EDITORIAL
Updating the Dermatologic Nomenclature: Names That Are Good or Bad
Parish and Witkowski

ORIGINAL CONTRIBUTIONS
Serum Lipid Level in Iraqi Patients With Psoriasis
Aldhalimi, Almuhanna, and Alrikabi
Clinical Features and Treatment of Dermatosis Papulosa Nigra in Migrants to Italy
Calcaterra, Franco, Valenzano, Fazio, and Morrone

REVIEWS
Acute Generalized Exanthematous Pustulosis
Pecina and Cappel
Sporotrichosis: Part I
Schechtman

COMMENTARIES
Sentinel Lymph Node Biopsy in Melanoma: The Gulf Between Presentation and Reality
Thomas
Sentinel Lymph Node Biopsy in Melanoma: Coping With Incomplete Information; Call for Further Investigations
Lambert

LETTER TO THE EDITOR
Prolactinoma Can Be Associated With Gynecomastia
Cohen, Robinson, and Gray

DEPARTMENTS
NEW THERAPY UPDATE
Zyclara (Imiquimod) Cream, 3.75%
Gupta, Cooper, and Abramovits

PERILS OF DERMATOPATHOLOGY
Newtonian Dermatopathology: When the Reaction to a Lesion Obfuscates the Diagnosis
Rojas, Sarkissian, Heller, and Lambert

CONGRESS REPORT
Highlights From the 7th EADV Spring Symposium, Cavtat, Croatia, May 13–16, 2010
Lipozenčić

CASE STUDIES
Segmental Cutaneous Piloleiomyomata
Cook-Norris, Rodriguez, Kovach, Boyd, and Zic
Vulvoperineal Crohn’s Disease: Response to Metronidazole
Khaled, Ezzine-Sebai, Fazaaz, Zeglaoui, Zermani, and Kamoun
Folliculocentric Lichen Sclerosus et Atrophicus
Mann, Vergili-Kalner, Wasserman, and Petronic-Rosic
Poorly Growing Hair in a Child
Bolotin, Ortel, and Stein
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**TABLE OF CONTENTS**

**EDITORIAL**

*Updating the Dermatologic Nomenclature: Names That Are Good or Bad*

Lawrence Charles Parish, MD, MD (Hon); Joseph A. Witkowski, MD  

199

**LETTER TO THE EDITOR**

*Prolactinoma Can Be Associated With Gynecomastia*

Philip R. Cohen, MD; Floyd W. Robinson, BS; James M. Gray, MD  

201

**ORIGINAL CONTRIBUTIONS**

*Serum Lipid Level in Iraqi Patients With Psoriasis*

Muhsin A. Albalimi, CABDV; Sadiq J. Almuhanna, FICMS; Samir H. Alrikabi, MSc  

204

*Clinical Features and Treatment of Dermatosis Papulosa Nigra in Migrants to Italy*

Roberta Calcaterra, MD; Gennaro Franco, MD; Mariacarla Valenzano, MD; Raffaella Fazio, MD; Aldo Morrone, MD  

207

**REVIEWS**

*Acute Generalized Exanthematous Pustulosis*

Jennifer L. Pecina, MD; Mark A. Cappel, MD  

210

*Sporotrichosis: Part I*

Regina Casz Schechtman, MD, PhD  

216

Self-Test Review Questions (p. 221)

**COMMENTARIES**

*Sentinel Lymph Node Biopsy in Melanoma: The Gulf Between Presentation and Reality*

J. Meirion Thomas, MS, FRCP, FRCS  

222

*Sentinel Lymph Node Biopsy in Melanoma: Coping With Incomplete Information; Call for Further Investigations*

W. Clark Lambert, MD, PhD  

226

**DEPARTMENTS**

**NEW THERAPY UPDATE**

William Abramovits, MD; Aditya K. Gupta, MD, Section Editors

*Zyclara (Imiquimod) Cream, 3.75%*

Aditya K. Gupta, MD, Elizabeth A. Cooper, HBSc; William Abramovits, MD  

227

**PERILS OF DERMATOPATHOLOGY**

W. Clark Lambert, MD, PhD, Editor

*Newtonian Dermatopathology: When the Reaction to a Lesion Obfuscates the Diagnosis*

Javier Rojas, MD; Navèr Sarkissian, MD, PhD; Debra S. Heller, MD; W. Clark Lambert, MD, PhD  

231
DEPARTMENTS (continued)

CONGRESS REPORT
Marcia Ramos-e-Silva, MD, PhD, Section Editor

Highlights From the 7th EADV Spring Symposium, Cavtat, Croatia, May 13–16, 2010 ................................... 235
Jasna Lipozencić, MD, PhD, Chairperson

CASE STUDIES
Vesna Petronic-Rosic, MD, MSc, Section Editor

Segmental Cutaneous Piloleiomyomata .................................................. 238
Robert H. Cook-Norris, MD; Adrian O. Rodriguez, MD; Bradley T. Kovach, MD; Alan S. Boyd, MD; John A. Zic, MD

Vulvoperineal Crohn’s Disease: Response to Metronidazole .................. 240
Aida Khaleed, MD; Nadia Ezzine-Sebai, MD; Becima Fazaa, MD; Faten Zeglaoui, MD; Rachida Zermani, MD; Mohamed Ridha Kamoun, MD

Folliculocentric Lichen Sclerosus et Atrophicus .................................. 242
David J. Mann, MD; Irene J. Vergilis-Kalover, MD; Justin R. Wasserman, MD; Vesna Petronic-Rosic, MD, MSc

Poorly Growing Hair in a Child ............................................................... 246
Diana Bolotin, MD, PhD; Bernhard Ortel, MD; Sarah L. Stein, MD

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EDITORIAL

Updating the Dermatologic Nomenclature: Names That Are Good or Bad

Lawrence Charles Parish, MD, MD (Hon); Joseph A. Witkowski, MD

DERMATOLOGY probably has the largest vocabulary of any of the medical specialties, a statement to which we can attest when we reviewed aspects of the Dermatology Lexicon project. Some terms are derived from Latin or Greek and present spelling problems to all but a select few. Examples include acrokeratosis verruciformis and pterigium. Other diseases carry names that are so a mouthful that few can call them out without the interruption of breathing. These might include erosio interdigitalis blastomycetica and exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe. No wonder the former is now referred to simply as candidosis, or is it, candidiasis, and the latter as oid-oid disease or Sulzberger-Garbe disease.

BAD NAMES

Be that as it may, we would like to focus on disease names that we should consider avoiding, because they unnecessarily conote ideas that are not germane to patient welfare. These diseases can be easily called by other terms.

• Chondrodermatitis nodularis chronica helicis: This may sound more important in its Latinate form; simplifying the diagnosis to chondrodermatitis of the ear is much more understandable. The cartilage can still be inflamed, and the annoying pain and tenderness will exist with the simplified terminology.

• Senile keratoses: These represent the overproduction of keratin due to excessive exposure to sunlight. While it may take many years of such exposure, not every patient with this possible premalignant condition is approaching Alzheimer’s disease. Even knowing that the histopathology demonstrates squamous cell carcinoma, grade 1 or 2, use of the term actinic keratosi would be preferred.

• Senile purpura: While nonpalpable purpura is often seen in older patients, there is no reason to cast aspersions on the chronologically challenged. Possibly, just calling the red collections, often found on the arms, nonpalpable purpura would suffice. Chronic purpura is just not helpful.

MEDIocre NAMES

• Neurodermatitis denotes red scaling patches on the body, often with lichenification. Should there be history of allergic rhinitis or asthma, a new diagnosis might be used: atopic dermatitis. This has its problems, however, as the causative allergens are rarely found, contrary to the case with hayfever or asthma. Neurodermatitis is better than the synonym of lichen simplex of Brocq, but, once again, the person is led astray into believing that “nerves” or the proverbial stress is the etiologic agent.

• Lichen sclerosus atrophicus represents an atrophic process that is often found on the female genitalia. Its male counterpart is called balanitis xerotica. Do the red, scaling, and atrophic lesions really need 9-syllable terminology, let alone challenges to the spelling capabilities of the clinician?

• Paget’s disease would seem to be a harmless eponym, honoring Sir William Paget who described:
  o Bone disease
  o Squamous cell carcinoma in situ of the areola, being more common in women
  o Squamous cell carcinoma in situ in areas other than the breast (extramammary)

Using the word Paget then denotes 3 different diseases. Were not the terms so well established, it might be more appropriate to select nomenclature that was less confusing and possibly more explicit.

GOOD NAMES

• Basal cell carcinoma is a very descriptive name, an improvement over basal cell epithelioma, and a significant change for the better over rodent ulcer. The patient is anxious enough over the possible scarring to be caused by the surgical removal of this malignancy. There is no good reason to add to the worry by suggesting that a rat created the problem.

• Acne represents a sebaceous gland disorder where many of...
the lesions can be pointed and so, the misconstruing of acne to acme is not so terrible. Acne vulgaris is another mouthful that is unnecessary to perpetuate, while acne rosacea does not provide more information over the one-word, rosacea.

- Contact dermatitis says just what it means: a reaction due to contact with a substance. Adding irritant or allergic to the terminology may be informative, but equally so, causes problems for the simplicity of the term contact dermatitis.

CONCLUSIONS
Perhaps, we have just scratched the surface. While we may not have reformed dermatologic nomenclature, we have presented some of our thoughts.

REFERENCE

WAX MOULAGE

Kerion celsi, Trichophytia profunda capillitii. Moulage Nr. 218, made by Otto Vogelbacher ca. 1920 at the Dermatology Clinic in Freiburg i.Br. (Germany). Museum of Wax Moulages Zurich, www.moulagen.ch

Courtesy of Michael Geiges, MD
To the Editor:

Dr Kapoor’s review provides an excellent summary of the cutaneous manifestations that characterize the systemic conditions associated with gynecomastia. In addition, the pathogenesis of gynecomastia in the included chronic metabolic disorders (cirrhosis and chronic renal failure), endocrine disorders (Graves’ disease and hypopituitarism), systemic infections (leprosy and human immunodeficiency virus), gastrointestinal malignancies, genetic syndromes (lentiginosis syndrome and Klinefelter syndrome), and alcohol abuse is discussed. We respectfully add prolactinoma to the conditions that can be associated with gynecomastia.

Prolactinoma, the most common secretory pituitary tumor, can be classified by tumor size: microadenoma (<10 mm), macroadenoma (>10 mm), and giant (a macroadenoma >40 mm). Clinical symptoms are secondary to either tumor-associated hyperprolactinemia (gonadal and sexual dysfunction) or adenoma-related growth (visual field defects, cranial nerve palsies, and headaches). Prolactinoma typically presents as a microadenoma with amenorrhea, infertility, and galactorrhea in women. In men, since the prolactinoma is more often diagnosed as a macroadenoma, initial symptoms may be associated with the tumor’s larger size: neurologic and vision dysfunction. Endocrine-related symptoms from hyperprolactinemia (such as hypogonadism, infertility, and impotence with decreased libido and erectile dysfunction), however, can be the presenting finding or a subsequent manifestation in men. In addition, albeit less common, gynecomastia, galactorrhea, and abnormally sparse body hair can occur.

Prolactinoma-associated gynecomastia results from tumor-associated hyperprolactinemia. Prolactin inhibits the pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that are necessary for the production of androgens, resulting in decreased testosterone levels and increased estradiol levels. These changes lead to decreased libido, impotence, and gynecomastia.

In this case, a 36-year-old Ukrainian man presented with unilateral galactorrhea and fatigue. At 13 years of age, he had been exposed to radioactivity for 2 weeks following the Chernobyl nuclear power plant reactor 4 explosion. White liquid, elicited by palpation of the breast, is visible on the left nipple and areola. A large intrasellar macroadenoma (2.6 × 2.7 × 2.5 cm), which neither compressed the optic apparatus nor invaded the cavernous sinuses, was detected on the brain magnetic resonance imaging scan. His serum testosterone level was decreased (147 ng/dL, normal = 214–827 ng/dL) and his serum prolactin level was markedly increased (3440.2 ng/mL, normal = 3.0–30.0 ng/mL); the latter observation confirming the suspected diagnosis of prolactinoma. Follow-up evaluation after 6 weeks of cabergoline treatment showed diminished left nipple lactation and decreasing serum prolactin level (200 ng/mL).
of gonadotropin-releasing hormone from the hypothalamus, resulting in suppression of the hypothalamic-pituitary-gonadal axis. In addition, prolactin directly impairs gonadal steroidogenesis by inhibiting the pituitary release of follicle-stimulating hormone and luteinizing hormone.

Prolactinoma can be associated with the coexistence of parathyroid and pancreatic neoplasms in patients with multiple endocrine neoplasia type 1 syndrome; however, the adenoma usually presents as a sporadic tumor. For example, we recently observed a man with previous radiation exposure who subsequently developed a prolactinoma that presented with unilateral galactorrhea (Figure) and fatigue.

Currently, “no risk factors have been identified for sporadic prolactinomas.” We hypothesize, however, that a previously unrecognized risk factor for prolactinoma is exposure to accidental or therapeutic radiation. We therefore suggest that patients who present with sporadic prolactinoma be asked whether they have a prior history of radiation exposure.

In summary, gynecomastia can either be the presenting symptom or a subsequent development in men with a prolactinoma. Sparse body hair, secondary to hyperprolactinemia-associated hypogonadism, is a cutaneous manifestation that can be observed in these individuals.

A prior history of therapeutic or accidental exposure to radioactivity should be sought in all patients with sporadic prolactinoma.

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Psoriasis is a chronic inflammatory skin disorder that affects more than 2% of the population worldwide. It is characterized by an increase in keratinocyte proliferation and alterations in dermal and epidermal T cells, monocytes/macrophages, and neutrophils. Although several previous studies suggest that patients with psoriasis have abnormalities of plasma lipids and lipoproteins as an important risk factor for cardiovascular disease, many of the results remain controversial. Many of these reports suggest that persons with psoriasis have proatherogenic lipoprotein profile that includes hypertriglyceridemia, raised plasma concentrations of low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and lipoprotein (a) and a lowered high-density lipoprotein cholesterol (HDL-C) concentration. High HDL-C concentrations are well established as a major protective factor against coronary heart disease because of their ability to remove unesterified cholesterol from cells and other lipoproteins, where it may have accumulated, and return it to the liver for excretion in the bile.

The aim of this study was to investigate the plasma lipid profile in psoriasis in the Middle Euphrates region in Iraq in comparison with nonaffected persons.

**PATIENTS AND METHODS**

The study was done in the dermatology outpatient department at Al-Sadr Teaching Hospital, Najaf, Iraq, during the period from January to August 2007. It is a cross-sectional study that included 50 adult patients with psoriasis and 50 sex-, age-, and body mass index (BMI)—matched healthy individuals as the control group. The diagnosis of psoriasis was mainly clinical and all doubtful cases were excluded. Smokers, alcoholics, pregnant women, and those with a BMI >30 kg/m² were not included in the study. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Weight and height were recorded as the persons were wearing light clothes and not wearing shoes.

Psoriasis area severity index (PASI) was evaluated using the standard formula. Mild PASI score was defined as 0.1 to 10.9 and moderate PASI score was defined as 11 to 49.9. Patients with severe (PASI >50), erythrodermic, and pustular types of disease were excluded from the study. Other exclusion criteria included patients with diseases that may cause secondary hyperlipidemia such as diabetes mellitus, hypothyroidism, nephritic syndrome, chronic renal insufficiency, obstructive liver disease, and connective tissue diseases, as well as patients taking medications such as β-blockers, thiazide diuretics, corticosteroids, cyclosporine, retinoids, and lipid-lowering agents in the past 6 months.

Blood samples were taken after 12 hours of overnight fasting. Serum levels of total cholesterol, triglycerides (TGs) and HDL-C were assessed in both groups. The patient and control groups each consisted of 39 men and 11 women. The serum triglyceride, cholesterol, LDL, and very LDL levels were significantly higher in psoriatic patients (P<.05) but not for high-density lipoprotein (P>.05). Serum lipid level was found to be significantly higher in Iraqi patients with psoriasis. It may be useful to do early screening and treatment of hyperlipidemia in psoriasis to prevent atherosclerosis and its complications.

**ORIGINAL CONTRIBUTION**

**Serum Lipid Level in Iraqi Patients With Psoriasis**

Muhsin A. Aldhalimi, CABDV; Sadiq J. Almuhanna, FICMS; Samir H. Alrikabi, MSc

**ABSTRACT**

Psoriasis is a chronic inflammatory and proliferative dermatosis. Previous studies have demonstrated that patients with psoriasis may have an increased risk of occlusive vascular disease. High serum lipid level has been suggested in the pathogenesis of this phenomenon. In this study, the authors assess the lipid profile in Iraqi patients with psoriasis and compare it with that of nonaffected persons. This study was designed and conducted as a cross-sectional study with 50 cases in the patient group and 50 patients in the control group. It was performed in the department of dermatology at Al-Sadr Teaching Hospital in Najaf, Iraq. The lipid profile, including serum levels of triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein, were assessed in both groups. The patient and control groups each consisted of 39 men and 11 women. The serum triglyceride, cholesterol, LDL, and very LDL levels were significantly higher in psoriatic patients (P<.05) but not for high-density lipoprotein (P>.05). Serum lipid level was found to be significantly higher in Iraqi patients with psoriasis. It may be useful to do early screening and treatment of hyperlipidemia in psoriasis to prevent atherosclerosis and its complications.
This study was approved by the ethics committee of our university, and all patients gave their informed consent.

**STATISTICAL ANALYSES**

Values are presented as mean ± standard deviation. Comparison between patients with and without psoriasis was performed by Student t test and Pearson correlation coefficients. P value <.05 was considered statistically significant.

**RESULTS**

The age of the patients ranged from 20 to 67 years, with a mean of 37.6 years. There were 39 men and 11 women. The age of the control group ranged from 21 to 65 years, with a mean of 37.4 years. The sex distribution was the same as that of the patients. PASI score ranged from 2.3 to 24.7, with a mean of 19.6. The mean duration of disease was 5.45 years (range 0.8–19 years). There was no difference between patients and the control group with regard to BMI, systolic and diastolic blood pressures, and physical activity. Serum lipid levels in patients with psoriasis and in controls are shown in the Table. In the patient group, serum total cholesterol, LDL-C, VLDL-C, and TG levels were significantly higher than those of controls (P <.05). HDL-C was slightly higher in the control group, but the difference was not statistically significant (P >.05). There was no significant association between PASI and serum lipid profile in the present work (Pearson correlation coefficients P >.05).

**DISCUSSION**

In spite of an increasing number of studies dealing with plasma lipid levels in patients with psoriasis, the results are still conflicting.3–13,15–18 It is still controversial whether changes in lipid composition are primary events or secondary to psoriasis or perhaps due to medications such as cyclosporine and retinoids.5,7,19

In this study we tried to assess this relation in a group of Iraqi patients. The measured lipid parameters in this work were significantly higher in patients with psoriasis than the control group, apart from HDL-C, which was slightly higher in the control group. The results of previous studies were greatly variable. High,3,11,17,19 low,20 or even normal4,5,7,18 values of serum cholesterol levels in patients with psoriasis have been reported. In this study we found a significantly higher level of total cholesterol values in patients with psoriasis (P <.05). Similar conflicting results of plasma TG level were observed in the published literature. The previous results varied from high3,4,7,17 to low20 or even normal5,6,8,18,19 values. This work showed a significant higher value of serum TG levels in the psoriatic group. A similar controversy was found regarding HDL-C and VLDL-C values in patients with psoriasis. Normal4,5,7,8,17–19 and low3,10,12 levels of serum HDL-C and high3,6,11,12 levels of VLDL-C have been reported. Although the values of HDL-C in the present study were lower in the psoriatic group than in the control group, the difference was not statistically significant (P >.05). The recorded values of VLDL-C level in this work were significantly higher in the psoriatic group (P <.05).

The discrepancy in data from different studies may be due to the fact that patients included in statistical analysis have different phases and forms of psoriasis and undergo various treatments. The other cause may be a result of differences in lipid referential values, such as sex and age, which considerably change the results when young and old patients and men and women are collectively investigated.3 Different methods used in disease scoring and laboratory assessment may be another cause of the discrepancy.

The values of serum lipid in psoriatic patients have been studied since almost half a century ago. Lea and colleagues21 reported increased serum lipid concentrations in patients with psoriasis. Since then, much research has been performed in this area, most of which consistently points to a raised prevalence of lipid abnormalities in individuals diagnosed with psoriasis. The exact cause of these changes in lipid metabolism in patients with psoriasis is not yet confirmed. The activation of the immune system in psoriasis

### Table. Comparison of Lipid Profile Between Patients With Psoriasis and Control Patients

<table>
<thead>
<tr>
<th></th>
<th><strong>Patients With Psoriasis (N=50)</strong></th>
<th><strong>Control Group (N=50)</strong></th>
<th><strong>P Value</strong></th>
</tr>
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<tr>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>216.4 ± 20.16</td>
<td>208.8 ± 22.09</td>
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<td>Triglycerides, mg/dL</td>
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<td>139.7 ± 13.93</td>
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<td>HDL-C, mg/dL</td>
<td>39.62 ± 3.76</td>
<td>43.88 ± 3.52</td>
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<tr>
<td>LDL-C, mg/dL</td>
<td>146.22 ± 25.62</td>
<td>134.56 ± 23.73</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>VLDL-C, mg/dL</td>
<td>34.52 ± 12.35</td>
<td>27.9 ± 11.67</td>
<td>&lt;.05</td>
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</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; VLDL-C, very low-density lipoprotein cholesterol.
may cause some changes in patients' lipid profiles. They may be related, however, to some structural and functional abnormalities in the digestive system, which are shown to be found in nearly all the segments of the digestive system. These abnormalities may cause alteration in decomposition, modification, and synthesis of many organic compounds, including lipids. Knowing that psoriasis is a genetic disorder, however, there is a possibility that genetic alterations in the HDL-C and/or apolipoprotein A-I genes may be linked with this disease. This genetic hypothesis is supported by a study on lipid and lipoprotein profile among Swedish patients with psoriasis at the initial stages of the disease. It demonstrated that patients with psoriasis manifest significant lipid abnormalities and support the notion that the abnormal lipid profile seen in such patients might be genetically determined rather than acquired.

Previous studies have shown a high prevalence of atherosclerosis in psoriatic patients. High serum lipid level has been suggested in the pathogenesis of this phenomenon. Early assessment and treatment of abnormal lipid profile may reduce atherosclerosis and cardiovascular accidents in these patients.

REFERENCES
Dermatosis papulosa nigra (DPN) is a nevoid condition of the pilosebaceous apparatus that predominantly affects adult black persons.1,2 It is characterized by black or dark brown flattened or cupuliform papules, with a diameter ranging from 1 mm to 5 mm. The lesions do not itch or hurt (are asymptomatic) and occur on the face, neck, and trunk. DPN is a frequent disease among black persons, above all Africans and African-Americans, but is also common in Native Americans and persons from Malaysia.

Despite the diagnosis being easily made at medical examination, DPN is characterized by a chronic and worsening course. Therefore, even though DPN is a benign disease, the lesions are unaesthetic and the therapeutic options are quite inefficient. A prospective study was carried out during a period of 24 months (January 2006 to December 2007) at the Department for Preventive Medicine for Migration, Tourism and Tropical Dermatology of San Gallicano Dermatological Institute in Rome. Among 58 patients, 41 (71%) were women and 17 (29%) were men. The mean age was 33.5 years (range, 8–45 years). One pediatric patient was observed. This study is the first in Italy that, in recent years, has observed an important growth of the migration. The classic female predominance, family predisposition, and photodistribution of the lesion were found. DPN is frequently associated with patient discomfort, therefore the education of patients to reduce self-treatment is important. (SKINmed. 2010;8:207–209)

Dermatosis papulosa nigra (DPN) is a benign epithelial tumor that is common in dark-skinned people. Although the diagnosis is easily made on medical examination, DPN is characterized by a chronic and worsening course. Therefore, even if DPN is a benign disease, the lesions are unaesthetic and the therapeutic options are quite inefficient. A prospective study was carried out during a period of 24 months (January 2006 to December 2007) at the Department for Preventive Medicine for Migration, Tourism and Tropical Dermatology of San Gallicano Dermatological Institute in Rome. Among 58 patients, 41 (71%) were women and 17 (29%) were men. The mean age was 33.5 years (range, 8–45 years). One pediatric patient was observed. This study is the first in Italy that, in recent years, has observed an important growth of the migration. The classic female predominance, family predisposition, and photodistribution of the lesion were found. DPN is frequently associated with patient discomfort, therefore the education of patients to reduce self-treatment is important. (SKINmed. 2010;8:207–209)
Clinically, the lesions that we found were round, smooth, brown or black papules, ranging in size from 1 mm to 5 mm. Rarely we observed, only on the trunk, nodules or pedunculated papules (14%).

These lesions were commonly asymptomatic, although 5 patients (8.4%) reported transitory itch.

Twenty-three women (39.6%) reported the application of bleaching cream (most containing high-strength corticosteroids) for a period ranging from 4 months to 5 years, without any improvement. The histopathologic examination was performed in 3 cases and confirmed the diagnosis of DPN (Figure 3).

Regarding psychological impact, discomfort described by these patients, above all among young adults and women, was remarkable. In fact, aesthetic considerations were the reason for consultation in 43 patients (74%), 35 of whom were women. Moreover, in 37 patients (63.8%), DPN caused anxiety and fear of professional concerns.

All patients were informed that the treatment may be temporary and could result, above all in black skin, in important dyschromia. Electrosurgery was performed in 20 patients after the application of 30 minutes of lidocaine-prilocaine cream. At 1-month follow-up examination, hypochromia in 15 patients and hyperchromia in 5 patients were detected. At 3-month follow-up, dyschromia persisted in only 2 cases; 3 patients were lost to follow-up.

DISCUSSION

DPN was first described by Castellani in 1925 while visiting Central America and Jamaica. He noted that this condition was common in adult black persons and was usually localized on the face.1

Different from that previously reported, we found that DPN occurs in all people with high Fitzpatrick skin phototype classification (skin phototype IV, V, or VI), not only in African descendants.1

The incidence of DPN among black persons rises from about 5% to 40%, and women, especially adolescents, are more commonly affected than men.1,3-5

The lesions usually develop during puberty and become more pronounced by the sixth decade; they are rare during childhood. Some studies have demonstrated the family predisposition of DPN.

DPN is likely to be genetically determined, with 40% to 54% of patients having a family history of involvement. DPN is believed to be caused by a nevoid developmental defect of the pilosebaceous follicle. Some researchers have suggested that DPN should be classified within the group of epithelial nevi.6,7

Clinically, the single lesions are 1-mm to 5-mm black or dark brown cupuliform and usually asymptomatic. DPN is localized on the malar regions and on the forehead, is rare on the lower
parts of the face and the chin, and can sometimes be found on the neck, chest, and back.

The differential diagnosis of DPN include melanocytic nevi, warts, acrochordons, adenoma sebaceum, follicular hamartoma, and seborrheic keratosis.

The diagnosis may be confirmed by biopsy, with DPN resembling an acanthotic seborrheic keratosis.

Lesions of dermatosis papulosa nigra have the histologic appearance of seborrheic keratoses; they display hyperkeratosis, irregular acanthosis, keratin-filled invaginations of the epidermis (horn cysts), and marked hyperpigmentation of the basal layer. Although most lesions are of the acanthotic type and show thick interwoven tracts of epidermal cells, they may have a reticulated pattern in which the tracts consist of a double row of basaloid cells.\(^8,9\)

Although DPN could exhibit thick interwoven tracts of epithelial cells, the proliferation of small basal cells is not common in DPN, such as in seborrheic keratosis.

Treatment is seldom requested because of DPN’s benign nature, but patients often request some treatment to improve their aspect and reduce discomfort.

The papules may be removed with diathermy or cautery; cryotherapy has also been used, but it is important to inform the patient that all this treatment may be temporary and could result in, above all in black skin, important hypopigmentation or hyperpigmentation and sometimes in keloids.\(^10\)–\(^13\)

Other therapies include keratolytic creams associated with electrodessication, electrodessication, fractional photothermolysis, and long-pulsed 1064 nm Nd:YAG laser.\(^14\)–\(^15\)

We performed excision using fine-needle electrosurgery to minimize the risk of unaesthetic scarring, and the use of anesthetic cream was permitted to treat more lesions at the same time.

**CONCLUSIONS**

Although DPN is benign and the treatment, however easy to perform, is not always required, it is important to promote the knowledge of this condition common among black persons to provide the right assistance and treatment.

**REFERENCES**

First described as a distinct entity in 1968,1 acute generalized exanthematous pustulosis (AGEP) is a relatively uncommon cutaneous reaction pattern typically precipitated by medication exposure. The disease has been variably termed pustular drug rash, generalized pustular dermatosis, and toxic pustuloderma. The current nomenclature was proposed in the French literature in 1980.2

CLINICAL PRESENTATION

AGEP is characterized by acute onset of an edematous erythematous dermatitis with overlying small pustules, frequently accompanied by a temperature >38°C. Leukocytosis is common, predominantly as neutrophilia, although eosinophilia may also occur. Serum chemistry values may show a slight elevation in hepatic transaminases, hypocalcemia, and a transient decrease in creatinine clearance.3

The typical dermatologic appearance is that of an edematous erythematous dermatitis that frequently begins on the face or in intertriginous regions. Patients often describe the dermatitis as burning and pruritic. This dermatitis is followed by the appearance of numerous small (<5 mm) nonfollicular sterile pustules in the involved areas (Figure 1). By definition, the pustules in AGEP are sterile, but, as with any diffuse dermatitis, staphylococcal and other bacterial superinfections can occur. Mucous membrane involvement occurs in 20% of the patients. Occasionally, blisters, target lesions, and purpura are seen.3 Individual pustules can expand and coalesce, thereby forming larger confluent pustules. Biopsy may be required to confirm the diagnosis, and histopathology typically shows spongiform subcorneal pustules or intraepidermal pustules with papillary dermal edema and perivascular infiltrates of neutrophils and sometimes eosinophils.4

An AGEP validation score proposed for diagnosis is based on a combination of features of the morphology, histopathology, and clinical course (Table I).5 Often, however, patients with cutaneous drug reactions have been simultaneously exposed to multiple new medications, making determination of the particular causative agent challenging. Inadvertent reexposure has been reported to provoke recurrent episodes of AGEP; thus, rechallenge could be used to confirm clinical suspicions of a causative agent.3,6 Re-exposure is potentially unsafe, however, and may raise ethical concerns. Since patch testing results are positive in 50% of patients, it is a reasonable method for attempting to elucidate the inciting medication.7 Patch tests are generally considered safe, although an AGEP reaction provoked by patch testing has been reported.8

INCIDENCE

The incidence of AGEP is estimated to be approximately 1 in 5 cases per million per year, and all age groups may be affected.5 Two studies suggested a female predilection, but this has not been a consistent finding3,9,10 One study found a disproportionate association with the HLA B51, DR11, and DQ3 genotypes compared with the general population. A personal or family history of psoriasis is slightly more common than would be expected in the general population, but most cases of AGEP occur in patients without any psoriatic history.

ETIOLOGY

The underlying pathogenic mechanism for AGEP remains unclear; however, on the basis of several studies, a T-cell–mediated process has been hypothesized. In vitro tests have demonstrated that drug-specific T lymphocytes from AGEP patients produce chemokines that attract neutrophils as well as prolong their
survival, thus leading to the sterile inflammatory pustules that are clinically observed.\textsuperscript{11,12} AGEP is precipitated by systemic drugs in approximately 90% of patients. Historically, β-lactam and macrolide antibiotics are the most frequent causative agents, although multiple drugs have been implicated (Table II). AGEP has been reported to occur from multiple antibiotics within the same class: in 1 patient, AGEP developed from 2 different macrolides,\textsuperscript{13} and in another patient, AGEP developed from 3 different β-lactam antibiotics (piperacillin, ceftazidime, and meropenem).\textsuperscript{15} A bimodal pattern has been seen for the interval to onset after starting administration of an inciting drug. With antibiotics, the onset of dermatitis usually occurs within 2 days (mean, 2.5 days), whereas with other medications there is often a delay of 1 to 3 weeks (mean, 18 days).\textsuperscript{3} AGEP has been associated with viral infections (including enteroviruses, cytomegalovirus, and human parvovirus B19),\textsuperscript{3} spider bites,\textsuperscript{2,3} and mercury exposure.\textsuperscript{3}

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of AGEP includes various dermatoses that have a pustular component with a background of diffuse erythema. Folliculitis, impetigo, and Sweet syndrome can appear pustular but are typically not associated with a background of diffuse erythema. Blistering diseases such as Sneddon-Wilkinson disease, immunoglobulin A pemphigus, and pemphigus foliaceus can form pustules but often have more chronic and discrete lesions. Impetigo typically presents with larger, flaccid, and non-sterile pustules that remain relatively localized. Sweet syndrome can occur suddenly and the lesions may appear pustular, but these lesions are also relatively localized and discrete. Pustular contact dermatitis, superinfected eczematous dermatitis, pustular psoriasis, staphylococcal scalded skin syndrome, and drug rash with eosinophilia and systemic symptoms can present with diffuse erythematous dermatitis associated with pustules. Staphylococcal scalded skin syndrome is associated with staphylococcal infection, and drug rash with eosinophilia and systemic symptoms is associated with significant systemic symptoms. Both tend to be characterized by exfoliation rather than pustule formation. Most of the above entities are easily distinguished from AGEP on the basis of clinical findings and history. The primary disease process to be excluded is generalized pustular psoriasis (von Zumbusch psoriasis) (Figure 2), which has a longer clinical course than AGEP and is not associated with drug administration.

**TREATMENT**

Treatment consists of discontinuing use of the suspected offending agent and providing supportive care. If they are not thought to be causative agents, antipyretics and antihistamines can be used for symptomatic relief. Various topical treatments, including topical corticosteroids and cool compresses, can also be considered, but they may provide only mild symptomatic relief. Systemic corticosteroids may be empirically used, but supportive evidence is lacking. In at least two published reports, pretreatment with corticosteroids did not prevent AGEP from occurring.\textsuperscript{6,18} Paradoxically, there are also reports of corticosteroids provoking an AGEP reaction.\textsuperscript{19,20} Patients should be counseled to avoid use of the offending drug in the future, and their

![Figure 1. Acute generalized exanthematous pustulosis. Anterior surfaces of legs (A); back (B).](image-url)
adverse reaction should be documented in their medical record. Although no specific guidelines are available, it may be prudent to recommend that patients avoid future exposure to medications in the same class.

OUTCOMES

Outcomes in AGEP are uniformly excellent. The dermatitis is topographically self-limited in distribution and usually spontaneously resolves in less than 15 days. Resolution is followed by pinpoint cutaneous desquamation and eventual healing. No data exist on cross-sensitization between similar classes of medications (eg, penicillins and cephalosporins). Serious consequences are extremely rare: an early article reported a 5% mortality rate, but this has not been substantiated in later reports. Two cases of AGEP-related death have been described; however, 1 patient died of hepatic coma and had other comorbidities and the other died of acute renal failure and sepsis.

CONCLUSIONS

AGEP is a relatively rare dermatologic disease typically provoked by medication exposure. Specific criteria exist for establishing the diagnosis. Symptoms usually spontaneously resolve after withdrawal of the precipitating medication.

REFERENCES


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Table II. Drugs and Miscellaneous Causes Reported to Be Implicated in Acute Generalized Exanthematous Pustulosis

<table>
<thead>
<tr>
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8 Mashiah J, Brenner S. A systemic reaction to patch testing for the evaluation of acute generalized exanthematous pustulosis.


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A New Tretinoin Therapy
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Sporotrichosis is the most common subcutaneous mycosis in South America. Classic infection is associated with traumatic inoculation of soil, vegetables, and organic material contaminated with *Sporothrix schenckii*. Animals of various species, including humans, are affected by this disease. This subcutaneous mycosis is an infection of implantation. The most frequent clinical form is the lymphocutaneous form. The fixed cutaneous form is characterized by infiltrated nodular, ulcerated, or erythematousquamous lesions located on exposed areas where fungal inoculation occurred. The disseminated cutaneous forms have mainly been observed among immunosuppressed patients, especially human immunodeficiency virus–positive individuals. Sporotrichosis is the only subcutaneous mycosis for which direct examination or histology is of little or no value for diagnosis. The diagnosis rests solely on the isolation of *S. schenckii* in culture. Since 1998, researchers from Brazil suggested that feline transmission of sporotrichosis was associated with a large and long-lasting outbreak of the disease in the city of Rio de Janeiro. (SKINmed. 2010;8:216–220)

**HISTORY**

In 1898, Bernard Schenck first isolated and described *S. schenckii*. He was attending medical school at Johns Hopkins University at the time, and he had the assistance of a US Department of Agriculture mycologist, Erwin Smith, who identified the organism and classified it as "sporotricha." In 1900, the disease was reported for the second time by Hektoen and Perkins, who classified the etiologic agent as *S. schenckii*, with the pathogen being isolated from a specimen aspirated from the cutaneous lesions of a patient. In Europe, the first case was described in 1903, and more than 200 cases were reported during the following 10 years.

The first sporotrichosis in Brazil was reported in 1907 by Lutz and Splendore, who also found that it was possible to culture the yeast form in vitro. The dimorphic transition of this fungus was described by Howard in 1961.

**TAXONOMY**

*S. schenckii* is, therefore, a dimorphic pathogenic fungus and the etiologic agent of human and animal sporotrichosis. The fungus
belongs to the subdivision Deuteromycotina, class Hyphomycetes. According to Mariat and Taylor, the fungus Ceratocystis stenoceras (Ophiostoma stenoceras) presents a conidial stage similar to that of S. schenckii; however, no conclusions exist regarding the description of the teleomorphic phase of this species. Other investigators have recently postulated that stenoceras may correspond with the teleomorph of S. schenckii. Previous studies based on DNA hybridization experiments, however, provided strong evidence that stenoceras is not the teleomorph of S. schenckii. The degree of hybridization observed among S. schenckii and O. stenoceras DNAs was as low as 30% while a high degree of cross-hybridization was observed among 4 S. schenckii strains studied.

**EPIDEMIOLOGY**

*S. schenckii* is widely distributed in nature and can be found in soil associated with plant organic matter (e.g., thorns, dry leaves, and wood), water, and decomposing organic matter, among others. *S. schenckii* is present in the soil throughout the world. Sporotrichosis is more frequent in tropical and subtropical countries, however, and is endemic in many parts of Latin America. Sporotrichosis has been mainly reported in tropical and temperate zones. It is endemic in Mexico, Central America, and South America, as well as other areas such as South Africa. It can also occur in temperate climates such as in southern United States, Japan, and Australia. In the south of the American continent, the disease more frequently occurs in humid autumn or summer seasons, whereas in Mexico, the highest incidence is observed in cold and dry seasons. No seasonal difference, however, has been reported by other authors.

Sporotrichosis can affect persons of all ages, and the number of cases involving men and women varies from region to region. In some regions, the difference in the distribution of cases according to age and sex might be explained by the type of fungal exposure, but no association has been found in other regions.

Generally, infection results from inoculation of the fungus through thorns, splinters, scratches, and small traumas during leisure and occupational activities such as floriculture, horticulture, gardening, fishing, hunting, farming, and cattle raising, mining, and wood exploration. Laboratory professionals can be accidentally infected while manipulating *S. schenckii* cultures. Sporotrichin skin test is mainly applied for epidemiologic studies and is not commercially available in Brazil.

**EPIDEMIC OUTBREAKS**

Sporotrichosis usually occurs in isolated cases or in small family or professional outbreaks. Epidemics are rare and, if present, have been related to a single source of infection. The largest reported epidemic occurred in South Africa, with about 3000 gold miners infected with the fungus, which occurred in the wood girders of the mine structure. Another epidemic burst affected 84 workers who participated in reforestation programs in 15 states of the United States.
Sporotrichosis: Part I

United States and was associated with the sphagnum moss used to store the seedlings that originated from Pennsylvania.%

Zoonotic Sporotrichosis

Human sporotrichosis has been sporadically related to the scratch or bite of animals.21,28 The presence of the fungus in the mouth or nails of the animals, however, was not demonstrated in any of the cases described.28,29 Since the 1980s, domestic cats have gained importance in the transmission of the mycosis to humans.20,30–34 Between animals, the acquired infection is reported in various species such as horses, rats, dolphins, cows, and fish.2 Animal to human transmission is rare, however, and there are few reports on animal transmission of sporotrichosis to humans, with the exception of some cases of armadillo transmission in Uruguay35 and feline transmission in Brazil. Other risk groups include animal health personnel, such as veterinary doctors and technicians, and animal owners as a result of the increasing number of sporotrichosis case reports transmitted by domestic cats. Domestic cats can acquire the disease following traumatic injury from infected street cats during fights or from direct inoculation of environmental organisms that inhabit soil and vegetation. They transmit the infection to humans in the domestic environment through biting or scratching human skin and consequently inoculating the organisms that are present under the nails. Another way of transmission is through direct contact of human skin with the infected cat skin, mucous membranes, or exudates from open lesions. Domestic dogs have been identified with sporotrichosis, probably transmitted by domestic cats.14

Pathogenesis

This subcutaneous mycosis is an infection of implantation. In most cases it develops following traumatic injury, especially by vegetation such as thorns and wood, and the inoculation of environmental organisms into the host where they affect the subcutaneous tissue, skin, and other adjacent structures. Certain occupational groups such as those who handle plant materials or soil are frequently exposed to the organism and have been known to become infected.

Multiple inoculations may occur simultaneously, not to be confused with spread of a single primary lesion. The presentation and course of sporotrichosis depends on the host immune response as well as the size and virulence of the inoculums. In hosts not previously inoculated, involvement of regional lymphatic ensues. In those with a prior history of exposure to S. schenckii, no lymphatic spread occurs and a “fixed ulcer” develops at the site of inoculums or granulomatous plaque (particularly on the face).36

Extensive cutaneous disease with or without systemic involvement is also possible, especially in an immunocompromised host. Cases of inhaled sporotrichosis have been reported with systemic and cutaneous dissemination, similar to disseminated histoplasmosis and other dimorphic fungal infections.

Clinical Features

Sporotrichosis has diverse clinical manifestations, and investigators disagree regarding the clinical classification of the disease.2 The most frequent clinical form (about 80%) is the lymphocutaneous form. The initial presentation of sporotrichosis is that of a single papule at the precise location of injury, most commonly on the hand, that

Figure 4. Sporotrichosis. Fixed cutaneous form. Infiltrated nodular eroded papule on the leg.

Figure 5. Sporotrichosis. Fixed cutaneous form. Infiltrated nodular eroded papule on the nose.

SKINmed. 2010;8:216–220

Sporotrichosis: Part I

218
appears several weeks after inoculation. The lesion then becomes eroded or ulcerated with purulent drainage, and is generally not painful (Figure 1). Weeks after development of the initial lesion, additional lesions appear, typically as dermal and subcutaneous nodules and ulcers along the path of lymphatic drainage (often up the arm) (Figure 2). This clinical description led to naming the disease as “ascending nodular lymphangitis.” This is the well-known “sporotrichoid” pattern (Figure 3). Usually, lesions located in the deep dermis or subcutaneous tissue result in skin scars.

In general, the fixed cutaneous form is characterized by infiltrated nodular, ulcerated, or erythematous nodules located on exposed areas where fungal inoculation occurred (Figure 4 and Figure 5). The lesions of fixed cutaneous sporotrichosis can appear granulomatous (Figure 6), and disseminated lesions typically present as subcutaneous nodules. The disseminated cutaneous forms have mainly been observed among immunosuppressed patients, especially human immunodeficiency virus–positive individuals. Mucosal involvement is not common but may occur and preferentially affects the ocular mucosa (Figure 7). Among the extracutaneous forms, osteoarticular and pulmonary involvement are the most common, but there are reports of cases of severe hematogenic dissemination with involvement of multiple organs.

DIFFERENTIAL DIAGNOSIS

Due to the diversity of the clinical forms of sporotrichosis, there is also a vast set of differential diagnoses with other pathologic conditions. Examples include leishmaniasis, nocardiosis, chromomycosis, tuberculosis, rosacea, noninfectious granulomatous diseases, and psoriasis, among others.

When there is a sporotrichoid pattern, the major entity to be excluded in endemic areas from Brazil is leishmaniasis. In Europe, Canada, and the United States, the major differential diagnosis is an atypical mycobacterial infection, in particular Mycobacterium marinum. Other less common causes are rhinoscleroma, granuloma inguinale, histoplasmosis, leishmaniosis, and Penicillium marneffei infection.

The differential diagnosis of fixed plaque sporotrichosis and disseminated lesions is broad and includes other granulomatous disorders, both infectious and inflammatory.

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SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Editor

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

1) Sporotrichosis is most commonly transmitted to humans by contact with:
   a. cats
   b. dogs
   c. hamsters
   d. lice
   e. snakes

2) The “sporotrichoid pattern” is best described as a/an:
   a. acral ulcerating dermatosis
   b. ascending nodular lymphangitis
   c. dependent edematous erythema
   d. nodular intertrigo
   e. reticulated mucinosis

3) Of the following, the most common mucosal site to be involved with sporotrichosis is the:
   a. conjunctiva
   b. oral cavity
   c. urethra
   d. vagina
   e. vulva

4) Of the following, the organ most likely to be involved by extra-cutaneous sporotrichosis is the:
   a. colon
   b. kidney
   c. liver
   d. lung
   e. stomach

5) Of the following, the tissue most likely to be involved by extra-cutaneous sporotrichosis is:
   a. central nervous system tissue
   b. endometrial tissue
   c. osteoarticular tissue
   d. peritoneal tissue
   e. retroperitoneal tissue

ANSWERS TO SELF-TEST REVIEW QUESTIONS:
1) e
2) c
3) a
4) d
5) c

From the Departments of Pathology and Dermatology, UMDNJ-New Jersey Medical School, Newark, NJ
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Patients with newly diagnosed melanoma are frightened and vulnerable. At times of crisis, pessimism prevails and patients inevitably consider the worst possible outcome as one of the range of possibilities. That fear is compounded when they realize that, unlike most other malignancies, there is no systemic therapy that can prolong overall survival. In this frame of mind, patients are offered sentinel lymph node biopsy (SLNB), which, like ultrasound, in the best of hands, is an effective staging and prognostic tool. Inevitably, many patients accept SLNB in the hope that their disease proves to be sentinel node (SN)–negative; however, during the consent process, 3 other possible benefits of SLNB in melanoma may be mentioned that are either speculative or unproven.

First, it is suggested that even if the disease is SN-positive, then immediate (early) lymphadenectomy vs delayed lymphadenectomy (when the nodal disease becomes palpable) may provide a survival advantage. This was a conclusion of the first Multi-center Selective Lymphadenectomy Trial (MSLT-1), but the observation is better explained by an incidence of false-positivity within the SN. Second, it is suggested that immediate vs delayed lymphadenectomy provides a benefit in disease-free survival (DFS), but this outcome is an inevitable consequence of the MSLT-1 trial design and does not amount to a therapeutic advantage for patients. Third, it is suggested that immediate lymphadenectomy is associated with fewer complications than delayed lymphadenectomy. This contribution will address these 3 issues and will argue that the benefits of SLNB in melanoma have been overstated. It will conclude that the procedure is merely a staging and prognostic tool and, for most patients, represents excessive and unnecessary treatment.

FALSE-POSITIVITY IN THE SN

It was the matched-pair analysis that first concluded that immediate vs delayed lymphadenectomy provided a survival advantage. In that study, a survival advantage of 22%, 32%, and 37% at 5, 10, and 15 years, respectively, was claimed for immediate lymphadenectomy comparing 2 computer-selected groups of patients matched for all other prognostic factors. Sadly, this survival advantage was not confirmed by the results of MSLT-1, which showed no difference in overall survival from the point of randomization, when immediate and delayed lymphadenectomy were compared in the context of a randomized controlled trial. The authors of these papers have declined to explain the large difference in survival between the 2 studies, but the most likely explanation is that some of the minimally involved SNs in the matched-pair analysis were prognostically false-positive, which means that they were destined for dormancy or destruction and not for progression to palpable nodal recurrence.

Breast cancer is another disease where SN status directs treatment options, but microscopic tumor deposits in the SN are believed to be of no adverse prognostic significance and, according to size, are not an indication for completion lymphadenectomy nor necessarily for adjuvant systemic therapy. In biological terms, why should it be assumed that tiny subcapsular deposits of melanoma in the SN will behave so differently and require more radical treatment?

The authors of MSLT-1 and others refuse to consider the possibility of false-positivity in the SN in melanoma, possibly because the statistical analysis of MSLT-1 assumes, without proof, that all positive SNs will inevitably progress to palpable nodal recurrence if not removed. The incidence of false-positivity in the SN in MSLT-1 at the third interim analysis has been estimated to be 24% for patients with intermediate thickness tumors and 34% for all patients entered into the trial. These figures suggest that a large number of patients may have been wrongly up-staged and may have had unnecessary completion lymphadenectomy and possibly unnecessary adjuvant therapy.

In a remarkable paper, investigators describe performing delayed SLNB in 6 patients at a median of 3.9 years after wide excision of the primary melanoma. Two patients were found to have tiny subcapsular deposits of melanoma in the SN 4 years...
and 4.9 years after the removal of their primary tumor (Figure). Were these patients destined for late nodal recurrence, or is this a perfect, if unintended, illustration of prognostic false-positivity?

**DISEASE-FREE SURVIVAL**

Neither is it correct to claim, as was published,\(^2\) that immediate vs delayed lymphadenectomy provides an advantage in DFS. A benefit in DFS in the biopsy arm of MSLT-1 was inevitable due to trial design.\(^3\) The most likely site of first recurrence in patients with intermediate thickness primary melanoma (1.2 mm to 3.5 mm) is the regional lymph nodes, and, in the biopsy arm of MSLT-1, the patients most likely to develop nodal metastases were identified as being SN-positive at the outset and were treated with prophylactic lymphadenectomy. Therefore, it is inevitable that there are more regional node recurrences as site of first recurrence in the observation arm. When the incidence of first recurrence was broken down by site,\(^2\) nodal recurrence was more than 3 times more common in the observation arm than in the biopsy arm. Consequently, the advantage in DFS simply amounts to lead-time bias and is of no therapeutic advantage. This error was successfully challenged with the National Cancer Institute (NCI), who funded the MSLT trials. They issued guidance in June 2007\(^4\) that stated the following:

We agree that in a trial where one arm has nodal disease removed at the outset, and the other arm does not, calculation of either distant DFS or exclusion of nodal recurrences from the DFS calculation is appropriate. We have indicated to Dr Morton our belief that he should include a DFS analysis in the next update of study, that excludes nodal recurrences.

Patients who die of melanoma succumb to distant metastasis; therefore, the most important end point for the fourth interim analysis and (fifth) final analysis of MSLT-1 is distant DFS. Despite this guidance from NCI, the authors of MSLT-1 and others have continued to stress the importance of DFS as previously calculated.\(^9\)–\(^13\) It is surprising that this crucial error was not identified before publication.\(^2\)

**COMPARING MORBIDITY FOLLOWING LYMPHADENECTOMY**

Patients are also encouraged to undergo SLNB for the following reason:

We must also understand the safety and efficacy of salvage node dissection at the time of nodal relapse. Available data suggests that lymphadenectomy performed for clinically evident nodal disease is associated with more complications and poorer regional control rates than when the same procedure is done for microscopic disease.\(^13\)

**Figure.** Delayed sentinel lymph node biopsy: subcapsular deposits of melanoma in the sentinel node 4 years (A) and 4.9 years (B) after wide excision of the primary tumor.\(^8\)

Statements similar to this are used frequently by advocates of SLNB but are not evidence-based. The only randomized controlled trial of immediate vs delayed lymphadenectomy is MSLT-1, which does not describe any greater morbidity following delayed lymphadenectomy in patients with intermediate thickness tumors.\(^2\) It is conceded that retrospective studies of therapeutic lymph node dissection do show a high incidence of complications, but this is due to the inclusion of patients who, for a variety of reasons, present with advanced, neglected nodal disease and who, unlike patients in the observation arm of MSLT-1, did not undergo regular follow-up, with or without ultrasound surveillance, after wide excision of their primary tumor. In other words, there is no evidence that patients who are closely observed by clinical or ultrasound surveillance following wide excision of their primary melanoma and who then develop palpable nodal recurrence, have more complications or more nodal basin recurrences following delayed lymphadenectomy.

**EXCESSIVE AND UNNECESSARY SURGERY**

Patients must understand that the SLNB procedure involves excessive and unnecessary surgery for the vast majority, and that SLNB alone carries a risk of immediate and late complications. We know that the incidence of SN-positivity is about 20% and that only 20% of SN-positive patients will have positive non-SNs on completion lymphadenectomy. Of 100 patients undergoing SLNB, at least 80 will be SN-negative and will have had an unnecessary operation. The prevailing opinion among SLNB experts is that all patients with positive SNs should have completion lymphadenectomy, irrespective of the tumor burden\(^12\),\(^13\); therefore, 16 patients will have unnecessary completion lymphadenectomy and only 4 of the original 100 patients will have the exact amount of surgery required. In terms of complications of SLNB alone, 13.8% of patients will have minor complications\(^14\) and 12% will have permanent lymphedema at 6 years.\(^15\) Patients should also understand that although SN status is an important
prognostic factor, it is no guarantee of remaining disease-free. In MSLT-1, approximately 17% of SN-negative patients had recurrence by 5 years and 9.7% had died of metastatic melanoma.

CONCLUSIONS

When considering complex management issues, physicians and patients have the right to expect accurate information from opinion leaders, untainted by personal preference, creative statistical interpretation, or unjustified extrapolation. Patients who consider the SLNB procedure should understand that it is a staging and prognostic tool and nothing more. There is no evidence at present that the procedure offers an advantage in DFS or that any subgroup of patients benefits from a survival advantage. There is also no evidence that delayed lymphadenectomy results in more complications than immediate lymphadenectomy, providing that patients are effectively followed-up after wide excision of their primary tumor by regular clinical examination, preferably with ultrasound surveillance. There has been a reluctance to disclose and discuss the arguments against SLNB in melanoma, and it has even been suggested that “… to deny the patient the opportunity of a successful SLNB may have medicolegal consequences.”

Prognostic false-positivity in the SN in melanoma is potentially the most serious error in the SLNB hypothesis, a suggestion that advocates of the procedure refuse to consider at present. Some tiny deposits of melanoma in the subcapsular sinus of SNs are of no adverse prognostic significance and are destined for dormancy or destruction. Such patients are at risk for being wrongly up-staged with the inevitable consequences described. This risk has been compounded by the 2009 American Joint Committee on Cancer melanoma staging classification, which classifies all micrometastasis in the SN, including solitary tumor cells, as node-positive. Inevitably, this change, which is not evidence-based, will result in more unnecessary completion lymphadenectomies and will not enrich the pool of patients most suitable for studies of adjuvant therapy.

This commentary highlights clinical, biological, and ethical issues relating to the initial treatment of melanoma. The term standard of care has no authenticity in medicine. Physicians and patients should focus on reality rather than presentation.

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The commentary in this issue of SKINmed, “Sentinel Lymph Node Biopsy in Melanoma: The Gulf Between Presentation and Reality,” makes a very valid point: that in evaluating sentinel lymph node biopsies (SLNBs), statistical analyses performed to date have lumped together all positive biopsies, regardless of whether only a few cells (ie, a “micrometastasis”) or larger masses of tumor cells have been detected. Some or all of those biopsies read as positive on the basis of only small tumor volumes may not be prognostically significant, and this may, in turn, lead to unnecessary surgery to remove whole fields of lymph nodes with attendant morbidity.

LIMITATIONS
This may also limit the value of SNLBs as a starter. The author correctly points out that breast surgeons have recommended that small metastases in lymph node biopsies may not be considered significant, and may not recommend additional surgery in some instances.

It may also be self-serving for the physician to recommend SLNB, as well as additional surgery, if the biopsy is positive, even with a micrometastasis. He or she becomes more important, and he or a colleague gets paid for the surgery.

The problem is that no one knows whether such micrometastases in SNLBs of melanomas can or should be ignored. The studies simply have not been performed as of this date. Thus, the physicians recommending further surgery after detecting such metastases may in fact be benefiting the patient, even if they are not without bias in recommending this course of action.

RECOMMENDATIONS
What is needed are additional studies to examine the point raised by the author. Until these are done, it may indeed be proper to advise patients differently who face the prospect of a possible SLNB. They are indeed “frightened and vulnerable,” but with good reason. Thus, a recommendation for more restraint in advising the patient needs to be carefully considered.

It may be appropriate for the patient to be advised differently before giving consent for an SNLB. It may also be advisable for the patient to be advised differently if a micrometastasis is found. The patient should be told objectively of the potential risks and benefits at each step, allowing them to make decisions based on the best evidence available. They may well still opt for the procedure, and then may or may not opt for further surgery if a micrometastasis is found.

One of the major problems with SNLB is that it is still relatively new, and much relevant data have not yet been compiled and analyzed. We need to give patients our best information and advice in the meantime.

CONCLUSIONS
Knowing what I know, I would probably accept SNLB, even though I may well have less faith in it than the physician who recommended it to me. If a metastasis is found it may be larger than a micrometastasis, making the decision for further surgery less challenging. If I were a patient in this situation, even if informed that SNLB has value only as a staging procedure, I might opt for it simply so that I could have better knowledge of my prognosis. This may not only affect my anxiety level, but also influence decisions such as whether to have more children or to hurry up in writing that “great American novel.” We need to give patients the best advice we can and allow them to make such decisions. Most importantly, as much as possible, we need to remove our own self interests from all of this, as the accompanying commentary states very clearly. I know a name for this, it is called “honesty.”

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**DESCRIPTION**

Zyclara has recently been approved by both the US Food and Drug Administration (FDA) and Health Canada as a new topical therapy for multiple actinic keratoses (AKs) of the face and balding scalp. Topical imiquimod 5% cream (Aldara cream, 5%) has been available for many years as a 25 cm² field treatment for AKs. Dosage uses application 2 times per week for periods of 8 to 10 hours for 16 weeks.\(^1\,^2\) The lower concentration of imiquimod in Zyclara allows for a daily-use schedule and application over larger areas than the 5% cream, with a much shorter application period of 6 weeks.

AK lesions appear in areas of sun-damaged skin and have some potential to transform into squamous cell carcinoma, although there are currently no markers to indicate which lesions may become malignant.\(^3\) Treatment of all AKs is therefore prudent in prevention of more serious outcomes. The mode of action of imiquimod is stimulation of immune response to destroy abnormal cells within the field of drug application. The resultant immune response to imiquimod can also reveal subclinical lesions not previously detected in the sun-damaged areas, providing effective early destruction that may help sustain clearance rates post-treatment.\(^3\) Overall, imiquimod cream provides good field destruction of multiple AKs.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Although the mechanism of action of imiquimod has not been studied or conclusively defined in AK, there are many known actions produced by imiquimod that may be involved. Imiquimod is a toll-like receptor-7 agonist and has been shown to induce the release of interferon-α and other cytokines from human monocytes/macrophages and keratinocytes in vitro.\(^3\,^4\) The upregulation of cytokines may enhance apoptosis of neoplastic epidermal cells and upregulation of DNA repair enzymes after UV damage.\(^3\)

It may also increase antigen-presenting cell antigen presentation to T cells, leading to a strong T-helper type I immune response.\(^5\)

**Pharmacokinetics**

Mean peak serum drug concentration for patients with AK (n=17) was approximately 0.323 ng/mL at the end of a 3-week treatment period, using once-daily applications of Zyclara (2 packets, 18.75 mg) to the entire face and/or balding scalp.\(^4\,^5\) Steady state levels were achieved in 2 weeks, and the T_max ranged from 6 to 9 hours.\(^4\)

**Clinical Studies**

Clinical efficacy was studied for both a 2.5% and a 3.75% formulation of imiquimod (Zyclara), compared with placebo (identical excipients to the active formulations). The treatment regimen for all arms was once-daily application for two 2-week cycles, with a 2-week no-treatment interval between cycles.\(^6\) Eligible patients had 5 to 20 visible or palpable AK lesions in an area >25 cm² on either the face or the balding scalp, but not both. Patients applied cream to either the total face or the total balding scalp, but not both, as selected by the investigator. A total of 479 patients were enrolled in the trial (3.75% cream = 160 patients; 2.5% cream = 160 patients; and placebo = 159 patients).

**Efficacy**

Final efficacy was evaluated 8 weeks after the end of treatment.\(^5\) Primary efficacy measured was complete clearance, defined as proportion of patients with zero lesions in the treatment area. Complete clearance was found in 35.6% of patients in the Zyclara group, vs 30.6% in the 2.5% imiquimod group and 6.3% in the placebo group. Both active formulations showed significantly higher complete clearance than placebo (P<.001 for pairwise comparison vs placebo). Considering partial clearance (≥75% reduction in AK lesions compared with baseline), the clearance rates were 59.4% for Zyclara, 48.1% for 2.5% imiquimod, and 22.6% for placebo.
Again, both active treatment groups showed significantly higher partial clearance rates than placebo (P<.001), and Zyclara showed higher partial clearance than the 2.5% imiquimod (P=.047).

**SAFETY/ADVERSE EVENTS**

No unexpected safety issues were found in any group, and vital sign measurement/physical examination did not show any significant safety issues during the trial. The most frequently reported adverse events (AEs) on nonapplication sites with use of 3.75% imiquimod were headache (6.3%), fatigue (4.4%), nausea (3.8%), and pyrexia (3.1%). Treatment-related AEs were reported in 19.4% of the 3.75% cream group (31 of 160), compared with 11.9% in the 2.5% cream group and 2.5% in the placebo group.

One case of severe diarrhea was reported as probably related to use of Zyclara. Local skin reactions (LSRs) were independently collected of other AEs/application site reactions (ASRs) and were reported in almost all patients using Zyclara (Table). Severe erythema was found in 25.2% of Zyclara patients, with severe scabbing/crusting in 13.8%. The other LSR groups had severe grades in approximately 5% to 10% of patients. The mean erythema score increased during the treatment periods but was reduced below baseline level during the follow-up period for both imiquimod groups. ASRs were reported in 10.6% (17 of 160) of the 3.75% cream group, compared with 6.3% in the 2.5% cream group and 1.3% in the placebo group. Pruritus was the most frequently reported ASR in the Zyclara group (4.4%), followed by irritation (3.1%), pain (3.1%), and swelling (1.3%).

Of the 6 patients who discontinued the study due to AEs, 2 were in the Zyclara group. Only 2 AEs leading to discontinuation were considered related to study treatment: 1 Zyclara patient had headache, fatigue, pain, and application site pain, and 1 placebo patient had headache.

Patients receiving Zyclara showed a higher frequency of need for a rest period during treatment, with 10.6% (17 of 160) requiring at least 1 treatment rest period, compared with 6.9% in the 2.5% cream group and 0% in placebo.

In postmarketing surveillance of imiquimod 5% cream, rare reports have been received of either onset or exacerbation of autoimmune conditions (including thyroiditis, multiple sclerosis, spondyloarthropathy, psoriasis, and ulcerative colitis).

A second Zyclara study used a similar design to investigate two 3-week application cycles, with a 3-week no-treatment interval between cycles, vs 2.5% imiquimod cream and placebo. Although the safety profiles were similar between 2-week and 3-week cycles, the increased duration of use did not appear to increase efficacy compared with the 2-week cycle.

Use of imiquimod may reveal the presence of subclinical AKs during therapy. This was noted as a transient increase in AK counts during trial therapy and did not reduce treatment efficacy. This effect has been noted in previous imiquimod studies. The clearance of subclinical lesions may result in sustained lesion clearance and could be an advantage compared with other treatment methods that do not reveal subclinical lesions, reducing the need for future treatment.

Almost half of patients treated with Zyclara (78 of 160) were 65 years and older. No overall differences in safety or effectiveness were detected in these patients vs younger patients, although greater sensitivity of some older individuals cannot be ruled out.

**INDICATION, DOSAGE, AND ADMINISTRATION**

Zyclara is indicated for the topical field (area) treatment of multiple clinically typical, visible, or palpable actinic keratoses, presented at start of therapy or revealed during therapy, of the face or balding scalp in adults. The cream is provided in 250-mg single-dose packets containing 9.4 mg of imiquimod (3.75% w/w). Up to 2 packets are applied once daily before bedtime.
to the affected treatment field for 2 treatment cycles of 2 weeks each, separated by a 2-week no-treatment period. Prior to application, patients should wash the treatment area with mild soap and water and allow the area to dry thoroughly. A thin film of imiquimod should be applied to the entire treatment area and rubbed in until the cream is no longer visible, and hands should be washed after application. Use near eyes, lips, and nostrils should be avoided, and the application site should not be occluded. Zyclara should be left on the skin for approximately 8 hours overnight and then removed by washing the area and hands with mild soap and water.

Most patients will experience some LSRs, which may include erythema, scabbing/crusting, flaking/scaling/dryness, and edema. These LSRs may require an interruption of dosing for several days if the reaction is severe or produces intolerable patient discomfort. Treatment may be continued after consulting with a physician. The dosage period should not be prolonged to make up for missed doses and rest periods.

SAFETY AND PRECAUTIONS

Some patients may experience flu-like signs and symptoms including fatigue, nausea, fever, myalgias, arthralgias, and chills preceding or accompanying LSRs. A patient assessment should be considered, and dosing may need to be interrupted or adjusted.

Patients should minimize or avoid natural or artificial sunlight exposure during treatment, due to concerns of heightened sunburn susceptibility and reports of shortened tumor formation time in an animal photocarcinogenicity study. Protective clothing (eg, hat) should be used during treatment.

Safety in immunosuppressed patients has not been established, and imiquimod should be used with caution in patients with pre-existing autoimmune conditions including thyroiditis, multiple sclerosis, spondyloarthropathy, psoriasis, and ulcerative colitis.

Safety has not been established in pregnant women, and use should be restricted to cases where the potential benefit outweighs the potential risk to the fetus. It is not known whether topical imiquimod is excreted in human breast milk, therefore caution should be used in nursing women.

The maximum treated area tested is approximately 200 cm². Safety and efficacy of application over larger areas has not been established and is not recommended.

DISCUSSION

The new imiquimod formulation provides a lower potency preparation and a less taxing protocol of therapy for the patient (2 weeks on, 2 weeks off, 2 weeks on, and stop). This results in a shorter course of therapy, with no loss of efficacy in eradicating actinic keratoses. This formulation should be a welcome addition to the dermatologist’s armamentarium for the management of actinic damage.

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Sir Isaac Newton’s third law states that for every action there is an equal and opposite reaction.¹ The same may be said of many biological phenomena, except that the reaction is rarely equal and may, in fact, vastly exceed the impetus. Causes include trauma, stasis, and masses, including tumors. Many of the latter, such as desmoplastic basal cell carcinomas and melanomas, induce marked connective tissue reactions. Other such reactive phenomena include vascular reactions, several types of inflammation, and reactions including granulation tissue. In the preceding column in this series we examined ways in which the latter, on the surface, may obfuscate diagnosis of a skin or mucus membrane biopsy.² We now consider how such reactions in deeper tissues may produce similar diagnostic misdirection.

CASE 1

A painless, slightly tender bluish nodule on the upper lip of a 48-year-old human immunodeficiency virus–positive woman was biopsied and read by the referring pathologist as an angiosarcoma, possibly Kaposi sarcoma. Review of slides received in consultation showed a poorly defined nodular lesion composed of numerous dissecting vascular channels lined by a single layer of prominent endothelial cells (Figure 1). Further evaluation revealed overlying lichen simplex chronicus, indicative of chronic trauma or manipulation, and areas in which the lesion was bounded by a thin remnant of a venous wall. The final diagnosis was Masson tumor (Masson pseudotumor; intravascular papillary endothelial hyperplasia).

A Masson tumor is formed when a venous thrombus is invaded by normal reactive endothelial cells attempting to recanalize the lesion. Diagnosis in early lesions is facilitated by the presence of fibrin within the connective tissue. Diagnosis in later lesions is made by identification of the remnant of a venous wall at the border of the lesion, but chronic trauma may cause the thrombus and, therefore, the reactive lesion to extend beyond the vessel wall in places. Thus the lesion is not actually a tumor (neoplasm) and is not papillary, and the terms Masson tumor and intravascular papillary endothelial hyperplasia are not really appropriate.

A Masson tumor may occur anywhere a venous thrombus may arise. It commonly occurs in the hemorrhoidal veins. We have previously reported its occurrence on the vulva.³

CASE 2

A painless, nontender deep nodular lesion on the thigh of a 38-year-old man was biopsied near its edge. Histopathologic examination showed a somewhat storiform spindle cell lesion (Figure 2), which was initially suspected to be a possible dermatofibrosarcoma protuberans. A CD34 immunohistochemical stain, which is characteristically positive in dermatofibrosarcoma protuberans, was reactive in lesional cells (Figure 3), consistent with this diagnosis. This stain also

Figure 1. Case 1: Dissecting endovascular channels (Hematoxylin and eosin stain, magnification ×380).
decorates endothelial cells, however, and immunohistochemical staining with CD31, which stains only the latter, was also positive. Further examination of deeper levels revealed a part of the lesion consistent with a leiomyoma, and this diagnosis was confirmed by immuno-

histrochemical staining for smooth muscle actin within this portion of the lesion (Figure 4). The final diagnosis was leiomyoma with a peripheral vascular reaction.

Although leiomyomas may be tender, many lack this characteristic. Notifying the pathologist that the lesion was biopsied at its periphery may have helped in its evaluation. Cutaneous leiomyomas may arise from multiple sites within the skin and subcutis, including blood vessels and pilar erectus muscles, and may occur anywhere.

**DISCUSSION**

The issue of whether a lesion or tissue reacting to it is biopsied is very much a matter of discussion between the dermatopathologist and the clinician, because, unless an excisional biopsy is performed, the clinician chooses which portion of the lesion to biopsy. In addition to obtaining diagnostic tissue, this decision is influenced by factors such as cosmetic result and other disabilities resulting from the biopsy. If a lesion is biopsied at its edge, or at another special site, this information needs to be communicated to the pathologist.

As the dermatopathology laboratory continues to become more remote from the clinical setting, the lines of communication between clinician and dermatopathologist may become more tenuous. Use of electronic medical records, whatever their other advantages and limitations, may facilitate this process, provided that a complete and accurate record of the biopsy procedure is entered into the patient’s record and this portion of the chart is transmitted to the pathologist.
HISTORICAL DIAGNOSIS & TREATMENT

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

Pediculosis Vestimentorum

Synonyms: Pediculosis vestimenti seu vestimentorum; Phthiriasis capitis; Vagabond's disease; Body-lousiness.

**DIAGNOSIS:** The discovery of a louse or the nits in the seams of the underclothes is sufficient, but even in their absence,—as when the patient has recently changed his clothing,—the distribution of the lesions, the punctiform hemorrhages, parallel excoriations and pigmentation make the diagnosis comparatively easy.

**TREATMENT:** Attention should be directed mainly toward the clothing and bed linen, which are to be immersed in boiling water or subjected to a temperature of 165° or 170° F. in an oven. To destroy any nits that may be present on the body, the latter should be anointed with a 20 per cent ointment of staphisagria, made by adding two drachms of the freshly powdered seed to the ounce of hot lard, which is then to be strained and cooled.
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The 7th Spring Symposium of the European Academy of Dermatology and Venereology (EADV) took place with more than 2000 participants, gathering at the Congress Centre of the Hotel Croatia in Cavtat (antique Epidaurus) near Dubrovnik (antique Ragusa and called “South Pearl of the Adriatic Sea”). The locale is located on the beautiful Croatian coast, which boasts of 1244 islands and peninsula sand overwhelmed with rich and unique vegetation.

BACKGROUND
This 7th EADV Spring Symposium was organized under the high auspice of the president of the Republic of Croatia, Professor Ivo Josipović. Participants came from 78 countries worldwide.

We wanted to achieve harmony in dermatology and venereology, and we succeeded with a successful blend of the scientific program and the social events. The president of EADV, Professor Andreas Katsambas, expressed his sincere thanks to each and every one of the organizers and board members for their support and valuable input for Cavtat (Figure 1). He congratulated them for “their amazing job in organizing such a terrific meeting.” There were positive comments from the many who attended the meeting, giving proof of its success. “Everything was more than perfect” (Figure 2).

In the opening ceremony, the traditional good spirit of Dubrovnik was demonstrated by the folk dance Ensemble Lindo with two performances and by the renaissance Ragusæum Ensemble Plazzarius with three presentations: La Magdalena, Branle, and T roto.

The biggest confirmation for the organizers of the 7th EADV Spring Symposium was the compliment paid that we have done for Croatian dermatology today just as the famous Academician Franjo Kogoj (1894–1983) did in his time.

SCIENTIFIC PROGRAM
The highlights of the Symposium were the opening lectures by Professor Amir Muzur entitled “Milestones in the History of Croatian Dermatology and Venereology” and by Professor Stefan Beissert entitled “Nowdays and Future of Dermatovenereological Research.”

Figure 1. Jasna Lipozenčić (center, left) and Andreas Katsambas (center, right) during the welcome reception with Penny Emmanouil (far left) and Electra Nikolaidau (far right).

Figure 2. From left to right: Bruce Thiers, Stefan Beissert, Angela Robinson, and Steingrimur Davidsson at the opening reception.
Friday, May 14, 2010, had a packed program with:

- Free Communications
- Case Report Sessions
- Scholarship Ceremony
- Continuing Medical Education/Continuing Professional Development
- Media Committee
- Scientific Programming Committee
- Fostering Trainee Committee
- Euromelanoma Meeting
- Fostering Skill Specialists Committee
- Statutes Committee
- Forum Session
- Update on Melanoma Management
- Psoriasis
- Skin Conditions and Endocrinology
- Workshops
  - Syphilis: The Resurgence of an Old Problem
  - Pearls in Dermatological Surgery
  - Novel Drugs and Adverse Reactions in Dermatovenerology
- Plenary Sessions
  - Allergy, Environment, and the Skin
  - Brain-Skin-Axis
  - Immunotherapy for Skin Diseases in the Molecular Era
- Satellite Symposia
  - Azithromycin in Dermatovenerology
  - Optimizing Psoriasis Treatment Outcomes With Adalimumab
  - Dilemmas in Prevention of Superinfections in Dermatology
  - General Topics in Sirolimus
  - New Approach in Sun Protection for Allergy-Prone Skin
  - Topical Retinoids in Treatment of Acne
  - What’s New in Photoprotection in 2010?
  - The Human Papillomavirus (HPV) Vaccine—Impossible Without Dermatology and Venereology
- Focus Sessions
  - Botulinum Toxin: Use and Misuse
  - The Skin and Internal Malignancy
  - Test Yourself in Dermoscopy
- Forum Sessions
  - Practical Considerations in Cutaneous Lymphomas
  - Hair and Nail Diseases
- Symposia
  - Acne and Rosacea
  - Bullous Diseases Revisited
  - Skin Diseases in the Mediterranean
- Workshops
  - Approaches to Wound Healing and Leg Vein Treatment
  - Management of Chronic Urticaria
  - Vitiligo and Pigmentary Disorders

On Saturday, May 15, 2010, the program was just as exciting:

- Free Communications
- Poster Forum (awards given to presenters from Denmark, Iran, and Moldavia)
- Case Report Sessions
- President’s Symposium
  - Metabolic Comorbidities and Psoriasis
  - Cumulative Experience From the Sexually Transmitted Disease Clinic
  - Melanocytes and Melanogenesis: News to Tell
- Symposia
  - Skin Clues of Systemic and Connective Tissue Diseases
  - Photodermatology
  - Atopic Dermatitis
  - Nonsurgical Treatment of Non-Melanoma Skin Cancer
  - Human Immunodeficiency Virus Infection in Dermatology
  - Dermatomycoses
- Workshops
  - Laser Therapy
  - Sexually Transmitted Infections (STIs)
  - Pediatric Dermatology
  - Psyche and the Skin
  - Facial Rejuvenation
  - HPV in Dermatovenerology
- Plenary Sessions
  - Novel Imaging Techniques for Diagnosis of Skin Disorders
  - Exogenous Acne Revisited
  - STIs: Progress, Challenges, and Opportunities
- Focus Sessions
• Managing Adult-Onset Acne
• STIs and Adolescence
• Office-Based Cryotherapy
• Practical Consideration in Treating Cutaneous Lupus Erythematosus

• Forum Sessions
  • Biologicals in Psoriasis: When and Which to Use?
  • Dermatoses in the Genital Area

Closing Ceremony

• What’s New Sessions
  • What’s New in Clinical Dermatology
  • What’s New in Venereology
  • What’s New in Pediatric Dermatology

CONCLUSIONS

As one participant remarked: “It was a wonderful meeting! Perfectly organized, good science, nice atmosphere. I not only enjoyed the EADV Spring Symposium but I also found the organization to be perfect” (Figure 3).
Cutaneous piloleiomyomata (CPL) are benign smooth muscle tumors most commonly presenting as multiple, grouped, red to dark brown, firm, dermal papules and nodules, typically no larger than 1.5 cm. An unusual and suggestive clinical finding is sharp, shooting pain, resulting from cold contact, emotional stress, or physical trauma. CPL tends to occur in the second and third decades without sex predilection. Common lesion locations include the extensor surfaces of the extremities, trunk, and face. Linear or segmental distribution is rare. Some authors have described the segmental pattern as zosteriform leiomyomatosis but, as stated by some experts, the term segmental is preferred since the lesions do not follow a true dermatomal distribution. The pathophysiology of segmental cutaneous leiomyomatosis (SCL) is unknown but may represent an autosomal dominant genetic mosaicism. SCL has since been divided into two distinct segmental patterns, type 1 and 2, based on a loss of wild-type allele(s) following a mutational event. Type 1 SCL manifests as purely segmental lesions reflecting heterozygosity for the underlying mutation. In type 2 SCL, a postzygotic mutation in a heterozygous embryo results in a loss of heterozygosity, leading to a segmental pattern superimposed on disseminated areas of involvement. Our patient, with only segmental lesions, would best fit type 1 SCL. The etiology of the pain associated with CPL is unclear but thought to be either the result of smooth muscle contraction, an increased number of nerve bundles, or pressure on surrounding cutaneous nerves.

Treatment depends on the severity of symptoms and extent of skin involvement. Surgical excision is possible in patients with limited skin involvement. Recurrence is common, however, particularly in patients with multiple lesions. If extensive involvement is present,
medications including nifedipine, nitroglycerin, and phenoxybenzamine have been used with limited success.7

This rare neoplasm is likely clinically underrecognized,7 particularly when presenting in a segmental distribution. Increased awareness of this unusual presentation is important due to the associated risks of uterine fibroids and aggressive renal malignancies in these patients and their offspring if germline mosaicism is present.

REFERENCES


Figure 2. Photomicrograph showing abundant spindle-shaped smooth muscle cells (hematoxylin and eosin original magnification [A] ×4 and [B] ×40).
CASE STUDY

Vulvoperineal Crohn's Disease: Response to Metronidazole

Aida Khaled, MD;1 Nadia Ezzine-Sebai, MD;1 Becima Fazaa, MD;1 Faten Zeglaoui, MD;1 Rachida Zermani, MD;2 Mohamed Ridha Kamoun, MD1

A 46-year-old woman with a medical history of chronic juvenile arthritis with bilateral prosthetic hips presented with vulvoperineal ulcerations of 3 years’ duration. There was no diarrhea or recent weight loss. Cutaneous examination showed asymmetrical vulvar edema of the labia minora and labia majora with deep and linear ulcerations having verrucous borders located on the inguinocural regions and the buttocks fold (Figure 1). On physical examination there was bilateral limited mobilization of the hips. A biopsy specimen was taken from the border of the vulvar ulceration and histologic examination showed under a hyperplasic epidermis an epithelioid granuloma with multinucleated giant cells of the dermis without caseification. Laboratory analyses and results from chest x-ray were normal. Results for Koch bacilla in the spittle, microbiologic studies (staining for microorganisms and cultures), and tuberculin intraderm reaction were negative. There was no Crohn's disease aspect on colonoscopy, and there was normal small bowel enterography. Systematic intestinal biopsies were also with normal aspect. Based on the clinical data and granulomatous histologic characteristics, the diagnosis of metastatic Crohn's disease without digestive involvement was obtained. The patient was started on metronidazole 1 g/d. After 6 months of treatment, there was an almost-complete healing of ulcerations (Figure 2). Treatment was well-tolerated.

Vulvoperineal involvement in Crohn's disease is rare and may constitute the sole manifestation of the disease since it may precede bowel symptoms by several months to years in 20% of cases. In this localization, treatment of Crohn's disease is difficult and not standardized.1 We report a case of vulvoperineal Crohn's disease that responded to metronidazole in a 46-year-old woman.

Our patient had cutaneous Crohn's disease without digestive involvement. Diagnosis may not be obvious if vulvoperineal involvement precedes active bowel disease. Abscesses, draining sinuses, edema, and sharply demarcated ulceration of the perineum and/or vulva with usually verrucous borders (as demonstrated by our case) are the characteristic manifestations of the disease. They are caused by direct extension from the involved bowel or by granulomas separated from the bowel by normal tissue. The latter form is usually named metastatic Crohn's disease. In the absence of digestive involvement, the diagnosis is based on clinical and histologic aspects and on the absence of other clinical and paraclinical signs of a specific infection. Because of the scarcity of this topographic form of Crohn's disease, and in the absence of randomized essay, treatment remains not standardized.1 Multiple treatments have been tried. They include corticosteroids, which can be injected either topically or locally or administered orally. They are often efficient with a frequent corticodependence and multiple side effects.
especially for oral steroids. Sulfasalazine may lead to a partial healing of cutaneous lesions but is more efficient in digestive forms. Immunosuppressive agents such as azathioprine, methotrexate, and cyclosporine are also efficient, but a long-term treatment may expose the patient to severe side effects. Immunosuppressive treatments should be indicated for digestive involvement and may be an ultimate option in resistant forms of vulvoperineal Crohn’s disease. Thalidomide also leads to a satisfactory result in refractory vulvar ulcerations associated with Crohn’s disease. Recently, investigators stated that infliximab is a good therapeutic option for recalcitrant vulvar Crohn’s disease, but no optimum regimen was provided. Only a few small studies have evaluated metronidazole for the treatment of Crohn’s disease with low convincing results. A better activity has been demonstrated in colonic disease and for perianal fistulas. Metronidazole seems to be a good therapeutic option since it has led to complete healing of perineal lesions with a persistent result in our patient and in several uncontrolled reports. Its efficiency is due to antibacterial, antiinflammatory, and immunosuppressive action. As demonstrated by researchers, the efficacy of metronidazole is dependent on the dose and duration of the treatment. According to the largest follow-up study, the optimal dose is 20 mg/kg/d and the duration is at least 12 months, with a maximum duration of 36 months. The most commonly reported side effects are digestive and hematologic, but also reversible sensory peripheral neuropathy.

REFERENCES


Figure 2. Almost-complete healing of the ulcerations after 6 months of metronidazole treatment.
SA is a chronic inflammatory scarring disease, described clinically by Hallopeau in 1887 and histologically by Darier in 1892. The etiology of the disease still remains unknown. While it can be seen in all age groups, LSA affects women more commonly than men, with a bimodal peak of incidence: the first occurs between 8 and 13 years of age and the second between the fifth and sixth decade, both in women with physiologically low estrogen states.

LSA has a predilection for the anogenital region, seen in approximately 85% of cases. While 15% to 20% of those have extragenital lesions,1 the folliculocentric distribution of the lesions in our patient is unique and the generalized distribution itself is uncommonly reported and thus less well understood. We report a case of extragenital LSA that had a folliculocentric and generalized clinical presentation in a patient with antinuclear antibodies.

DISCUSSION

Extragenital LSA without accompanying genital involvement is uncommon and has been reported in 2.5% to 15% of patients.2,3 Extragenital LSA is histologically identical to the more common genital presentation of LSA and is characterized by homogenization of papillary dermal collagen, extensive edema, a band-like lymphocytic infiltrate, and thinning of the overlying epidermis. Clinically, this results in atrophic or sclerotic ivory white papules, which often coalesce into large plaques that, aside from dryness and itching, are generally asymptomatic.

The lesions typically occur on the trunk and proximal extremities, often favoring the neck, shoulders, and wrists, although the tongue and oral mucosa may also be involved.1,2 Occasionally, microguttate lesions have been reported. Early on, the white sclerotic or atrophic papules are found between hair follicles and then often coalesce into larger plaques. This case is unusual given its folliculocentric clinical appearance and generalized distribution.

The cause of LSA remains undetermined but it is believed to be multifactorial, with genetic, hormonal, and infectious influences, including Borrelia burgdorferi infection.4,5 Patients of both sexes with LSA have a high incidence of systemic autoimmune disease, most commonly autoimmune gastritis and Hashimoto’s thyroiditis.6–10 An exuberant immunologic reaction to an as-yet unidentified antigen has been proposed to be responsible for the characteristic disease manifestations. Supportive evidence for this hypothesis includes the occurrence of a lymphocytic vasculitis and a T-lymphocyte–dominant inflammatory infiltrate with monoclonally rearranged γ-chain gene of the T-cell receptor detected in skin lesions of lichen sclerosus and occasionally in blood.11–14
A 1981 study of 50 women with histologically confirmed LSA showed that 37 (74%) had tissue autoantibodies and 17 (34%) had at least 1 autoimmune disease. A second study in 1988 confirmed this finding, as 147 of 350 (42%) women with LSA had tissue autoantibodies, 74 (21.1%) had ≥1 first-degree relatives with an autoimmune disease, and 75 (21.4%) had ≥1 autoimmune diseases (by history). No identifiable difference in clinical features was found among women who developed autoimmune related phenomena, nor was it clear whether screening for such diseases was justifiable, as only a small percentage developed autoimmune diseases after the diagnosis of LSA.

First-line treatment for LSA includes ultrapotent topical steroids and intralesional triamcinolone injections. Alternative therapies that have been reported include photodynamic therapy with aminolevulinic acid (effective in relieving pruritus) in one study and phototherapy for extragenital LSA, with a marked reduction or clearing after treatment with 40 sessions of UV-A at 20 J/cm² in 10 patients with extragenital lichen sclerosus without adverse effects. There are other recent case reports of successful therapy using thrice-weekly narrowband UV-B. It is believed that both UV-A and narrowband UV-B work by increasing matrix-metalloproteinase levels.

Vitamin D and vitamin A derivatives have also been reported in the treatment of LSA. One study demonstrated a marked reduction in the number of hypertrophic plaques in a patient within 3 weeks of beginning treatment with calcipotriol 0.005% ointment applied twice daily under occlusion. Systemic vitamin A has shown some success with both oral and parenteral administration. This is thought to work by inhibiting transforming growth factor β, which decreases collagen synthesis by fibroblasts.

Topical testosterone or progesterone is no longer recommended given the conflicting data and possible adverse effects. Likewise, earlier studies showed no benefit of using penicillin, other antibiotics, or penicillamine. Additional treatment options reported to be effective include adrenocorticotropic hormone, hydroxychloroquine, sulfasalazine, oral calcitriol, and topical retinoids. Surgery is typically reserved for symptomatic patients who have failed multiple medical modalities. Recent research has focused on the use of topical tacrolimus for LSA, with one successful report of treating extragenital LSA with 0.1% tacrolimus ointment and psoralen plus UV-A.

We find this presentation to be of interest due to the unique folliculocentric and generalized clinical presentation. A diagnosis of LSA should be considered in the differential of perifollicular hypopigmentation.
REFERENCES


HYPERTRICHOSIS

Medications reported to cause excessive hair growth

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Adapted from Litt, JZ. Curious, Odd, Rare, and Abnormal Reactions to Medications. Fort Lee, NJ: Barricade Books; 2009:162.
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Loose anagen syndrome (LAS) is a hair disorder that is primarily diagnosed in childhood. The most frequent complaint on presentation is poor hair growth and thin hair, although other symptoms include unruly lusterless hair. In most cases, patients tend to be blonde, although a few dark-haired patients have been described. Three different patterns of LAS have been reported, all of which show loose anagen hair (LAH) phenotype on hair pull test. Patients with type A phenotype have sparse

A healthy 5-year-old Caucasian girl presented to the pediatric dermatology clinic for poor hair growth. The patient's father described slow hair growth and finely textured hair since birth. The patient had her first haircut 1 month before presentation. The family denied bald areas on the scalp, significant hair shedding, and sores on the scalp. The child did not scratch at her scalp or pull her hair. She ate a normal diet and had normal growth and development otherwise. She was not taking any medications or over-the-counter supplements. There was no family history of hair disorders. On physical examination, the patient had short, fine, reddish blond hair that was of different lengths (Figure 1). There were no papules, pustules, scale, or crust on her scalp. Lymphadenopathy was absent. She had normal eyelashes and eyebrows. There were no lesions on her oral mucosa. No tooth or nail abnormalities were present. The rest of the physical examination was normal. The hair pull test resulted in 4 easily pulled hairs (3 anagen and 1 telogen). A hair mount was performed (Figure 2). The hair mount analysis revealed anagen hairs with distorted bulbs and ruffled cuticles extending a short distance distally from the bulb, consistent with loose anagen hair (Figure 2). All of the anagen hairs on the pull test demonstrated the above findings. Based on the patient's clinical presentation and the findings seen on light microscopy of the hair mount preparation, the patient was diagnosed with loose anagen syndrome.

**Figure 1.** Reddish brown fine hair of variable lengths was appreciated on the scalp.
Hair with poor growth; patients with type B phenotype present with sparse, dull, and unruly hair; and patients with type C phenotype present with increased hair shedding.³

The pathogenesis of LAS remains largely unclear. One study has found a mutation in a hair keratin K6hf, present in the companion cell layer of the outer root sheath, detected in 3 of 9 families with LAS.⁴ It is unclear, however, whether other keratins or adhesion molecules in the inner root sheath may also be responsible for this hair disorder. In addition, it remains to be seen whether genetic differences account for the various subtypes of LAS.

Diagnosis of LAS is based on the combination of characteristic clinical findings as well as the presence of microscopically defined LAH on hair pull test.¹ On light microscopy, LAH hairs show misshapen hair bulbs, absence of root sheaths, and the characteristically ruffled cuticle.¹²⁵,⁶ It is thought that anywhere from 70% to 100% of hairs in patients with LAS demonstrate LAH features.³ It should be noted, however, that up to 10% of cases of LAH have been reported in normal individuals, although it is unclear whether these individuals may have a milder expression of LAS. A biopsy is usually nondiagnostic for this condition, although one characteristic feature is premature keratinization of the Henle and Huxley layers of the inner root sheath.¹⁵

The clinical severity of LAS tends to improve with age, with some cases leading to complete resolution.¹² Generally, aggressive treatment is not warranted, and gentle hair care is recommended for these patients.

REFERENCES

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**INDICATIONS AND USAGE**

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

**WARNINGS AND PRECAUTIONS**

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

Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infections develop. Discontinue use if irritation develops.

**ADVERSE REACTIONS**

The most common adverse reactions (>1%) are HPA axis suppression and application site reactions. The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria, and telangiectasia.

**USE IN SPECIFIC POPULATIONS**

Pregnancy

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

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

Nursing Mothers

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

Pediatric Use

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

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

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (two times daily) for which Locoid Lipocream is indicated. Five of the 82 evaluable subjects (6.1%) demonstrated laboratory evidence of suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Suppressed subjects ranged in age from 3 months to 16 years and, at the time of enrollment, had 25% to 95% HPA involvement. These subjects did not develop any other signs or symptoms of HPA axis suppression. At the first follow up visit, approximately one month after the conclusion of treatment, cosyntropin stimulation results of all subjects had returned to normal, with the exception of one subject. This last subject recovered adrenal function by the second post treatment visit, 65 days post-treatment.

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

**Geriatric Use**

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

**PATIENT COUNSELING INFORMATION**

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

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

Rub in gently. Avoid contact with the eyes. Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician. Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may constitute occlusive dressings. Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician. If no improvement is seen within 2 weeks, contact your physician. Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.

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

**BRIEF SUMMARY**

**For Topical Use Only**

**Locoid Lipocream® Cream, 0.1% Rx Only**

**ADVERSE REACTIONS**

The most common adverse reactions (>1%) are HPA axis suppression and application site reactions. The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.
Now younger eczema patients have something to smile about

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

Locoid Lipocream®
(hydrocortisone butyrate 0.1%) Cream

The power of an ointment with the elegance of a cream

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

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

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

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