateral lower eyelid edema, erythema, and superficial erosions with frank green purulent drainage from both eyes and crusting along the lower lash line.
in association with acute colitis, which were sterile and larger than the usual pinhead-sized pustules of bacterial folliculitis. The lesions occurred predominantly on the face, eyelid margins, and scalp, and did not break down or ulcerate like pyoderma gangrenosum. Although our patient complained of associated pain, there was no pathergy, and the lesions resolved rapidly with treatment of his Crohn’s disease. The differential diagnosis considered was broad; however, all other entities were carefully excluded through examination and systemic evaluation.

Drug eruption was readily excluded as our patient was not taking any systemic medications at the time of onset except for prednisone. The distribution of his lesions was not consistent with pustular bacterid of Andrews, which is primarily palmoplantar, nor did he have a primary bacterial infection that could account for a bacterid. All wound and blood cultures were negative for herpes simplex and varicella zoster viruses, in addition to bacterial, fungal, and mycobacterial infections. Behçet’s syndrome classically manifests with oral and genital ulcerations and pathergy, whereas reactive arthritis manifests with uveitis, arthritis, and urethritis. Our patient did not have any of these features during evaluation. His cutaneous eruption may be considered a distinct clinical entity or can be alternatively thought of as an example of pustular PG, as it has been described in the past.

The histopathologic features of the pustular eruption of Crohn’s disease are not diagnostic.

Nonetheless, a skin biopsy is necessary to exclude other infectious and noninfectious causes. Skin biopsy demonstrates subcorneal and dermal neutrophilic infiltration with subepidermal edema that indicate a range of changes within the same disease, reflecting the timing of the biopsy in disease evolution.¹

CONCLUSIONS

The diagnosis of pustular eruption of Crohn’s disease is difficult to prove, as is pustular PG, because of the lack of specificity of the cutaneous clinical and histopathologic signs. Exclusion of the fundamental pustular eruptions leaves a clinical scenario in which the physician can be comfortable diagnosing and treating the acutely febrile patient with bloody diarrhea and pustules for Crohn’s disease.

REFERENCES

6 Powell FC, Si D, Perry HO. Pyoderma gangrenosum: classification
Figure 3. Skin biopsy from a papulopustule on the central upper back showing a subcorneal pustule with areas of eroded epidermis (hematoxylin-eosin stain, original magnification ×4) and dermal infiltration (A). Dermal infiltrate consisting predominantly of neutrophils (hematoxylin-eosin stain, original magnification ×20) (B).

A 41-year-old human immunodeficiency virus (HIV)–positive man was hospitalized with complaints of a 4-week history of nausea and vomiting, associated with decreased oral intake, and a 4-day history of frontal headache and fever. His medical history was significant for a gunshot wound to the head 3 years prior, with a residual seizure disorder. He also had two previous hospitalizations, both for culture-negative bacterial meningitis; the first episode occurred 12 months before admission and the second episode occurred 5 months later. At that time, he was found to be positive for serum antibodies against HIV and a CD4+ T-lymphocyte count of 126/mm³. He had no known drug allergies and was not receiving any medication. On admission, the patient was febrile (104.0°F) and hypotensive (blood pressure, 92/40 mm Hg). Pertinent physical examination findings included cachexia with bitemporal wasting, dry mucus membranes, adherent white patches on the oral mucosa, and negative Kernig’s and Brudzinski’s signs. His laboratory results revealed macrocytic anemia, a decreased serum sodium of 125 mEq/L, and a normal total leukocyte count with a CD4+ T-lymphocyte count <50/mm³. Lumbar puncture opening pressure was elevated at 160 mm Hg, and cerebrospinal fluid analysis showed an increased white cell count of 97/µL (84% lymphocytes), a decreased glucose level of 26 mg/dL, and a decreased protein level of 42 mg/dL. The patient was started on empiric therapy that included intravenous ampicillin and cefotaxime, oral Bactrim, and clotrimazole lozenges for thrush. Cerebrospinal fluid culture was positive for Escherichia coli, sensitive to cefotaxime. Two days later, the patient developed fine, erythematous, nonblanchable macules primarily on his abdomen, with minimal involvement of his thorax and back. His skin lesions remained unchanged for the next 2 weeks. Repeat lumbar puncture was performed after 14 days of cefotaxime. The cerebrospinal fluid analysis showed an elevated white cell count of 7/µL (100% lymphocytes), a decreased glucose level of 53 mg/dL, and a decreased protein level of 33 mg/dL. The cerebrospinal fluid culture was now positive for Pseudomonas aeruginosa resistant to cefotaxime. The patient was started on imipenem. On day 34 of his admission, the patient became tachypneic with complaints of dyspnea. A chest roentgenogram revealed bilateral patchy infiltrates. He was transferred to the intensive care unit and intubated for hypoxemic respiratory failure (arterial blood gas values on 6 L of oxygen: pH, 7.46; bicarbonate, 23; and oxygen saturation, 37). That evening, the patient was also noted to have diffuse petechiae and purpura in a reticulated pattern over his abdomen (Figure 1A and 1B), most heavily concentrated in the periumbilical region, extending to the axillae and upper thighs. A 3×3-mm punch biopsy from abdominal skin demonstrated Strongyloides stercoralis larvae in the dermis (Figure 2A and 2B). His sputum specimen was teeming with adult S. stercoralis worms (Figure 3) and, subsequently, numerous S. stercoralis larvae were observed not only from the bronchoalveolar lavage but also from the nasogastric fluid specimen. These findings confirmed the diagnosis of disseminated strongyloidiasis. On hospital day 35, the patient was doing poorly and was started on thiabendazole (1250 mg twice daily for 28 days). Nine days later, ivermectin (4.5 mg once daily for 3 days for 2 courses) was also added. He continued to clinically deteriorate. The patient died 31 days after systemic antihelminthic treatment was initiated.

**Strongyloides stercoralis** is an intestinal nematode commonly known as the human threadworm that infects millions of people worldwide.² It is endemic to tropical and subtropical areas of the world, including the southeastern United States.¹ The unique life cycle of *S. stercoralis* can result in cutaneous, gastrointestinal, and pulmonary manifestations in humans.¹ Disseminated strongyloidiasis, also known as hyperinfective strongyloidiasis, develops most commonly in patients with suppressed immunity, including infection, such as HIV or tuberculosis; iatrogenic, such as long-term corticosteroid therapy or patients undergoing chemotherapy; or malignancy, such as leukemia or lymphoma.³–⁶

Human infection occurs when the infective larvae penetrate the skin, enter the bloodstream, and travel to the alveoli of the lungs. From the lungs, the larvae ascend the tracheobronchial tree, are...
swallowed by the human host, and subsequently localize to the favored habitat of the small bowel. The female nematode produces larvae that are either (1) excreted in the stool of the host or (2) penetrate the intestinal mucosa or perianal area, resulting in autoinfection. This cycle of autoinfection allows persistence of the parasite for decades without additional exposure of the host to exogenous infective larvae. Even with chronic infection, however, healthy individuals are usually asymptomatic. It is when the parasite is coupled with a defective cell-mediated immunity that disseminated disease, or hyperinfection syndrome, can occur.

Disseminated strongyloidiasis is associated most commonly with severe infection (pneumonia, meningitis, bacteremia) with enteric organisms from a suspected intra-abdominal source. Strongyloides hyperinfection has also been observed in patients with dermatologic conditions associated with immunodeficiency such as bullous pemphigoid, pemphigus vulgaris, and systemic lupus erythematosus.

The primary cutaneous manifestations of the parasitic infection include larva currens and disseminated *S. stercoralis* (Table). The term larva currens was initially coined in 1958 to describe the swift migration of *S. stercoralis* larvae within the skin. The cutaneous finding is commonly described as a pruritic, erythematous, papulonodular, or linear lesion. It is due to an allergic reaction to the filariform larvae that travel in the skin, producing serpiginous urticaria. These lesions are most commonly identified over the buttocks, proximal thigh region, and lower abdomen due to the perianal source of autoinfection. The rate of migration has been cited to be 5 to 15 cm/h. Nondisseminated *S. stercoralis* infection can also present as chronic urticaria.

Cutaneous manifestations of the disseminated helminthic disease have been described as rapidly progressing petechia and purpura. Skin lesions most commonly involve the abdomen but can also occur on the thorax and proximal extremities. Massive numbers of larvae migrate through the intestinal mucosa to disseminate throughout the body.

The vascular distribution of the *S. stercoralis* lesions observed in disseminated disease resembles the clinical picture of caput medusae of chronic liver disease in patients who have portal hypertension. In the setting of portal hypertension, increased portal pressure results in retrograde flow through the periumbilical portal systemic anastomoses. Our patient was placed on mechanical ventilation before the development of the periumbilical purpura. As described previously, it is thought that there is a rise in portal pressure secondary to the positive-pressure ventilation. This increase in portal pressure shunts blood, carrying numerous *S. stercoralis* larvae, through the periumbilical portal systemic anastomoses. When the larvae reach the dermal vasculature, extravasation of red blood cells occurs, resulting in periumbilical purpura that resembles multiple thumbprints, commonly referred to as the thumbprint sign.

The mortality associated with disseminated *S. stercoralis* has been reported as high as 77% to 85% worldwide, but, in recent years, endemic areas of the United States have a 31% mortality rate. A better prognosis is associated with early detection of the parasitic infection and prompt initiation of anthelminthic medication. In patients with a negative stool culture, anti-strongyloides immunoglobulin G enzyme immunoassay can be valuable for early diagnosis of strongyloidiasis. With a sensitivity and specificity >90%, the rapid test can readily identify the parasitic infection early in the course of the disease in patients at risk for disseminated disease.

Treatment for strongyloidiasis includes the anthelminthic drugs ivermectin, thiabendazole, and albendazole. Strongyloidiasis treatment in immunocompetent patients consists of either ivermectin 200 μg/kg orally for 1 day, thiabendazole 25 mg/kg orally twice a day for 3 days, or albendazole 400 mg orally twice a day.

**Figure 1.** Distant (A) and closer (B) views of nonpalpable purpura with extensive involvement of the abdomen in an immunocompromised patient with disseminated strongyloidiasis.
for 3 days. Ivermectin is considered first-line therapy due to better tolerance and decreased hepatotoxicity. Disseminated S. stercoralis requires multiple-dose treatments for an extended period, usually lasting several weeks until all specimens (nasogastric aspirates, pulmonary secretions, or stool) are free of nematode.

CONCLUSIONS

The population of immunocompromised patients is increasing with the progressively higher prevalence of HIV infection, increased organ transplants, and the extensive use of corticosteroids, immunomodulators, and cancer chemotherapy. Clinicians should maintain a high index of suspicion for strongyloidiasis when an immunocompromised patient presents with a serious infection caused by enteric organisms and nonspecific abdominal or pulmonary symptoms. In the setting of immunosuppression, periumbilical purpura (the thumbprint sign) is considered diagnostic of disseminated S. stercoralis.

REFERENCES

Table. Cutaneous Manifestations of *Strongyloides stercoralis*

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>LARVA CURRENS</th>
<th>DISSEMINATED <em>S STERCORALIS</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated disease²</td>
<td>None</td>
<td>Immunocompromised</td>
</tr>
<tr>
<td>Location¹³,¹⁵</td>
<td>Buttocks, proximal thigh region, and lower abdomen</td>
<td>Abdomen primarily, with extension to thorax and proximal extremities</td>
</tr>
<tr>
<td>Morphology¹⁵</td>
<td>Pruritic, erythematous, and serpiginous or linear</td>
<td>Rapidly progressing periumbilical petechia and purpura¹³</td>
</tr>
<tr>
<td>Pathology¹³,¹⁵</td>
<td>Allergic reaction from <em>S stercoralis</em> larvae migration; larvae often missed on biopsy</td>
<td><em>S stercoralis</em> larvae readily identifiable in a dermal biopsy</td>
</tr>
<tr>
<td>Treatment²,¹⁶</td>
<td>Ivermectin³ 200 µg/kg PO for 1 dose, thiabendazole 25 mg/kg PO BID for 3 d, or albendazole 400 mg PO BID for 3 d</td>
<td>Multiple-dose treatment for an extended period³</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; PO, orally. ³Commonly referred to as the thumbprint sign. ¹⁴ ³Considered first-line therapy due to better tolerance and decreased hepatotoxicity. ¹⁷ ³Ivermectin 200 µg/kg PO for 1 dose per day for 1 to 3 days, may repeat treatment weekly for 2 total courses; thiabendazole 25 mg/kg PO BID or albendazole 400 mg PO BID for 2 to 4 weeks.²,¹⁶

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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 skin 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. Systemic 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 (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.

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