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0 = no change, 1 = mild improvement, 2 = moderate improvement, 3 = significant improvement

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*Statistical significance reached on all measurements observed (P<0.01).

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Marcia Ramos-e-Silva
President of the Congress

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Dirt is everywhere. We wash our dirty hands. We use dirt in which to grow vegetables. If we use too many dirty words, we might have our mouths washed out with soap. If we do not wash behind our ears, there could just be enough dirt for growing carrots. And, a wound that becomes infected is dirty.

THE DIRT EXHIBIT
A recent exhibit at the Wellcome Collection in London was entitled The Filthy Reality of Everyday Life: Dirt.1 This extraordinary presentation pictured a panorama of dirt from street dirt to filthy clothes (Figure 1). There were illustrations of sanitation workers disinfecting a city street to eliminate cholera, posters advertising soap and how to use a cleaning agent not only to rid the body of filth but also to make the home “spic and span,” and photographs of mud wrestling, all of which pointed toward the old adage, “cleanliness is next to godliness.”

Health is intertwined with corralling dirt. Take, for example, the development of sewers to make cities healthier and less filthy, or prostitutes being forced to clean city streets in Switzerland as penance (Figure 2). The International Hygiene Exhibition in Dresden, Germany, in 1911 led to the development of a museum that focused on cleanliness, as a “public venue for health care education.” Water, itself, can be contaminated and cause more harm than good (Figure 3).

DIRT AND MEDICAL PERSONNEL
As for medical personnel and the hospital environment, that represents a totally different kettle of fish. Nosocomial infections caused by multidrug-resistant organisms are growing problems in many health care institutions. Colonization of potentially pathogenic organisms on various objects, such as pagers, mobile phones, keyboards, clothing of the hospital staff, nurses’ uniforms, and even the white coats of physicians have been repeatedly reported.2

The neckties traditionally worn by doctors have recently attracted attention because, in most cases, they are rarely cleaned and, therefore, might carry more bacteria than other items of clothing. The same goes for mobile phones and touch screens. These contaminated objects have been suggested as vectors or possible vectors for transmission of nosocomial pathogens from health care workers to patients and from one patient to another.3

DIRT AND DERMATOLOGY
Skin disease is frequently associated with dirt. Scabies and pediculosis are considered preventable, if the patient were only clean. Patients with atopic dermatitis or stasis ulcers might not have problems if the skin were made dirt-free, or maybe not. There is a school of thought that supposes that eating dirt may even be helpful in reducing atopic dermatitis.4 Additionally, those filthy maggots may be beneficial in treating leg wounds.5 Of course, sexually transmitted diseases would not exist, except for dirty sexual proclivities.

Skin shedding and its accumulation have been explored from the psychological point of view, as well. If the skin were kept clean, then the sebaceous glands might not be covered with debris that dirt could affect, and acne might be minimal. Warning the adolescent not to touch the pimples may connote that this sebaceous gland disorder is somehow associated with dirt.6

A review of the literature has called attention to dermatitis neglecta, where the debris mimicked a nevus.7,8 A 13-year-old girl presented with brownish pigmentation surrounding the areola of both nipples. Until the areas were washed with alcohol, the crusts, being made up of stratum corneum being shed and moistened with sebum and perspiration, looked just like a nevus. Recently, there has been renewed attention drawn to a condition called terra firme-forme dermatosis (TFFD), first described a few decades ago and most likely the same as dermatitis neglecta.9 The entity, also known as Duncan’s dirty dermatosis in honor of the first dermatologist to describe the entity,10 is characterized by brownish black debris smattered on the skin.

TFFD is frequently localized to the trunk, where the differential diagnosis may include confluent and reticulated...
dermatosis of Gougerot and Carteaud, or the neck, where it mimics acanthosis nigricans. It also has been found on the ankles, knees, pubis, axillae, and elbows. When TFFD presents as small areas on the scalp, it has been confused with seborrheic keratoses or even pigmented basal cell carcinomas. Histologic examination of TFFD shows "prominent lamellar..."
hyperkeratosis with focal areas having compact orthokeratosis arranged in whorls.\textsuperscript{11}

This embarrassing condition often does not seem to be removed by soap and water, but light rubbing with an isopropyl alcohol pad removes the unwanted material and returns the skin to its natural appearance (Figure 4). TFFD can afflict all age groups, although it may be more common in children. It does not have a gender predilection, and this dirty condition is not associated with any underlying disease.

CONCLUSIONS

Dirt may not be the root of all evil, and it may have little effect on most dermatologic entities. Keeping clean may be only esthetic, but it beats being thought of as dirty.

REFERENCES


**Figure 4.** The dirty debris of terra firme-forme dermatosis found on the legs of a 52-year-old man who has chronic stasis dermatitis. Note the area cleared by wiping vigorously with alcohol.

**FORMULARY OF DR GEORGE C. ANDREWS**

**Soothing Emulsion**

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Submitted by Douglas D. Altchek, MD, New York, NY.
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Content

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Psoriasis is a common disease encountered in dermatology practices. In addition to the classic plaque variant, it has a variety of presentations, including guttate, pustular, seborrheic, and erythrodermic. Despite the often widespread nature of this condition, affecting the scalp, trunk, extremities, nails, and, less commonly, the face and genitalia, lesions affecting the lips and oral mucosa are uncommon. Fissured tongue and geographic tongue are the most common clinical presentations of oral psoriasis. Psoriatic involvement of the lips is a very rare presentation, with only a handful of cases reported in the literature. Lip involvement can be associated with other cutaneous and/or oral lesions of psoriasis, or can be the sole presentation of psoriasis.

CLINICAL FINDINGS

In the current issue, Sehgal and colleagues report a case of lip psoriasis in a 16-year-old woman who had fissuring and flaking lips for approximately 6 years. Clinical and pathologic investigations led to a diagnosis of psoriasis affecting the lips. In her case, the lips were affected exclusively. Although there were no other physical symptoms or cutaneous manifestations, her lip psoriasis was associated with significant psychiatric morbidity and profound negative effects on her emotional and social quality of life.

Her initial presentation was related to chewing a dish made of salted and roasted corn. This potentially irritating substance suggests the possibility of Koebnerization, similar to a presentation in a case caused by protruding teeth. Although prior topical and systemic treatments were ineffective, the young woman in Sehgal's paper was treated to excellent effect with a combination of topical tacrolimus, calcipotriene, and betamethasone dipropionate.

The patient in Sehgal's paper received a dose of oral fluconazole due to concern of possible concomitant fungal infection; however, her clinical presentation was likely the result of psoriasis alone. Loose, thick scale around the mouth might be colonized coincidentally with bacteria and fungi, a finding that may be observed incidentally on histology. We believe that further investigation for infection is not needed if the diagnosis of psoriasis can be made.

Despite the rarity of this condition, we have recently consulted on a similar case. A 20-year-old man presented with 18 months of crusting, peeling lips. He attributed the onset of his disease to exuberant rubbing of his lips during a basketball game secondary to an unusual “burning and tingling” sensation; there was no other identifiable antecedent event or medical or environmental exposure. Within 2 weeks, he developed exuberant yellow-white scale affecting the entirety of both lips. He initially attempted to treat this with self-debridement and moisturization, to no effect. He was then evaluated by multiple physicians, including his primary care physician and a dermatologist, who prescribed a variety of oral and topical steroids, antifungals, and antivirals, all to minimal or no effect. Our patient underwent an incisional biopsy of the lower lip that was interpreted as actinic cheilitis, prompting referral to us for further evaluation and treatment.

Our clinical evaluation demonstrated minimal edema and minor erythema of the lips, with striking crusting and peeling of a yellow-white, plate-like scale (Figure). The scale was easily dislodged without pain and, with the exception of the minimal edema and erythema, the underlying lip was normal in appearance. The typical irregular, thin scale of actinic cheilitis at the vermillion border was absent; further, the patient was African American and only 20 years old, making actinic cheilitis an unlikely diagnosis. Subsequently, we obtained the outside histopathology, which was interpreted as showing parakeratotic scale and psoriasiform epithelial hyperplasia without evidence of actinic cheilitis.

RECOMMENDATIONS

We proposed a diagnosis of psoriasis involving only the lips. We prescribed treatment with combination calcipotriene 0.005%
and betamethasone dipropionate 0.064% ointment applied twice a day for 2 weeks, followed by 6 weeks of twice-a-day usage on Mondays and Thursdays; this regimen was repeated as disease activity required. We also prescribed tacrolimus 0.1% ointment twice a day on other days. He used white petrolatum as needed for moisturization and as a barrier. Additionally, we asked him to reduce physical manipulation of the lips and to use Biotene dental care products (GlaxoSmithKline, Research Triangle Park, NC).

He initially had excellent resolution of his disease; however, the condition currently has a waxing and waning course, worsened by cold or dry weather and physical manipulation, such as lip licking and biting. He has had significant improvement overall and is happy with his treatment.

Oral involvement of psoriasis is rare, and, with the inclusion of the two cases in this issue, only 6 patients presenting exclusively with lip involvement have been reported, two of whom went on to develop lesions elsewhere.\textsuperscript{8,9,11,13} Although rare, lip psoriasis has a striking clinical presentation (see Figure and clinical photos in Sehgal et al).

Substantial psychiatric morbidity was experienced by both our patient and the patient described by Sehgal and colleagues. Our patient became withdrawn from friends, lost interest in his pastimes, quit college and his job, moved out of his apartment and in with his family, and took to wearing a mask while in public. With improvement of his disease, his psychiatric morbidity has significantly decreased. In addition to no longer wearing a mask in public, he is again engaging in social relationships, employed, and living independently.

Given the rarity of this condition, the prevalence, distribution, natural history, and most effective treatments are unknown. Lip psoriasis is worsened by cold or dry weather, physical manipulation such as lip biting and exuberant rubbing, and by irritating substances, suggesting the Koebner phenomenon.\textsuperscript{9,11} Although the two patients presented in this issue were relatively young, lip involvement has been described in patients from the second to seventh decade of life.\textsuperscript{9,14} This condition occurs in a variety of populations; patients have been reported in Russia, Europe, America, India, and Turkey.\textsuperscript{7–11,14}

Although this condition is apparently unresponsive to mild topical steroids such as those frequently prescribed for the lips, it frequently responds well to more potent steroids.\textsuperscript{8,9} Additionally, the use of topical vitamin D analogues and tacrolimus has been beneficial, as reported by Sehgal. Our patient had suboptimal response to topical clobetasol alone, but he had an excellent response to a treatment regimen of calcipotriene-betamethasone and tacrolimus.

CONCLUSIONS

Psoriasis should be in the differential diagnosis of lip lesions presenting with fissuring and scale, especially in the setting of a personal or family history of psoriasis, although these are not always present. Clinical suspicion is required to detect this disease because it may be confused with more common conditions, such as candidiasis, irritant or actinic cheilitis, bacterial infection, or atopic dermatitis.

Disclosures: This paper is supported by alumni donations to the University of Michigan Department of Dermatology. The authors declare that they have no significant conflicts of interest relating to the material presented in this manuscript.

REFERENCES

Psoriasis of the Lips

COMMENTARY

May/June 2012


WAX MOULAGE

Pemphigus seborrhoicus (Senear Usher). Moulage No 1372, made by Elsbeth Stoiber in 1960 in the Department of Dermatology, University Hospital Zurich. Museum of Wax Moulages, Zurich, www.moulagen.ch

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

References:
Burning mouth syndrome (BMS) consists of chronic pain and/or a burning sensation of the oral cavity but with no clinically visible lesions. It is the most common disesthesic pain of middle-aged adults, with a marked female predominance. The tip of the tongue is the most frequently affected site in patients with BMS, accounting for two-thirds of cases. The lips may also be involved in burning mouth disorders, especially the lower lip. These symptoms can last for years, and spontaneous resolution is exceedingly rare. It is almost fully resistant to few currently available (drug) treatments.

**CLINICAL FEATURES OF BMS: DEFINITION AND CLASSIFICATION**

BMS is clinically defined as a painful and burning (intraoral) sensation of the tongue, even if these symptoms occur simultaneously in other parts of oral mucous membrane. BMS is frequently associated with symptoms such as sensation of dry mouth (xerostomia) and increased thirst. Some patients with BMS may experience an intraoral itchy sensation (allokinesis). Taste disturbances (dysgeusia) are often, but not always, reported. Although there are many ways of classing the syndrome, BMS is usually classified according to Lamey's criteria on clinical grounds. BMS type 1 involves symptoms that worsen throughout the day, BMS type 2 includes persistent symptoms during the day, and BMS type 3 involves intermittent pain and symptom-free days. The average age at the diagnosis of BMS is approximately 60 years. Currently, the risk of BMS is more than 2 times as high among women as men (ratio of women/men ranges from a low of 3:1 to a high of 15:1). A conservative estimated prevalence of BMS has been reported to be 5% (range from 2% to 15%) with a peak in the fifth and sixth decades of life. At this time, there is no evidence of racial or ethnic background differences. The diagnosis of many cases of BMS is frequently delayed or even missed because symptoms overlap with those of more common oral diseases. Spontaneous complete remission of BMS is known to occur but is rare.

**ETIOLOGY**

Our understanding of the cause and pathogenesis of BMS is largely unknown, although many hypotheses have been advanced including those involving postmenopausal state, anxiety, depression, and previous dental treatments. It is also thought to be associated with both peripheral neuropathy and central nervous system disturbances. In our view, direct exposure to metal antigens (eg, mercury, palladium, gold, silver, and chromium) released from dental metal alloys may trigger neurogenic inflammation in individuals who are predisposed to allergy to metals. Although local factors have been suspected to be the cause, this has been difficult to document. The risk factors for BMS are postmenopausal age, anxiety, depression, and previous dental treatments. From a dermatologic point of view, BMS may be the first sign of oral lichen planus in some patients.

**INVESTIGATION AND DIAGNOSIS OF BMS**

The most consistent immunologic abnormality associated with BMS is rheumatoid factor and autoimmunity as manifested by a rise in titers of autoantibodies to nuclear and nucleolar antigen. Thus, underlying rheumatologic conditions should be ruled out on presentation and follow-up. B12 deficiency and plasma holotranscobalamin along with plasma homocysteine should be assessed and corrected (when possible). Serologic testing for celiac disease should be performed to exclude this autoimmune enteropathy as well as gluten sensitivity, because both may cause small fiber neuropathy. Patients should visit their dentist to explore possible local factors and, in particular, rule out local toxicity as well as allergic sensitization caused by dental alloys. Some patients (about 5%) in our retrospective cohort study, received an initial diagnosis of BMS a few months before cancer diagnosis. Another concurrent disease associated with BMS is monoclonal gammopathy. From a dermatologic viewpoint, on the basis of our experience, BMS has been associated with various skin manifestations in adults such as oral lichen planus, systemic contact dermatitis, and baboon syndrome. In our view, BMS should not be classified as a psychogenic and/or somatoform disorder given that clear organic causes can almost always be identified.

**MANAGEMENT OF BMS**

Patients should optimize their oral health and avoid alcohol and cigarette smoke. They should visit their dentist to explore possible local factors into their oral cavity and in particular rule out local toxicity as well as allergic sensitization caused by dental alloys.
Various local drug treatments are not effective. As supportive measures, two of the preferred drugs include pregabalin and amilsulpride. These drugs have some value in alleviating BMS symptoms.

REFERENCES


Figure. Oral lichen planus (OLP) arising from buccal mucosa in a patient with burning mouth syndrome (BMS). Images of right buccal mucosa obtained in a patient who received a clinical diagnosis of BMS (type 1) in July 2004 (panels A and B). At that time, no visible signs of oral disease were observed. In April 2007, (panels C and D) the same patient developed OLP. OLP can develop before, concurrently with, or months after the diagnosis of BMS.
ABSTRACT

The Global Alliance to Improve Outcomes in Acne group recently published their recommendations for the management of this disorder. The consensus is that the combination of a topical retinoid and an antimicrobial agent is the preferred regimen for nearly all patients with acne who present with inflammatory lesions. The Global Alliance to Improve Outcomes in Acne group suggests that this therapeutic combination targets 3 of the 4 major pathogenic factors of acne: bacterial colonization of the pilosebaceous duct, inflammation, and abnormal keratinization within the follicle. Topical retinoids are also recommended for maintenance therapy (with benzoyl peroxide, if needed, for antimicrobial effect).

Adapalene is a naphthoic-acid derivative that is used topically for the treatment of acne. This agent was developed to provide enhanced stability and anti-inflammatory effects while maintaining effectiveness, reducing irritation, and improving tolerability (as compared with retinoic acid). Adapalene selectively binds to retinoic acid receptors and thus modulates cellular differentiation and keratinization. This medication also possesses anti-inflammatory effects and is known to inhibit the arachidonic acid cascade. Adapalene also inhibits polymorphonuclear leukocyte lipoxygenase activity, an important component of the inflammatory response to Propionibacterium acnes.

Previous studies have demonstrated a favorable side effect profile for adapalene. Tolerance has been established with the product, both as monotherapy and as combination therapy with other agents. Results from the pivotal trials showed that patients taking adapalene gel 0.1% experienced lower incidences and severity of erythema, scaling, dryness, and burning compared with those on a regimen of tretinoin gel 0.025%. Irritation related to adapalene tends to be transient and usually subsides within the first few weeks of initiating treatment. The low irritation potential of adapalene 0.1% cream is similar to that of the 0.1% gel formulation. Taken together, these results indicate that adapalene 0.1% is well tolerated.

Two large 12-week studies involving a total of 1068 patients evaluated the safety and efficacy of the adapalene 0.1% lotion formulation. The lotion was superior to the vehicle lotion in both studies. The frequency distributions of worst scores of either 0 (none) or 1 (mild) for adapalene lotion were erythema (98.5%; 40.7%), scaling (100%; 73.5%), dryness (100%; 68.8%), and stinging/burning (98.5%; 100%). The most common treatment-related adverse event was dryness (study 1, cream 2.7% [2 of 75] and lotion 4.0% [375]); study 2, cream 2.9% [2 of 69] and lotion 4.3% [3 of 69]. Both the adapalene 0.1% cream and 0.1% lotion formulations were well tolerated and acceptable to the study participants. The adapalene 0.1% lotion provides clinicians with a retinoid for the treatment of acne in a lotion formulation.

ORIGINAL CONTRIBUTION

A Comparison of the Tolerability of Adapalene 0.1% Cream and Adapalene 0.1% Lotion in Healthy Individuals

James H. Herndon, Jr, MD; Thomas J. Stephens, PhD; Nathan S. Trookman, MD; Ronald L. Rizer, PhD; Norman Preston, PhD; Scott Caveney, MD, PhD; Ronald W. Gottschalk, MD

Two separate single-center, randomized, evaluator-blinded, bilateral (split-face) comparison studies compared the tolerability of adapalene 0.1% cream with adapalene 0.1% lotion in individuals with healthy skin treated once per day for 3 weeks. At each visit, the participants were graded on erythema, scaling, dryness, and stinging/burning (scale: 0 = none to 3 = severe). On the final study visit, the participants completed a Cosmetic Acceptability Questionnaire. Adverse events were recorded at each study visit. A total of 144 participants were enrolled and 130 completed the studies (study 1, n=66; study 2, n=64). The lotion formulation was non-inferior to the cream for the success rates and tolerability assessments in both studies. The frequency distributions of worst scores of either 0 (none) or 1 (mild) (study 1; study 2) for adapalene lotion were erythema (98.5%; 40.7%), scaling (100%; 73.5%), dryness (100%; 68.8%), and stinging/burning (98.5%; 100%). The most common treatment-related adverse event was dryness (study 1, cream 2.7% [2 of 75] and lotion 4.0% [375]); study 2, cream 2.9% [2 of 69] and lotion 4.3% [3 of 69]. Both the adapalene 0.1% cream and 0.1% lotion formulations were well tolerated and acceptable to the study participants. The adapalene 0.1% lotion provides clinicians with a retinoid for the treatment of acne in a lotion formulation.
control in terms of the Investigator Global Assessment success rate and lesion counts (total, inflammatory, and noninflammatory). The tolerability of adapalene lotion was similar to vehicle (erythema, scaling, dryness, stinging/burning), and skin irritation was transient. The most common adverse event (AE), dry skin, was seen predominately during the first month of treatment. The results from the patient surveys indicated that the lotion was easy to spread, easily absorbed, and pleasant to use. These results agree with previous studies that indicate that some patients find lotions easier to spread and more pleasant to use than other topical formulations such as creams and ointments.18,19

Adapalene (Differin, Galderma Laboratories, L.P., Fort Worth, TX) is currently available in gel, cream, and lotion preparations.20 The lotion formulation gave health care providers another acne treatment option for patients with varying vehicle preferences.17 The following report is based on two separate single-center, randomized, evaluator-blinded, bilateral (split-face) comparison studies that were conducted to compare the tolerability of adapalene 0.1% cream with adapalene 0.1% lotion in participants with healthy skin treated once per day for 3 weeks.

METHODS

This report comprises two single-center, randomized, evaluator-blinded, split-face comparison studies conducted concurrently over the course of 3 weeks. Study 1 was conducted at a clinical site in Texas and study 2 was conducted at a clinical site in Colorado. Clinic evaluations were conducted on Monday through Friday for 3 consecutive weeks in January and February.

INCLUSION CRITERIA

Participants of either sex, aged 18 years and older, with healthy skin as determined by the clinical grader qualified for study participation.

EXCLUSION CRITERIA

Excluded from participation were individuals with a degree of skin pigmentation that interfered with the reading of skin reactions, individuals with a known allergy to one of the components of the test materials, and those with a washout period for topical treatment on the treated area less than 1 week for corticosteroids and/or 4 weeks for retinoids. Individuals with current sunburn, eczema, atopic dermatitis, perioral dermatosis, or rosacea on the area to be treated were also excluded from these studies. Both studies were conducted in accordance with the principles stated in the Declaration of Helsinki. The study participants signed informed consent forms and understood that they were free to withdraw from the study at any time and for any reason. The IntegReview Institutional Review Board approved both study protocols. The studies were registered on www.clinicaltrials.gov as NCT01046396 and NCT01046565.

TREATMENTS

Participants cleansed their faces with Cetaphil Gentle Skin Cleanser (Galderma Laboratories, L.P.), applied Differin (adapalene) 0.1% cream to the other half of the face, and applied Differin (adapalene) 0.1% lotion to the opposite side of the face once daily for 3 consecutive weeks (21 days). Application of test materials to each side of the face was determined by a randomization design (to which the evaluator was blinded). The participants performed test material applications on each Monday through Friday clinic visit (under the supervision of clinic personnel), excluding the final study visit, and at home on each Saturday and Sunday. Each participant was assessed by the same evaluator throughout the course of the study.

TREATMENT COMPLIANCE

Clinic personnel weighed test material units before and after clinic applications. Participants were also provided with weekend diaries to record test material application and comments.

TOLERABILITY

Evaluators graded erythema, scaling, dryness, and stinging/burning using a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). The evaluators were trained together and every attempt was made to encourage them to use the same criteria for rating.

STATISTICAL ANALYSES

The primary variables of interest were the worst post-baseline scores for local tolerability parameters (erythema, scaling, dryness, and stinging/burning) across the study visits. The worst post-baseline local tolerance scores for each parameter (regardless of time point) were summarized. A Wilcoxon signed rank test was used to compare treatment groups. The primary analysis for the worst post-baseline local tolerability scores consisted of dichotomizing each assessment as a success (score = 0) or failure (score ≥1). A 95% confidence interval for the difference of success rates between treatments was calculated. A 15% margin of noninferiority was used to assess the noninferiority between the two treatment groups. The sign test was used to compare patient responses of the Cosmetic Acceptability Questionnaire.

No statistical determination for sample size was conducted. Seventy-five participants were enrolled in study 1 and 69 were enrolled in study 2 to ensure that at least 60 participants completed the study. The tolerability survey analyses were taken from the per-protocol population (study 1, N = 66; study 2, N = 64). The safety
analyses were conducted on the safety population (study 1, N = 75; study 2, N = 69).

RESULTS

PATIENT DISPOSITION
Seventy-five participants were enrolled in the study, 9 of whom discontinued study participation; leaving 66 who completed study 1. Sixty-nine participants were enrolled, 5 of these withdrew, and 64 completed study 2. There were no major protocol violations or deviations during either study.

DEMOGRAPHICS
Most of the participants were white women with a Fitzpatrick classification of type II or III (Table I).

TOLERABILITY ASSESSMENT
The majority of participants (with the exception of patients with erythema in study 2) were assessed as having none (score of 0) or mild (score of 1) erythema, scaling, dryness, and stinging/burning (Table II). Moreover, there were no significant differences between the two adapalene formulations in terms of the mean of the worst scores from the tolerability assessment parameters within either study (Figure 1). The frequency distribution of worst scores from the tolerability assessments showed that adapalene 0.1% lotion was not inferior to adapalene 0.1% cream in both studies (Table II). Each individual study reported equivalent success rates for adapalene 0.1% lotion and adapalene 0.1% cream (Table III). The results from both studies demonstrated that adapalene 1% lotion was noninferior to adapalene 1% cream.

Figure 1. Results from the mean (± standard deviation) worst scores from the tolerability assessment parameters. Skin tolerability was assessed using the following scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Table I. Demographics and Baseline Characteristics (Per-Protocol Population)

<table>
<thead>
<tr>
<th>Mean Age, y</th>
<th>Study 1 (N=66)</th>
<th>Study 2 (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>51</td>
<td>38</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Female</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Fitzpatrick Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Type II</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Type III</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Type IV</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Type V</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Type VI</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
At the final study visit, participants completed a Cosmetic Acceptability Questionnaire on product aesthetics and preference. There was a slight numerical preference for the cream compared with the lotion for all study questions except two (Which side left the least amount of residue on your skin, study 1; Which side had less odor, study 2); however, there were large percentages of participants who showed no preference for either formulation (Figure 2).
Figure 2. Cosmetic Acceptability Questionnaire results. These surveys were completed on day 22 or at the early termination visit, if applicable.

Adverse Events
AEs were assessed from the time of first test material application until exit from the study. Overall, 7 participants who used adapalene cream and 9 who used the lotion experienced treatment-related AEs (Table IV). The most common treatment-related AE in both studies was dryness.

Table IV. Summary of Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Study 1 (N=75)</th>
<th>Study 2 (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adapalene 0.1% Cream, No. (%)</td>
<td>Adapalene 0.1% Lotion, No. (%)</td>
</tr>
<tr>
<td>Bumps</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Burning</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Burning/stinging</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Dryness</td>
<td>2 (2.7)</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Erythema</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>1 (1.3)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Redness</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Scaling</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Patients with treatment-related adverse events, No.</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
DISCUSSION
Results from the two concurrent studies provide evidence regarding the tolerability, acceptability, and safety of the new adapalene 0.1% lotion compared with the 0.1% cream preparation. For each study, success rates were comparable between the two adapalene formulations. Within each study, worst scores assessments produced equivalent results for the two formulations. The majority of participants were assessed as none or mild for the parameters evaluated in the tolerability assessment. Each study, success rates were comparable between the two adapalene formulations. It is interesting to note that participants in study 2 (which was conducted in Colorado) showed a tendency toward higher tolerability scores (ie, more patients were classified as moderate or severe) and a lower percentage of successes than study 1. This may have been attributed to the colder, dryer climate at the first study site, as the studies were conducted concurrently in January through February. The differences in geographic location and climate may have played a role in the differences in scores observed between the two studies. In addition, it is possible that there were subtle differences inherent in the way evaluators assessed the skin, but we believe this to be a minor factor. Overall, the adapalene 0.1% lotion was noninferior to the 0.1% cream with respect to tolerability measurements evaluated in these studies.

Cosmetic acceptability was favorable for both adapalene preparations. A considerable proportion of the participants reported no preference for one formulation of adapalene over the other.

Adapalene has shown a favorable tolerability profile in several previous clinical trials that employed typical dosing schedules.21–23 Adapalene 0.1% cream was shown to be well tolerated with a low incidence of cutaneous AEs over the course of 12 weeks.22 Another study reported that adapalene 0.1% cream was well tolerated over 12 weeks, with low percentages of patients reporting dryness (8%), burning (5%), peeling (2%), facial irritation (2%), and erythema (2%).23 The frequency and severity of AEs in the current studies was consistent with those reported in earlier trials for these two adapalene formulations.20,21,24,25 As was observed in the current studies, the most common AE reported for the cream23,26 and lotion24,25 formulations has been dryness. Overall, treatment-related AEs with these two products tend to be predominantly mild to moderate in severity.23–26

Patient acceptability toward adapalene skin care regimens has been favorable.27,28 There is no waiting period necessary between facial cleansing and application of the product, which could translate into greater convenience for the patient.12 Compliance to a skin care regimen can be poor when the medication is inconvenient to use or if the patient has concerns about medication adverse effects or efficacy.29 The favorable tolerability profile for adapalene and its high rate of patient acceptability could result in improved compliance.17 In order to enhance compliance, providing patients as well as their caregivers a choice of vehicle options has been recommended.30

LIMITATIONS
The current studies had some limitations that should be kept in mind when drawing conclusions from their results. Each study was conducted at a single site; therefore, there was variability in the evaluator assessment scores. Some of these differences in tolerability assessment scores may have been caused by climatic or geographic factors.

CONCLUSIONS
Overall, both adapalene 0.1% lotion and adapalene 0.1% cream were well tolerated. The cosmetic acceptability questionnaire results were not significantly different between the two preparations for any question. AEs with both agents were predominantly mild to moderate in severity. The adapalene 0.1% lotion provides clinicians with a retinoid for the treatment of acne in a lotion formulation.

Acknowledgements and disclosure: Julie Crider, PhD, assisted in the medical writing. Galderma Laboratories, L.P., provided editorial support. Funding for the two studies was provided by Galderma Laboratories, L.P.

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28 Cook-Bolden F. Subject preferences for acne treatments containing adapalene gel 0.1%: results of the MORE trial. Cuts. 2006;78:26–33.
A New Tretinoin Therapy
From Onset Dermatologics
Anti-infective prevention has become a public health priority for several years; thus, strict standards of hygiene, including the use of disinfectants, detergents, and antiseptics (DDA) is now prevalent. According to their chemical classification,1–5 these products can stop the proliferation or inactivate various types of microorganisms. These specific effects are required in different processes (Table). The main components found in these products are aldehydes, quaternary ammoniums, alcohols, oxidants, phenolics, biguanides, diamides, and carbanilines.

In the health care environment, disinfectants are used for disinfecting purposes in rooms (surfaces and floors) and for medical materials (medical instruments, optical systems, dialysis circuits, basins, and buckets for hospital waste), and antiseptics are used for healthy skin and wound antisepsis. The aim of these disinfectants and antiseptics is to decrease potential hazards of cross transmissions of infectious agents among patients, and thus to limit nosocomial infections. In the food industry, cleaning and frequent disinfection of food surfaces aim to ensure infection-free food. Cleaning and disinfecting processes, carried out at regular intervals, generally proceed in the following manner: (1) a “scraping” phase, with manual scraping or with pressurized tepid water; (2) a “cleaning” phase, by applying detergents; and (3) a “disinfection” phase, with the application of a disinfecting solution.

Dermatoses related to DDA exposure are various. The most frequent types1,2,6 are: irritant contact dermatitis, allergic contact dermatitis, contact urticaria, and atopic dermatitis (AD) flares. For this reason, we have been interested in the occupational dermatitis diagnosed for workers exposed to DDA products in the workplace. We carried out a retrospective and descriptive study of a bidisciplinary consultation of occupational dermatology by selecting patients who worked in the main industries exposed to these products (health care, food-processing, and cleaning industries). The purpose of this study was to assess the proportion of workers, exposed to DDA among all of the patients, seen in consultation, and to describe the subtypes of dermatoses found in these workers.

PATIENTS AND METHODS
A retrospective and descriptive study was performed investigating cutaneous ailments diagnosed at an occupational dermatology consultation service for patients working in the main sectors of industries exposed to DDA.
### Table. Various Uses of Disinfectants and Antiseptics According to Chemical Class

<table>
<thead>
<tr>
<th><strong>Chemical Class</strong></th>
<th><strong>Disinfection</strong></th>
<th><strong>Antiseptics</strong></th>
<th><strong>Use in Health Care Workers</strong></th>
<th><strong>Use in the Food Industry</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldehydes</strong></td>
<td></td>
<td></td>
<td></td>
<td>Formaldehyde + glutaraldehyde: Disinfection phase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complementary treatment for skin diseases</td>
<td>Quaternary ammoniums + glutaraldehyde or formaldehyde: Disinfection phase</td>
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<td></td>
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<td></td>
<td>Healthy skin washing and antiseptic</td>
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<td></td>
<td>Healthy skin</td>
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<td></td>
<td></td>
<td></td>
<td>Injection place</td>
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<td></td>
<td></td>
<td></td>
<td>To draw blood</td>
<td></td>
</tr>
<tr>
<td><strong>Quaternary ammoniums</strong></td>
<td>Ground and surface disinfection</td>
<td>Complementary treatment for skin diseases</td>
<td>Quaternary ammoniums + glutaraldehyde or formaldehyde: Disinfection phase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medical materials disinfection</td>
<td>Healthy skin washing and antiseptic</td>
<td></td>
<td></td>
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<td><strong>Alcohols</strong></td>
<td>Ethanol:</td>
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<td>Healthy skin</td>
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<tr>
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<td>Surface disinfection using spray process</td>
<td></td>
<td>Injection place</td>
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<td>To draw blood</td>
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<td><strong>Chlorinated products</strong></td>
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<td>Sodium, hypochlorite: Disinfection</td>
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<td></td>
<td>Hemodialysis generator disinfection</td>
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<td><strong>Iodide products</strong></td>
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<td>Antiseptic and surgical handwashing</td>
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<td></td>
<td></td>
<td>Detersion</td>
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<td></td>
<td>Healthy skin and mucous antiseptic</td>
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<td>Buccal, ophthalmologic, and genital mucous antiseptic</td>
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<td>Surgical surface antiseptic</td>
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<td></td>
<td>Complementary treatment of cutaneous affections</td>
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<tr>
<td></td>
<td></td>
<td>Superficial and minor burns</td>
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<td><strong>Oxidants</strong></td>
<td>Peracetic acid, hydrogen peroxide:</td>
<td>Hydrogen peroxide:</td>
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<tr>
<td></td>
<td>Hemodialysis machines</td>
<td></td>
<td>Used in dental surgery for its antiseptic and hemostatic effects</td>
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<tr>
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<td>Endoscopy cold disinfection</td>
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The investigation began in November 2002 in the Department of Dermatology at the University Hospital of Brest. It included joint consultations performed by a dermatologist and an occupational physician. The synergistic activity of these two doctors allowed for a singular approach to the dermatologic conditions, both on a cutaneous and on a socio-professional level. The collaboration also allowed for indexing of patients at the same time, wherein some cases would have been addressed separately by each of these services. Patients were thus directed to this consultation by their general practitioner, a specialist (dermatologist or occupational physician), or a hospital consultant.

The consultation proceeded as follows:

- Patients were seen at a joint consultation by the dermatologist and an occupational specialist to obtain a clinical history (particularly, personal or family history of atopy: asthma, atopic rhinoconjunctivitis, or dermatitis).
- A clinical examination was carried out with a complete cutaneous assessment and, if possible, an examination of the cutaneous lesions when present.
- Patch tests were performed in necessary with either the hospital-standardized tray (European standard), specific-allergen trays, or specific patches prepared with samples of products used in the workplace and supplied by the patient. Dilution and preparation were occasionally carried out before application on the skin in order to be sure of the non-irritating effect of the compounds (compatibility of the pH, non-abrasive physicochemical characteristics).

To confirm the diagnosis of occupational dermatosis, we focused on the 7 Mathias criteria, which include the following questions:

- Is the clinical appearance compatible with contact dermatitis?
- Are there workplace exposures to potential irritants or allergens?
- Is the anatomic distribution of the eruption compatible with contact dermatitis?
- Is the temporal relationship between exposure and onset consistent with contact dermatitis?
- Have non-occupational exposures been excluded as causes?
- Does the dermatitis improve away from work exposure to the suspected irritant or allergen?
- Do patch or provocation tests identify a probable allergic cause?

A positive answer to 4 of these questions allowed for the reasonable conclusion of an occupational etiology.

The main industries where workers are exposed to DDA products are in the health care, food, and cleaning industries. Patients who worked in these sectors and who were seen in the occupational dermatology consultation clinic from November 2002 to April 2007 were included in the study. For each patient, we utilized a computerized database to evaluate the consultations and reported the following points: occupation, allergy antecedents (atopic subject or AD), allergens identified by patch testing, and final dermatologic diagnosis.

RESULTS

From November 2002 to April 2007, a total of 291 outpatients were referred to the occupational dermatology consultation clinic at the University Hospital of Brest. A total of 61 of the 291 patients (20.9%), working in a DDA-exposed industry, were included in the study: 50 in health care and 11 in the food and cleaning industries. An occupational origin for their skin disease was proven for only 39 health care workers. The 11 non-professional patients with dermatoses included 6 patients with psoriasis, 2 cases with dyshidrosis, 1 with chronic urticaria, 1 with dermatophytosis, and 1 with onychodystrophy. As a result, 17.8% (50 of 280) of cases of occupational dermatitis diagnosed included patients exposed to DDA in the workplace: 13.9% (39 of 280) in health care and 3.9% (11 of 280) in the food and cleaning industries. Among workers with occupational dermatitis, 26 of 50 (52%) had an atopic history (28% with AD); 5 of 11 (45%) for workers in the food and cleaning industries (1 with AD and 4 with an atopic history without any cutaneous marks); and 21 of 39 (54%) for health care workers (13 with AD and 8 with an atopic history without any cutaneous marks). Fourteen of 50 patients (28%) had AD and 12 of 50 (24%) had an atopic history without any cutaneous marks.

Among persons working in health care institutions, 14 cases of dermatitis were diagnosed in nurses, 11 in nurses’ aids, 8 in ward clerks, 4 in laboratory technicians, and 2 in radio-operator manipulators. These cases of dermatitis included isolated irritant contact dermatitis for 17 patients (43.6%), isolated allergic contact dermatitis for 12 patients (30.8%), irritant contact dermatitis associated with allergic contact dermatitis for 8 patients (20.5%), AD flares after exposure to irritants for 1 patient (2.5%), and contact urticaria for 1 patient (2.5%). Results from additional allergy testing (ie, prick test when testing natural rubber latex and patch test for the other products) were positive 47 times.

- Disinfectants and antiseptics (12 positive)
  - Ammonium IV: commercial solution called hexanios (concentrated in ammonium IV) (2), commercial solution...
called aniosurf (concentrated in ammonium IV) (1), ammonium IV (1), benzalkonium chloride (1), cetalkonium chloride (1)

Aldehydes: formaldehyde (3), glyoxal trimer (2), glutaraldehyde (1)

• Nickel (11)
• Balsam of Peru (4) and fragrances (4)
• Rosin (3), latex solution (3), isothiazolinone (3), lanolin (3)
• Dodecyl gallate (1), potassium bichromate (1), professional soap (1), paraben (1)

Among 20 patients with allergic contact dermatitis (isolated or associated with irritant contact dermatitis), 10 (50%) patients had an atopic history (asthma, atopic rhinitis, or AD). Among patients working in the food and cleaning industries, 4 cases of dermatitis were diagnosed in workmen, 4 in maintenance personnel, and 3 in kitchen workers. The diagnoses included irritant contact dermatitis in 4 patients (36.4%), allergic contact dermatitis in 3 patients (27.3%), irritant contact dermatitis associated with allergic contact dermatitis in 1 patient (9%), AD flare after exposure to irritants in 2 patients (18.2%), and contact urticaria in 1 patient (9%). Intradermal tests, scratch tests, and patch tests revealed 10 results for sensitization, and the following allergens were identified: disinfectants (3 positive tests: aldehyde [2] and ammonium IV [1]), soap (3), isothiazolinone (1), thiuram (1), lanolin (1), and neomycin (1).

Among 4 patients with allergic contact dermatitis (isolated or associated with irritant dermatitis), 1 had an atopic history (asthma, atopic rhinitis, AD).

DISCUSSION

In the course of our investigation, we observed a large population (almost 20% of patients) with occupational dermatitis who worked in health care institutions or food and cleaning industries. These departments are known to employ the use of DDA, suggesting that the employees in these environments were exposed to DDA in the workplace.

This can be explained in several ways. First, these areas are subject to strict standards of hygiene that have gradually led to intensive cleaning and disinfection processes, including the use of many DDA products. Such DDA agents are employed in the food industry to ensure that products do not transmit infectious agents and in the health care sector to decrease nosocomial infections. The use of DDA products raises the workers’ exposure to these irritating and sensitizing agents, which explains why a high number of occupational dermatitis cases are found in these industries. In addition, employees are not often informed about the nature of the products they use or about the necessary protective measures to be used.

The misuse of disinfectants (eg, increasing the active agents to obtain a better quality of cleaning in a shorter period) and the lack of adequate protection (eg, wearing too small gloves or those with holes, involving skin contact with the product) increase the risk for employees to develop cutaneous lesions.

Workers exposed to DDA in our study could be overrepresented, compared with the number that may be found in a non-hospital environment. Initially, our examination took place in a hospital, therefore, making it more accessible for health care workers who work in hospitals. This explains the significant proportion (13.9%) of these employees present at the consultation. Secondly, dermatoses related to DDA are infrequently diagnosed out of the hospital, and often, non-hospital dermatologists are not very informed about these diseases. In our community, many dermatologists are reluctant to conduct allergy testing, preferring to refer their patients to a hospital service.

Irritant contact dermatitis is the most frequently reported dermatitis, affecting 42% (21 of 50) of the patients included in our study. These employees regularly handle DDA agents. Such products are, for the majority, skin irritants and most likely responsible for the appearance of irritating lesions in these patients; however, many such irritant co-factors may be found in these sectors of employment: These may include:

• Chemical factors: industrial professional soaps and detergents, which cause skin barrier dysfunction and increase skin permeability and are reported to be the first cause of occupational cutaneous irritation.

• Mechanical factors: aggressive and repeated handwashing, particularly for health care workers, to clean or disinfect their hands.

• Physical factors: wet environments, the occlusion effect of protective gloves, and exposure to cold and moisture, particularly in the food industry. Repeated exposure to water, frequent contact with detergents, and mechanical abrasive factors of repeated actions in these working areas represent the most significant risk factors for irritation dermatitis. In addition, working in a damp environment can be defined in different ways: regular work with hands in a damp environment (about 2 hours a day), regular use of occlusive gloves (about 2 hours a day), and/or frequent and intensive handwashing.

In Singapore in 2003–2004, researchers reported a significant increase in workers from the food industry among patients experiencing occupational dermatitis caused by detergents and damp working conditions.
Irritant contact dermatitis associated with allergic contact dermatitis is also frequent, coexisting for 20.5% of health care workers and 9% of workers in the food and cleaning industries. Such dermatoses, with failure of the protective skin barrier, facilitate the invasion of allergens into the dermis and support sensitization with a potential allergen. This would explain why irritation and allergy frequently coexist.16

Allergic contact dermatitis affected 30% (15 of 50) of the employees in our study. Irritating lesions are not the only lesions to support the appearance of allergic contact dermatitis; however, AD also represents a risk factor for allergic contact dermatitis. A history of AD contributes to the development of cutaneous symptoms. The relationship between AD and allergic contact dermatitis is reported in various studies, both in the health17 and in the food industry.18 Our results are consistent with these data. If we consider all workers presenting with occupational dermatitis in this study (50), we found that 52% among them presented with an atopic history, whereas only 30% (10% to 24%) of the overall population is atopic. A total of 28% of the patients in our study had a history of AD, whereas estimates are 20% in the overall population. We can, therefore, assume that the existence of an atopic history (and more precisely of AD) represents a risk factor for developing occupational dermatitis.

A study in Germany from 1990 to 1999, concerning 3730 occupational dermatitis cases revealed that 37% of the patients had an atopic history (and more precisely of AD) represents a risk factor for developing occupational dermatitis. A history of AD contributes to the development of cutaneous symptoms. The relationship between AD and allergic contact dermatitis is reported in various studies, both in the health17 and in the food industry.18 Our results are consistent with these data. If we consider all workers presenting with occupational dermatitis in this study (50), we found that 52% among them presented with an atopic history, whereas only 30% (10% to 24%) of the overall population is atopic. A total of 28% of the patients in our study had a history of AD, whereas estimates are 20% in the overall population. We can, therefore, assume that the existence of an atopic history (and more precisely of AD) represents a risk factor for developing occupational dermatitis.

A study in Germany from 1990 to 1999, concerning 3730 occupational dermatitis cases revealed that 37% of the patients had atopic skin, whereas in the overall population, the prevalence was estimated to be 20%.19 The investigators concluded that 21.6% of occupational dermatitis cases were attributable to the existence of AD and that supervision of these patients was necessary to prevent the development of occupational dermatitis. On the physiological level, this can be explained. In atopic patients the barrier function of the skin is compromised, which facilitates the penetration of environmental allergens and, therefore, sensitization (which can be humoral or delayed). In a 3-year prospective cohort of food industry apprentices, investigators18 revealed that the proven cutaneous atopic history multiplied by 4 to 5 times the risk of developing hand dermatitis; they did not find any association with other endogenous factors, such as respiratory atopy or metal sensitization. According to other investigators,20 respiratory atopy could also be a significant risk factor for developing immediate type I allergic responses.

Nurses were the most affected in our study, mostly with irritant contact dermatitis. Many factors of irritation are found in professional health care practices, including contact with antiseptics (antisepsis of the skin prior to injection, disinfection of wounds, hydroalcoholic solutions, or solutions for hand hygiene), wearing protective gloves for extended periods,21,22 and repeated and aggressive handwashing. Irritant lesions lead to allergic contact dermatitis, which would explain why these dermatoses coexist in health care workers.

Disinfectants and antiseptics are the most common allergens identified in our study. They account for 26.3% of the allergens identified in health care and food workers. Other main allergens were found, especially nickel, but also preservatives (isothiazolone and parabens) and perfumes, which are components of many disinfectant and detergent solutions.2 Detergents were not identified among allergens identified in our study, however, which is not surprising, considering the very weak prevalence of contact allergies related to detergents, reported in past studies.23 Among disinfectants and antiseptics, quaternary ammoniums and aldehydes are the main allergens.

In September 2000, researchers24 reported that health care workers were significantly more sensitized to glutaraldehyde and benzalkonium chloride than nonexposed persons (who did not work in health care environments). The data-processing network of the German dermatologic private clinics25 showed that the sensitizing rate to formaldehyde is higher in food workers, compared with the general population. In our study, health care workers were more sensitized to glyoxal and formaldehyde than to glutaraldehyde, because 5 results were positive for glyoxal and formaldehyde, compared with only 1 positive result for glutaraldehyde in health care workers.

In 2005, investigators26 found a significantly higher sensitization rate to glutaraldehyde in exposed individuals compared with nonexposed persons, whereas they did not note a significant difference concerning formaldehyde, which showed that glutaraldehyde is more sensitizing than formaldehyde. The decrease in glutaraldehyde sensitization in health care workers could be explained by the reduction of exposure to these products. For the past few years, health care institutions have greatly reduced the use of glutaraldehyde, primarily to protect the health of exposed workers, because glutaraldehyde handling not only can result in respiratory (reactive airway dysfunction syndrome in the event of strong inhalation) or dermatologic (sensitization risk) affections, but also because it is ineffective as nonconventional infectious agents for endoscope disinfection, evolving as a substitute for this product by other disinfectants, especially peracetic acid.27 The decrease in glutaraldehyde use in health care institutions has resulted in limiting health care workers’ exposure to this product and, thus, should explain why the sensitizing rate is decreasing in health care workers.

Previous studies also support our results. Researchers28 who reported similar findings found relatively comparable results in a study performed in a private dermatology clinic among 135 patients with
occupational dermatitis: health care, cleaning, and food industries accounted for 30% of occupational dermatoses and quaternary ammoniums and aldehydes were found to be the main allergens identified, in addition to nickel, thiuram mix, and neomycin. On the other hand, the proportions of the types of dermatoses were reversed compared with our study, with higher rates of allergic contact dermatitis compared with irritant contact dermatitis.

CONCLUSIONS

This study suggests that workers exposed to DDA could represent a large proportion of employees with occupational dermatitis. The relationship between occupational exposure to these products and the appearance of irritant dermatitis is difficult to prove because many other cofactors exist, including many mechanical factors that could irritate the skin (maceration, frequent glove changing, microtrauma) and lead to irritant dermatitis. In addition, if workers present with this kind of dermatitis, especially patients with a history of AD, they are often tempted to remove their protective gloves due to the unpleasant sensations of maceration and discomfort. This could lead to increased exposure to irritant products (DDA) in these sectors.

Many factors, including use of DDA products, can play a part in generating irritant dermatitis. For allergic contact dermatitis, patch testing confirmed the role of these products in the appearance of skin disorders. These cases of dermatitis can have serious occupational consequences, resulting, for most serious cases, in incapacity to work.10 More frequently, these dermatitis cases can lead to repeated sick leaves, making it important to have effective preventive measures for reducing the appearance of dermatitis for workers exposed to these products, including:

• To remind exposed workers about the simple rules for handwashing and glove wearing: to wash hands as infrequently as possible, to use a nonirritant soap, to dry hands well, to avoid detergents, to regularly apply emollient creams,14 to avoid wearing gloves for a long period, and to wear thick gloves with nitrile or vinyl polychloride with long sleeves for cleaning and disinfection processes. The use of creams must be explained to make the difference between skin protection products, which must be applied regularly (about every 3 hours) during activities that are harmful to the skin, in contrast with skin care products, which are used to promote the skin’s ability to regenerate itself and are used on clean skin after exposure.

• To limit, if possible, workers’ exposure to irritating products, substituting them with less-irritating products, or using other disinfection processes, particularly automated disinfection of medical materials.

• To develop, for exposed workers, educational programs about occupational dermatitis: anatomical and physiological concepts of the cutaneous barrier, the clinical aspects of dermatitis, and preventive measures.29–31 These educational programs have already been created for health care workers in various countries; ie, Finland32 and Germany.33,34 They have been shown to be effective in primary prevention, when training, by reducing dermatitis appearance in future health care workers, but also in secondary prevention, by significantly improving the incidence of dermatitis compared with employees receiving only traditional treatment. The development of these educational programs, complemented by traditional dermatologic treatment, should result in improving practices and should thus decrease the frequency of dermatitis in workers exposed to hazardous products.

Finally, it would be interesting in further studies to determine the true incidence of dermatitis related to DDA in exposed professional areas and to assess the occupational consequences of these dermatitis cases on incapacity of work, new vocational guidance, and sick leave within the framework of an international-wide medical vigilance.

REFERENCES


9th World Congress of Cosmetic Dermatology

By the International Academy of Cosmetic Dermatology

Athens, Greece
June 27-30, 2013

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The pathogenesis of keloid formation is poorly understood; however, agreement exists concerning how keloids generally result after injury or inflammation within the skin of predisposed individuals. It is thought that keloids may develop as early as 1 to 3 months after trauma, but there have been reports of keloid formation up to a year after an inciting event.1

Distinguishing keloid histopathologically from normal skin is straightforward. Keloids differ from normal skin and normal scars by rich vasculature, high mesenchymal cell density, inflammatory cell infiltration, and thickened epidermal cell layer.2 In keloids, the collagen fibers are organized in swirls, and these fibers are composed of numerous fibrils closely packed together with the resulting fibrous growths invading normal dermis that produce tissue masses in subcutaneous tissue.3 Few macrophages are present, while some lymphocytes exist.4

Studies on the role of dermal fibroblasts in keloid formation have determined that keloid-derived fibroblasts differ from normal skin–derived fibroblasts in the production of collagen I and factors associated with fibrotic conditions, including transforming growth factor (TGF) β.3 The fibroblasts continue to multiply even after the wound repairs, and are characterized by a persistent dermal fibroproliferative reaction and excessive extracellular matrix (ECM) production, especially type I collagen deposition, resulting in a net deposition of matrix long after re-epithelialization occurs. Moreover, the rate of collagen synthesis per fibroblast as well as the activity of enzymes remodelling intracellular collagen biosynthesis is greater in keloid-derived fibroblasts than in normal-derived fibroblasts.6

Real-time reverse transcription polymerase chain reaction (RT-qPCR) is the most commonly used method for quantitatively measuring gene expression. This method provides good sensitivity, accurate quantification of transcript numbers, and increasingly higher throughput capabilities.7 Quantification of gene expression can determine genes responsible for the progression of a disease and can provide valuable insight into the characteristics of a particular disease. Current studies identify reference genes that are validated for each tissue type and these genes can be selected by evaluating data from RT-qPCR statistical algorithms such as geNorm.8 The principle of the geNorm algorithm is that from an initial group of candidate reference genes tested across all the cell types (normal and diseased), the expression ratio of the two functionally distinct reference genes that display the most similar expression across all the conditions are chosen as reference genes.

ABSTRACT

The pathogenesis of keloid formation is poorly understood. The fibroblasts in keloid patients continue to multiply even after initial wound repair and are characterized by a persistent dermal fibroproliferative reaction and excessive extracellular matrix production. Most studies concentrate on the type of collagen produced within keloids and the cytokines that dominate the disease. There have been considerably fewer studies in the expression of messenger RNA level in key cell cycle genes of the keloid fibroblast. The aim of this study was to measure the messenger RNA expression of the key regulators of cell cycle, cell cycle cyclins, and cyclin-dependent kinases, and their inhibitors. (SKINmed. 2012;10:152–159)
The purpose of this study was to investigate the expression of cell cycle regulatory genes in keloid fibroblasts vs fibroblasts derived from normal scars. Initially, we identified the most stable reference genes for use in RT-qPCR experiments investigating cell cycle regulatory gene expression in fibroblasts. In an attempt to determine the role of cell cycle candidate transcripts, these reference genes were used to measure the relative expression of key cell cycle regulatory components of cell cycle by comparing differences in the expression of cell cycle candidate transcripts in keloid fibroblasts and normal scar fibroblasts.

METHODS AND MATERIALS

SAMPLE COLLECTION

A keloid scar was defined as a dermal tumor that spread beyond the margin of the original wound, continued to grow over time, did not regress spontaneously, commonly recurred following excision, and had been present for at least a minimum of 1 year.

All cases (N=5, aged 13–42 years, with an average age of 29.4 years) were personally assessed by an experienced surgeon. There were 4 women and 1 man participating in this study who were from different ethnic backgrounds (Table I). A full medical history was taken and each scar lesion was examined in detail. The local and hospital ethical committees had given approval for the study protocol. Written consent was obtained from all individuals entered into the study.

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Abbreviations: AP, Asian Pakistani; BA, Black African; BC, Black Caribbean; F, female; K, keloid study; M, male; N, normal; W, White Caucasian.

In the control (nonkeloid) sample, 2 men and 3 women participated in this study with different ethnic backgrounds (N=5, aged 22–62 years, with an average age of 49.6 years). All control patients were clinically assessed to ensure that any existing scars did not resemble keloid. The local and hospital ethical committees gave approval for the study protocol and written consent was obtained from all individuals entered into the study.

TREATMENT OF EXCISED SCAR TISSUE

After the removal of the scar, depending on its size, the scar was divided into a maximum of 4 regions. Many of the scars were too small and so no divisions were made. These scars were exempted in this study as our interest was to find differences in gene expression across different sites. Where it was possible, normal skin was also taken for the purpose of internal control.

The top layer consisted of the upper layer of the epidermis, which is normally 1 mm in thickness (variable thickness according to the exact anatomical body site). The middle layer was the collagen-rich region of the scar in the epidermis region of variable thickness. The bottom layer was the region where the collagen-rich layer came in contact with the fatty layer. The margin layer was the region where the normal skin and the keloid scar met and the normal skin was considered to be located beyond the keloid scar but in exactly the same anatomical site.

Skin was also taken from nonkeloid regions termed the external control. In this study, skin was taken from patients who did not have any evidence of abnormal skin conditions. Many of these patients were women who had undergone surgery to remove stretch marks.

CELL CULTURING

Following harvest of the lesions, the skin samples were extensively washed in phosphate buffered saline (PBS) (1% antibiotics and fungicide) for 15 minutes at room temperature. Using two scalpels, the remaining skin was finely diced into 1-mm² pieces and added to 0.25% to 0.5% collagenase A for 2.5 to 3 hours at 37ºC. The resulting cell suspension was then put through a 100-μm cell strainer (optional additional step) and the enzyme neutralized with the addition of fibroblast cell culture media containing 10% fetal calf serum (plus 1% penicillin and streptomycin and 1% nonessential amino acid. The solution was then centrifuged at 1200 rpm for 5 minutes and resuspended in 12-mL fibroblast media. This was added to a 75-cm² tissue culture flask with approximately 4x10⁵ cells and incubated at 37ºC in 5% carbon dioxide for 48 hours. Cell confluence was assessed by observing the growth of the fibroblasts under a light microscope and media was either changed every 2 to 3 days or culture
was trypsinized and passaged. Once the cells reached confluence, they were washed with PBS (1% antibiotics and fungizone) and trypsin was added. Cells detached, were pelleted at 1200 rpm for 5 minutes, and the supernatant discarded. Once the media was removed, 1 mL Trizol (Invitrogen, Grand Island, NY) was added to the pellet and was mixed with the aid of pipette. The resulting cell culture present in the tube was then suitable for RNA extraction.

RNA EXTRACTION FROM SAMPLES

The RNA was extracted using the Qiagen RNeasy Mini Kit (Qiagen, Austin, TX) according to manufacturer’s instructions. Final elution of the total RNA was performed using 30 μL of RNase-free water, and repeated to maximize the amount of RNA eluted. Total RNA samples were stored at −80°C until use. The concentration of total RNA representing each sample was quantified by using a NanoDrop ND1 spectrophotometer (NanoDrop Technologies Ltd, Wilmington, DE). All RNA samples were determined to have no or mild loss of integrity (RNA integrity number > 7.6) and were thus deemed suitable for use in the following experiments.

PCR ASSAY DESIGN

The real-time PCR assays were performed on a Roche LightCycler 480 (LC480; Roche Diagnostics, Basel, Switzerland). Primer and probe sequences were designed for 8 of the most commonly used control (reference) genes4 using the Universal Probe Library Assay Design Centre (http://www.roche-applied-science.com). Transcript sequences were obtained from the National Centre for Biotechnology Information (NCBI). Primers and matched probes were synthesized by Metabion International AG (Martinsried, Germany). Where possible 400 ng of RNA was used to synthesise cDNA. The mRNA was converted into cDNA by using the SuperScript™ III first-strand synthesis supermix for qRT-PCR (Invitrogen, UK). Where possible 400 ng of RNA was used to synthesise cDNA. Otherwise the maximum volume (maximum of 8 μL of total RNA) was used to synthesis cDNA. The concentration of RNA from all samples was quantified using the NanoDrop* ND-1000 UV/visible Spectrophotometer (NanoDrop Technologies).

The real-time PCR assays were all performed in triplicate using 384-well plates on cDNA from total RNA that had been DNase I–digested. No template controls were used for each assay. Each assay well had a 10-μL reaction volume consisting of 5 μL 1 × probe master mix (FastStart Taq DNA polymerase) and reaction buffer, dNTP with 3.2mM MgCl2 (Roche Diagnostics), 0.1 μL 20 μM FP , 0.1 μL 20 μM RP , 0.7 μL of sterile reaction buffer, RNA, and 4 μL of sample cDNA or water for negative controls.

The PCR amplifications were performed according to the standard protocol with initial Taq activation at 95°C for 5 minutes and 45 cycles of 95°C for 10 seconds and 58°C for 30 seconds, finishing off with 40°C for 30 seconds.

All the probes were supplied by Roche Diagnostics and primers were synthesized by Metabion International AG (Martinsried, Germany).

REVERSE TRANSCRIPTION

The mRNA was converted into cDNA by using the SuperScript™ III first-strand synthesis supermix for qRT-PCR (Invitrogen, UK). Where possible 400 ng of RNA was used to synthesise cDNA. Otherwise the maximum volume (maximum of 8 μL of total RNA) was used to synthesis cDNA. The concentration of RNA from all samples was quantified using the NanoDrop* ND-1000 UV/visible Spectrophotometer (NanoDrop Technologies).
DATA ANALYSIS
Following the RT-qPCR assays, the levels of expression (Cq value) for each of the candidate reference genes were converted into relative quantities ($2^{ΔΔCq}$) using the algorithm described by Vandesompele and colleagues. These relative quantities were then entered into a data input file that could be analyzed by the geNorm software package to identify which of the assayed genes for a given tissue type exhibited the most stable relative expression. Gene expression stability measures (M value) of each individual gene within the tissue evaluated was calculated by the geNorm software. The pairwise variation (V value), which is an indication of the influence on the stability attributed by addition of a gene to a group of reference genes, was also calculated by the geNorm software package. Genes with the lowest M value are the most stably expressed.

WESTERN BLOT
Protein was extracted and a total of 20 mg of protein was resolved by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to a nitrocellulose membrane (Sigma, Aldrich Co Limited, Gillingham, Dorset, UK). Primary antibodies anti-CDC2 (sc-954, Santa Cruz Biotechnology, Santa Cruz, CA) and β-actin (A1978, Sigma) were incubated for 1 hour at room temperature, and were decanted and followed by incubation with horseradish peroxidise–conjugated secondary antibodies; rabbit anti-CDC2 (172-1019, Bio-Rad, UK) and mouse anti-β-actin (172 1011, Bio-Rad) all diluted 1:1000 at room temperature for 1 hour. After washing, ECL Advance Western Blotting Detection Kit (RPN 2135, GE Healthcare, Waukesha, WI) was applied and proteins were visualized using the enhanced chemiluminescence detection system (Kodak Biomax Light Film, Sigma). The film was developed by Fujifilm FPM 800A.

RESULTS
IDENTIFICATION OF REFERENCE GENES FOR FIBROBLASTS
The data from the GeNorm software analysis showed a V value threshold <0.15 for reference genes, which suggested high stability of expression across the reference transcripts (Figure 1). Genes in order of least to most stable expression are GAPDH, ACTB, B2M, RPL32, RPL13a, SDHA, HPRT1, and HMBS.

From these data, two reference genes were used to normalize data: HPRT1 and HMBS.

The PCR results for gene expression of 16 genes are shown in Table II. Initially the average Cq values were normalized against the average of reference genes and the value was negatively rooted to the base of 2 to convert into natural numbers. Both one-way analysis of variance (ANOVA) and Kruskal-Wallis analysis were performed to look for significant $P$ values. Kruskal-Wallis values were more satisfactory than one-way ANOVA because the Kruskal-Wallis test is most commonly used when there is one nominal variable and one measurement variable, and the measured variable does not meet the normality assumption of ANOVA. A one-way ANOVA may yield inaccurate estimates of the $P$ value when the data are very far from a normal distribution. The Kruskal-Wallis test does not make assumptions about normality. The $P$ values for both of these tests are shown in Table II.

The results showed 7 genes with significant $P$ values for one-way ANOVA while significance was seen for 5 genes when using Kruskal-Wallis. The Tukey test was performed on these results to find significant differences across the genes. The Tukey test is a single-step multiple comparison procedure used to find which means are significantly different from one another. The Kruskal-Wallis test showed close relation with the Tukey test; therefore, from both the Kruskal-Wallis and Tukey tests it was possible to conclude the following: CDC2 is down-regulated throughout all sites in keloid compared with external control. P27 is up-regulated while cyclin A and cyclin E are significantly down-regulated in the bottom section of the keloid scar. The $P$ value generated
The origin and pathogenesis of keloid scars continues to be poorly understood. Despite some similarity with equine sarcoïds, a major problem faced by researchers is the absence of an animal model, as keloid disease affects only humans. Based on the histological observation of excess and irregular deposition of ECM, most of the work so far has been focused on the characteristics of keloid fibroblasts. Keloid fibroblasts are found to overproduce fibronectin and collagen when compared with normal fibroblasts.9,10 Other cells such as the keratinocytes are thought to also have a potential role in pathogenesis of keloids, and support exists for epithelial-mesenchymal interactions being instrumental in modulating fibroblast behavior in keloids by paracrine signalling. Cytokines are also considered to be involved in the pathogenesis of keloid scars. TGF-β1 and TGF-β2 are the main cytokines responsible for stimulating the synthesis of collagen and fibronectin in keloid scars.

### Table II. Gene Expression Studies: Fold-Change Relative to Reference Genes in 16 Transcripts in Keloid Patients (K1–K5) Across 5 Different Sites and Normal Nonkeloid Patients (N1–N5)

<table>
<thead>
<tr>
<th>GENES (2δCq)</th>
<th>CDK</th>
<th>CDK INHIBITORS CYCLIN FAMILY REGULATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>CDC2</td>
<td>CDC2</td>
</tr>
<tr>
<td>N1 External control</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>N2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>N3</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>N4</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>N5</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>K1 Bottom</td>
<td>0.2</td>
<td>1.9</td>
</tr>
<tr>
<td>K2</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>K3</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>K4</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>K5</td>
<td>0.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Abbreviation:** CDK, cyclin dependent kinase.
“Cell cycle” denotes the orderly sequence of events required for cell duplication. The main engine that drives the cell cycle is controlled by the family of serine/threonine protein kinases called cyclin-dependent kinases (CDKs). As indicated by the name, its association with the regulatory subunit known as cyclin is an absolute requirement for kinase activity. To strictly control the proper progression of the cell cycle, besides CDKs and cyclins, mammalian cells have developed a number of regulatory pathways collectively known as “cell-cycle checkpoints” that serve to control the order and timing of cell-cycle transition and ensure that critical events are completed without any error. When one cell cycle has not been successfully completed, checkpoints will delay progression until the error is corrected and only then can cell cycle progress toward completion. Defects in cell-cycle checkpoint pathways result in genomic instability and have been implicated in transformation of normal cells into cancer cells.

The focus of this study was to look at the gene expression of some of these key regulators of cell cycle in fibroblasts. Fibroblasts from different regions of keloid scar as well as fibroblasts from nonkeloid patients were harvested and primary cultures produced in tissue culture flasks. The division of keloid scars into 4 regions is novel and was set up to look for differentiation within different regions of the scar. Two controls were used to compare the gene expression: one internal and one external. The internal control comprised cells retrieved from normal tissue from keloid patients while the external control came from patients who had no previous history of keloid or any skin diseases.
A reference gene screen was carried out to see which genes were expressed constantly throughout the samples. HPRT1 and HMBS were found to be the most stably expressed, while GAPDH, which is a gene employed as a reference gene in many other studies, was the least stably expressed.

From this study, mRNA expression of some of the genes investigated were seen to be different than the external normal control material. For example, CDC2 mRNA expression showed down-regulation across all keloid sites including internal normal compared with the external normal controls. This could suggest that people who are susceptible to forming keloid scars may have underexpression of this mRNA and encoded protein. Western blot confirmed this relationship, showing that the protein expression of CDC2 is only present in very small amounts in sample K2 normal and not present in any other sample (Figure 3). The down-regulation of this mRNA, and hence its protein, may be due to other factors that were not investigated in this study, but this could be further investigated for use as a biomarker to distinguish keloid fibroblasts from normal fibroblasts.

Fibroblasts from the bottom section of the keloid scar show down-regulation in cyclin E2 and cyclin A, and might imply that this part of the scar is the most suppressed region, fitting with the surgical term of the quiescent replication region of the scar. Although the Tukey test shows no significant change in cyclin B1 mRNA expression, it displays the lowest expression in the same bottom section. The only gene that showed up-regulation of mRNA in comparison to the external control was p27 in the bottom region of surgically excised keloid tissues. The p27 protein binds to and prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes. Again, the only region where this may carry significance is in the bottom of the scar. This study cannot link down-regulation of cyclin A and E2 with up-regulation of p27, but it is highly probable that up-regulation of one CDK inhibitor could lead to cascades of events that might cause down-regulation of the cyclin family in an indirect manner.

The Kruskal-Wallis test fitted the data much better than one-way ANOVA. The reason for this is that the Kruskal-Wallis test does not assume a normal population.

CONCLUSIONS

This study uniquely analyzed fibroblast mRNA expression across different sites of keloid scars. From the transcript levels it is suggested that the discrimination and dissection of the sites was carried out with relative care. This is shown where the level of mRNAs associated with cell cycle suppression is mostly detected in the bottom region of the scar, and where expected. The margin, however, which is known as the most proliferative part of the scar, did not show any major change in the level of mRNA expression. This observation was not expected and may be a reflection of the inappropriate selection of transcripts to reveal active cell proliferation. Figure 4 summarizes these findings. The diagram is a schematic representation of a keloid scar. The numbers relate to the number of genes that showed significant difference in expression. The bottom shows 4 of 4, indicating that all 4 genes exhibited altered expression at this site, while other regions of the keloid scar only scored 1 of 4.
CDC2 down-regulation in the lower regions of keloid scars has been the prominent finding in this study. Employing carefully selected reference transcripts, the levels of CDC2 expression were very low compared with the external normal across all the sites, including internal normal. This observation was further confirmed at protein levels with Western blotting. Although further validation is required, these data could suggest that people who develop keloids have low CDC2 expression.

Acknowledgement: Dr Yun Xu, University of Manchester, assisted with one-way analysis of variance and Kruskal-Wallis analysis.

REFERENCES


HISTORICAL DIAGNOSIS & TREATMENT: SYPHILIS PRIMARIA. (continued from page 142)

SYNONYMS: CHANCRE; HARD CHANCRE.

Spirochaeta pallida finds its way into the system by inoculation. After a period of incubation that may last for two to ten weeks but is usually about three, at the point of entry the first evidence of syphilis arises and is the chancre. About one week after the appearance of the primary lesion on the penis the inguinal glands become discretely and painlessly enlarged and hard. As a rule the chancre starts as a macule, scratch or erosion, beneath which a papule soon forms and increases in size to that of a finger nail. It is usually surrounded by a red dark areola. The surface may be dry and crusted with layers of exfoliated epidermis or it may be superficially or deeply ulcerated. Most often it is merely abraded, polished and raw looking or slightly moist and partly covered by a gray film or adherent pseudomembrane. The most marked, constant and typical characteristic of the chancre is its induration. Surrounding or underlying the surface lesion is an extended or more often a sharply circumscribed region of superficial or deep infiltration. This usually becomes palpable the fifth to tenth day after the appearance of the chancre and reaches its maximum in another week when the infiltrated tissue may be of almost cartilaginous hardness. The infiltration may remain long after any ulceration has healed, even for several months, though generally both the ulceration and the induration disappear in four to six weeks and the glandular swelling subsides soon afterwards. The chancre does not leave a scar unless it has been deeply ulcerated. In men three-fourths of all genital chancres are located on the cervix of the penis, on the glans near the frenum, or on the margin of the preputial opening. The others are at or about the meatus or upon the skin of the penis, scrotum or groin. The chancre is usually single; two or more may be acquired at the same time, but it is unusual for one chancre to produce others by auto-inoculation.

DIAGNOSIS: Secondary or mixed infection may effectually obliterate all of the characteristics of a syphilitic sore, and a nonspecific herpetic erosion or a chancroid may at times closely resemble a typical chancre. A lesion which develops less than five days after exposure to contagion is not a chancre even if syphilis was acquired at that time. A sore which appears more than ten days after the last coitus is probably a chancre. However in no case is it justifiable to start constitutional syphilitic treatment until Spirochaeta pallida can be identified in the secretion expressed from the sore, or unless secondary syphilitic lesions are present to confirm the diagnosis.

TREATMENT: The chancre heals promptly when the general mercurial treatment is begun. Usually the only local treatment required for an uncomplicated chancre is cleansing with soap and water and dusting with calomel. If the sore ulcerates iniform may be used or a wet dressing of one to three thousand mercuric chloride. As regards the use of arsenic in the treatment of syphilis, it will require many years to determine whether or not certain arsenic compounds which are now being extensively substituted for mercury, are as harmless in themselves and as certain in results as the old and well tried remedies.
Paget’s disease of the breast affects the areola and/or the nipple, usually with unilateral lesions resembling eczematous dermatitis. Most cases are associated with an underlying invasive breast neoplasm.1,2

HISTORY
The disease was first described in England by Sir James Paget in 1874, with lesions in the breast areola being eczematous and initially benign but demonstrating neoplastic changes in 1 to 2 years.3 In 1904, Jacobaeus investigated three cases of Paget’s disease of the breast and demonstrated the epidermotropism of malignant cells of an underlying mammary adenocarcinoma disclosed by histopathology.4

Epidemiology
Paget’s disease occurs mainly in women, in a proportion of 1:100. It has been described in patients aged from 26 to 82 years, being rare in women in their 40s, but frequent in the following 2 decades.1 It is an uncommon presentation of a breast neoplasm, representing 0.5% to 5% of all mammary tumors.5 Most cases are related to an underlying neoplasia, whether in situ or ductal invasive carcinoma. Recent studies have demonstrated an association of 67% to 100% of Paget’s disease with underlying neoplasias.6 Despite its comparative rarity, Paget’s disease may be associated with neoplasms in the contralateral breast. The first case of the disease was described appearing years after a radical mastectomy carried out in the other breast.7

Breast cancer is rare in men, representing only about 1% of cases. Paget’s disease, observed in men between 43 and 81 years,8 is still infrequent, with fewer than 50 cases published in the medical literature.9 The majority are associated with carcinoma of the underlying breast, with only two isolated cases8 and one with bilateral lesions.9 When affecting other areas, it is called extramammary Paget’s disease, representing about 6.5% of cases. In this form, the vulva is the most typical location, which is responsible for 65% of the cases and rarely associated with underlying neoplasia.10,11 There are 4 reported cases of an association between breast and vulvar Paget’s disease12 and 14 cases of extramammary associated with neoplasia of the breast.6

IMMUNOPATHOGENY
The histogenesis of Paget’s disease is an extremely controversial issue. There are two main theories, both plausible, that aim to elucidate its pathogenesis and have influenced the therapeutic approach. The first one, called the epidermotropic theory, suggests that the Paget cells are originally apocrine ductal cells that became malignant, originating in a ductal carcinoma migrating through the breast epidermal basal membrane of the underlying ducts. This theory is based on the presence of breast neoplasia associated with intraductal or invasive carcinoma of the breast in the majority of patients. Superexpression of oncoprotein c-erb...
B2 in Paget cells may suggest the hypothesis that the keratinocytes release a chemotactic factor that attracts Paget cells to the epidermis.5,13

The theory of in situ malignant transformation proposes that Paget cells are transformed malignant keratinocytes. Paget’s disease is an in situ carcinoma, regardless of the associated breast neoplasia.13 This is a process that affects the epidermis of the nipple in the same way it does the underlying breast parenchyma, sometimes with lesions without dermal alterations or without direct connection with the tumor.5

**Clinical Presentations**

Paget’s disease can be seen in three different forms: (1) alterations restricted to the skin of the nipple and areola (some authors call it “extramammary Paget’s disease of the breast”10); (2) alterations in nipple and/or areola associated to an underlying palpable mass; and (3) isolated breast tumor (subclinical Paget’s disease).13

The initial clinical picture can be nonspecific or discreet, appearing with pruritus, burning, and paresthesia of the nipple and areola; small crusts; and, more rarely, serous-blood papillary discharge and a palpable mass (Figure 1A and Figure 1B). In its progression, an eczematous or psoriasiform lesion appears, with raised borders and irregular contour, along with exudate and crusting limited to the nipple and areola but also extending to the breast. The lesion is usually unilateral, with exceptional bilateral occurrence.14 There is a case of a lesion on an accessory nipple.15 In the more advanced stages, the crusts and exudate are more exuberant with the possibility of ulcerations and changes to the nipple and areola architecture.10,16,17 The nipple can be retracted or even deformed and a mass or nodule can be palpable deep in the breast. Pruritus is the prevailing symptom and can be associated with excoriations.10

About 50% of the patients present a palpable mass in the breast and 90% to 94% of these are already in an advanced stage of the disease. The lymph nodes should be examined, with special attention to the axillary and supraclavicular nodes. In cases not associated with a clinically detectable breast mass, which is seldom palpable, the tumor is frequently detectable only in more advanced stages.10

Evolution of the cutaneous lesions is slow, and patients often postpone visiting the physician for at least a year or more.

There are about 34 cases of Paget’s disease with pigmented lesions reported in the literature.18 They present as asymptomatic punctiform lesions, macules, or plaques of light brown to black, sometimes with intermingled erythematous areas and irregular format showing slow and progressive growth.19–24

**Histopathology**

The histopathology of Paget’s disease is marked by the presence of Paget cells. These are large round or oval intraepidermal structures comprising abundant and clear cytoplasm, with large, hyperchromatic, eccentric, and pleomorphic nuclei with visible, although not protuberant, nucleolus. After periodic acid-Schiff stain, abundant intracellular mucopolisaccharides are observed while intercellular bridges are absent.1

Paget’s cells can be found in all levels of the epidermis in small numbers or occupying whole portions of the epidermis. They can be found isolated or in small aggregates, without forming nests, sometimes pressing but preserving the basal layer. They can extend to the follicular epithelium of the gland ducts. Mitoses are frequent and can be atypical.1,18 It is suggested that the morphology of those cells is identical in both mammary and extramammary Paget’s disease, with differences only regarding the immunophenotype.25

Tokor cells are intraepidermal cells present in 10% of normal nipples with clear and abundant cytoplasm, as well as small and eccentric nuclei. They are usually located in the basal layer, around the milk duct orifices, but in case of hyperplasia, they
extend to the upper layers, forming aggregates that can be mistaken for Paget cells. It has been proposed that these cells are present in cases with no underlying neoplasia. Immunohistochemistry of these cells is similar to that of Paget cells. Morphology is the main form for their differentiation.26

In the epidermis, acanthosis, hyperkeratosis, and parakeratosis can be present, and in advanced cases, ulceration. In the dermis, it is possible to observe mononuclear inflammatory infiltrate and vascular neoformation (Figure 2A and Figure 2B).5

In cases of pigmented lesions, Paget’s cells contain abundant melanin granules19 due to melanocytic proliferation and an increase of pigment synthesis. The responsible mechanism for this occurrence is not completely understood, and it has been suggested that the neoplastic cells produce melanocyte chemotactic factors and fibroblast growth factor, which stimulates the proliferation of melanocytes.27 These characteristics, however, are insufficient to classify such lesions as melanocytic.1

The pagetoid aspect of the cells present in this disease simulates other intraepidermal neoplasias, such as malignant melanoma, pagetoid cells in situ squamous cell carcinoma, mycosis fungoides, cutaneous tumors of the adnexa (sebaceous gland carcinoma or porocarcinoma), Merkel cells carcinoma, Langerhans cells histiocytosis, and some cutaneous epidermotropic metastases.1,19

Immunohistochemistry can be useful as an aid in the diagnosis and to establish the differential, especially with malignant melanoma (Figure 3).

Cytokeratin (CK) 7 is the more sensitive marker, present in more than 90% of the Paget cells, but not entirely specific.25,26,28 In normal nipples, Toker and Merkel cells can be CK7 positive.28 CK8 and CK18 can also be positive (Figures 4 and 5).

Oncoprotein c-erb B2 is expressed in up to 90% of the cases of breast Paget’s disease and seems to be correlated with the presence of underlying mammary neoplasia and with a worse prognosis.5,17,29,30

Patients with cutaneous lesion, but without palpable mammary mass, can have the diagnosis of Paget’s disease of the breast excluded if epithelial membrane antigen (EMA) and c-erb B2
are not detected or highly suggested, when both are expressed. In cases where EMA expression by the Paget cells occurs, but not c-erb B2, a breast adenoma or associated in situ ductal carcinoma can be suggested.30

The expression of mucin core protein (MUC) glycoprotein can be helpful in the diagnosis of Paget's disease. MUC1 is expressed in almost all cases of the mammary and extramammary disease, while MUC2 is usually negative in extramammary and positive only in cases associated with an underlying gastric adenocarcinoma. MUC3 is positive in about 75% of the cases of Paget's mammary disease and rarely expressed in extramammary cases.25 MUC5AC does not usually present positivity in mammary cases, and is controversial in extramammary cases (40% to 100%). The cases associated with underlying neoplasia can show different immunophenotypes.25,31–33 The expression of each of these glycoproteins may be related to the behavior and prognosis of underlying mammary neoplasm.34

Protein S100, HMB 45, and Melan A are not expressed in the Paget cells and are fundamental for the differential diagnosis with malignant melanoma. Additionally, Paget cells are not marked by CD1a, CD5, and CD68, contributing to other differential diagnoses.20,23,24 Paget cells can also demonstrate reactivity for the carcinoembryonic antigen (CEA) in approximately 35% of the cases.5,26,35

In one report, the androgen receptors could be detected in 88% of cases of mammary and in 78% of extramammary Paget's disease. The estrogen receptor was positive in 10% of the mammary cases and negative in all progesterone cases.33

**DIAGNOSIS**

Diagnosis requires careful clinical evaluation when suspecting unilateral eczema-like lesions in the nipple, which do not respond to adequate therapy. It is necessary to perform a biopsy for histopathologic examination, preferably of the nipple. The full thickness of the epidermis and dermis should be included and immunohistochemistry should be performed.

Dermatoscopy of these lesions does not illustrate, so far, an effectively defined pattern, but some reports demonstrated irregular areas of brown pigmentation with dots and globules, gray-bluish areas or red-milky areas with irregular vascular pattern. These findings make the differential diagnosis of melanoma almost impossible.20,21 Confocal microscopy reveals large atypical cells arranged in pagetoid form, resembling malignant melanocytic lesions, associated with epidermal disarray of poorly defined borders and suggestive of extensive superficial melanoma.19 The histopathologic and immunohistochemical examination are fundamental to obtain differentiation.20

Breast imaging with ultrasound, mammography, nuclear magnetic resonance, and nuclear medicine can be useful in detecting or discarding underlying neoplasias. The majority of cases demonstrate that about 50% of the patients with Paget's disease do not show alterations in their mammographies.5,13 Its sensitivity, however, is extremely high (97%) in the presence of a palpable mass in the breast; this has small significance (50%) in cases of disease confined to the nipple without a palpable mass. Mammographic findings include thickening of the skin, nipple, and areola; retraction of the nipple; subareolar microcalcifications or diffuse calcifications; masses; and distortion of the architecture. Bilateral examination is required for precise detection of the suspicious lesions and for evaluation of the other breast. This is needed in order to exclude a multifocal disease or other associated neoplasias and to serve as a control for cases where a conservative treatment option is chosen.5

Ultrasound should be considered at the beginning of the investigation, especially in cases in which mammography did not detect alterations.5 There is presence of an underlying breast tumor in 67% of 52 patients with histologically evidenced Paget's disease. Of these, 2% have normal mammography.13 Nuclear magnetic resonance of the breast can detect hidden mammary tumors confined to the retroareolar tissue, involving the nipple and/or areola without clinically suspicious expression.5 Nuclear medicine can be useful in the detection of nipple diseases, through the capture of 99m Tc MIBI by the proliferative intraductal Paget cells; however, this is still a limited technique that requires more study.5 Such examinations, however, can be normal even with prevalent disease, emphasizing the role of the clinical and histopathologic role in the diagnosis.
DIFFERENTIAL DIAGNOSIS

Paget’s disease should be differentiated from nipple contact dermatitis, psoriasis, melanoma, basal cell carcinoma, squamous cell carcinoma, Bowen’s disease, scabies, dermatophytosis, and bullous diseases, among others. Contact dermatitis of the nipple is the main differential diagnosis. It is usually bilateral, has raised borders and superficial hardening, and shows a good response to topical corticosteroid therapy. Basal cell carcinoma and Bowen’s disease, despite being rare in the nipple, may be clinically similar to Paget’s disease, requiring histopathologic examination for differentiation. A differential diagnosis with malignant melanoma of the areola can result in a real clinical, dermatoscopic, and histopathologic enigma. In addition to immunohistochemistry, it requires histopathologic examination with a fragment that includes the entire thickness of the epidermis and dermis. In melanoma, the neoplastic cells involve the dermal-epidermal junction, extending to the papillary dermis and positive immunohistochemistry for HMB 45 and protein S100. Concerning Paget’s disease, the invasion is in the upper epidermal cells and positive immunohistochemistry for CEA, AE1/AE3, anti-HER2, or c-erb B2 (in about 80% to 90% of cases) and CK7 (almost 100% of cases). The treatment of choice is surgical excision of the lesions and skin and later affect the mammary tissue and lymph nodes with possible metastases. The most important positive factor for a better prognosis in the evolution of Paget’s disease of the breast is its early diagnosis and removal, together with the underlying intraductal carcinoma. It is necessary to warn women regarding this type of cancer, which can remain for long periods as a purely cutaneous lesion without relevance, but may only be the “tip of the iceberg” of a malignant tumor.

REFERENCES


TREATMENT

The treatment of choice is surgical excision of the lesions and underlying neoplasia, if present. Photodynamic therapy and topical imiquimod, despite being therapeutic options for an extramammary disease, should not be used in cases of Paget’s breast disease due to the risk of existence of an underlying neoplasia. The decision to perform a radical or conservative mastectomy, adjuvant therapies (radiotherapy, chemotherapy, and hormone therapy), and axillary or sentinel lymph node emptying should remain at the discretion of the oncologist, considering in each case the extension of the disease and the associated comorbidities. The evolution of Paget’s disease of the breast is its early diagnosis and removal, together with the underlying intraductal carcinoma. It is necessary to warn women regarding this type of cancer, which can remain for long periods as a purely cutaneous lesion without relevance, but may only be the “tip of the iceberg” of a malignant tumor.

SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

Instructions: For each of the following numbered questions, choose the appropriate lettered response(s). Unless directed to choose only one lettered response, all, some, or none of the responses may be correct.

1) The main clinical differential diagnosis of mammary Paget's disease is: (Choose the single best response.)
   a. amelanotic melanoma.
   b. basal cell carcinoma.
   c. Bowen's disease.
   d. contact dermatitis.
   e. dermatoxytosis.
   f. scabies.

2) Dermoscopy of lesions of Paget's disease: (Choose the single best response.)
   a. allows ready differentiation from amelanotic melanoma.
   b. allows ready differentiation from melanotic melanoma.
   c. has not been reported, to date, to reveal an effectively defined pattern.

3) Photodynamic therapy and topical imiquimod are reasonable therapeutic options for: (Choose the single best response.)
   a. mammary Paget's disease.
   b. extramammary Paget's disease.
   c. both.
   d. neither.

4) Which of the following immunohistochemical stains are often positive in mammary Paget's disease? (Answer as many as apply.)
   a. AE1/AE3
   b. CD1a
   c. CD5
   d. CD68
   e. c-erb B2
   f. CK7
   g. Anti-HER2
   h. HMB 45
   i. MUC1
   j. Protein S100

5) Toker cells: (Answer as many as apply.)
   a. are equivalent to Merkel cells in non-nipple skin.
   b. are present in the upper dermis in 10 percent of normal nipples.
   c. have clear and abundant cytoplasm.
   d. in cases of Toker cell hyperplasia, may be mistaken for Paget's disease.
   e. may readily be distinguished from Paget's cells using immunohistochemistry.

ANSWERS TO SELF-TEST REVIEW QUESTIONS:

1) d; 2) c; 3) b; 4) a, e, f, g, i; 5) c, d

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Poget's Disease of the Breast
Calciphylaxis occurs due to calcium deposition in arterioles, which leads to ischemic ulceration of overlying skin. Two-year mortality rates from sepsis ranges from 50% to 80%. Calciphylaxis is most common in hyperparathyroidism secondary to chronic renal impairment and rarely occurs in the setting of normal renal function. Biopsy of the calciphylaxis ulcer reveals calcium deposits lining the vascular intima. Tissue calcification may also be seen on plain radiographs. Calcium-phosphate metabolism should be normalized by treating any underlying hyperparathyroidism with bisphosphonates, parathyroidectomy, and/or cinacalcet in addition to dialysis in chronic renal failure. Intravenous sodium thiosulfate has been used successfully to treat renal and normo-renal calciphylaxis. Sodium thiosulfate displaces calcium ions from calcium deposits to form calcium thiosulfate, which is excreted by the kidneys or dialyzed. Systemic glucocorticoids may prevent ulceration of early plaques of calciphylaxis. Hyperbaric oxygen, skin grafting, and iloprost infusions are useful adjuncts in the management of this debilitating condition.

Calciphylaxis (synonym calcific uremic arteriolopathy) results from calcification of arterioles and subsequent thrombosis and skin ischemia. Extensive skin ulceration and sepsis causes death in up to 80% of patients with end-stage renal failure and up to 50% of patients with normal renal function.

POSTULATED PATHOPHYSIOLOGIC MECHANISMS
Hyperparathyroidism, hypercalcemia, and hyperphosphatemia in combination with hypertension and arteriosclerosis promotes calcification of both large and small blood vessels. These risk factors, which congregate in chronic renal disease patients, put these patients at high risk for developing calciphylaxis, hence the synonym calcific uremic arteriolopathy.

Hepatic disease also increases the risk for calciphylaxis, but the mechanism remains unclear. A possible reason is that vitamin K is reduced in liver disease, which is required for post-translational gamma-carboxylation of matrix gamma-carboxyglutamic acid protein, fetuin or growth arrest–specific gene 6. These are calcification inhibitors produced by vascular smooth muscle cells. Warfarin, which inhibits vitamin K–dependent carboxylation of these calcification inhibitors, is thought to encourage vascular calcification in this way.1,2

Liver disease and body mass index >30 kg/m² were significantly associated with calciphylaxis in multivariate analysis comparing dialysis patients with calciphylaxis and dialysis patients without calciphylaxis. Use of systemic corticosteroids was significant only in univariate analysis but not significant in multivariate analysis.

Warfarinization, hypertension, diabetes mellitus, vitamin D, calcium supplementation, phosphate-binding agents, estrogen, and iron supplementation were not statistically significant risk factors for calciphylaxis.3

HYPERPARATHYROIDISM IN CHRONIC RENAL DISEASE
Hyperparathyroidism leads to increased serum calcium and decreased serum phosphate. This is because parathyroid hormone stimulates the release of calcium and phosphate from bone, and increases calcium but decreases phosphate reabsorption in the kidneys. Parathyroid hormone also increases 1,25-dihydroxyvitamin D₃ production in the kidney, which stimulates intestinal calcium and phosphate absorption.

Secondary hyperparathyroidism in chronic kidney disease occurs due to insufficient renal 1,25-dihydroxyvitamin D₃. Low serum calcium levels stimulate release of parathyroid hormone. Increasing the serum calcium levels still exerts a negative feedback effect on parathyroid hormone production, but after prolonged secondary hyperparathyroidism, the parathyroid gland becomes hyperplastic and autonomously secretes excessive parathyroid hormone. This is tertiary hyperparathyroidism.

DIAGNOSIS
Early calciphylaxis presents as painful plaques often on the lower legs or on fatty areas (breasts, buttocks, thighs). There may or may not be surrounding livedo reticularis as it starts to ulcerate,
Diagnosis and Treatment of Calciphylaxis

REVIEW

May/June 2012

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Figure 1. Small ulcer on the posterior calf with livedo reticularis apparent on the medial aspect of the left lower leg. The biopsy suture is visible.

Figure 2. Calcium crystals within an arteriole in subcutaneous fat, from skin biopsy of the ulcer shown in Figure 1.

and biopsy would be useful to exclude vasculitis (Figure 1). Histological evidence of calcium deposits within pannicular arterioles confirms the diagnosis of calciphylaxis (Figure 2). Vascular calcium deposits have been demonstrated to comprise mainly calcium phosphate in the form of calcium hydroxylapatite and calcium carbonate.

Biopsy of an early calciphylaxis plaque, however, can trigger ulceration, and there are several reports that recommend plain radiography to demonstrate soft tissue calcification for diagnosis particularly for early plaque-type calciphylaxis in chronic kidney disease. Listed in Table I are diagnostic tests helpful in identifying biochemical abnormalities that increase the risk of calciphylaxis.

TREATMENT

RENAL REPLACEMENT THERAPY

Increasing the frequency and duration of hemodialysis sessions, using low calcium dialysate, or temporarily switching to continuous veno-venous hemofiltration may improve outcome in rapidly ulcerating calciphylaxis associated with chronic kidney disease.

MANAGEMENT OF HYPERPARATHYROIDISM

Primary and tertiary hyperparathyroidism generally require parathyroidectomy. Mild secondary hyperparathyroidism is treated by vitamin D supplementation (calcitriol or alfacalcidol) and calcium supplementation. Calcium-free phosphate binders, eg, sevelamer, are used to reduce phosphate absorption from the gut. The aim is to keep the calcium-phosphorus product below 55 mg²/dL², as a level higher than this is associated with higher risk of calciphylaxis. Vitamin D and calcium supplements, however, are best avoided if calciphylaxis ulceration or plaques are already present.

Table I. Summary of Recommended Investigations

<table>
<thead>
<tr>
<th>Investigation</th>
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<tbody>
<tr>
<td>Full blood count</td>
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<tr>
<td>Urea and creatinine</td>
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<tr>
<td>Liver function</td>
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<tr>
<td>Corrected calcium</td>
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<tr>
<td>Phosphate</td>
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<tr>
<td>Calcium-phosphorus index (&lt;55 mg²/dL²)</td>
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<tr>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>Coagulation profile</td>
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<tr>
<td>Thrombophilia screen (factor V Leiden, anti-cardiolipin Ab, lupus anticoagulant, protein C, protein S, homocysteine)</td>
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<tr>
<td>Skin biopsy</td>
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<tr>
<td>Plain radiographs</td>
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<tr>
<td>Technetium-99 scintigraphy to exclude visceral calcification</td>
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CINACALCET
Cinacalcet is a calcimimetic and increases the sensitivity of calcium-sensing receptors on the parathyroid gland, subsequently reducing parathyroid hormone production. Cinacalcet is used as adjunctive treatment in dialysis patients with refractory secondary hyperparathyroidism, i.e., parathyroid hormone levels >800 pg/mL (or 85 pmol/L) despite a normal or high adjusted serum calcium, and if parathyroidectomy is contraindicated.\(^7\) Cinacalcet was successfully used to treat calciphylaxis ulceration due to secondary hyperparathyroidism in several case reports where parathyroidectomy was delayed or contraindicated.\(^8,9\) Cinacalcet should be discontinued if the parathyroid hormone level is chronically suppressed below 1.5 times the upper limit of normal to reduce the risk of adynamic bone disease (renal osteodystrophy).\(^10\) This is a condition caused by a low turnover of bone, which results in bone being unable to take up circulating calcium and consequent osteopenia and bone resorption.

BISPHOSPHONATES
There are three case reports on the successful use of bisphosphonates in treating calciphylaxis ulcers in patients undergoing hemodialysis. Two of these used oral etidronate 200 mg/d for 14 days\(^11,12\) and one used intravenous (IV) pamidronate 30 mg for five treatments over a 2-week period.\(^13\) All these patients had secondary hyperparathyroidism with high calcium-phosphorus indices. There is one case report on pamidronate for normo-renal calciphylaxis, but this patient had mild hyperparathyroidism (parathyroid hormone 89.7 pg/mL) and mildly raised serum alkaline phosphatase, which may be secondary to vitamin D deficiency. Plain radiography of this patient’s legs also revealed calcification of major arteries in the legs including the anterior tibial, posterior tibial, and fibular arteries.\(^14,16\)

How a bisphosphonate could reduce vascular calcification is not fully understood, but alendronate and ibandronate have both been shown to inhibit vascular calcification in a rat model that used vitamin D to induce vascular arterial calcification.\(^15\)

OTHER DRUGS
SODIUM THIOSULFATE
There are multiple case reports on sodium thiosulfate in calciphylaxis ulceration both in the setting of end-stage renal failure\(^16-19\) and in normo-renal calciphylaxis.\(^6,20\) Sodium thiosulfate has also been successfully used to treat calciphylaxis in children undergoing dialysis.\(^5\) There is one case report on progression of calciphylaxis due to tertiary hyperparathyroidism and end-stage renal failure resulting in death despite thrice-weekly hemodialysis, parathyroidectomy, and 10 weeks of IV sodium thiosulfate (25 g thrice weekly).\(^21\) The other case where sodium thiosulfate failed to heal calciphylaxis ulceration was in an obese patient with type II diabetes mellitus undergoing peritoneal dialysis who experienced a stroke with subsequent epilepsy and aspiration pneumonia.\(^22\)

Sodium thiosulfate is an established antidote to cyanide poisoning (12.5 g or 50 mL of a 25% solution at a rate of 3 to 5 mL/min). In 1985, it was demonstrated that oral sodium thiosulfate 20 mmol/d reduced the incidence of kidney stones from 100 stones in a 3-year control period to 3 stones during a 4-year treatment period (n=34 patients).\(^33\) Subsequently, daily 10 to 20 mmol of oral sodium thiosulfate and/or 10 to 20 mmol IV sodium thiosulfate at the end of hemodialysis for 3 to 15 months caused symptomatic and radiological dissolution of articular (4 patients), as well as penile and perineal soft tissue calcification (1 patient).\(^24\)

Sodium thiosulfate is thought to act by displacing calcium from calcium phosphate to form calcium thiosulfate, which is much more soluble than any of the other calcium salts (sulphate, citrate, carbonate, phosphate, and oxalate). Calcium thiosulfate is then excreted in the urine by the kidneys or via hemodialysis.\(^23\)

The theoretical chemical equilibrium reaction between sodium thiosulfate and calcium phosphate is as follows: \(3\text{Na}_2\text{S}_2\text{O}_3 + \text{Ca}_3(\text{PO}_4)_2 \leftrightarrow 3\text{CaS}_2\text{O}_6 + 2\text{Na}_2\text{PO}_4\). The prompt relief of pain following sodium thiosulfate infusions may stem from vasodilatation, leading to relief of tissue ischemia as evidenced by improved transcutaneous partial oxygen pressure and thermography.\(^25\)

DOSAGE AND ADMINISTRATION OF SODIUM THIOSULFATE
The commonly used regimen is 25 g IV sodium thiosulfate via a central venous catheter over 30 to 60 minutes 3 times per week in adults infused after dialysis sessions.\(^16,18,19,26,27\) Normo-renal calciphylaxis was treated with IV sodium thiosulfate 5 g daily or 25 g 3 times per week.\(^20\) The dose used for children or young adults in end-stage renal failure is 25 g/1.73m\(^2\) body surface area, again after thrice-weekly dialysis.\(^5\)

There is no evidence that sodium thiosulfate needs to be administered via a central venous catheter and it is usually given via peripheral cannulae for cyanide poisoning. As the sodium thiosulfate infusions need to be given over a period of weeks, however, a peripherally inserted central catheter provides longer-term IV access.

Side effects include anion gap metabolic acidosis due to the generation of thiosulfuric acid, nausea, vomiting, rhinorrhea, and sinus congestion. Most of the patients did not develop alterations of calcium or phosphate levels. In one case report, a patient developed a low ionized calcium level of 0.88 mmol/L causing a prolonged QT interval following low-calcium dialysate for hemodialysis and sodium thiosulfate infusions.\(^5\)
PENTOXFYLLINE

Pentoxifylline was used at 400 mg twice daily along with intensive wound care to successfully manage a case of normo-renal calciphylaxis with alcoholic liver cirrhosis and elevated calcium and phosphate.28

SYSTEMIC GLUCOCORTICOIDS

Oral prednisone 30 to 50 mg once daily for 3 to 5 weeks has been used successfully only in early nonulcerative plaques of calciphylaxis. Systemic glucocorticoids are contraindicated in patients with ulcerating calciphylaxis or peripheral vascular disease and patients at high risk for infection.4

INTENSIVE WOUND CARE

Wound infections should be treated with appropriate antibiotics, and gentle wound debridement with silver sulfadiazine or enzymatic debridement20,28 has been advocated. Conversely, some researchers advise against any surgical debridement of calciphylaxis ulcers.29

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy involves breathing 100% oxygen at up to 2.5 atmospheres of pressure in a sealed chamber that is pressurized to the same degree. A monoplace chamber is pressurized with 100% oxygen and a mask need not be worn, while a multiplace chamber is pressurized with air and each individual wears a mask that delivers pressurized 100% oxygen. Each session lasts between 60 to 90 minutes and is typically carried out daily for many weeks.

Hyperbaric oxygen therapy has been shown to help in healing calciphylaxis ulcers. In one report, 8 of 9 calciphylaxis patients undergoing dialysis who tolerated hyperbaric oxygen treatment healed completely after 20 to 108 sessions. The remaining patient had progressive disease requiring amputation.30 In another study, researchers reported 2 of 5 patients recovering from calciphylaxis, with the responders achieving transcutaneous oxygen levels >33 mm Hg when breathing normo-baric 100% oxygen.31

SKIN GRAFTING

Split-thickness skin grafting after aggressive deep shave of the ulcer32 or autologous fibroblast and keratinocyte culture in combination with iloprost infusions (1 μg/kg/min over 4 hours for 35 consecutive days)33 have been used to accelerate healing of calciphylaxis ulcers. Skin grafting, however, is only practical for limited disease.

CONCLUSIONS

The treatment of calciphylaxis is not straightforward and is summarized in Table II. It is important to normalize the parameters of calcium metabolism particularly in renal disease using phosphate binders, parathyroidectomy, calcimimetics, and bisphosphonates. Renal replacement therapy should probably be intensified in cases of quickly worsening ulceration. There is growing evidence for sodium thiosulfate to treat both renal and normo-renal calciphylaxis. Intensive wound care is paramount whilst hyperbaric oxygen therapy, skin grafting, oral pentoxifylline, and iloprost infusions are helpful adjunctive treatments. Epidemiological data on risk factors for calciphylaxis and the efficacy of therapeutic strategies is being collected in several calciphylaxis registries worldwide to improve evidence-based treatment of this debilitating disease with a poor survival rate (Table III).

Table II. Summary of Management of Calciphylaxis

<table>
<thead>
<tr>
<th>Aim to normalize calcium metabolism</th>
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<tbody>
<tr>
<td>Intensify renal replacement therapy</td>
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<tr>
<td>Calcium-free phosphate binders</td>
</tr>
<tr>
<td>Bisphosphonate</td>
</tr>
<tr>
<td>Calcimimetic (hyperparathyroidism only)</td>
</tr>
<tr>
<td>Parathyroidectomy (hyperparathyroidism only)</td>
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<table>
<thead>
<tr>
<th>Dissolve calcium deposits</th>
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<tr>
<td>Intravenous sodium thiosulfate</td>
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<table>
<thead>
<tr>
<th>General wound care</th>
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</thead>
<tbody>
<tr>
<td>Analgesia</td>
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<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Gentle debridement of ulcers</td>
</tr>
<tr>
<td>Dressings</td>
</tr>
<tr>
<td>Hyperbaric oxygen therapy</td>
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<tr>
<td>Skin grafting</td>
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</tbody>
</table>

Table III. Calciphylaxis Registries

<table>
<thead>
<tr>
<th>United States: Calciphylaxis Registry, KU Medical Center, University of Kansas</th>
</tr>
</thead>
<tbody>
<tr>
<td>www2.kumc.edu/calciphylaxisregistry/</td>
</tr>
<tr>
<td>United Kingdom: UK Calciphylaxis Registry, International Collaborative Calciphylaxis Network</td>
</tr>
<tr>
<td><a href="http://www.calkiphylaxis.org.uk">www.calkiphylaxis.org.uk</a></td>
</tr>
<tr>
<td>Germany: Calciphylaxis Register, International Collaborative Calciphylaxis Network</td>
</tr>
<tr>
<td><a href="http://www.calkiphylaxis.de">www.calkiphylaxis.de</a></td>
</tr>
</tbody>
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REFERENCES


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The diagnosis of cutaneous lesions often involves histological analysis of biopsy specimens. These biopsy specimens are read by dermatologists, general pathologists, and dermatopathologists, with some controversy surrounding whether dermatologists and general pathologists have the proficiency to read dermatopathologic sections. The American Society of Dermatopathology has reported that 25% of dermatology residency training is devoted to dermatopathology and that dermatopathology represents 25% of the dermatology board-certifying examination.1 This information, along with the report that dermatologists receive more dermatopathology training than general pathology residents,2 has led many dermatologists to read their own histopathologic sections. In contrast, some dermatologists, particularly on the east coast,3 have their histopathologic sections read by a dermatopathologist. Both groups of dermatologists face unique pitfalls in diagnosis and management of cutaneous lesions.

“I ALWAYS READ MY OWN SLIDES”

While dermatologists receive dermatopathology training in residency, they do not receive the same level of training as dermatopathologists, who spend 1 to 2 years focusing on dermatopathology. While some dermatologists assert that they can interpret the easy slides and send out the difficult ones, sometimes the most difficult interpretations are found in sections that superficially appear easy.

Grant-Kels notes that the easy cases are often the most frightening, as one may miss a melanoma hidden in an obvious seborrheic keratoses.4 With misdiagnosis of melanoma one of the most common causes of lawsuits in histopathology,5 dermatologists must be wary when ruling out malignant melanoma in their own slides.

Other histologic diagnoses can also be misleading, with Merkel cell carcinoma often superficially resembling basal cell carcinoma (Figure A and B). In addition, dermatologists who read their own slides face the ethical concerns inherent in self-referral. LeBoit addressed this issue, questioning whether dermatologists are less apt “to fire their dermatopathologist” after mistakes, if they are themselves acting as the dermatopathologist.6

“I NEVER READ MY OWN SLIDES”

Although dermatopathologists are more experienced at reading histologic sections, the dermatologist has the advantage of correlating the histologic findings with the clinical findings. This correlation is especially important given that dermatopathology requisition forms often do not encourage physicians to provide specific clinical information.

A study investigating requisition forms for melanocytic lesions found that none of the forms requested a full description of the lesion, using the ABCDE checklist, or mentioned whether the specimen was a partial or complete biopsy, while few provided information on a history of a cutaneous neoplasm.7 Without this information, the dermatopathologist cannot make a full interpretation of the lesion.

In addition, dermatopathologists are often vague and inconsistent when describing biopsy specimens. Sellheyer and Bergfeld note that some dermatopathologists comment, inappropriately, on the margins of a shave or punch biopsy, while others use
equivocal language to describe margins in order to satisfy the clinician but avoid medicolegal responsibility. These deficiencies in communication between the dermatopathologist and the dermatologist can have detrimental effects on diagnosis and management of skin lesions.

CONCLUSIONS

To read or not to read your own slides is an important question for dermatologists, with both medical and legal implications. We suggest perhaps that dermatopathologic sections should be read by a dermatopathologist with the slide(s) also read by the dermatologist. This system allows for expert analysis of the slide by a dermatopathologist, while maintaining clinical checks and balances from the dermatologist. In addition, we recommend that dermatopathology requisition forms contain specific questions about the morphology of skin lesions. This should include the ABCDE checklist for a pigmented lesion, the patients’ dermatologic and general medical history, and whether the biopsy specimen represents a complete excision or a partial resection.

REFERENCES

Recently, I reviewed two early US textbooks of dermatology and the lives of their authors (A Practical Treatise on Diseases of the Skin, 4th ed, and Diseases of the Skin). I became particularly interested in the discussion of pellagra in these two texts because pellagra, now a forgotten disease in the United States, was epidemic in the early 20th century in the Southern United States, killing more than 100,000 people between 1900 and 1940. It was fresh in the minds of the senior faculty members of the medical school that I attended in the late 1940s. We were taught that pellagra was a disease of the “4 Ds”: dermatitis, diarrhea, dementia, and death. The authors of the two texts above, particularly Ormsby, discuss pellagra at great length, while contemporary textbooks of dermatology devote but a paragraph or two to pellagra. Practitioners of today should be interested in the clinical descriptions and photographs of this disease because they are difficult to access, because of pellagra’s historical importance in the United States, and because it still is seen in poverty- and famine-stricken parts of the world.

A CONSTITUTIONAL EPIDEMIC DISORDER

Hyde and Montgomery considered pellagra to be:

a constitutional epidemic disorder, accompanied by an exanthem. Usually first noted in the spring, symptoms are prodromic and characterized by marked fatigue, malaise and, occasionally, fever. Soon the face, neck and back of the hands (when exposed to sun) are affected with an erythema of a dull lurid hue…which may be accompanied by desquamation, occurring in successive years chiefly in the summer…. Simultaneously, an extraordinary degree of muscle feebleness is noticed…. The fingers gradually become semi-flexed into the palms and gastro-intestinal derangements supervene [with] colicky pains and diarrhea. Disorders of the nervous system are betrayed by melancholia, disturbed vision, idiocy, convulsions and symptoms of meningitis.

Hyde and Montgomery were unsure of the etiology of pellagra. They mentioned the possibility of maize as a cause, but noted that some patients who experienced pellagra had never eaten maize:

The exact etiology of the malady should rather be traced by the statesman and politico-economist. The wretchedness, poverty, poor food, and hopeless moral and social conditions of the inhabitants of the pellagrous districts, many of them toiling under a burning sun, half starved, emaciated and despairing, should explain largely the symptoms of the scourge which affects them. In districts where the disease prevails extensively, the mortality has been frightful.

The authors mentioned Lombardy, Southern France, and Spain as the locations of pellagra but not the Southern United States. Although the exact etiology of pellagra, a vitamin deficiency, was not available to Hyde and Montgomery, they accurately described its underlying factors, namely the almost starving conditions of the poor in the countryside of Southern Europe.

Pellagra was first described in the 18th century as an epidemic in the poverty-stricken Spanish countryside by Gaspar Casal. Pellagra did not appear in the United States until the turn of the 20th century. It then ravaged the Southern United States and was not eliminated until the 1940s. This short report will reduct the descriptions of pellagra in two early textbooks of dermatology. The first, published in 1897 before cases of pellagra were recognized in the United States, and, the second, published in 1915 in the midst of the epidemic. The text published in 1915 described in detail the medical signs and symptoms of pellagra particularly as they relate to the skin, as well as speculations as to its cause. The complicated story of the socioeconomic situation of the Southern United States and the hunt for the cause of pellagra will also be discussed briefly.
OLIVER ORMSBY’S DESCRIPTION

Pellagra became endemic in the United States in about 1907. The southern states have furnished the majority of cases. It was only since 1907 that pellagra has assumed important proportions in this country. The earliest symptoms may be connected with the skin or gastrointestinal tract. Occasionally, the patient suffers what is presumed to be a sunburn and is indisposed for a short time. The symptoms then clear up, to return the next years or at some future date.

In other cases, a moderately sore mouth, with some gastrointestinal disturbance, particularly diarrhea, occurs, but is considered to be of no consequence, and in the course of a few weeks, the symptoms subside, only to recur at some future time. During the winter months the patients are often entirely well. With each recurrence, the symptoms are apt to be exaggerated, although at times they have been noted to be more mild.

A certain proportion of cases begin with gastrointestinal symptoms, consisting of chronic and often severe diarrhea with more or less stomatitis. These symptoms in certain cases have lasted for one or two months before the appearance of the dermatitis. In such cases the latter is usually exaggerated and of the bullous type. In other cases the disease runs a more chronic course, exhibiting mild symptoms. In still other cases the disease may be acute and severe (Pellagra typhosis), the patient having a high temperature, severe diarrhea, and stomatitis, delirium and other evidences of intense intoxication. Seasonal recurrence has been emphasized by all observers. The disease has been noted to occur most often in the spring and autumn. In a certain proportion of cases, after an attack has occurred in the spring, a recurrence takes place in the autumn.

In observing the development of these lesions, it is noted that at first there often occurs macular lesions, light or dark-red in tint, which soon fuse, forming a patch of dermatitis almost identical in appearance with that caused by the sun (Figure 1 and Figure 2). As the evolution of the disease advances, the color of the lesions deepens and they assume a reddish-brown or chocolate hue. In from seven...
to ten days, or a little longer, desquamation begins, at which time a roughened, scaling surface is present. Early in the process there is moderately marked swelling. In the more active cases, on the erythematous base, there develop bullous lesions, which often attain a large size, and which, after a few days, gradually dry, leaving a thickened crusted epidermis. Ecchymoses not infrequently complicate the process and secondary pyogenic infection may follow. In the vesicular and bullous severe cases, ulceration may ensue; in many cases the edema is sufficient to produce fissures. Whether erythematous or bullous, the lesions are always well defined. After the eruption has disappeared, the skin in some cases is pigmented; in other the pigment is lessened. In certain cases, where the process is less acute, the appearance is permanently thickened, hard, roughened, scaly and pigmented. The terminal stage is exhibited as a thin cicatricial, parchment-like integument, presenting striae parallel with the long axis of the hand.

The lesions are found on the exposed parts of the body chiefly, and their arrangement is characteristic. In the major portion, the dorsa of the hands, the wrists (Figure 3 and Figure 4) and some parts of the face, neck or scalp (Figure 5) are involved, the feet and ankle more rarely (Figure 6 and Figure 7). The arms and chest, and to a lesser extent the ears and other parts of the body, including the palms and the genital region, are also involved. The symmetry of the lesions is striking. On the hands often a solid area extends over the entire dorsal surface, involving the fingers, knuckles, and also the wrist on the extensor surface for a distance of about two inches. In this area, the lesions frequently sweep around and involve about two thirds of the flexor surface and then come to an abrupt ending. This partial gauntlet has been frequently observed. That the rays of the sun are a factor in determining the localization of the lesions is accepted by all observers. Subjective symptoms, as a rule, are not marked, and are exhibited as burning rather than itching, the surface practically never showing evidence of scratching.

In the gastro-intestinal system, diarrhea is a constant concomitant in severe cases; in mild cases this may be absent and constipation [may] be present. The appearance of the tongue is important. This becomes swollen and denuded, presenting a dry appearance, with, in severe cases, more or less superficial ulceration along its edges and upon its under surface with yellowish sloughing, which bleeds easily. A resemblance to the aphthous stomatitis seen in other debilitated states is noted. The ulcers are very superficial and heal without scar formation. In mild cases, the tongue is reddened and presents smooth areas especially along

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**Figure 3.** Pellagra. Ormsby, Figure 90, page 437. The hands and wrists are involved with pellagra “gloves.”

**Figure 4.** Man with pellagra “gloves.” Courtesy of James C. Babcock Collection. Waring Historical Library, Medical University of South Carolina. Charleston, South Carolina.
the tip and along the margins, a condition to which the
term “bald tongue” has been applied. The nervous system
chiefly presents the symptoms induced by acute intoxica-
tion…. In the terminal stages of pellagra the symptom
complex [is] that belonging to central neuritis.

In the recurrences that take place from year to year, the
general symptoms become more marked. The gastro-
intestinal are indicated by dyspepsia, pains in the abdomen
and dysentery. Pains are described as occurring in vari-
ous parts of the body, particularly the head, epigastrium,
and feet, with burning sensations in these same areas.
Tenderness on pressure over the spinal cord; muscular
weakness and loss of muscle power, particularly in the
legs; tremors of the head and arms, mental worry and
depression, anxiety and discontent, loss of memory, ver-
tigo, and vague feelings of pressure, weight or pulsation
about the head, all may occur. In some cases the subjects
are excitable and irritable, in others stupid and morose…. 
In the terminal stage, extreme weakness and emaciation,
from the preceding severe gastro-intestinal disturbances,


deprofused prostration, delirium, with involuntary evacu-
atation of the bladder and bowels, close the scene…. The
duration of the disease extends over periods varying from
one to twenty years. Five years is probably the average.

ORMSBY’S SPECULATIONS

Ormsby then speculated about the etiology of pellagra. This
was, of course, before the vitamin deficiency case was proven.
He noted that it occurred more frequently in women, that field
laborers experienced it the most, and that the disease seemed to be
confined to tropical and warm zones. In Europe, only a few cases
occurred in the cities, while in the Southern United States, small
towns and mill villages were affected the most. Ormsby wrote that in Europe, poor hygiene, poor food sources, and poverty were unquestionably important factors in the etiology; however, in the United States these do not appear to be important. In the latter situation, the disease not infrequently attacks people in the best walks of life, where poor hygiene or lack of proper food is out of the question. Ormsby then discussed the corn theory of pellagra:

The various theories regarding the production of pellagra are those concerning maize or Indian corn and other agents. The corn theory has been most strongly advanced in Italy. The views relative to this hypothesis may be summarized as follows: (1) Indian corn is deficient in or lacks some nutrient principle necessary for health, and pellagra results from a diet limited too strictly to that cereal. (2) Corn contains some toxic substance which in susceptible individuals produces the disease. (3) Corn undergoes some form of decomposition in the intestine of certain individuals, as the result of growth of bacteria, the toxins thus produced exciting the disease. (4) Healthy corn is innocuous, but at some stage in its preparation for consumption, either in the ear, when stored, or after being cooked, it undergoes decomposition, as the result of the growth of certain fungi.... In the growth of these organisms it is supposed that toxins are produced which, when absorbed, induce pellagra. (5) Finally, that some of the organisms which are commonly found in the moldy or spoiled corn may be eaten with it, directly invading the body and producing the disease.

Ormsby concluded by noting that the disease is regarded by most observers as not contagious and that the pathologic findings of the skin and in post-mortem examination were not specific. Ormsby's only recommended therapy was improvement of nutrition as being of the highest importance, while internal medication has been of little value.
JOSEPH GOLDBERGER

Goldberger, an officer in the US Public Health Service (Figure 8), extensively studied pellagra in the South from 1914 until his death in 1929. In an investigation carried out in the mill villages of Spartanburg County, South Carolina, beginning in 1916, Goldberger and his colleagues Dr George Wheeler and the statistician Edgar Sydenstricker showed that pellagra was not a contagious disease. Rather, it was caused by a dietary deficiency, which, in itself, was directly related to the low wages that made the purchase of adequate food by the mill workers’ families impossible. Although Goldberger and his colleagues did not isolate the specific dietary factor that caused pellagra, they did uncover the gestalt of poverty and deprivation directly related to the incidence of the disease. It was not until the prosperity of World War II in the 1940s, with the improvement of the availability of good food, that pellagra was eliminated in the United States except for the occasional alcoholic and food faddist.

THE CORN STORY

Ormsby listed the various theories that incriminated the eating of corn in the etiology of pellagra. The traditional food preparation of corn (maize) by the Indians of Latin America required treatment of the grain with lime, an alkali (nixtamalization). This removes the husk, producing a softer product that is more easily ground, nixtamil (an Indian word). This process affords significant nutritional advantages over untreated maize. It converts some of the niacin (and possibly other B vitamins) into a form more absorbable by the body, improves the availability of the amino acids, and supplements the calcium content balancing maize’s excess of phosphorous.

When corn cultivation was imported to Europe in the 16th century, it became the staple of the poor in Southern Europe because it was cheaper than wheat. The benefits of the lime treatment were not understood; so, in Southern Europe, the exclusive diet of corn played an important role in pellagra. This was not true in the Southern United States where maize was not the staple food and the overall dietary deficiencies hid the shortage of niacin.

THE BIOCHEMICAL ANSWER

Virgil Preston Sydenstricker, a relative of Edgar Sydenstricker, the associate of Goldberger, wrote in 1958:

Osborne and Mendel in 1914 demonstrated that cystine and tryptophan are essential for nutrition and growth of animals and called attention of the scarcity of those amino acids in zein [a prolamine present in maize; it lacks chiefly the amino acids, L-tryptophan and L-lysine and is also low in cystine content].... The case was broken by Elvehjem, Madden, Strong and Wooley in 1937 when they identified the anti-black tongue [a disease in dogs similar to pellagra] factor in dogs in liver extract as nicotinic acid. The results were truly dramatic. No longer did patients die because they could not retain food, yeast or liver extracts. Nicotinic acid amide or sodium nicotinate could be given intravenously with life-saving effect. However, some dermatologic abnormalities persisted in patients while being maintained on an adequate diet supplemented with nicotinic acid. These phenomena were at the time thought to be evidence of relapse, but in December, 1938, Sebrell and Butler reported the experimental production of such lesions by a diet deficient in riboflavin.... It has been proved that both riboflavin and pyridoxine are required for the metabolism of tryptophan and that pyridoxine is essential for the synthesis of niacin from the amino acid.

While pellagra can develop without maize entering the picture, its prevalence in a maize-eating population can now be clarified. A diet low in good protein and containing large amounts of corn can actually increase the requirement for niacin and its endogenous production. If there is a deficiency of riboflavin and pyridoxine as well, the utilization of what little tryptophan may be available is impossible and the diet is rendered virtually niacin free.

REFERENCES

A 56-year-old woman presented with a 1-year history of painless swelling and nodules involving the dorsal and palmer aspects of her right hand. She gave a history of working on a sugarcane farm.

The patient was found to be negative for the human immunodeficiency virus. Skin biopsy, direct microscopy, and fungal culture confirmed black grain Madurella mycetomatis.

**Figure 1.** Ulcerated nodules of black grain mycetoma involving the right hand.

**Figure 2.** Multiple ulcerated nodules of black grain mycetoma on the right palm.

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**URTICARIA**

**Drugs that may cause urticaria M–N**

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Exclusive Plaque Psoriasis of the Lips: Efficacy of Combination Therapy of Topical Tacrolimus, Calcipotriol, and Betamethasone Dipropionate

Virendra N. Sehgal, MD; Shruti Sehgal, MDS; Prashant Verma, MD; Navjeevan Singh, MD; Farhan Rasool, MD

Fissuring was prominent but the buccal mucosa, surface of the tongue, gingiva, and palate were normal. The clinical examination did not reveal any evidence of skin and/or nail psoriasis/psoriatic arthropathy or any other systemic abnormality. Blood examination including total and differential leukocyte count, complete hemogram, and liver and renal function tests were normal. Biopsy of the representative lesion was subjected to serial sections. They were stained with hematoxylin-eosin to work up microscopic pathology. It revealed the presence of mounds of parakeratosis with numerous neutrophilic Munro microabscesses (Figure 2). Submucosal vessels were dilated and congested. Periodic-acid-Schiff (PAS) stain revealed fungal hyphae and spores within the parakeratotic layer. Colonies of Gram-positive cocci were also demonstrated on the surface of the mucosa. She was administered combination therapy, comprising topical tacrolimus (0.1%) ointment and calcipotriol hydrate (50 μg/g) plus betamethasone dipropionate (0.5 mg/g) twice a day for 7 days. A single bolus dose of fluconazole 450 mg orally was also administered. The response to treatment was favorable and the lesions showed regression (Figure 3).

From the Dermato-Venereology (Skin/VD) Center, Sehgal Nursing Home, Panchwati-Delhi; the Department of Conservative Dentistry and Endodontics, Government Dental College Raipur; the Department of Dermatology and STD; Department of Pathology; University College of Medical Sciences and Associated Guru Teg Bahadur Hospital Delhi, and Skin Institute, School of Dermatology, Greater Kailash, New Delhi, India Address for Correspondence: Virendra N. Sehgal, MD, A/6 Panchwati, Delhi-110 033 India • E-mail: drsehgal@ndf.vsnl.net.in

(see also page 130)
diagnosis is required to be supported by microscopic pathology, the characteristic of which is mounds of parakeratosis with numerous neutrophilic Munro microabscesses and dilated and congested submucosal blood vessels. PAS reaction is useful in ruling out fungal infection by the presence of hyphae and/or spores within the parakeratotic layer. In addition, the presence of colonies of Gram-positive cocci may also be indicative. Previous workers with contrasting results had embarked on this procedure. These investigations are recommended for future diagnosis of the condition. It is worthwhile to emphasize that exclusive involvement of the lips, as seen in our case, is uncommon and we are aware of only two examples in the literature.

Combination therapy of topical tacrolimus immunomodulator and calcipotriol (vitamin D₃ analog), which acts on the nuclear receptors of keratinocytes, was chosen for their synergistic action. Betamethasone dipropionate cream was added to facilitate rapid remission.

REFERENCES

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**CASE STUDY**

**“Eruptive” Facial Syringomas: An Inflammatory Skin Reaction?**

Husein Husein-ElAhmed, MD; J. Aneiros-Fernandez, MD; J. Aneiros-Cachaza, MD

A 26-year-old woman exhibited multiple, 1- to 3-mm eruptive asymptomatic papules, symmetrically distributed on the face. None of her family members had similar lesions. The papules first appeared in 2006 and gradually increased in number, particularly during her first pregnancy. She stated that the development of lesions was preceded by dermatitis. Physical examination revealed many flesh-colored or slightly reddish, smooth-surfaced papules around the eyes, both cheeks, and temples (Figure 1 and Figure 2). The differential diagnosis included syringomas in an atypical location, cutaneous sarcoidosis, and periorificial dermatitis. Histopathologic examinations revealed aggregation of small tubular structures lined by two rows of epithelial cells, most of which were characterized by comma-like tails, giving them a tadpole shape. They were embedded in a fibrous connective tissue stroma in the dermis. These histopathologic findings were consistent with syringoma (Figure 3).

Syringomas are traditionally considered benign adnexal tumors derived from the intraepidermal portion of eccrine sweat ducts. The variety of clinical presentations reported in the literature, however, cast doubt upon the neoplastic nature of syringomas. In addition, the presentation of eruptive syringomas is a rare neoplastic process. Some studies have suggested the intraepidermal portion of the eccrine gland as the origin of syringomas. Supporting this hypothesis, we present this case of facial eruptive syringoma in a 26-year-old woman.

This case suggests that some of the so-called *eruptive syringomas* may start as an inflammatory process of the upper portion of the eccrine duct. As a result of the inflammatory process, a hyperplastic reaction of the eccrine duct ensues, resulting in tortuous proliferative changes. Our hypothesis is supported by numerous reports of cutaneous conditions unlikely to be neoplastic, cases of diffuse alopecia and melanocytic nevi. In addition, there are cases reported of eruptive syringoma associated with milia and alopecia, suggesting that a diffuse inflammatory process could also involve the pilosebaceous units. The etiology of the inflammatory reaction could not be established in our case.

The higher incidence of syringomas in women and the frequent development of the lesions before or around puberty, as well as occasional exacerbation of the lesions during pregnancy, may imply a hormonal role in some cases. In our case, an increase in number and size of the lesions was observed during pregnancy; furthermore, a strong expression of progesterone receptor by immunohistochemistry was noted in two studies.

**CONCLUSIONS**

We think eruptive syringoma is a reactive hyperplastic process of the eccrine duct following an inflammatory cutaneous process,
and this rare condition should be considered when a histological pattern resembling a syringoma is observed on skin biopsies after an inflammatory skin reaction.

REFERENCES


Verrucous carcinoma, first described in 1948 by Lauren V. Ackerman,1 is a rare and well-differentiated variant of the classical squamous cell carcinoma (SCC). It appears on the skin and mucosa, with the oral cavity as the preferred site.2 It is clinically characterized by whitish, verrucous, and exophytic lesions, with well-defined borders and painless growth. Ulceration is uncommon.2 The diagnosis is both clinical and histopathologic, requiring several histologic sections, because such examination may disclose characteristics that are not only intermediate between hyperplasia and neoplasia3 but also foci of SCC.2 Correct diagnosis is essential to define the treatment and prognosis. Presently, surgery is the treatment of choice.4–6

Oral verrucous carcinoma (OVC) represents only 9% of oral SCC.7 This neoplasm usually affects men older than 50 years2 who have risk factors such as infection by the human papillomavirus (HPV), chronic tobacco use, constant trauma, betel chewing, and snuff useage.7 Poor dental hygiene magnifies the problem.8 Another factor may be the association with chronic lichen planus.9,10

A study of 23 patients with OVC, in whom the genotypic characteristics of HPV and expression of p53 were assessed, concluded that the process of carcinogenesis may involve HPV infection of both high- and low-risk serotypes, as well as fast replication during hyperkeratinization. Inactivation by p53 that is associated with the infection by HPV may be involved in this process.11 Viral carcinogenesis probably occurs by suppression or mutation of the p53 gene, because that gene would be responsible for the tumor cell suppression activity.7

Histologic examination shows hyperkeratosis, massive acanthosis with a verrucous surface, and well-differentiated epithelium with minimal atypia and rare mitoses. A dense chronic inflammatory infiltrate in the connective tissue in contact with rounded borders of epithelial cells is frequent, as opposed to the irregular epithelial masses and small epithelial extensions usually observed in classical SCC. It is a clinical and histopathologic diagnosis, and thus clinical recognition immediately allows the diagnostic suspicion. Our patient's tumor was compatible with the diagnosis of OVC. Her advanced age and the use of dental prostheses were risk factors; the morphology and the painless evolution of the lesion are characteristic.

The main differential diagnosis should be made with SCC that presents with aggressive behavior, frequently with metastasis to the cervical region,12 and where radiotherapy is used with or without chemotherapy and/or surgery. In opposition, its verrucous variant, despite being malignant, has a good prognosis, with rare detection of metastases. Surgery with wide excision is the treatment of choice1 without radiotherapy, because some

CASE STUDY

Verrucous Carcinoma of the Tongue

Fernanda Aguiar Santos Vilela, MD;1 Beatriz Moritz Trope, MD, PhD;1 Paula Cabral Menezes Gurfinkel, MD;1 Juan Manuel Piñeiro-Maceira, MD, PhD;2 Marcia Ramos-e-Silva, MD, PhD1

A 75-year-old woman with full dentures had a progressive growth on the tongue for the past 15 years. She reported ulceration of the lesion 4 months prior that was accompanied by pain and odinophagia. She denied addiction to alcohol or tobacco. On examination, there was an ulcerated, vegetating, verrucous lesion, with yellow-whitish areas intermingled with erythematous areas, being infiltrated and having well-defined borders, on almost all areas of the back of the tongue (Figure 1). No adjacent lymphadenopathy was found. Biopsy of the tongue was compatible with verrucous carcinoma demonstrating squamous cell neoplasia with prevailing areas of rounded borders. There were “tunnels” filled with parakeratotic material surrounded by an extensive inflammatory response, plus isolated foci of neutrophils inside the tumor (Figure 2). There were relatively well-differentiated neoplastic cells with little cytopathological atypia. In addition, there were several foci of individual or grouped dyskeratotic cells (Figure 3), plus tunnelling of parakeratotic material and an intratumor inflammatory response (Figure 4). Following surgical removal, the woman underwent chemotherapy and radiation treatment.
authors believe that radiotherapy has the potential for inducing anaplastic transformation.\textsuperscript{9,13,14}

In a retrospective study, 101 patients with OVC were analyzed (79\% men with an average age of 53.9 years). The local recurrence rate was 68\%, and survival rate free of the disease after 5 years of surgical treatment was 77.6\%. The prognosis of OVC with appropriate surgical treatment may be considered excellent.\textsuperscript{15} Recently, successful treatments have also been reported either with intra-arterial infusion of methotrexate\textsuperscript{16} or photodynamic therapy utilizing 5-aminolevulinic acid.\textsuperscript{17} Other treatment options are intraleional bleomycin and laser surgery.\textsuperscript{14}

Histopathologic diagnosis is difficult due to the high grade of cellular differentiation that can lead to the wrong diagnosis of pseudoepitheliomatous hyperplasia.\textsuperscript{3} Additionally, about 25\% of this variant presents foci of classical SCC.\textsuperscript{2}

**CONCLUSIONS**

Despite the fact that OVC represents only 9\% of oral SCCs, a correct differential diagnosis between them is required for definition of the prognosis and therapeutic modalities. The diagnosis is based on the clinical-histopathologic correlation. In general, the careful analysis of several histologic sections is needed for the appropriate diagnosis due to the pseudocarcinomatous hyperplasia.
REFERENCES


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To the Editor:

Skimming the table of contents of the November/December 2011 issue of SKINmed, my eyes were attracted to the question of alcohol-based disinfectants and by the supplemental line on the next page “right for the wrong reason.”

I must say I did enjoy the collection of papers that Wolf, Parish, and Parish put together,1,2 but although I agree that it is important “to dispel the concern that ABHR damages, dries, and irritates the skin more than hand washing with ordinary soap,” I think this statement is “right for the wrong reasons.”

Washing with detergent or soap solubilizes the skin oils, essentially dissolving them in a detergent and water emulsion, and then washes the detergent/soap/skin oil mixture right down the drain. Thus, upon drying the hands, one is left with an outer keratin layer that has no, or much diminished, protective superficial surface lipid. This allows evaporation, dehydration, desiccation, and numerous minute cracks, which, when exposed to the next application of the alcohol-based product, stings as one would expect.

When one uses an alcohol-based hand rub (ABHR), on the other hand (or actually both hands), one solubilizes the natural oils on the skin surface, the alcohol sterilizes the bacterial content of that oil right on the skin surface, and then the alcohol simply evaporates. This leaves the skin oils behind, to continue to serve as the barrier to evaporation that they were designed to provide.

I shared the trepidation of many when alcohol-based products were introduced, but I have found personally, as a sensitive atopic with easily desiccated hands, working in New England in a very dry environment in the winter, that I can maintain my skin oil on my hands much more satisfactorily using alcohol-based products than soap and water. The reasons are pretty straightforward, and I am delighted to see science once again catching up with natural logic.

Thank you for the opportunity to comment.

REFERENCES


—F. William Danby, MD, FRCPC, Department of Dermatology, Geisel School of Medicine at Dartmouth, Hanover, NH • E-mail: billd860@gmail.com
**BRIEF SUMMARY**

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

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

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

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

Initiate appropriate therapy if concomitant skin infections develop.

Discontinue use if irritation develops.

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

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

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

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

**Nursing Mothers**

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

**Pediatric Use**

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

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

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

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

**Geriatric Use**

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

**PATIENT COUNSELING INFORMATION**

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

- Apply a thin film to the affected skin two or three times daily for corticosteroid-responsive dermatoses in adults. Consult with your physician to determine if treatment is needed beyond 2 weeks. Apply a thin film to the affected skin areas two times daily for atopic dermatitis in patients 3 months of age and older.

Safety of Locoid Lipocream in pediatric patients has not been established beyond 4 weeks of use.

- Rub in gently.
- Avoid contact with the eyes.
- Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician.
- Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may act as occlusives.

- Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician.
- If no improvement is seen within 2 weeks, contact your physician.
- Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.

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Locoid Lipocream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, including the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older. Safety and effectiveness in pediatric patients below 3 months of age have not been established. Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.