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Head lice infestation remains a major problem in the 21st century, with an estimated 6 to 12 million people affected annually in the United States alone. Despite aggressive attempts to eliminate this parasite, including education and even the questionable “no-nit” policy in schools, pediculosis capitis remains a common presentation not only in dermatology clinics but also in family practices and emergency units.

INCIDENCE

Head lice (caused by the arthropod Pediculus humanus var. capitis) is a significant worldwide problem, having the dubious distinction of being the most prevalent global parasite. It is difficult to assess worldwide prevalence, as there are insufficient data; however, these villains could afflict at least a few billion people globally, with children younger than 12 being the most commonly afflicted. Figures for some individual countries do exist, however, with the United States experiencing a staggering 6 to 12 million new cases each year. In the United Kingdom, more than 50% of 7- and 8-year-olds are affected, with a yearly incidence of 37% and a 2% prevalence. In Germany, around 1 in 6 children (1500 of 10,000) are known to be infested at any one time.

While pediculosis corporis is predominately prevalent in countries with cold climates, pediculosis capitis is global. Tropical countries are not spared, but there are higher recordings of head louse infestations during the colder months.

CONTRIBUTING FACTORS

In the mid-20th century, head lice were mainly observed in the lower socioeconomic classes. This was attributed to the usual culprits: poverty, poor hygiene, lack of access to health care facilities, and overcrowding. A Jordanian study in 2000 confirmed the notion of a higher prevalence in the lowest socioeconomic class. It also revealed an increased incidence in higher socioeconomic classes, but here the source was linked to housemaids and all of the families were promptly treated. In poorer families, parents, due to the social stigmata of head lice infestations, tended not to seek treatment, which may have resulted in the higher infestation rates.

Worldwide pediculosis capitis is now found in all social classes. The principal mode of transmission is head-to-head contact for a minimum of 1 minute. Head lice infestations have the highest prevalence in young children (preschool to primary school age), which may be related to the activities performed by this age group, with the most amount of head-to-head contact, eg, the games “tag, you’re it” and round and round the mulberry bush:

Round and round the mulberry bush
The monkey chased the weasel
The monkey stopped to pull up its socks
And pop goes the weasel

The above verse, whereby children dance around in a group and then attempt to tag one another, exemplifies how head lice are transmitted.

The incidence in girls is around twice as high as that in boys. This has been attributed to the idea that girls play activities such as the plaiting of their friends’ hair and sharing hats or headcarves. Another method now documented is the changing of sweatshirts in school gym classes. In younger children, the incidence between girls and boys is similar, perhaps due to the nature of the hair at this age (fine and short), thus making visual diagnosis easier.

In the United States, African American children are rarely found with head lice. This has been attributed to the idea that girls play activities such as the plaiting of their friends’ hair and sharing hats or headcarves. Another method now documented is the changing of sweatshirts in school gym classes. In younger children, the incidence between girls and boys is similar, perhaps due to the nature of the hair at this age (fine and short), thus making visual diagnosis easier.

In the United States, African American children are rarely found with head lice. Theories include differences in the morphology of the hair. It is proposed that clinging to the hair shaft is more challenging for the louse on African American scalps. The racial
differences observed in the United States are inconsistent with findings in other countries. In Brazil, there is no difference in prevalence between the ethnic groups, and in Africa infestation rates are rife, perhaps due to modification of the louse.11

ENTOMOLOGY

*P. capitis*, averaging 1 mm to 4 mm, is confined to hair on the scalp, eyebrows, and eyelashes, where it is attached by a chitinous substance (Figure 1). To survive, the 6-legged parasite must feed on its host's blood multiple times daily, using its pincer-mouthparts to pierce the skin and secrete saliva, which contain anticoagulation and vasodilating substances, enabling it to feed successfully. When not feeding, the head louse will scurry at a rate of 23 cm a minute and cling to the hair shaft. If the head louse is unable to feed successfully, it will only survive for up to 3 days and nits (eggs) (Figure 2) survive around 10 days.12

CLINICAL FEATURES

Pruritus is the classical symptom of head lice, typically affecting the occipital and post-auricular regions (Figure 3 and Figure 4). A significant proportion of patients are asymptomatic for up to 4 to 8 weeks after initial infestation due to the delayed hypersensitivity reaction from the saliva passed along the hypopharynx.13 As the head louse can produce up to 300 eggs within 10 days, there can be a heavily infested population, even before a physician is consulted. The date on which the eggs hatch can be calculated, as hair grows at approximately 0.4 mm/d.13 Most nits are visualized 1 mm to 2 mm from the scalp. *P. pubis*, in addition to pubic hair, can be visualized on eyelashes and eyebrows but is less likely to be detected on the scalp due to the high density of scalp hair.2

Interestingly, pediculosis capitis and corporis are similar and can mate, whereas *P. pubis* cannot. It is postulated this is due to the likelihood of conspecificity between *P. capitis* and *corporis*, with both parasites sharing the same haplotypes. This has led to discussion about whether the head and body louse are indeed

Figure 1. Adult head louse showing the carb-like claw that grasps the hair. With permission from Warren Rosenberg, photographer, 123rf.com, Houston, Texas.

Figure 2. The nit of the head louse.
separate species. Of note, patients infested with *Pthirus* may become sensitive to *Pediculus*. Complications, especially from inadequate treatment, include infection, malaise, and anemia and can result in children underperforming; hence, the derogatory term “nit-wit.”

TREATMENT

Before commencing treatment, a correct diagnosis should be established to ensure complete eradication of the cooties. Dermatoscopy or fine-tooth combing to remove the louse for direct microscopy can aid diagnosis confirmation. Identification of nits is not a prerequisite for treatment. Health care workers should be wary of finding eggs months after therapy, due to the length of time it takes for nits to move along the hair shaft towards the surface.

Treatment for pediculosis capitis should be commenced only in patients with an active infestation. Management is two-fold: medication/fine-tooth combing and prophylaxis. Medication varies between countries but can be subdivided into topical and oral therapies. Topical treatments may include permethrin 1% (currently first choice) and/or a combination of pyrethrin and piperonyl butoxide (both available over-the-counter), as well as lindane 1%, malathion 0.5%, benzyl alcohol 5%, and spinosad 0.9%, which was approved by the Food and Drug Administration (FDA) in January 2011.

Other topical agents, not currently approved by the FDA include crotamiton 10%, permethrin 5%, and newer therapies such as cetaphil and dimeticone 4%. Cetaphil is postulated to work by suffocation, as it blocks the louse’s spiracles and dimeticone 4% by interfering with the insects’ water regulation. Resultz, licensed in Canada, is another therapy used to treat head lice by eroding the louse’s exoskeleton with consequent dehydration and death.

Oral therapies include the anti-helminthic drug ivermectin, gaining momentum for both oral and topical application, the later was given FDA approval in February 2012. Cotrimoxazole, which is postulated to work by direct toxicity or by causing vitamin B deficiency through killing the symbiotic gut bacteria, is currently not licensed, nor is its combination with permethrin 1%.

To diminish resistance development, patients and their caregivers should be counseled on the appropriate treatment regimen. Inadequate treatment in the past has been the likely cause of the development of resistance. Similarly, prophylactic use of pediculicides for family or close friends is not recommended, but contacts should be examined and treatment commenced if necessary.
Combing the hair regularly, using a fine-tooth comb, with subsequent inspection, to detect dead nits from live ones (grey and white, respectively) has proved a useful alternative to the forenamed medications and has none of the associated side effects sometimes seen with medication use.

All material that has had head contact, eg, pillows, headscarves, should be washed at 130°F for 30 minutes or tightly contained in a plastic bag for 2 weeks. Other fomites, such as headphones or combs should also be cleansed with isopropyl alcohol. Opinion is divided on whether floors at home or in schools should be cleaned, with a recent Australian study showing no benefit after vacuuming a known infested room.

Prophylaxis, by educating parents, teachers, school nurses, and assistants at daycare facilities is essential.

**CONCLUSIONS**

Head lice and their escapades remain a concern, being nondiscriminatory and affecting everyone from all ages, classes, ethnicities, nationalities, and sexes. It is a worldwide problem costing some countries millions of dollars. Pediculosis capitis infestations are not pleasant clinically, due to the itching and secondary pyoderma and, in part, to the hysteria produced by the thought of the infestations. Head lice, unlike body louse, have never been implicated in causing disease. As unpleasant as the head louse is, it, like other arthropods, has been around for longer than homosapiens and will likely be here forever.

**REFERENCES**

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Wrinkling of the palms is a physiological response to prolonged water immersion occurring on average 11.5 minutes after exposure to water.\(^1,2\) Aquagenic wrinkling of the palms (AWP) is excessive and early palmar wrinkling that occurs within a few minutes of exposure. It may be associated with discomfort and functional impairment and leave the palms with whitish papules and a macerated appearance.\(^3,4\)

Several names have been given to the presentation including transient reactive and acquired papulotranslucent acrokeratoderma, aquagenic palmoplantar keratoderma, and aquagenic syringal acrokeratoderma.\(^5–8\)

**ETIOLOGY AND PATHOGENESIS**

AWP is associated with cystic fibrosis (CF) and the CF carrier state\(^1,3,4\) palmar hyperhidrosis,\(^2,5\) marasmus,\(^9\) Raynaud phenomenon,\(^2,10\) atopy,\(^7\) and use of rofecoxib\(^10\) and aspirin.\(^7\) In non-CF patients, AWP has been mainly reported in adolescent girls.\(^3\)

The etiology is unknown. An abnormality of sweat ducts, hyperkeratosis, hyperkeratosis secondary to friction, and an abnormality of the barrier effect of the stratum corneum have been suggested as potential causes.\(^7,11\) Increased epidermal sodium concentrations have been implicated in patients with CF taking rofecoxib and aspirin.\(^9,10\)

Experimentally, it has been shown in physiologic aquagenic wrinkling that increasing the tonicity of the water in which the hands are immersed causes an increased time to wrinkling.\(^2\) This implies that passive movement of water into the skin is important in initiating palmar wrinkling. An intact sympathetic nerve supply to the palms is required for physiologic aquagenic wrinkling to occur.\(^2,12\) Possibly, a critical volume of water must accumulate in the palmar skin to initiate wrinkling via a pathway that stimulates sympathetic nerve fibers.\(^3\)

Between 44% to 80% of CF patients and up to 25% of CF carriers have AWP.\(^1,13\) In CF, loss of functional CF transmembrane conductance regulator (CFTR) results in reduced electrolyte reabsorption in the eccrine ducts and, thus, hypertonic sweat.\(^14\) This hypertonicity may lead to an increased rate of diffusion of water into the palmar skin and hence AWP. Alternatively, CFTR abnormalities may affect flux of water into the skin via a different mechanism. CFTR has been shown to activate aquaporins, and aberrant aquaporin 5 expression has been demonstrated in the sweat glands in AWP.\(^15,16\)

**CLINICAL FEATURES**

**HISTORY**

Patients presenting to a dermatologist with AWP describe paraesthesia followed by thickening and wrinkling of the palms shortly after immersion in water. Hand movements may be painful, with discomfort and wrinkling persisting from minutes to hours. Warm weather, hyperhidrosis, and occlusion exacerbate the wrinkling. AWP may fluctuate with exacerbations and periods of complete resolution. Patients with AWP subsequently diagnosed with CFTR mutations do not necessarily have a history of chronic respiratory disease or gastrointestinal complaints.\(^1,14\) AWP has been the presenting complaint in atypical CF\(^17\) and CF carriers.\(^4\)

In patients already known to have CF, AWP is often present with no associated discomfort or functional impairment. The majority of these patients are aware of, but not affected by, the early and excessive aquagenic wrinkling.

**EXAMINATION**

On examination, the dry palms may be normal or may show mild hyperlinearity with subtle central nonscaling and whitish to translucent papules, 2 to 3 mm in diameter (Figure 1). There may be areas of keratolysis in the web spaces and on the nail folds.\(^4\) After approximately 2 minutes of submersion, the palms, web spaces, and lateral aspects of the fingers become thickened with exaggerated wrinkling (Figure 2). The whitish papules become more prominent and new papules may appear. The papules may peel, leaving scattered superficial erosions, particularly in the web spaces and nail folds. Patients may present with their hands immersed, the “hand in the bucket sign,” keen to demonstrate their AWP.\(^3\)
The diagnosis is easily made on history and clinical examination. Histology may be normal or may show dilated eccrine ostia and hyperkeratosis. Screening tests for CF include sweat chloride testing and CFTR mutation analysis. These are performed after genetic counseling and consultation with a respiratory physician.

Management
Management of AWP has included twice-daily applications of aluminium chloride hexahydrate 20% in anhydrous ethyl alcohol and Botulinum toxin injection with some success. Ionophoresis, 12% ammonium lactate cream and mometasone furoate have also been tried.

Because patients presenting with AWP, including apparently healthy patients, have an increased risk of having CF or the CF carrier state and because patients with mild forms of CF may develop late-onset or slowly progressive lung disease, identifying these patients and respiratory referral and interventions are important to minimize future morbidity.

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When faced with a patient from the tropics who has lymphedema, most clinicians’ first thoughts will be of lymphatic filariasis (LF), a parasitic infection spread by mosquitoes that affects 120 million people worldwide. Dermatologists and family doctors in the United States, however, are recognizing another important cause of lymphedema in patients arriving from the tropics: podoconiosis or endemic nonfilarial elephantiasis (Figure 1).

**BACKGROUND**

The story of the gradual identification of podoconiosis from LF is fascinating and has been described in detail by Ernest W. Price, the “father of podoconiosis.” A form of elephantiasis distinct from LF was first clearly identified in 1938, when on the basis of repeated negative test results for bacteria and microfilaria among Guatemalan patients, Robles inferred that the disease (which he called pseudo-lepra) was associated with walking barefoot. The location of the next set of investigations into nonfilarial elephantiasis was western Ethiopia, where in the 1960s, Oomen described a type of elephantiasis caused neither by onchocerciasis nor filariasis. He noted that most cases were found at an altitude between 1000 m and 2000 m, but was unable to fully resolve questions about etiology. Through the 1980s, Price pursued research across several disciplines to establish the association of this nonfilarial elephantiasis with certain types of volcanic soil. He also demonstrated the predominance of very small particles in soils of endemic areas, the presence of mineral particles in patients’ lymph nodes, and the irritant effect on lower limb lymphatics of silicate suspension in animal models. Price did not stop at etiology, and described the clinical signs and natural history of the disease he had by this stage named podoconiosis. Although most of Price’s research was done in Ethiopia, he traveled across tropical Africa to produce a map of podoconiosis occurrence still apparently valid today. Price’s work forms the backdrop to current research and intervention in Ethiopia, the country most heavily affected with podoconiosis.

**DIAGNOSIS**

For the clinician aiming to make a diagnosis of podoconiosis, much rests on history. The condition develops in people exposed over many years (typically at least 9 years) to irritant red clay soils, typically unable to afford shoes. These soils are found in highland tropical areas where previous volcanic deposits weather at high altitude (over 1000 m) under conditions of heavy rainfall (over 1000 mm/y). Podoconiosis is therefore associated with high elevation, and LF with lower altitudes at which transmission of the parasite by mosquitoes can occur. Countries with a high rate of podoconiosis, and from which patients may have originated include Ethiopia, Uganda, DR Congo, Rwanda, and Cameroon. Further distinction between podoconiosis and LF can be achieved through the patient’s account of early symptoms. In podoconiosis, symptoms (aching and burning) are almost always reported from the foot first, and the swelling progresses from the foot slowly up the lower leg, only rarely reaching above the knee. This is in contrast to patients’ reports in LF, where symptoms frequently originate in the groin, and swelling may be noticed anywhere in the leg, often above the knee. Examination of midnight blood for microfilaria or use of a rapid antigen test will help exclude LF if there is doubt.

**TREATMENT**

Treatment of podoconiosis includes measures to avoid contact with irritant soil (chiefly use of shoes, which may no longer be an issue for the patient who has moved to the United States) and a simple lymphedema treatment regimen. Daily foot washing, use of a simple emollient, and bandaging can result in dramatic improvements in leg volume and skin function (Figure 2 and Figure 3).
CONCLUSIONS

Recognition of podoconiosis as such, and not LF, will spare patients unnecessary drug therapy. Explaining the nature and cause of podoconiosis to the patient may enable him or her to relay this information back to their home setting, where many misconceptions may surround the condition. As a preventable and treatable cause of lymphedema in the tropics, podoconiosis deserves wider recognition.

REFERENCES

Herpes simplex virus (HSV) is one of the most common viral agents, affecting patients of all ages. It is classified as HSV type 1 (HSV-1) and HSV type 2 (HSV-2), being characteristically responsible for oral and genital herpes, respectively. Acyclovir (ACV) is the drug of choice for prevention and treatment of HSV infection either by oral or intravenous route. ACV-resistant HSV strains have been identified since 1982 and is more commonly detected in immunocompromised patients such as transplant recipients and patients with AIDS and rarely in immunocompetent patients. Before the use of ACV prophylaxis, HSV was isolated from 75% to 90% of bone marrow transplant patients. The prophylactic use of ACV in this group of patients resulted in a decreased incidence of HSV excretion. The routine use of HSV susceptibility testing is fundamental in the clinical suspicion of resistance not only for the knowledge of the incidence of HSV resistance in Brazil, but also to understand the mechanism of HSV resistance.

**OBJECTIVES**

The goal of this study was to demonstrate the presence of an HSV-resistant strain in Brazil, entailed by the growing number of transplanted patients and those with the human immunodeficiency virus and an absence of reports on HSV resistance to ACV.

**STUDY DESIGN**

**Clinical Isolates and Patients**

A total of 83 clinical samples from oral mucositis or from HSV-like skin lesions were obtained from 47 hematopoietic stem cell transplant (HSCT) recipients and 36 nontransplanted immunocompetent patients at the Clementino Fraga Filho Hospital of the Federal University of Rio de Janeiro. Patients were eligible to participate in the study if they signed an informed consent.
form. All swabs were transported to the laboratory in a transport media (1 mL of MEM-Eagle with 400UI penicillin, 30 μg/mL of gentamicin and 5 μg/mL of amphotericin B) and stored at –80°C until inoculation.

**HSV ISOLATION IN CELL CULTURE**

For the HSV isolation, VERO cells monolayer (African green monkey kidney cells monolayer), maintained in MEM-Eagle containing penicillin (100 UI/mL), gentamicin (10 μg/mL), and amphotericin B (2 μg/mL) and supplemented with 2% of fetal calf serum, were inoculated. After inoculation, cell cultures were examined daily for the presence of characteristic HSV cytopathic effect (CPE). In the absence of CPE, after 2 weeks of daily microscopic observation, cells monolayer blind passages were performed. Samples were considered negative after 3 consecutive blind passages without evidence of HSV CPE.

**VIRUS TYPING**

Direct immunofluorescence method (dIF) was performed to confirm and identify the HSV serotype. VERO cells monolayer presenting 80% of CPE were carefully shaken for cell detachment and centrifuged (1500 rpm for 3 minutes). The pellet was suspended in PBS pH 7.2 and 200 μL of the obtained cell suspension (10⁶ cells/mL) were centrifuged onto a glass slide by the aid of a cytocentrifuge and fixed in a 100% cold acetone. Fixed cells were stained with specific monoclonal antibodies (HSV-1 and HSV-2) and observed for the presence of viral inclusions with a fluorescence microscope (×400).

**DYE-UPTAKE SUSCEPTIBILITY TESTING**

The 27 HSV isolates from HSCT and nontransplant patients were tested for susceptibility to ACV, by the Dye-uptake method, previously described. Briefly, 200 μL of a Vero cells suspension (1×10⁶ cells/mL) were dispensed into each well of a 96-well plate, then 50 μL of a 2-fold dilutions of acyclovir (ACV) prepared in MEM-Eagle were added to each well. Finally 50 μL of MEM-Eagle, containing 100DU₉₀/mL of HSV were dispensed to the respective wells. The dilution series of ACV resulted in a final concentration of 0.125 μg/mL to 4 μg/mL and 8 replicates were used for each dilution. Drug, virus, and cells controls were used in each assay. Following the incubation of the plates for 72 hours at 37°C in a 5% carbon dioxide atmosphere, 50 μL of a neutral red dye solution (0.15% in saline buffer, pH 5.5) were added to each cavity of the 96-well plate. After incubation for 45 minutes, the excess dye was removed by washing wells once with phosphate buffered saline (PBS pH 6.5). The neutral red incorporated into the viable cells was eluted with 100 μL of citrate ethanol buffer (disodique citrate 30 mM in ethanol 50%). Optical densities were read at 540 nm with a spectrophotometer. The 50% inhibiting concentration of the drug was calculated by linear regression analysis. The final inhibiting concentration of each sample was the average of each of the two results since samples were tested twice simultaneously. Any assay in which the ED₉₀ of the control strain was outside the range of ±2 standard deviation, ie, 2.5-fold greater than the mean, was repeated. Samples with discrepant results were also retested.

**STATISTICAL METHODS**

The chi-square test for proportional difference was used. Significance was indicated by a *P* value <.010.

**RESULTS**

From a total of 83 inoculated samples, 27 (32.5%) showed suggestive HSV-CPE, confirmed by the dIF. Three HSV isolates (11.1%) were from HSCT (3 of 47) and the other 24 (88.9%) were from the nontransplant group (25 of 37). The dIF technique used for HSV serotype identification revealed that 23 HSV isolates (85.2%) were of serotype 1 (HSV-1) and 4 (14.8%) of serotype 2 (HSV-2). Two of the 4 HSV-2 isolates were obtained from the genital region and the other two from the orolabial region (Table I).

<table>
<thead>
<tr>
<th>Characteristics, No.</th>
<th>HSV Samples</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (N=83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontransplanted patients (n=36)</td>
<td>24/36 (66.7%)</td>
<td>.001</td>
</tr>
<tr>
<td>Transplanted patients (n=47)</td>
<td>3/47 (6.4%)</td>
<td>&lt;.001</td>
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<tr>
<td>HSV-isolated samples (n=27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontransplanted patients (n=24)</td>
<td>24/27 (88.9%)</td>
<td>.010</td>
</tr>
<tr>
<td>Transplanted patients (n=3)</td>
<td>3/3 (100%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

| Site of lesion | | |
| Oral vesicles (n=18) | 16¹/2² | |
| Oral mucositis (n=3) | 1¹ | |
| Genital vesicles (n=2) | 2¹ | |
| Perianal vesicles (n=3) | 3¹ | |
| Skin vesicles (n=1) | 1¹ | |
| Total (N=27) | 23¹/4² | .010 |

¹Viral isolation-positive samples. Virus typing by direct immunofluorescence method.
²Herpes simplex virus type 1.
³Herpes simplex virus type 2.
The dye-uptake method used to evaluate HSV sensitivity to ACV revealed that from the 27 HSV isolates, 25 (92.6%) showed sensitivity to ACV concentrations <1.5 μg/mL, one HSV isolate (3.7%) between 1.5 μg/mL and 2 μg/mL, and one (3.7%) showed sensitivity to ACV concentrations >2 μg/mL (Table II).

**DISCUSSION**

The frequent use of ACV for the treatment and prophylaxis of HSV infection increased the emergency of HSV-resistant strains. Consequently, the routine monitoring of HSV sensitivity to ACV turned out to be an important tool in the knowledge of clinical and epidemiological outcomes of ACV-resistant strains of HSV.

Several methods have been used to evaluate the sensitivity of HSV to ACV; nevertheless, the plaque reduction assay and the dye-uptake method are the most commonly used. In this report, the dye-uptake assay, based in the uptake of neutral red dye by living cells but not by virus-killed ones, was the method of choice to test HSV sensitivity to ACV. It has proved to be valuable and labor-saving as suggested by other authors.7,8

In our study, from the 27 HSV isolates, 3 (11.1%) were obtained from the HSCT and 24 (88.9%) from the nontransplant patients (Table I). The reduced incidence of HSV isolates in the transplanted group was probably a consequence of the prophylactic use of ACV (125 mg/m², intravenously, every 6 hours) that is now widely performed in nontransplant patients. The literature shows that before the prophylactic use of ACV, HSV could be isolated from 75% to 90% of bone marrow transplant patients.5,9 As reported by other authors, ACV decreases the incidence of HSV infection but does not eliminate HSV excretion; therefore, in our study, even in the course of ACV prophylaxis, 6.4% transplanted patients (3 of 27) showed HSV excretion. These patients had prolonged fever, but none had grade 4 mucositis.

The immunocompetent patients with HSV-1 resistant to ACV (ED₅₀ > 2 μg/mL) experienced recurrent erosive perianal skin lesions and received long-term treatment with ACV (ACV cream or ACV oral treatment). Resolution was observed after ACV was discontinued.

Our results show that the sensitivity to ACV of the 27 HSV clinical isolates varied from 0.15 μg/mL to 2.29 μg/mL. All the HSV-2 isolates were sensitive to lower concentrations of ACV. Concerning the different threshold of resistance, established by different authors for HSV-1, the threshold of 1.5 μg/mL, determined by past researchers10,11 is somewhat arbitrary and was not correlated with the level at which resistance becomes clinically significant.12,13 On the other hand, the cut-off level of 2 μg/mL for the HSV-1 was well correlated with the ACV therapy failure.12,13 Taking the threshold of 2 μg/mL as the cut-off level of resistance, the 27 HSV isolates could be placed in 3 distinct groups (Table II). In the first group, there were 25 HSV-1 and HSV-2 isolates (92.6%) sensitive to ACV concentrations <1 μg/mL; in the second group, there was one HSV-1 isolate (3.7%) that was sensitive to ACV concentrations between 1.5 μg/mL and 2 μg/mL; and the third group contained the HSV-1 isolate (3.7%) that was considered resistant to ACV (ED₅₀ > 2 μg/mL), and was isolated from an immunocompetent patient with frequent HSV recurrence (Table II).

It is known that the heterogeneity of the HSV population, due to the coexistence of sensitive and resistant strains, detected in vitro by phenotypic tests, facilitates the selection of ACV-resistant strains in patients receiving prolonged and repeated treatment with ACV.14 Since the acquisition of HSV strains resistant to ACV remains rare, it is suggested that the frequent use of ACV in self-medication, during HSV recurrence, originates resistance.15-17

Our results showed no resistance in the transplanted group but the presence of HSV resistance in one immunocompetent patient (4.1%), in contrast to the literature that shows a prevalence of HSV resistance from 0.1% to 0.3% in immunocompetent patients and from 3.5% to 6.3% in the immunocompromised patients.4,14,18-20 This observed difference could be explained by the small number of patients and, according to the literature, the frequent use of ACV in self-medication by the patient showing the resistant HSV isolate, could also explain that resistance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;1.5 μg/mL</th>
<th>&gt;1.5 AND &lt;2 μg/mL</th>
<th>&gt;2 AND &lt;3 μg/mL</th>
<th>&gt;3 μg/mL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV 1</td>
<td>21</td>
<td>1b</td>
<td>1c</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>HSV 2</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25 (92.6%)</td>
<td>1b (3.7%)</td>
<td>2c (3.7%)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Patient status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplanted</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nontransplanted</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

a Inhibitory drug concentration (ED₅₀).
b ED₅₀ = 1.56 μg/mL.
c ED₅₀ = 2.29 μg/mL.
CONCLUSIONS

The routine monitoring of patients at risk for developing resistance will allow the adaptation of therapeutic care to the needs of our hospital. Nevertheless more extensive studies will be required with a greater number of patients to investigate the real prevalence of HSV resistance in the Brazilian population.

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REFERENCES

“A transparent and open League working first hand with all of the world’s dermatologic & aesthetic surgery professionals and their National Societies.”

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ABSTRACT

It is known that one side of our body is not identical to the other.1 This includes the feet. Toenail unit changes secondary to shoe friction or trauma were first discussed by Dr Miguel Allevato in 1975 (Allevato M, personal communication, 1975) and again in 2010.2 In 1980, Gibbs first suggested abnormal foot biodynamics as a possible cause of toenail changes.3 Baran and Badillet in 1982 described partial hallux onycholysis,4 Gibbs in 1985,5 and Mortimer and Dawber6 and Murray and Dawber in 20027 described the foot biodynamics in detail, as the cause of toenail changes. The recovery from abnormal toenail unit changes of dermatophyte fungi, which cause more than 90% of cases of “onychomycosis,” has always been unacceptably low.8–10 The present report shows evidence that dermatophyte fungus-negative abnormal toenail unit signs are the result of toe friction in a closed shoe in patients with an asymmetric walking gait. These toenail signs should signal to the clinician that there is a skeletal asymmetry in the patient, which ultimately results in dysfunction of unilateral foot biodynamics. If not diagnosed and subsequently corrected, the asymmetry will worsen with age. Fleeting lower back pain is a typical symptom that is often disregarded by the patient. Initially, these toenail signs are unilateral, but with time may be seen bilaterally, and are always worse at the original site.

There are 4 clinical signs that can occur individually and in combination: (1) onycholysis, with or without (2) nail bed (NB) subungual keratosis, sometimes accompanied by (3) irregularities of the surface and or shape of the nail plate (NP) and (4) abnormalities of the stratum corneum of the hyponychium skin of the toes.

While observing some of these patients in private practice, it was noted that the skin of the tips of the toes were callused, suggesting shoe trauma. After examination of the shoes of these patients (Figure 1E and Figure 4K), it was obvious that the wearmarks on the soles were different, with the greater wear present on the sole of the shoe of the foot showing the clinical signs.

To identify the anatomic underlying cause of an unequal foot biodynamics, we examined the possible causes (unilateral flat foot, hyperflexion of the smaller toes forefoot inversion/eversion, pes cavus, tibial varum, vertical talus, scoliosis, clubbed foot, tarsoal coalition, and past trauma or surgical procedure).

METHODS

CLINICAL EXAMINATION

Clinical toenail signs (onycholysis, NB subungual keratosis, NP surface damage, and damage to the skin of the toes) were evaluated in our patients.

MYCOLOGICAL EXAMINATION

Routine samples from the involved nail unit (NB and NP) were cultured in dermatophyte test medium (DTM), and a direct microscopic examination using 20% potassium hydroxide with dimethyl sulfoxide (DMSO) was performed. Samples were not sent for
histochemical identification of glycogen by the periodic acid-Schiff reaction, as this is not diagnostic of a “dermatophyte” fungus and would stain positive for all members of the Mycota family.

**Radiologic Examination**

An x-ray was taken of the pelvis, the lumbar vertebral column, and both acetabulums, with the patient standing barefoot on a horizontal surface with their knee joints locked (code DCDG 724.2), when clinically indicated.

Limb length was measured by digitally creating a horizontal line in the x-ray from the superior surface of one femur to the other femur. If this horizontal line did not coincide with the superior surface of the opposite femur, then there was a differential in the limb length (measured in millimeters). Any spinal abnormalities, such as scoliosis, were also noted.

**Results and Interpretation**

All the clinical signs presented here are dermatophyte fungus–negative (by DTM culture and direct examination) and assumed to be due to the asymmetry of the foot biodynamics of the patient’s stance and walking gait and by repeated friction and pressure of the foot by the closed shoe. Skin changes secondary to friction are well accepted, but nail unit changes secondary to friction have not been appreciated as an alternative to clinical signs of onychomycosis. All 49 patients who underwent x-ray, aged 15 to 89 years, exhibited various degrees of onycholysis (Figures 1B–D), NB keratosis (Figures 2A–F and Figures 3Da-c), NP abnormalities (Figures 3A–C, 3F–G), and indistinguishable clinical appearance to distal lateral subungual onychomycosis (Figures 4A–C, Figures 4Da-c, and Figures 4E–J), as well as the skin of the tips of the affected toes exhibiting calluses or hyperkeratosis, or any combination of these signs mostly in the hallux but not restricted to it. Of these 49 patients, 6 (12%) did not have a functional “shorter” limb. Thirty (61%) had a functional limb length discrepancy (LLD) of 1 mm to 5 mm, 7 (14%) had an LLD of 6 mm to 10 mm, and 6 (12%) had an LLD >10 mm.

A correlation between the functional shorter limb (1–5 mm) and the severity of the nail clinical signs were seen in 6 of 13 patients (46%), and between the shorter limb (>5 mm) in 12 of 13 patients (92%). Nail unit abnormalities were unilateral on the foot of the functionally shorter limb in 67% of patients, except in one patient. In 23% of the patients, nail changes were bilateral; however, the toes of the functional shorter limb in the majority of these patients were more severely involved as compared with the toes of the other foot.

With reference to scoliosis, 15 (30%) of the 49 patients had scoliosis (Figures 2G and 4E). Six had no LLD and, of these, 2 (33%) had scoliosis. Thirty patients had LLD of 1 mm to 5 mm, of which 8 patients (27%) had scoliosis. Seven patients had 6- to 10-mm LLD and 2 (29%) had scoliosis, and of the 6 patients who had LLD >10 mm, 3 (50%) had scoliosis.

Two had severe skin calluses in the hyponychium area, with more severe clinical changes in the toes of the shorter limb. Eight patients had unequal flat feet (Figure 1K). Of the total number of patients studied, 10 families presented similar abnormalities in one parent and offspring. In our experience, these changes occur at an early age and worsen with aging.

Because of the multiple factors that can affect the walking gait, these figures are presented because they seem to show a trend but are not suitable for statistical evaluation.
DISCUSSION

The data presented in this article indicate that the specific clinical nail unit changes (that resemble and may be mistaken for onychomycosis) are commonly produced by friction of the toes against the closed shoe, apparently as the result of an anatomical asymmetry that tilts the body, so that one side has dysfunctional foot biomechanics when walking.

Published studies on the prevalence of a shorter limb in the general population vary from 77%, reported by Rush and Steiner in 1946 using a full length standing method designed among army personnel, and 40% by Subotnick, who studied...
4000 athletes and coined the term short leg syndrome. In 2006, investigators compared scanning vs the full-length standing method and found them comparable. A full-length standing radiographic technique was used in our patients. There is no established data to suggest that scoliosis is secondary to the short limb syndrome.

Patients who have distal subungual onychomycosis (DSO) may also have abnormal foot biomechanics and present additional clinical nail unit changes (asymmetric gait nail unit syndrome [AGNUS]) that are indistinguishable from the category of onychomycosis termed distal lateral subungual onychomycosis (DLSO) and even show lateral margin involvement (Figures 4A, B, C, D, G, and I). This would guarantee failure to completely achieve a 100% clinical cure when systemic antifungal treatment is given to patients with both dermatophyte onychomycosis and AGNUS. This should be of particular interest to investigators who treat DSO in studies for pharmaceutical companies, because these findings would explain why a patient with DSO after an apparently successful treatment with a systemic antifungal will remain clinically abnormal yet mycologically negative. Furthermore, the evidence presented in this paper would negate the need for a re-definition of “cure,” as has been proposed by a group of dermatologists, podiatrists, and Pharma-associated individuals, in a recent consensus paper regarding the persistence of clinical signs in successfully treated mycological (dermatophyte)–negative patients.

The nail-shoe trauma is most often the result of an asymmetric gait unsuspected by both the patient and the clinician. It is unlikely that onychomycosis itself leads to an asymmetric walking gait. One might also speculate that an asymmetric walking gait could favor the onset of dermatophyte onychomycosis in the onycholysis secondary to AGNUS. This assumption, however, might be serendipitous. In a larger series of patients with fungus-negative nail changes, causes other than an asymmetric gait (dysfunctional biomechanics) may surface.

**CONCLUSIONS**

Evidence is presented indicating that commonly seen toenail lesions, that may resemble onychomycosis but are in fact dermatophyte-free, are caused by the friction of the toe and the closed shoe in patients who have variable, often correctable skeletal abnormalities resulting in an asymmetric walking gait due to dysfunctional foot biomechanics. Many of these patients are misdiagnosed as having onychomycosis and are treated with no subsequent improvement in their abnormal clinical toenail. Both dermatophyte onychomycosis and AGNUS can occur together for independent reasons. One may speculate that some of the opportunistic fungi described in the dermatologic literature clinically resembling DSO may occupy and flourish in the onycholysis secondary to AGNUS. Early recognition of the characteristic toenail signs may contribute to the health and quality of life of the patient who has some (one of many) skeletally correctable abnormalities and have onset in the early years that gets worse with age.

**Acknowledgements:** Dock Anderson, DPM and Martin N. Zaiac, MD at the Mount Sinai Medical Center contributed to the preparation of this presentation.
REFERENCES

Female pattern hair loss (FPHL) as a distinctive entity was first described about 30 years ago. The objective of this study was to perform a systematic review of all randomized controlled trials for treatment of FPHL. A preliminary search was carried out in several databases up to August 2008 to identify all randomized controlled trials on nonsurgical interventions for treatment of FPHL. Studies reporting fewer than 10 patients and non-English articles were excluded. Additionally, references of relevant articles and reviews were checked manually in search for additional sources. Among 238 citations found in the preliminary search, 12 fulfilled all criteria to be included in the systematic review. Topical minoxidil 1% to 5% for 24 to 48 weeks was shown to be effective in FPHL and its effect was not related to age or androgen level of patients. In addition, it may be effective in women with FPHL, both with and without hyperandrogenism, and in young and old premenopausal or postmenopausal. In patients with increased serum androgens, oral flutamide but not finasteride or cyproterone acetate was more effective than no treatment. Topical minoxidil is effective in patients with FPHL, with or without hyperandrogenism, but there is limited evidence for the efficacy of antiandrogens. (SKINmed. 2012;10:218–227)

METHODS

SEARCH STRATEGY AND SELECTION CRITERIA
All evidence was reviewed in accordance with the evidence hierarchy in which the RCTs were identified as the most acceptable evidence.

ABSTRACT

Female pattern hair loss (FPHL) as a distinctive entity was first described about 30 years ago. The first chosen term androgenetic alopecia, which has been known for many years, is debatable because hair loss does not necessarily only occur in women with hyperandrogenemia. Although balding has been observed in hyperandrogenic women who often have other manifestations of androgen excess such as hirsutism or menstrual disorders or severe and recalcitrant acne, some studies have detected normal androgen levels in many women with pattern hair loss. Genetic susceptibility also has not been recognized as a leading factor in many patients. The term FPHL is thus preferred.

FPHL may begin at any time after menarche or adrenarche and usually its frequency and severity increase with age, from 3% to 6% in women younger than 30 years to 29% to 42% in women 70 years and older. In some such cases, the clinical impact of hair loss has considerable societal and psychological costs for patients.

FPHL usually presents with progressive thinning and loss of hair over the crown and frontal scalp. The frontal hairline is usually preserved in patients with FPHL. The affected zone varies from a small area to the entire scalp. In contrast to its frequent involvement in male pattern hair loss, vertex is rarely affected in FPHL. Several classification methods of pattern hair loss have been suggested, which all have limitations. One of the most commonly used classifications has been proposed by Ludwig (Figure 1). FPHL can be observed in men as an uncommon presentation of hair loss.

Laboratory evaluation of women presenting with hair loss should be pursued after ruling out any other possible differential diagnoses such as telogen effluvium, diffuse or reverse ophiasis, and alopecia areata. Screening tests usually include a complete blood cell count, work-up for iron deficiency, and hypothyroidism. In a subset of women who show other features associated with androgen excess such as hirsutism, menstrual irregularities, or difficult-to-treat acne, testosterone and dehydroepiandrosterone sulfate (DHEAS) should also be measured as a screening tool for making the diagnosis of possible underlying disorders.

Many different forms of treatment and a variety of protocols have been tried for FPHL. In this study, a systematic review of all randomized controlled trials (RCTs) in the treatment of FPHL was performed.

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Since to the best of our knowledge no published systematic review on this topic existed at the time of our study, the main sources of evidence were individual RCTs. To locate all studies apropos of FPHL in women, a preliminary search was carried out in the following databases (to August 2008): Ovid MEDLINE, PubMed MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL).

Search strategy to locate RCTs in Ovid and PubMed MEDLINEs was based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision), using following key (filter) words in their special format for each MEDLINE: randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial AND humans.

Search strategy to locate FPHL in women in all databases was: androgen OR male pattern OR female pattern OR hereditary AND alopecia OR hair loss OR baldness AND female OR woman OR girl.

After initial search, the titles and abstracts of extracted articles were reexamined. If it was that a clinical trial had not been relevant to nonsurgical interventions in FPHL treatment in women, it was excluded before appraisal. Concerning critical appraisal, two researchers assessed the included studies independently of each other to determine the articles that were completely related to the subject and were performed methodologically (ie, to see if they were RCTs in FPHL treatment in women). The studies reporting fewer than 10 patients were excluded. The search became limited to full-text articles in English. Abstracts and non-English articles were skipped. In addition, references of relevant articles and reviews were checked manually in search for additional sources.

**RESULTS**

Figure 2 shows the number of articles obtained from the preliminary search, number of articles included for systematic review, and the number of excluded articles and the reason for exclusion. No more articles were identified by hand searching. Table I shows the characteristics of 12 articles included in this systematic review and Appendix 1 shows the list of excluded articles and the reason for exclusion (37 articles). Includes the CAT forms for all 12 articles included in this systematic review. The results of these articles are summarized in Table I. Assessment of methodological quality of these studies based on the Jadad assessment scale is presented in Table II. In 11 of these 12 studies, patient selection was based on physical examination and distinctive features of FPHL and only one study exclusively included hyperandrogenic women. Various methods were used for assessing the effect size of interventions in these studies that makes any comparison impossible.

**PREMENOPAUSAL WOMEN**

In 7 studies, patient selection was only based on the distinctive features of FPHL, and patients were not screened for hyperandrogenism. In 6 studies including 1378 patients, comparing topical application (1 mL) of minoxidil 1%,12,17 2%,13–15 2% and allocation concealment method of study that is considered sufficient if the intervention in each participant can not be predicted; blinding (has blinding been employed in study or not and who has become blinded [ie, participant, physician, results assessors, analyzer or health care provider]); how many participants have been excluded and have the participants been analyzed based on primary group to which they were assigned in randomization or not; and intention-to-treat analysis with proper and sufficient follow-up.

In the process of selecting the relevant studies, disagreements among authors were solved by reaching to consensus.

The next step was extraction of necessary data, which was also performed independently by two authors, and exchange of idea between all authors solved disagreements. According to the assessments, a description of quality for each selected article was issued and a Critical Appraisal Topic (CAT) form was provided for each article. The gathered data were entered into Review Manager (RevMan) software for statistical analysis. Meta-analysis was not possible due to incompatibility of the studies. The effects of therapeutic methods in different studies were compared using random effects model. For dichotomous results, relative risk (RR) and 95% confidence interval (CI) were reported. For continuous results, weighted mean of difference (WMD) and 95% CI were reported.
5%\textsuperscript{16} twice daily for 24 weeks,\textsuperscript{17} 32 weeks,\textsuperscript{12-14} or 48 weeks\textsuperscript{16} with placebo, in all except one study,\textsuperscript{13} minoxidil was superior to placebo. In the only minoxidil dose-finding trial, minoxidil 5% was more effective than minoxidil 2%; however, the difference was not statistically significant.\textsuperscript{16}

In a double-blind, randomized, placebo-controlled study\textsuperscript{20} on 40 women with diffuse or androgenetic alopecia, 1 mL of a 0.1% melatonin or placebo solution was applied on the scalp once daily in the evening for 6 months. The trichograms showed a significant increase in anagen hair rate in occipital hair of patients with androgenetic alopecia treated with melatonin compared with the placebo group. The increase in anagen hair rate in frontal hair in women with androgenetic hair loss was not significantly different from the placebo group.

Researchers\textsuperscript{19} studied 66 patients, aged 18 to 34 years, randomly assigned into two groups: 33 received morning and evening local applications (2 mL) of topical minoxidil 2% plus combined oral contraception for 21 of every 28 days and 33 were treated with cyproterone acetate 50 mg/d for 20 of every 28 days plus cyproterone-ethinyl estradiol for 21 of every 28 days for 1 year. Based on phototrichogram data, the minoxidil group was superior to the cyproterone group. This was seen in the increase in hairs of diameter >40 μm and the total number of hairs in the minoxidil group. In the subgroup analysis, however, minoxidil was more effective in patients with isolated alopecia and in the absence of menstrual cycle irregularities and other signs of hyperandrogenism, and cyproterone acetate was more effective when menstrual cycle irregularities and other signs of hyperandrogenism were present and when body mass index was elevated.

Investigators\textsuperscript{19} randomized 48 women with alopecia and increased serum androgens (testosterone, free testosterone, DHEAS) higher than the mean ±2 standard deviations to 1 of 3 treatments: 12 were treated with cyproterone acetate 50 mg/d from day 5 to day 15 of the cycle and ethinyl estradiol 25 μg from day 15 to day 25 of the cycle; 12 were treated with flutamide 250 mg/d; 12 were treated with finasteride 5 mg/d; all for 1 year. Twelve patients who were recruited for the study refused any treatment and were observed without any treatment for 1 year. Thirty normal ovulatory women, matched for age and weight, were used as controls. After 1 year, flutamide was modestly superior to the control group, whereas finasteride and cyproterone were not effective.

**POSTMENOPAUSAL WOMEN**

Three studies included 282 postmenopausal women. In one study,\textsuperscript{21} oral administration of finasteride 1 mg/d for 12 months did not increase hair growth or slow the progression of hair thinning in postmenopausal women with androgenetic alopecia.

In another study\textsuperscript{22} to evaluate the efficacy of topical estrogens for androgenetic alopecia in menopausal women, estradiol valerate 0.03% was applied as 15 drops on the affected area of the scalp every day for 4 weeks and then every other day for 12 or 24 weeks. The results suggested that estradiol valerate was significantly more effective than placebo regarding anagen/telogen ratio. Furthermore, a 12-week course of estradiol valerate did not differ significantly from a 24-week course.

Additionally, 30 μL/cm² of fulvestrant 70 mg/mL solution twice daily for 16 weeks was not associated with any statistically significant differences in favor of its use over placebo.\textsuperscript{23}

Another study\textsuperscript{24} also included women 20 years and older with an average of 56 to 57 years; however, the results have not been presented according to menstrual status and, therefore, postmenopausal women cannot be identified.

**DISCUSSION**

FPHL is a common disease. The role of androgens in this disease is not clear. In one study, only 40% of women with FPHL had elevated serum androgens.\textsuperscript{1} In another study, patients with alopecia had lower serum levels of androstenedione and DHEAS,
lower salivary testosterone, and higher levels of sex hormone–binding globulin than patients with hirsutism, but total testosterone was not significantly different. So the term FPHL has replaced the older term of androgenetic alopecia. Few RCTs for the treatment of FPHL were found in our search in the English literature. The response to treatment may differ in patients with hyperandrogenism and also in postmenopausal women.

**Premenopausal Women without Hyperandrogenism**

Seven RCTs have included women with FPHL without any evaluation of hyperandrogenism. The diagnosis in these studies was based only on the clinical pattern of hair loss. In 5 of these studies, twice-daily application of 1 mL of minoxidil 1% or 2% was compared with placebo. The duration of treatment was 24 weeks in one RCT and 32 weeks in 3 RCTs. In all of these studies except for one, minoxidil was more effective than placebo in reduction of hair loss and increase in hair growth. No follow-up after discontinuation of treatment was reported in any of them.

In one dose-finding RCT, minoxidil 5% induced more hair regrowth than minoxidil 2% after 48 weeks, but the difference was not statistically significant. In men with male pattern hair loss, minoxidil 5% proved to be more effective than 2%. No serious systemic side effect has been reported with topical application of minoxidil. It may cause redness and itching of scalp in approximately 5% of women. This dermatitis is usually a nonspecific irritant contact dermatitis, although rare cases of true allergic contact dermatitis with minoxidil have also been reported. Hypertrichosis of face and body may occur, which is more frequent with 5% minoxidil and in patients with dark complexion. It usually subsides after discontinuation of treatment.

The mechanism of action of minoxidil in FPHL is not completely understood. Several mechanisms have been proposed including vasodilation, angiogenesis, enhanced cell proliferation and DNA synthesis, potassium channel opening, antiandrogen effect, collagen synthesis suppression, and immunosuppression.

Although a 1-year prospective study did not find any adverse pregnancy outcome in women using topical minoxidil, it is considered as pregnancy category X and should not be used by pregnant or lactating women.

In one RCT, including 66 women with FPHL, treatment with 1 mL minoxidil 2% applied twice daily plus combined oral contraceptive for 21 of every 28 days was compared with cyproterone acetate 50 mg/d for 20 of every 28 days plus cyproterone-ethinyl estradiol for 21 of every 28 days. The duration of treatment was 12 months and no follow-up was reported. Hair counts in phototrichography showed better response to minoxidil.

In subgroup analysis, response to minoxidil was better in patients who had normal menstruation cycle, but in the group treated with cyproterone, more hair growth was observed in patients who had abnormal menstruation cycle. Patients included in this study were not assessed for the level of serum androgens.

One RCT did not find any significant difference between topical melatonin 0.1% solution applied 1 mL daily and placebo after 6 months in the frontal area, which is androgen-dependent, although melatonin was more effective in the occipital area. Interestingly, the same study showed more efficacy of melatonin compared to placebo in frontal area but not in occipital area in women with diffuse hair loss. In vitro studies have shown a positive effect of melatonin on hair matrix cell proliferation and hair growth and an induction of anagen phase.

**Premenopausal Women With Hyperandrogenism**

Only one RCT has included exclusively patients with definite evidence of hyperandrogenism who had serum level of DHEAS, testosterone, and free testosterone more than twice the standard deviation of mean in normal controls. A total of 48 patients were treated in 3 equal groups with cyproterone acetate 50 mg/d from day 5 to day 15 of the cycle and ethinyl estradiol 25 μg from day 15 to day 25 of the cycle or with flutamide 250 mg/d or with finasteride 5 mg/d and 1 group was left untreated as control. The duration of treatment was 1 year. At the end of the study, only patients treated with flutamide showed significant improvement compared with the control group. Flutamide is a strong competitive inhibitor of androgen receptors and has been used successfully for the treatment of hirsutism. Considering the risk of hepatotoxicity of flutamide, and the prolonged duration of treatment for FPHL, flutamide can not be a suitable option in the treatment of FPHL. Finasteride is a selective inhibitor of 5-reductase type II and has been approved for the treatment of male pattern hair loss at a dose of 1 mg daily. Although a few case reports have shown the efficacy of finasteride in FPHL patients with or without hyperandrogenism or postmenopausal women, this RCT and also another RCT in postmenopausal women could not show any superiority of finasteride over placebo.

**Postmenopausal Women**

Three RCTs have exclusively evaluated postmenopausal women with FPHL. In these studies, oral finasteride 5 mg daily for 12 months, topical estradiol valerate 0.03% for 12 to 24 weeks, and topical fulvestrant 70 mg/mL for 16 weeks were compared with placebo. None of them showed any significant difference between these treatments and placebo. Fulvestrant is a “pure” estrogen receptor antagonist that causes telogen follicles to enter anagen, thereby causing hair growth.
Table I. Characteristics of 12 Randomized Controlled Trials for Treatment of Female Pattern Hair Loss (12–23)

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>Sample Size</th>
<th>Age (Mean, Years)</th>
<th>Ludwig</th>
<th>Experimental Intervention</th>
<th>Sample Size</th>
<th>Control</th>
<th>Sample Size</th>
<th>Treatment Duration</th>
<th>Follow Up</th>
<th>Primary Outcome</th>
<th>Mean Difference in Change From Baseline % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>28</td>
<td>18–44</td>
<td>I, II</td>
<td>Topical minoxidil 2%, 1 mL bid</td>
<td>14</td>
<td>Placebo</td>
<td>14</td>
<td>32 weeks</td>
<td>—</td>
<td>Nonvellus hair count in 1 cm²</td>
<td>29.5 (10.3 to 48.7), P = 0.006</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
<td>20–44</td>
<td>I, II</td>
<td>Topical minoxidil 2%, 1 mL bid</td>
<td>15</td>
<td>Placebo</td>
<td>13</td>
<td>32 weeks</td>
<td>—</td>
<td>Nonvellus hair count in 1 cm²</td>
<td>8.0 (~58.5 to 74.5), P &gt; 0.05</td>
</tr>
<tr>
<td>14</td>
<td>294</td>
<td>18–45 (33.6)</td>
<td>I, II</td>
<td>Topical minoxidil 2%, 1 mL bid</td>
<td>155</td>
<td>Placebo</td>
<td>139</td>
<td>32 weeks</td>
<td>—</td>
<td>Nonvellus hair count in 1 cm²</td>
<td>14.0 (9.6 to 18.5), P = 0.0001</td>
</tr>
<tr>
<td>15</td>
<td>256</td>
<td>17–46 (34)</td>
<td>I, II</td>
<td>Topical minoxidil 2%, 1 mL bid</td>
<td>128</td>
<td>Placebo</td>
<td>128</td>
<td>32 weeks</td>
<td>—</td>
<td>Nonvellus hair count in 1 cm²</td>
<td>12.0 (5.9 to 17.5), P = 0.0004</td>
</tr>
<tr>
<td>16</td>
<td>261</td>
<td>18–49 (37)</td>
<td>I, II, III</td>
<td>Topical minoxidil 2%, 1 mL bid</td>
<td>102</td>
<td>Placebo</td>
<td>51</td>
<td>48 weeks</td>
<td>—</td>
<td>Nonvellus hair count in 1 cm²</td>
<td>15.1 (9.3 to 20.9), P &lt; 0.001</td>
</tr>
<tr>
<td>17</td>
<td>273 ≤20</td>
<td>I, II</td>
<td>Nonvellus (hairs &gt;40 μ diameter) hair count in 1 cm²</td>
<td>137</td>
<td>Placebo</td>
<td>136</td>
<td>24 weeks</td>
<td>—</td>
<td>Nonvellus hair count in 1 cm²</td>
<td>6.1 (3.3 to 9.0), P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>52 26±4 (26.4 ± 4.8)</td>
<td>I, II, III</td>
<td>Topical minoxidil 2%, 2 mL bid + Oral combined OCP Daily for 21 of 28 days</td>
<td>27</td>
<td>—</td>
<td>25</td>
<td>12 months</td>
<td>—</td>
<td>Hair (&gt;40 μ diameter) hair count in 0.36 cm²</td>
<td>8.9 (5.0 to 12.8), P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>48 25±2</td>
<td>I, II, III</td>
<td>Flutamide 250 mg/d 5–15 of cycle + ethinyl estradiol 25 μg, day 5–25 of cycle</td>
<td>12</td>
<td>—</td>
<td>12</td>
<td>12 months</td>
<td>—</td>
<td>Ludwig score</td>
<td>17b</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Finasteride 5 mg/d</td>
<td>12</td>
<td>—</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−1b</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Sex</td>
<td>Treatment</td>
<td>No.</td>
<td>Treatment</td>
<td>Duration</td>
<td>Outcome Description</td>
<td>Occipital</td>
<td>Frontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>----------------------------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>12</td>
<td>20–70</td>
<td>Topical 0.1% melatonin-alcohol solution, 1 mL daily</td>
<td>6</td>
<td>Placebo</td>
<td>6 months</td>
<td>Anagen hair count</td>
<td>2.9&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>125</td>
<td>59±</td>
<td>Oral finasteride, 1 mg/d</td>
<td>62</td>
<td>Placebo</td>
<td>63</td>
<td>Hair count in 1 cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-2.1 (-18.7 to 14.6),&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P &gt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>62</td>
<td>48–71</td>
<td>Estradiol valerate 0.03% (12w)</td>
<td>23</td>
<td>Placebo</td>
<td>20</td>
<td>Mean anagen/telogen ratio</td>
<td>42.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>70</td>
<td>49–72</td>
<td>Estradiol valerate 0.03% (24w)</td>
<td>20</td>
<td>Placebo</td>
<td>36</td>
<td>Hair count in 1.8 cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Final number of participants evaluable.
<sup>b</sup>Confidence interval (CI) is not calculated due to lack of standard deviation report in the paper.
<sup>c</sup>Minoxidil 5% vs 2%: 3.80 (-1.6 to 2.9), P > 0.05.
<sup>d</sup>The odds ratio of anagen to nonanagen hairs in melatonin-treated women showed a significant effect at 1.90 (95% CI: 1.22–2.96; P = 0.012) compared with the odds ratio in placebo-treated women in occipital area but it was 0.91 (95% CI: 0.52–1.61; P > 0.05) in frontal area.
One RCT evaluating topical minoxidil included women older than 20 years with a mean age of 56 to 57 years, but data on postmenopausal women were not separately reported, so no conclusion could be drawn on the efficacy of minoxidil in postmenopausal women.

Beyond the scrutiny on RCTs, which lay the foundation for evidenced-base practice, it is worthy to have an overview toward new horizons in FPHL treatment. There are a myriad of therapies under study. Spironolactone, although in off-label use beyond 20 years in FPHL, has been reemphasized recently. The Food and Drug Administration has recently approved low-level light therapy for hair loss. Despite being most probably safe, its safety and effectiveness has not yet been well elucidated. Some authors consider combination of antiandrogens with tricyclic contraceptives as the best choice.

Although not life-threatening regarding its enormous psychological impact, FPHL demands much more extensive basic and clinical research in order to achieve an effective solution.

### DISCUSSION

The only approved treatment shown to be effective in FPHL is topical minoxidil. Although the results are not very dramatic, not all respondents show regrowth but shedding arrest, all disappearing on treatment cessation. It seems the effect of minoxidil is not related to age or androgen level of patients and it may be effective in women with FPHL both with and without hyperandrogenism, in young and old, and premenopausal or postmenopausal. The maximum duration of treatment with minoxidil was 1 year in these RCTs, and none of them included a follow-up period after discontinuation of treatment. So it is not clear how long the effect of minoxidil lasts in FPHL. Similar studies in male pattern hair loss have shown that any beneficial effect of minoxidil is lost 4 to 6 months after discontinuation of treatment.

### CONCLUSIONS

In postmenopausal women with FPHL, treatment with antiandrogens such as estradiol, fulvestrant, and finasteride was not more effective than placebo. As the mechanism of action of
minoxidil is not related to androgen levels, it may be the only treatment option in these patients, although no RCT evaluating minoxidil in postmenopausal women is available. In patients with FHPL and hyperandrogenism, treatment with antiandrogens seems logical. But in the only available RCT, only flutamide was effective and finasteride and cyproterone did not show satisfactory results. In women with FHPL who have regular menses and no evidence of hyperandrogenism, there is no evidence to support use of antiandrogens.

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APPENDIX 1:

EXPERIMENTAL:


INTERVENTION ON MEN:


INCLUDED PATIENTS WITH OTHER KINDS OF ALOPECIA:


NOT ENOUGH SAMPLE SIZE:


NOT CLINICAL TRIAL:


NOT ENGLISH:

NOT RANDOMIZED :

PUBLISHED ONLY AS ABSTRACT:

REFERENCES


Eosinophilic Ulcer of the Oral Mucosa

Paula Cabral de Menezes Gurfinkel, MD; Andrea Cabral de Menezes Gurfinkel, MD; Tullia Cuzzi, MD, PhD; Marcia Ramos-e-Silva, MD, PhD

ABSTRACT

A 56-year-old woman presented with a painless lesion on the inner aspect of her upper lip. The clinical differential diagnoses were oral syphilitic chancre, tuberculosis, histoplasmosis, and neoplasia. A biopsy was performed, and the histopathologic diagnosis revealed an eosinophilic ulcer of the oral mucosa. Based on this case, we discuss the history, mechanisms of pathogenesis, clinical manifestations, histopathology, differential diagnosis, and therapy of eosinophilic ulcer of the oral mucosa. (SKINmed.: 2012;10:228–231)

DISCUSSION

Eosinophilic ulcer of the buccal mucosa (EUOM) is an uncommon and self-limiting benign disease rarely described in dermatology. Clinically, it is characterized by a solitary ulcer with raised and hardened borders located more frequently on the tongue, but it is also found on the buccal mucosa or lips. Its pathogenesis is still not defined, but it is believed that trauma may be involved in its appearance. Histopathologic findings are characteristic, being represented by a polymorphic inflammatory infiltrate, especially of eosinophils. When such findings are not present, it is necessary to use immunohistochemistry and molecular study. The lesion frequently involutes spontaneously within a week or up to 8 months, without need for treatment.

ILLUSTRATIVE CASE STUDY

A 56-year-old woman was referred for evaluation of a painless, rapidly growing lesion, present for 4 days on the upper lip. Examination revealed a hardened lesion with a central ulceration covered by fibrin and measuring approximately 1 cm (Figure 1). The patient denied trauma or participating in sexual activity for more than 10 years; however, she did have dental treatment 4 days before the appearance of the lesion, which resembled a syphilitic chancre.

Dark-field examination showed no spirochetes. Histopathologic study (Figure 2) showed epidermal acanthosis and ulceration. The conjunctive stroma was entirely occupied by polymorphic cellular infiltrate represented by monocytic and polymorphous nuclei, including numerous eosinophils. In the midst of those cells were some larger mononuclear cells with large and vesicular nuclei. Periodic acid-Schiff and Warthin-Starry stains did not add new data to those already described.

The immunohistochemical analysis evidenced positivity for CD3 (small cells), CD20 (small cells), and CD30 (large cells) and negativity for CD1a and ALK-1 protein. The lesion involuted spontaneously 3 weeks after its appearance.

HISTORICAL ASPECTS

EUOM was first described in adults by Popoff in 1956, who classified it in the spectrum of facial granuloma. Long before that, in 1881, Riga reported a similar disease on the tongue or inner aspect of the lower lip of children younger than 2 years. Fede studied its histopathology in 1890, and this become known as Riga-Fede disease. Some authors have proposed the name ulcerated granuloma eosinophilicum diutinum of the tongue. In 1970, Shapiro suggested that EUOM should be classified as a distinct entity, and it has received several names, such as ulcerative traumatic granuloma with tissular eosinophilia, Riga-Fede disease, ulcerated granuloma eosinophilicum diutinum of the tongue, traumatic granuloma of the tongue, and eosinophilic granuloma of the tongue.

PATHOGENESIS

The pathogenic mechanisms related to the appearance of the lesion are still unknown. A wealth of clinical and epidemiologic data suggest, however, that trauma has a role in the process. Among the findings are: (1) trauma precedes development of
EIOM in 39% of the cases; (2) the lesions are usually located on the tongue, a site of frequent trauma; (3) the existence of two incidence peaks: the first at 2 years of life, coinciding with the beginning of dentition, and another in the sixth and seventh life decade, when the absence of some teeth, poorly treated teeth, and/or the use of a prosthesis, facilitate occurrence of trauma. Additionally, experimental studies carried out with rats have demonstrated the appearance of similar lesions after repeated trauma to the tongue. Some authors suggest that trauma is only one of the factors that contribute to the development of EUOM. Possibly, it could act as a facilitator for penetration of viral and toxic agents into the dermis, promoting the formation of an inflammatory reaction in predisposed individuals; however, this has never been proven.

Arguments against trauma as being the sole etiologic agent include: (1) buccal mucosa trauma is much more frequent than the cases of EUOM, and (2) the existence of cases of multiple and recurrent lesions in multiple locations differ from the first lesion. In addition to these arguments, some authors consider that the history of trauma occurs in less than 50% of the cases, therefore reducing its relevance as a pathogenic factor. EUOM may encompass a spectrum of conditions presenting as a hardened ulcer with raised borders on the tongue, lip, and buccal mucosa.

**CLINICAL PRESENTATION**

The clinical picture is an ulcer of rapid growth, ranging from a few millimeters to several centimeters in diameter, with hardened borders. In a review of 154 cases of EUOM, the average lesion size was 1.6 cm². Perilesional erythema and a whitish or yellowish base with fibrin on the surface may be present. The lesion may be covered by a pseudo-membrane. In some cases, it appears only as a hardening. The lesion can be asymptomatic or extremely painful. If pain is present, it may interfere with eating. It affects any mucosa; however, the most frequent location is the tongue, a preferred site of the lesion in 50% of cases. The lesion appears especially on the lateral and dorsal surfaces. Other possible locations, in decreasing order are: lips, gingiva, palate, floor of the mouth, and retromolar area. The disease can occur at any age, with almost equal prevalence. The proportion seems to be 1.06 female to 1 male.

There is a pediatric variant, known as Riga-Fede disease, which may be associated with neurological alterations of the base, characterized by a loss of sensitivity and pain. The designation of Riga-Fede disease is only applicable to children younger than 2 years. The onset of lesions usually begins at 8 months, concurrent with the beginning of teething.

**HISTOPATHOLOGY**

Microscopic examination shows an ulcerated mucosa over tissue of poorly formed granulation, associated, in general, with polymorphic and dense submucosal inflammatory infiltrate. This infiltrate tends to extend in depth, affecting the underlying tissue, muscle fibers, and salivary glands. The inflammatory infiltrate is especially rich in eosinophils, but it also contains small and rounded lymphocytes, in addition to other inflammatory cells, such as neutrophils, plasmocytes, and histiocytes.
A population of large mononuclear cells, of still undefined origin, in which atypical nuclear cells are frequently observed, is associated with the infiltrate. Some authors state that this population of large mononuclear cells is heterogeneous, being positive for CD68 (histiocyte marker) and factor XIIIa (dendocyte marker). In an immunohistochemical study of 9 patients, there were no positive markers, with the cells being positive only for vimentin, suggesting that they could correspond to myofibroblasts. On the other hand, the presence of large mononuclear and atypical CD30+ cells suggests that the disease may be part of the spectrum of lymphoproliferative CD30+ diseases. The presence of atypical CD30+ cells, however, occurs in multiple nonneoplastic inflammatory diseases, and this finding perhaps is insufficient to define malignancy. It is believed that those cells found in EUOM correspond to a population of T lymphocytes activated in response to an inflammatory lesion. There are cases of EUOM that present with aggregates of CD30+ cells associated with a monoclonal rearrangement of the T-cell receptor γ gene, with those lesions being better classified in the spectrum of lymphoproliferative CD30+ diseases.

**DIFFERENTIAL DIAGNOSIS**

Several diseases must be listed in the differential diagnosis of EUOM. In the infectious group, primary syphilis, oral tuberculosis, and histoplasmosis stand out. Primary syphilis can be differentiated histopathologically from EUOM by the presence of an inflammatory infiltrate of perivascular prevalence and comprising mainly plasmocytes and lymphocytes. Oral tuberculosis is characterized by a necrotizing granuloma, and special stains and molecular study by polymerase chain reaction help in the diagnosis of this disease.

The presence of a rapidly growing oral ulcer leads also to the differential diagnosis of squamous cell carcinoma, Wegener's granulomatosis, sarcoidosis, discoid lupus, and histiocytosis of Langerhans cells in their localized form, known as eosinophilic granuloma. The latter can be differentiated from EUOM as affecting a younger age group (usually children) and for being located mainly in palate and gingiva and with little proneness to involution.

Histopathologically, EUOM may resemble atypical histiocytic granuloma (AHG), angiolymphoid hyperplasia with eosinophilia (ALHE), and Kimura's disease. AHG, in general, is a self-limiting ulcer in the gingiva and, microscopically, is characterized by submucous polymorphic infiltrate, different from EUOM by being a little more superficial. In ALHE, mucosal involvement is rare and, when present, is characterized by asymptomatic nodules. An inflammatory infiltrate is observed with many eosinophils and marked vascular proliferation with bizarre blood vessels. Kimura's disease is a chronic inflammatory process of unknown origin, usually affecting Asians. Clinically, it is characterized by deep subcutaneous intradermal nodules, adenomegaly, and eosinophilia. Mucosal involvement is rare. Histopathologically, it reveals an inflammatory infiltrate comprised of lymphocytes and eosinophils with the presence of atypical giant cells.

The observation of atypical lymphocytes can lead to the differential diagnosis of malignant lymphoproliferative diseases. Oral lymphomas are rare and are in most cases composed of B cells, mainly diffuse primary cutaneous lymphoma of giant B cells. As in some cases, there are large atypical CD30+ cells. It is necessary to differentiate them from the group of CD30+ lymphoproliferative diseases. These represent a spectral group of neoplasias situated between lymphomatoid papulosis and primary cutaneous lymphoma of large anaplastic cells (LCPGA), which corresponds to 30% of T-cell cutaneous lymphoma cases. Lymphomatoid papulosis is characterized by an auto-limited papulonodular eruption, rarely affecting the mucosa, other than LCPGA, manifested by a firm and solitary nodule. Differentiation between those two entities is clinical in most cases, because histopathologic differentiation is difficult.

**TREATMENT**

Because it is a self-limited disease, the most indicated treatment is observation of the lesion, which, in many cases, involves without the need for intervention. It is important, however, to exclude the possibility of malignant disease through biopsy. In case of repeated trauma from dental prosthesis or teeth in bad repair, the triggering factor should be removed. Despite its self-limiting character, several therapeutic possibilities have been discussed in the literature, with surgical excision of the lesion the most frequent, especially in cases of persistent lesion. Recurrence of the excised lesion is not usually observed; however, new lesions at other locations may occur. Besides surgical excision, topical or intralesional steroid treatment may be prescribed. There is a case of involution of the lesion in 3 weeks, after the use of intralesional steroid. Other therapeutic modalities described are curettage, cryotherapy, and radiotherapy.

**CONCLUSIONS**

EUOM is an uncommon entity, little known by the dermatologist and reported mainly in the literature relating to buccal pathology and bucomaxillary surgery. The pathogenic mechanisms of this entity are not yet defined. There are discussions involving the precise participation of trauma in its development. Due to its clinical characteristics, it requires making a differential diagnosis with several tumors, both benign and malignant.

The presence of CD30+ cells leads to the proposal of the classification of EUOM as a lymphoproliferative CD30+ disease.
or merely as a reactive pattern; however, the use of this marker alone is insufficient for a diagnosis of malignancy. There is still discussion about classification of EUOM as a distinct entity. Some authors support that it represents only a finding that may encompass several related diseases.3,4

REFERENCES
Cutaneous drug reactions (CDRs) have a wide spectrum of clinical manifestations that may be caused by multiple drugs by different mechanisms. The physiopathology of CDRs has been the subject of continuing debate. Its immunologic and nonimmunologic classifications are largely accurate, with the majority of CDRs conforming to the former. The well-recognized classifications include Gell and Coomb's hypersensitivity, type I; immunoglobulin E (IgE)-mediated immediate-type, type II; antibody-mediated direct cell toxicity, type III; immune complex-mediated activation of complement system, type IV; delayed-type cell-mediated immune response (Table). Type IV hypersensitivity has recently been subclassified into T-cell reactions. T cells release certain cytokines and chemokines, preferentially activating and recruiting certain cell types, which may explain the varied morphology of the T-cell–mediated reactions. Fas-Fas ligand and perforin pathways are some of the other well-appreciated immunologic mechanisms.

The genetic basis of CDRs has been delineated into two broad groups. The first group involves genes that drive pharmacologic mechanisms. Common mechanisms that underlie these severe CDRs are unusual drug accumulation in the target organ caused by polymorphisms in the drug-metabolizing enzyme and drug transporter genes, and an unusual sensitivity in the target organ caused by changes in drug target genes. The second category involves the immune system in a drug-induced allergic reaction. One important molecule for CDRs associated with immune reactions is the human lymphocyte antigen (HLA), which may play a key role in the initiation of immune responses, and killing target cells by presenting antigens to the T-cell receptor.

### METHODS
A Medline search (1959–2010) supplemented by PubMed was performed using the key phrase physiopathology of adverse CDR. Literature was reviewed for relevant text to update and define the current concepts.

### PHYSIOPATHOLOGIC CLASSIFICATION OF DRUG REACTIONS
The significant pathomechanisms of immunologic drug reactions are shown in the Table. Nonimmunologic mechanisms, predictable or unpredictable, may also be responsible for precipitating and/or triggering CDRs, which are mentioned below.

### PREDICTABLE
Predictable pharmacologic mechanisms are those caused by overdosage, altered metabolism, excretion, absorption, drug interaction, or side effects, which are a component of the pharmacologic action of the drug(s).

### DIRECT DRUG CYTOTOXICITY
Direct drug cytotoxicity occurs when the drug accumulates and leads to cellular destruction/malfunction, as in the cases of arsenical keratosis and methotrexate-induced hepatotoxicity.

### DRUG-DRUG INTERACTION
The drug-drug interaction between two drugs may occur ex vivo (in the infusion drip), in the blood, at tissue receptor sites (replacement of a bound drug by another), or indirectly as a result of acceleration or slowing of the metabolism in the liver of one drug/xenobiotic by another. The liver microsomal enzyme...
### Table. Gell and Coomb’s Classification of Drug Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Immune Reaction</th>
<th>Mechanism</th>
<th>Clinical Manifestations</th>
<th>Timing of Reactions</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (immunoglobulin E [IgE]-mediated)</td>
<td>Drug-IgE complex binding to mast cells with release of histamine and mediators including leukotrienes, prostaglandin D2, interleukin 5, and eotaxin&lt;br&gt;Chemical mediators activate and recruit eosinophils&lt;br&gt;Eosinophil degranulation results in further release of proinflammatory cytokines&lt;br&gt;Cytokines result in dilatation and increased permeability of microvasculature and bronchiolar smooth muscle contraction</td>
<td>Urticaria, angioedema, bronchospasm, inflammatory pruritus, vomiting, diarrhea, anaphylaxis</td>
<td>Min to h after drug exposure</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Specific IgG or IgM antibodies directed at drug–hapten-coated cells lead to complement activation</td>
<td>Hemolytic anemia, neutropenia, thrombocytopenia</td>
<td>Variable</td>
<td>Quinidine-mediated thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Penicillin- and sulfonamide-mediated hemolytic anemia</td>
</tr>
<tr>
<td>Type III (immune complex–mediated)</td>
<td>Tissue deposition of drug-antibody complexes with complement activation&lt;br&gt;Complement activation leads to release of vasoactive amines and proinflammatory cytokines from mast cells and basophils&lt;br&gt;Cytokines and other chemical mediators lead to increased vascular permeability and recruitment of neutrophils</td>
<td>Serum sickness, fever, dermatitis, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis, lupus erythema–like syndrome</td>
<td>1 to 3 wk after drug exposure</td>
<td>Hydralazine and procainamide lead to lupus erythema–like syndrome</td>
</tr>
<tr>
<td>Type IV reaction (delayed cell–mediated)</td>
<td>Major histocompatibility complex presentation of drug molecules to T cells with cytokine and inflammatory mediator release&lt;br&gt;Viruses may nonspecifically stimulate cytotoxicity, which affects target cells altered by any antigen</td>
<td>Allergic contact dermatitis, morbilliform dermatitis, fixed-drug eruption, Stevens-Johnson syndrome, erythema multiforme</td>
<td>2 to 7 d after exposure</td>
<td>Poison ivy dermatitis, phenytoin-induced exanthemes/bullous dermatitis</td>
</tr>
</tbody>
</table>

System is dependent on cytochrome P-450, which nonspecifically catalyzes a number of drugs by hydroxylation, oxidation, reduction, sulfoxidation, dehalogenation, deamination, desulfuration, and dealkylation. This metabolic pathway (hepatic microsomal) is nonspecific and a number of drugs are capable of stimulating (phenytoin, rifampicin) and inhibiting (chloromphenicol, phenylbutazone, allopurinol) the cytochrome P-450 system; therefore, this seems to be a potential site for drug interactions.
Metabolic
Cutaneous reactions, in addition, may occur as a result of alteration in the metabolic status, as in the case of xanthomas caused by isotretinoin therapy occurring as a result of raised levels of very low-density lipoproteins.3

Unpredictable

Pseudoallergic Reaction
Some drugs may directly release mast cell mediators to produce urticaria/anaphylaxis. Examples of these agents are codeine, atropine, quinine, hydralazine, radio-contrast media, pentamidine, and polymyxin-B.3

Idiosyncratic Reaction
Idiosyncratic reaction is an uncharacteristic response, neither predictable from animal experiments nor mediated by an immunologic mechanism. Genetic factors may play a role, of which glucose-6-phosphate dehydrogenase deficiency–mediated dapsone-induced hemolysis is a classical example.

Intolerance
Intolerance is simply the exaggerated effect to a very small dose of a drug.

Generation of Reactive Metabolites of the Drug in the Liver
The formation of neoantigenic determinants in the liver may either induce an immune response or an immune tolerance; however, large doses of a drug may result in the excessive production of its reactive metabolites, which may escape the tolerogenic hepatic environment via the lymphatic drainage to the local lymph nodes. Subsequently, the circulating metabolites may induce immune sensitization.15 Drug metabolism may also occur inside the keratinocytes and the antigen-presenting cells (APCs).

CDRs and Innate Immune System
A drug may stimulate the innate immune system either directly or by binding to the Toll-like receptors.18 In the latter case, the intracellular processing of a drug produces a hapten-like compound, which may attach to various intracellular structures and disturb their function.19,20 Subsequently, the altered signalling may upregulate the costimulatory molecules, CD86 or CD40, on the surface of an APC. Indeed, these markers have been used for screening the sensitizing potential of some compounds.21,22 Incubation of dendritic cells with sulfamethaxazole (SMX) in high concentrations is known to upregulate the CD40 molecules, which could be countered by inhibiting the metabolism of SMX.23 The metabolism of a drug that causes systemic immune reactions, therefore, can occur inside the APCs, and this may result in an enhanced antigen-presenting capacity of the metabolizing cells.24

A relatively large number of T and B cells are able to attach to hapten carrier complexes, and a vigorous immune response may arise. A predominant humoral immune response may occur if the hapten modification affects the soluble and cell-bound proteins, while a predominant T-cell response may arise if the hapten binds directly to the major histocompatibility complex (MHC) peptide complexes.7

T Cells and CDRs
There is increasing evidence to indicate that T cells play a vital role in the pathogenesis of drug reactions.25 The majority of drugs form chemically reactive metabolites, and there seems to be some relation between the extent of their metabolic activation and the potential of the drug to cause hypersensitivity, the pathways of which are defined below:

- Prior to systemic circulation, a drug may be metabolized by liver cells to highly reactive intermediate(s) that may haptenate proteins at the site of metabolic activation.26
- A free drug metabolite may attach to cutaneous proteins. Keratinocytes express high levels of cytochrome P-450s and can metabolize a drug.1,25 A proreactive metabolite, under conditions of oxidative stress or in an environment containing low levels of thiols/antioxidants, may undergo oxidation to electrophilic species.1 Electrophilic drug metabolites formed may stimulate T cells via the below three pathways.1

Pathway 1
The classical hapten mechanism (Figure 1),27–29 where a covalent interaction between nucleophilic moieties on cutaneous cell surface protein and the chemical, is a prerequisite for immune activation. The interaction between a drug and a protein is recognized as haptenation. The haptenated protein is taken up by professional APCs. Antigen-loaded, antigen-presenting cells migrate to the local lymph nodes, where they process a series of enzymatic reactions that break down the antigen to small peptide fragments and present the antigen on the MHC molecules to naive T cells.

Pathway 2
In pathway 2, the drug metabolites bind directly to the MHC molecules on the surface of the APCs and do not require antigen processing.28–30
PATHWAY 3

Pathway 3 does not require fragmentation of the drug into peptide fragments, and the drug has a capacity to bind the MHC molecules, eg, sulfamethoxazole and carbamazepine.28–30

Apparently, the preceding pathways are not sufficient to account for drug reactions that occur rapidly without an earlier drug exposure. Accordingly, an alternative model has been proposed that supplements the hapten/prohapten concept, termed the p-i concept, which stands for direct pharmacologic interaction of drugs with immune receptors (Figure 2). It implies that certain drugs bind specifically and reversibly to some of the highly variable antigen-specific T-cell receptors (TCRs) in a direct way, instead of co-valently modifying the MHC peptide complex. Such a drug-TCR interaction is independent of metabolism and processing and, in fact, may mimic drug interactions with other nonimmunologic receptors.26

Clonal T-cell expansion, a consequence of the aforementioned pathways, generates a population of antigen-specific T cells that migrate to skin following another exposure to a similar antigen. Secretion of cytokines and chemokines from inflammed skin and activated T cells control the nature of the cellular immune response, and hence the extent of tissue damage. Furthermore, the various clinical manifestations of T cell–mediated drug hypersensitivity may be explained by the distinct T-cell functions. Delayed hypersensitivity reactions (type IV) have been subclassified into T-cell reactions depending on the milieu of certain cytokines and chemokines, which has a capacity to preferentially activate and recruit monocytes (type IVa), eosinophils (type IVb), and neutrophils (type IVd).7

ANTIBODIES IN CDRs

Activated drug-specific T-cell clones may, in turn, stimulate the generation of a B-cell immune response directed to the hapten-carrier compound. Depending on the T-helper cell–secreted cytokine milieu, a B-cell class switchover may occur, subsequently leading to predominant IgE or IgG production. The former may ultimately result in type I hypersensitivity, while the latter may lead to either type II or type III hypersensitivity.

Skin is considered a unique target in hypersensitivity reactions regulated through several factors.

Keratinocytes express cytochrome P-450 and may contribute to the extrahepatic metabolism of drugs, thereby generating immunogenic haptens.31–33

Oral or parenteral uptake of drugs may lead to rapid distribution throughout the body. This aspect, in particular, has been well documented for skin, where antihistaminic drugs administered orally can reach tissue levels in the nanomolar range of 45 to 60 minutes.34

Skin is a border region with an enormously dense network of APCs and T cells and may promptly mount an immune response.35,36 Other organs do not have such highly reactive sentinel T cells. These cells may be characterized as chemokine ligand (CCL) 1 responders and express chemokine receptor (CCR) 8, while the immigrating inflammatory T cells are
CCL20 and CCR6+ responders, which are likely to be activated by the p-i mechanism. In drug hypersensitivity, the local concentration of drugs in the skin may lead to a successful TCR engagement by drugs directly interacting with the TCR (p-i concept) and supplemented by MHC interaction through close contact with the abundantly available epidermal APCs (dendritic and Langerhans cells).

Intercellular adhesion molecule 1, a surface ligand of keratinocytes, recruits T cells into the epidermis. Its expression may increase as a result of oxidative stress, viral infections such as the human immunodeficiency virus, and other second signals.37

Skin forms an interface with the external environment, thereby exposing it to high oxygen tensions, a source of free radicals.38 In addition, because skin is rich in polyunsaturated fats and continually exposed to UV rays, it may generate toxic free fatty acids.38

Lastly, the capillary circulation through the skin is sluggish, which may prolong the interaction between a drug with effector immune cells and keratinocytes.39

GENETICS AND ADVERSE DRUG REACTIONS

Hereditary forms of severe adverse drug reactions (ADRs) and reports of cases occurring in identical twins imply involvement of certain genetic factors in predisposing certain individuals to severe ADRs.40,41 The genetic basis of ADRs has been grouped into two categories. The first group entails genes that drive pharmacologic mechanisms, drug targets, drug-metabolizing enzymes, and drug transporters.11 Unusual drug accumulation in the target organ due to polymorphisms in drug-metabolizing enzyme and drug transporter genes and unusual sensitivity in the target organ caused by changes in drug target genes are the usual mechanisms.12 The second group includes the immune system in a drug-induced allergic reaction, regulated by an important molecule, the HLA. The latter plays a key role in initiation of immune responses and killing target cells by presenting antigens to the TCR.13

It has been realized that reactive metabolite generation from carbamazepine alone is not sufficient to cause Stevens-Johnson syndrome/toxic epidermal necrolysis.11 Whole genome polymorphisms have been incriminated in ADRs. Recently, a strong association between carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis and HLA-B*1502 allele has been reported.42 HLA-B*1502 screening is thus recommended for carbamazepine in clinical practice by the US Food and Drug Administration, and HLA-B*5701 screening is also recommended for abacavir by the Food and Drug Administration and the European Medical Agency.43

REFERENCES


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Contaminants, unintended tissue fragments, found on a slide along with an intended tissue section are a recurring problem in pathology laboratories. Tissue is processed similarly in every laboratory. Initially, it is grossed, in which it is inspected, described, and pared, before being fixed in a solution to prevent decomposition. Subsequently, the tissue is dehydrated, with the water being replaced by paraffin wax or plastic. The tissue is then embedded, forming the tissue block, and cut into sections. The sections of tissue are floated in a water bath, placed on a slide, and dipped in sequential staining baths. Contaminants can be imparted onto the slide during any step of this process.

CONTAMINANTS
There are two distinct types of contaminants, floaters and pickups, differentiated by their original source and presence or absence in the tissue block. Floaters are extraneous tissue fragments that adhere to the slide either when it is floated in the water bath or when it is dipped in the staining baths. In contrast, pickups are aberrant tissue fragments, acquired from forceps, scalpels, or cutting surfaces, that are embedded within the gross specimen and incorporated into the tissue block. Unfortunately, contaminants are quite common in pathology. A retrospective study found contaminants in up to 3% of diagnostic slides, while another found contaminants in approximately 8% of banked slides. These extraneous tissue fragments, ranging in size from a few cells to a few hundred cells, are problematic because they can lead to misdiagnosis and subsequent patient mismanagement.

If a contaminant is suspected on a histological slide, further investigation must be undertaken to confirm the identity of the tissue. Suspicion should be raised when the tissue is only at a single locus, is at a random orientation to the surgical specimen, is not consistent with the suspected pathologic condition, or exhibits a staining pattern inconsistent with the pathologic condition. In Mohs surgery, contamination should also be suspected if the tissue is located outside of the inked surgical margins. Clarification of a suspected contaminant begins by taking serial sections of the tissue block. If the suspected contaminant is found only in a single section of tissue, a floater is most likely the culprit. Identification of floaters becomes more cumbersome when the tissue is processed in one laboratory but read in another. Pickups, found in multiple sections of the tissue block, pose a greater challenge and require the pathologist to compare the suspected pickup with recently handled specimens (Figure 1). This process of identification is more difficult in busy pathology laboratories and when sections are read in different laboratories than those in which they were processed.

FLOATERS AND PICKUPS
To more accurately identify floaters and pickups, genetic testing for polymorphisms has been employed on the DNA of the intended specimen, the contaminant, and the tissue from which the contaminant is suspected to have originated. Despite the small size of tissue contaminants, and the DNA mutations commonly found in tumor cells, this genetic testing has proven successful. The ability to examine a miniscule tissue fragment makes polymerase chain reaction and molecular genetics particularly useful when a suspected contaminant changes the diagnosis from benign to malignant. In the case of Mohs surgery, DNA molecular testing is too time consuming and, thus, if the origin of the contaminant is in doubt, an additional Mohs stage should be performed.

Laboratories need established methods to minimize the risk of floaters and pickups. Frequent cleaning and changing of water...
Floaters and pickup baths are recommended. Particular attention should be paid to the first set of alcohol staining baths, which have the greatest prevalence of tissue discohesion and floaters. Meticulous cleaning of forceps and cutting surfaces is essential to reduce the risk of pickups. Since serrated forceps have tiny grooves that are apt to harbor tissue fragments, smooth tipped forceps, when feasible, should be used. In Mohs surgery, preoperative curettage is not recommended, due to the theoretic risk of introducing extraneous tissue into the surgical specimen. Finally, we recommend that at least two sections of tissue always be obtained in order to allow for easy recognition of floaters.

Floaters and pickups are an important challenge to dermatologists and dermatopathologists and have the potential to cause misdiagnosis, lost laboratory time, and malpractice lawsuits. One study analyzing malpractice lawsuits found that almost 1% of claims against pathologists involved misinterpretation of contaminants. This misinterpretation can lead to misdiagnosis of benign tissue as neoplastic. Investigators reported a patient initially diagnosed with B-cell lymphoma that was determined, 5 years later, to be a pickup. This patient refused chemotherapeutic treatment; however, she was subjected to yearly blood draws, examinations with an oncologist, and untold psychological harm. The risk for misdiagnosis of a neoplasm based on a contaminant is significant given that between 6% and 12% of contaminants consist of neoplastic tissue. It has been reasoned that floaters and pickups are more likely to contain neoplastic tissue because the friable nature of malignant tumors lends to their dissemination on laboratory benches, in the teeth of forceps, in water baths, and in staining solutions.

**CONCLUSIONS**

Contaminants are a persistent problem in pathology, with the potential to lead to misdiagnosis, lawsuit, and patient morbidity. Dermatopathologists and dermatologists need to be cognizant of contaminants during surgical excision, handling, and staining of specimens. While floaters can be easily prevented by frequent changing of water and staining baths, pickups are more challenging to prevent, requiring the dermatologist, dermatopathologist, and histotechnician to maintain clean equipment, clean workspaces, and proper surgical technique. When a contaminant is suspected, further investigation, including serial sectioning of the tissue block, examination of previously sectioned specimens, and genetic analysis, is warranted. In particular, Mohs surgery presents many opportunities for pickups to contaminate the surgical specimen. Since Mohs surgery is aimed at tissue conservation, prevention of pickups and floaters is particularly important to avoid unnecessary tissue excision.

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HISTORICAL VIGNETTE
Charles Steffen, MD, Section Editor

Entities and Eponyms: Two Each, and a Painter—“175” Years On
Karl Holubar, MD, FRCP, FRSM, GSE;1 Stella Fatovic-Ferencic, MD, PhD2

ABSTRACT

Time frames are always dictated by the calendar. Kaposi was born 175 years ago, Carl Heitzmann one year before, and lupus erythematosus (LE) just one year later. Strawberry Hill and its lord played not too small a role in unraveling some details of LE and the “hemorrhagic sarcoma to-be.”

Kaposi (1837–1902) lent his name to one of the above two syndromes, but he published extensively on both in the same year, same journal, and same volume (German Archives, volume 4, 1872).1

The literary “birth” of chronic discoid LE (CDLE) (1838) trails the master’s by one year. Carl Heitzmann’s birth precedes it, also by one—justification enough to deal with the three in one.

VIENNA, OCTOBER 2, 2011, CARL HEITZMANN’S 175 BIRTHDAY

Erythematous were described by Willan as much as by Alibert. To play with the calendar lends itself to these years: Willan died 200 years ago, Alibert 175 years ago and Kaposi was born in that year, Heitzmann the year before (October 2, 1836; 175 years ago). Alibert’s second-in-command was Laurent Théodore Biett (1781–1840) who took over in Saint-Louis, France, when Alibert became physician of the newly re-instated king of France. As was customary at the time, pupils published the teachings of their masters, as did Pierre Louis Alphée Cazenave and Henry Edward Schedel, in a first edition in 1828. LE-to-be was still unknown and there is no particular reference of what could be construed as cutaneous LE in hindsight. In the 1838 edition, Erythème Centrifuge, an entity was addressed and repeatedly referred to in later editions by Maurice Chausit. Eventually, in a case presentation published in the Gazette des Hôpitaux Civils et Militaires, July 27, 1850, Cazenave changed the term to lupus érythèmeux, confirmed one year later in his own journal (Annales des Maladies de la Peau, June 4, 1851). Thus, it remained, until Hebra in the first installment of his atlas in 1856, Latinized the term, to read now, lupus erythematosus, in fact a Graeco-Latin term. Seven years later, Hebra’s pupil Isidor Neumann coined another term with a Greek-only adjective, spelling it, lupus erythematodes.3 The latter became more popular in German-speaking countries; the Francophone world stuck to the original French version by Cazenave. Early on, Neumann also spoke of lupus Cazenavi as opposed to lupus Willani.

Kaposi, again out of Hebra’s department, authored the first extensive paper in 1872, mentioning for the first time dangerous systemic symptoms. This 32-page paper gained worldwide recognition and thereby the form of lupus erythematosus was immortalized outside the Francophonic.

Decades followed without any news breaking on the LE entity until the Libman-Sacks verrucous endocarditis described in 1924, and, after another lapse of decades, the LE cell and LE factor by Hargreaves at Mayo in 1948. Thomas Burnham first demonstrated immunoglobulin deposition along the basement membrane zone in lesional skin in 1963, which was soon confirmed worldwide. Anti-DNA antibodies were detected, the lupus anticoagulant was identified, lupus nephritis was diagnosed, and the whole spectrum of clinical symptoms became commonplace. Today, systemic lupus erythematous and CDLE are spoken of in the pertinent papers.

WHAT ABOUT STRAWBERRY HILL?

This relates to serendipity,4 today better known also in our latitudes/longitudes. On January 28, 1754, the envoy to the Hapsburg court in Florence, Horace Walpole, son of the famous prime minister Robert Walpole, wrote a letter to his lifelong pen friend Horace Mann in London,5 coining this word for the
English language and for world literature. We cannot go into that story, but 10,000 letters of Walpole are kept on the shelves of his wonderful estate near London in Strawberry Hill.

Joseph-Louis Pasteur Vallery-Radot (1886–1970) explains serendipity as “le hazard ne favorise que les ésprits prepares,” that is, an accidental sagacity of mind, letting observers find something “they were not in quest of.”4 Basis of the story is an old Oriental legend of the King of Serendip and his three sons (cp. the opposite: zemblanity,5 created by William Boyd, ie, finding unlucky, unhappy matters and taking the icy island of Novaya Zemlya as contrast to the spice island of Ceylon).

BACK TO LE!

Walter Lever’s book, in the first edition of this classic in 1949, Histopathology of the Skin, became the bible of generations of dermatopathologists to-be, listing liquefaction degeneration of the basal layer as 3 of 5 salient criteria for the diagnosis of CDLE. Hitherto, it was Gans’ illustration of a specimen from subacute LE that emphasized this point clearly, (Goeckerman and Montgomery on his heels). Its diagnostic value was not emphasized accordingly at the time. Only after Lever’s monography, no student would have passed his board examination without quoting this essential feature.

Serendipity, recently, let us run into a drawing in our own vaults. This picture is undated, unsigned, and was in fact published in the first-ever paper on LE pathology quoted above.3 No particular attention was paid to basement membrane zone (BMZ) as much as Neumann wrote “the English describe a homogeneous zone between corium and epidermis,” obviously the basement membrane. In fact, Neumann does not address such a structure but writes in his text, “in the corium, nuclear proliferations [he calls it “Kernwucherungen”] obfuscate the border between connective tissue and epithelium, at places.” This phenomenon is visible in Neumann’s illustration in one place but not specified. None of the famous texts of the late 19th century explicitly referred to that, nor Max Joseph. Pictures in these latter two, widely overlooked exquisite volumes of dermatopathology of 1899 and 1906 (recently addressed by Plewig and colleagues)6

Figure 1. Neumann’s picture from his 1863 paper.

Figure 2. Close up view of what Neumann described as “Kernwucherungen” (nuclear proliferations) but without any emphasis on destruction of the basement membrane zone.

Figure 3. A similar focus of “Kernwucherungen” (nuclear proliferation) as termed by Neumann in his text, Wiener Medizinische. Wochenschrift 1863 pages 643–645(c) is currently unpublished, but obviously made at the same time, by the same artist with the same handwriting on the frame. Neumann, in the preface of the 1870 edition of his textbook of skin diseases, explicitly states that all drawings were made by Dr Carl Heitzmann.
did not display BMZ destruction or comment on such. Neumann\textsuperscript{3} is obviously the first paper to depict BMZ destruction even without commentary (Figure 1). Another drawing in our files shows a small area of BMZ with clear destruction (Figure 2), apparently by the same artist, and also exhibiting the same ink and handwriting on the frame and the diagnosis of LE. In the preface of his volume, Neumann (1870 ed.) states that all drawings were made by Dr Carl Heitzmann, but the last drawing (Figure 3) was not published.

**OVER TO KAPOSI AGAIN!**

As we learned with LE, the same practice was held in Vienna wherein the assistants published the master’s observations, Kaposi for Hebra in this case. The first of the “hemorrhagic sarcomas” to-be cases was admitted to the Vienna department on April 25, 1868, well ahead of the paper in 1872. The patient was dismissed after a short time. Four years later, 5 patients were collected and this small series was published under the title of “multiple hemorrhagic sarcoma,”\textsuperscript{1} soon to bear the author’s name as an eponym.

Over the past decade we have busied ourselves with the publications of historical water colors, painted on site in Vienna, by doctors and still available in overabundance in medical facilities. Two books and several papers and posters of ours ensued: one volume about historical skin water colors as observed and judged by present-day celebrities, another following the same pattern, on ophthalmological illustrations. The skin volumes sold out quickly, but the eye volumes still sit on our Academy of Sciences’ shelves.\textsuperscript{7,8}

A short while ago, sifting through piles of research, we serendipitously found a sarcoma case, painted by Dr Carl Heitzmann (1836–1896). This water color was made before the paper by Kaposi was printed, in 1872.\textsuperscript{1} This news recently made it into The Lancet.\textsuperscript{9}

**HAIL WALPOLE, AGAIN**

Carl Heitzmann, was born in Croatia, and later became Doctor of Surgery of Vienna and a (dermato)pathologist in Vienna; he then immigrated to the United States in 1874. In September 1876, he became founding member of the American Dermatologic Association. He was a talented painter in the fields of dermatology, ophthalmology, pathology, and surgery during his Vienna years, and eventually practiced dermatology in New York City. (He left behind in Vienna his brother Julius, also a physician and painter, who died in 1922.)

Interestingly, pictures of the first-ever (ophthalmo)fundoscopical atlas by Eduard Jaeger in Vienna largely came from the same brushes. Owners today are the College of Physicians of Philadelphia. One contributor to our volume came from the present-day proprietors of whose namesake in Philadelphia was of Professor Edward Jaeger in Vienna. Other contributors were the great-grandson of Vienna’s first professor Georg Joseph Beer (1763–1821), and still another, the recently deceased nestor of British dermatology, Darrel Wilkinson (1919–2009).\textsuperscript{9}

William Faulkner put it, “The past is never dead. It’s not even past,” which is widely unbelieved in medicine today.

**REFERENCES**

Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of more than 20 neoplastic entities derived from mature T cells and natural killer cells involved in innate and adaptive immunity. T-cell lymphomas account for 10% to 15% of all cases of non-Hodgkin lymphoma in the United States (approximately 5000 to 6000 cases a year). PTCL represent approximately 12% of all non-Hodgkin's lymphomas in Western countries. With few exceptions, these malignancies, which may present as disseminated, cutaneous (CTCL), or predominantly nodal disease (Table), are clinically aggressive and have a dismal prognosis. Conventional therapies, historically based on protocols for aggressive B-cell lymphomas, deliver less than adequate outcomes. The majority of patients experience early relapse after front-line treatment and current 5-year overall survival is only 10% to 30%. Pralatrexate is a new chemotherapeutic agent that inhibits dihydrofolate reductase with promising activity in T-cell lymphomas and non–small cell lung cancer. It was approved by the Food and Drug administration (FDA) for use in the treatment of relapsed or refractory PTCL.

DESCRIPTION
Pralatrexate is an antineoplastic agent from the antifolates class, which includes methotrexate, pemetrexed, and raltitrexed. Pralatrexate is a 10-propargyl 10-deazaaminopterin derivative designed to have high affinity for the one carbon-reduced folate carrier (RFC-1), which leads to better cellular internalization of the drug and has a greater antitumor effect than methotrexate. Several clinical trials have been conducted to evaluate the use of this drug in PTCL and other malignancies such as non–small cell lung cancer. This review offers focused information for dermatologists about pralatrexate and its use as a novel treatment for relapsed or refractory PTCL.
**Mechanism of Action**

The polyglutanate metabolites of the antifolate class reversibly inhibit dihydrofolatereductase, the enzyme that reduces folic acid to tetrahydrofolic acid. This inhibition limits the availability of one-carbon fragments necessary for synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. Antifolates also cause an increase in intracellular deoxyadenosine triphosphate thought to inhibit ribonucleotide reduction and polynucleotide ligase, an enzyme concerned with DNA synthesis and repair. Tissues with high rates of cellular proliferation such as neoplasms, psoriatic epidermis, the lining of the GI tract, hair matrix, bone marrow, and fetal cells are most sensitive.

**Clinical Pharmacology**

The half-life of pralatrexate is 12 to 18 hours, and the total systemic exposure and maximum plasma concentration increase proportionally with the dosage (dose range 30–325 mg/m², including pharmacokinetics data from high-dose solid tumor clinical studies). The pharmacokinetics did not change significantly over multiple treatment cycles, and no accumulation in plasma was observed; it is approximately 67% bound to plasma proteins. In vitro, pralatrexate has a low potential to induce or inhibit the activity of CYP450 isozymes or hepatic glucuronidases. Approximately 34% of the drug is excreted unchanged in the urine following a single dose of 30 mg/m² administered as an intravenous push over 3 to 5 minutes.

**Clinical Trials**

Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma (PROPEL), the largest prospective, open-label, single-arm, multicenter, international trial was conducted in patients with relapsed or refractory PTCL who progressed following ≥1 course of prior therapy. Pralatrexate was administered by intravenous push at 30 mg/m²/wk for 6 weeks in 7-week cycles until disease progression or unacceptable toxicity developed, and was supplemented with 1 mg vitamin B12 administered intramuscularly every 8 to 10 weeks and oral folic acid 1.0 to 1.25 mg/d. The primary end point was overall response rate. Secondary end points included duration of response, progression-free survival (PFS), and overall survival (OS). A total of 115 patients were enrolled in the study, 111 patients were treated, and 109 patients were evaluable for efficacy. Patients were heavily pretreated, having failed a median of 3 regimens; 78 patients (70%) failed cyclophosphamide, doxorubicin, vincristine, and prednisone and 18 (16%) previously underwent autologous stem cell transplantation. Prior therapies also included etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin and bexarotene, denileukin difitox, and photopheresis. Approximately 27% (24%) had no evidence of response to any previous therapy. Seventy (63%) did not have evidence of response to their most recent prior therapy before entering the study.

**Efficacy**

The overall response rate in the 109 evaluable patients was 29% (n=32), including 11% complete responses (n=12) and 18% partial responses (n=20), with a median duration of response of 10.1 months. Median PFS and OS were 3.5 and 14.5 months, respectively. Initial response assessment was scheduled at the end of cycle 1. Of the responders, 66% did so within cycle 1. The median time to first response was 45 days (range 37–349 days).

**Adverse Reactions**

Pralatrexate was well tolerated, with 77 patients (69%) receiving full-dose therapy and 85% of all scheduled doses administered. The most frequent grade 3 and 4 adverse effects were thrombocytopenia (33%), mucositis (21%), and anemia (17%). Serious adverse effects included pyrexia, febrile neutropenia, and sepsis. Eight (7%) patients died during treatment or within 1 month of the last dose.

**Safety**

Pralatrexate is a pregnancy category D medication. It can cause fetal harm when administered to a pregnant woman. It was embryotoxic and fetotoxic in rats at intravenous doses of 0.06 mg/kg/d.
Pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions as well as a dose-dependent increase in postimplantation loss. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazard to the fetus.14

Pediatric patients were not included in the clinical studies. Thus, the safety and effectiveness in pediatric patients has not been established. Thirty six percent of patients (n=40) were 65 years and older. No overall differences in efficacy and safety were observed in patients based on age (younger 65 years compared with 65 years and older).

Liver function test abnormalities have been observed after administration. Persistent liver function test abnormalities may be indicators of liver toxicity and require dose modification. Caution is advised when administering to patients with moderate to severe impairment. Patients should be instructed to take folinic acid and receive vitamin B12 to potentially reduce treatment-related hematological toxicity and mucositis.

Complete blood cell counts and severity of mucositis should be monitored weekly. Dose-modification schedules should be followed based on the levels of neutropenia and mucositis. Serum chemistry tests, including renal and hepatic function, should be performed prior to the start of the first and fourth dose of a given cycle.14

CONCLUSIONS

Pralatrexate is interesting to the dermatologist treating CTCL and transformed CTCL as a form of PTCL when traditional options have failed. As we grow more comfortable as a result of increasing experience with the drug, pralatrexate may replace some of the more patient-taxing alternatives. Pralatrexate also offers treatment options for disease progression unchecked by phototherapy and other chemotherapeutic approaches. Even for dermatologists who do not foresee utilizing this type of medication in their practice, knowing that an effective and safe antifolate agent for CTCL and transformed CTCL should add value to their competence in the management of this disease.

REFERENCES

9TH WORLD CONGRESS OF COSMETIC DERMATOLOGY
BY THE INTERNATIONAL ACADEMY OF COSMETIC DERMATOLOGY
ATHENS, GREECE
JUNE 27-30, 2013
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Endometriosis is a relatively common condition defined by the presence of endometrial glands or stroma outside of the uterus. Most commonly, this condition affects the pelvic organs; however, implants of endometrial tissue have been reported in almost every organ system. The incidence of umbilical endometriosis has been reported to be between 0.5% to 4% in patients with endometriosis.

The complete pathogenesis of endometriosis is unknown, but several mechanisms have been proposed. These include Sampson’s hypothesis of retrograde flow, lymphatic spread, and the coelomic-metaplasia hypothesis. Cutaneous implants are also thought to involve these mechanisms as well as iatrogenic seeding. Our patient likely developed the umbilical implant from iatrogenic seeding at the time of her previous exploratory laparoscopy. Abdominal scar endometriosis related to prior hysterectomy, cesarean section, hernia repair, or exploratory laparoscopy has been well documented. Spontaneous umbilical endometriosis has also been reported. A case of umbilical endometriosis with demonstrated endometrial stroma in lymphatic channels has been reported.

A case has been reported of a patient with a mean age at presentation of 37.7 years, with symptoms occurring on average 18 months prior to presentation. Patients may present with pain, cyclical bleeding, or swelling. The lesions often appear to be brown, blue, purple, or red.

Histopathology of endometriosis may show glands in any stage of the menstrual cycle. Dermoscopy of cutaneous endometriosis has been described as homogenous reddish pigmentation with “red atolls.”

Treatment typically consists of surgical excision. Recurrences have been reported. Hormonal therapy is usually reserved for symptom control until surgical excision can be performed. Rare cases of malignant transformation have been described. Patients should be referred to a gynecologist to explore the possibility of coexisting pelvic endometriosis.

CONCLUSIONS
This case is unusual in that the patient had a bicornuate uterus—a nonobstructing mullerian anomaly. Obstructing mullerian anomalies are a known risk factor for endometriosis. Several studies have investigated the frequency of endometriosis in the infertile population. These studies showed an equal prevalence between infertile controls and those with nonobstructing mullerian anomalies. To our knowledge, however, no studies have investigated the role of nonobstructing mullerian anomalies and endometriosis in the general population. The prevalence...
of endometriosis is significantly elevated in the infertile pop-
ulation compared with the general population. A bicornu-
ate uterus occurs due to incomplete fusion of the mullerian
ducts, resulting in a single cervix with two endometrial cavities.
The differential diagnosis of any umbilical nodule should
include cutaneous endometriosis, umbilical hernia, Sis-
ter Mary Joseph nodule, nodular melanoma, and pyogenic
granuloma.49,13

Figure 1. Firm, tender, brown papule in the umbilicus mea-
suring 4 mm in diameter. Note the presence of an umbilical
piercing and gloved finger to the right and left of the umbilicus,
respectively.

Figure 2. Bicornuate uterus sliced coronally.

Figure 3. Hematoxylin-eosin stain (original magnification ×4)
showing branching tubular glands in the dermis.

Figure 4. Hematoxylin-eosin stain (original magnification
×10) showing glands lined by stratified columnar epithelium,
surrounded by small cells with scant cytoplasm, characteristic
of proliferative-phase endometrial stroma. Hemosiderin-laden
macrophages are seen in the gland lumen.
REFERENCES

Bacterial culture results of the blood and pustules content were negative. Shaved biopsy specimens from the pustular lesions revealed diffuse mild spongiosis with extensive subcorneal collections of neutrophils and confluent acantholysis forming intrepideral bullae (Figure 1 and Figure 2). This was accompanied by a superficial perivascular and interstitial lymphocytic inflammatory infiltrate showing mild exocytosis. No apoptotic keratinocytes or eosinophils were observed. No microorganisms were identified with periodic acid-Schiff and gram stains. Immunofluorescence studies were negative. Based on the histopathologic changes and the patients' history, a diagnosis of acute generalized exanthematous pustulosis (AGEP) concurrent with Hailey-Hailey disease (HHD) was made. The patient was not given any treatment except for withdrawal of the antibiotic clindamycin. The skin lesions and systemic symptoms resolved rapidly within 4 days, with mild desquamation. Rapid resolution of the skin lesions on withdrawal of the offending medication confirmed our diagnosis.

COMMENT

AGEP was first proposed as a distinct entity by investigators in 1968 and was further distinguished from pustular psoriasis by researchers in 1991. It is currently recognized as a unique reaction pattern associated with systemic medications in more than 90% of cases, particularly antibiotics. Other medications, including the antimiycotic agent terbinafine, the immune suppression agent azathioprine, and the COX-2 selective nonsteroidal anti-inflammatory drug minesulide, to name a few, and viral infection such as enterovirus, hepatitis virus B, and pavovirus B19, have been associated with the development of AGEP. Pathogenesis of AGEP seems to be mediated by T cells. Drug-specific T-cell–related expression of the potent neutrophil-attracting chemokine interleukin 8 has been shown to be elevated in keratinocytes and infiltrating mononuclear cells in AGEP.

The onset of AGEP is generally abrupt and the process is characterized by small (<5 mm), nonfollicular sterile pustules in the background of erythema over an extensive body surface, and it is typically associated with fever and elevated blood neutrophils. Histopathologic features of AGEP are that of a pustular dermatosis, mimicking conditions such as pustular psoriasis, subcorneal pustular dermatosis (Sneddon-Wilkinson), impetigo, and pustular drug eruption. Thus, the diagnosis relies on clinico-pathologic correlation. The correct diagnosis of this potentially life-threatening disorder is important in patient management because it requires simply withdrawal of the offending antibiotics, which will lead to complete resolution of the lesions within 2 weeks. The classic clinical and histopathologic features have been summarized in a validation score system developed by the EuroSCAR study group.

The most important differential diagnosis of AGEP is other pustular dermatoses, particularly pustular psoriasis. In fact, AGEP can be very difficult to distinguish from pustular psoriasis, and...
Acute Generalized Erythematous Pustulosis

CASE STUDY

July/August 2012

SKINmed. 2012;10:251–253

Acute Generalized Erythematous Pustulosis (AGEP), first described by Hailey-Hailey in 1939, is a rare skin disorder characterized by acantholysis of the epidermis. AGEP is inherited in an autosomal-dominant fashion with a great variation in the pattern and severity, but generally runs a chronic relapsing course typified by recurrent vesicles and erosions particularly involving the flexural areas such as the axillae, groin, neck, and submammary regions. Most individuals have the disease with a relatively limited extent, although widespread and severe involvement can occur. The underlying gene defect has recently been localized to mutations in the ATP2C1 gene on chromosome 3q21, which encodes a calcium pump. The mechanism by which mutant ATP2C1 causes acantholysis remains unknown, but it may be related to abnormalities of cytoplasmic as well as Golgi calcium levels that are critical in maintaining the integrity of the epidermis. From our search of the English literature, AGEP has not been associated with pustular dermatoses.

When AGEP develops in a patient with HHD, as in our patient, the clinical presentation and histopathologic changes can be confusing and the clinical and histopathologic diagnosis can be challenging. Clinically, pustules are unusual for HHD except for superimposed secondary infection. On histopathology, acantholytic changes are not a feature of AGEP and should suggest the differential diagnosis of acantholytic dermatosis and autoimmune blistering disorders. Clinical history and immunofluorescence studies are necessary for correct diagnosis.

CONCLUSIONS

We documented herein a drug-induced AGEP that developed in a patient with HHD, which presented a diagnostic challenge both clinically and histopathologically. Familiarity with the two disease entities made it possible to reach a prompt and accurate diagnosis, which led to proper management of the patient and rapid resolution of the lesions. To our knowledge, this is the first case of AGEP associated with HHD reported in the English literature.

REFERENCES


DISCUSSION

Wegener’s granulomatosis is a rare autoimmune disease classically characterized by granulomatous inflammation of the lower and upper respiratory tracts, pauci-immune glomerulonephritis, and necrotizing vasculitis of small and medium vessels. Patients may present with severe multisystem involvement or limited disease. Antineutrophil cytoplasmic antibodies directed at neutrophil proteinase 3 (c-ANCA) occur in approximately 80% of patients with severe disease and 60% of those with limited involvement. Although the pathogenesis of Wegener’s granulomatosis has not been fully elucidated, it is thought to be associated with a genetic predisposition, perhaps exacerbated by environmental exposures.

Levamisole is an antihelminthic medication that had long been used for its immunomodulatory effects in a broad variety of diseases, ranging from relapsing nephrotic syndrome to adenocarcinoma of the colon. Dermatologists had employed the drug in the treatment of bacterial, viral, and parasitic infections as well as collagen vascular diseases and inflammatory dermatoses with varied success. Levamisole was removed from the US market in 2000, but recently, it has been used increasingly as a bulking agent for cocaine and levamisole. Adverse events of levamisole reported in the literature range from general flu-like symptoms to agranulocytosis. Documented cutaneous side effects include hypersensitivity reactions, lichenoid, and fixed-drug eruptions and multiple reports of vasculitis. Investigators have reported large vessel necrotizing vasculitis of the bilateral ear lobes in a pediatric patient with nephrosis treated with levamisole. Other investigators described a child with heterozygous factor V leiden mutations that developed cutaneous...

CASE STUDY

Levamisole-Induced Wegener’s Granulomatosis Following Contaminated Cocaine Abuse

Sandra A. Kopp, MD; Whitney A. High, MD, MEng; Justin J. Green, MD

A 44-year-old woman with a medical history of chronic pain syndrome presented with a 3-day history of a painful “rash” that started on her face and spread to her legs. Further history revealed that she recently started a new medication, varenicline, 7 weeks prior to admission and had a long-standing history of intranasal cocaine use. Review of systems was significant for rhinitis, nasal congestion, joint pain, and a febrile episode 2 days prior to admission.

Physical examination revealed centrally violaceous, tender, stellate, and retiform purpuric patches and plaques on her extremities, nasal dorsum, and cheeks. Approximately 1.0-centimeter tender purpuric nodules were noted on her bilateral second proximal interphalangeal joints. She was afebrile.

Initial laboratory data revealed a mild leukopenia, normal serum urea nitrogen and creatinine without hematuria, and an elevated erythrocyte sedimentation rate. Further analysis showed a normal complement level, negative antinuclear antibody, human immunodeficiency virus, rapid plasma reagin, and hepatitis panel. Trace cryoglobulinaemia and a positive anti-streptolysin O were noted, along with a positive antineutrophil cytoplasmic antibody (c-ANCA) (>8.0 U) and perinuclear antineutrophil cytoplasmic antibodies, or p-ANCA (1.5 U). The hypercoagulable workup was negative. A skin biopsy taken from the left thigh was consistent with leukocytoclastic vasculitis.

After several weeks of high-dose oral prednisone taper, the patient’s symptoms improved, but flared upon discontinuation. On follow-up, she admitted to frequent relapses of cocaine abuse and had developed tender purpuric plaques on her nose, ears, and extremities, some with ulcerations (Figure 1 and Figure 2). She also had significant edema and joint pain that limited her ambulation. Further evaluation revealed normal chest x-ray results; however, computed tomography of her sinuses demonstrated thickened maxillary sinuses consistent with subacute/chronic sinusitis. She also developed hematuria. Mass spectrometry analysis of hair and urine samples tested positive for cocaine and levamisole. A presumptive diagnosis of levamisole-induced Wegener’s vasculitis was made. She was restarted on high-dose prednisone and methotrexate with improvement and advised to discontinue cocaine use, so as to avoid exposure to both substances. (SKINmed. 2012;10:254–256)

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Levamisole-Induced Wegener’s Granulomatosis

CASE STUDY

July/August 2012

SKINmed. 2012;10:254–256

In 2008, researchers described a German patient with c-ANCA positive for Wegener’s granulomatosis following cocaine abuse, without mention of levamisole toxicity. Recently, documented cases of p-ANCA–positive vasculopathy following cocaine abuse has led to the link of levamisole-induced vasculopathies once thought to be attributed to pure cocaine. Because it is difficult to detect levamisole secondary to its short half-life of approximately 5 hours, however, a causal relationship is difficult if samples are not taken within 48 hours of last use. Mass spectrometry has facilitated this detection. In addition, a recent report documented levamisole-laced cocaine causing occlusive necrotizing vasculitis of the ears.20

CONCLUSIONS

Our case highlights the importance of epidemiologic considerations when evaluating a difficult patient. According to the Drug Enforcement Administration, 69% of seized cocaine at US borders was found to contain levamisole. Physicians should be aware of this potential exposure in cocaine-abusing patients, and should recognize its potentially devastating effects.

To date there are only a handful of documented cases of presumed levamisole-induced vasculitis. Our report is one of the first to document levamisole exposure, by means of mass spectrometry, a vasculitis, and c-ANCA positivity, leading to the diagnosis of Wegener’s granulomatosis, likely exacerbated by the levamisole-containing illicit cocaine.

REFERENCES


SKINmed. 2012;10:254–256

Levamisole-Induced Wegener’s Granulomatosis

Figure 1. Purpuric patch on the right nasal sidewall secondary to vasculitis.

Figure 2. Purpuric patch on the right helix secondary to vasculitis.

necrosis with formation of p-ANCA and lupus anticoagulant after receiving long-term treatment with levamisole. Purpura of the ears was reported in five pediatric patients on long-term treatment with levamisole associated with anticytoplasmic antibodies, histologically ranging from leukocytoclastic and thrombotic vasculitis to vascular occlusive disease. Disseminated p-ANCA positive autoimmune disease without cutaneous involvement has also been reported during treatment with levamisole.

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DISCUSSION

Atypical PR occurs in one fifth of all patients with PR.\textsuperscript{1-3} Several unusual variants are reported in the literature depending on morphology and distribution.\textsuperscript{4}

We believe PR was an appropriate label for the eruptions in this patient. Other diagnoses such as dermatophytosis, secondary syphilis, atopic dermatitis, psoriasis, and contact dermatitis were unlikely in our patient. The abdominal eruption experienced by our patient 4 months prior was likely to be a herald patch, and axillary lesions were actually secondary eruptions of PR. The condition described here is pityriasis rosea of Vidal (PRV), an uncommon type of PR described by Jean Baptiste Vidal in 1882.\textsuperscript{4} This is also known as pityriasis circinata et marginata of Vidal.

PRV has a distinct presentation of multiple, large, oval or round, coalescent annular eruptions that are found on the groin or axillae within a few days. Individual lesions range from 3 cm to 6 cm in longest diameter and characteristically have central clearing and a rim of collarette scales with surrounding erythema. A prodrome may be noted before the onset of herald plaque. The trunk and extremities are spared in PRV. All of these features were present in our patient.

Herald plaque may be absent, inconspicuous, or, rarely, may be resolved by the time secondary eruptions appear. Secondary eruptions in PR generally follow a herald plaque within 2 weeks, but may be delayed up to 3 months.\textsuperscript{1,2} In our patient, the secondary eruptions in axillae appeared 4 months after the onset of the earliest lesion on his lower abdomen.

Our case illustrates two findings. Firstly, sudden onset of scaly axillary eruptions may be the result of PRV. Secondly, there may be a significant delay in the appearance of secondary eruptions of PR following a herald patch. The cause of such delayed eruptions remains a mystery in our immunocompetent patient. This patient did not demonstrate the recurrence during 6 months of observation. He was later lost to follow-up. (SKINmed. 2012;10:257–258)

CONCLUSIONS

PR may present with atypical clinical features. This often leads to misdiagnosis, especially when certain clues to the appropriate diagnosis are missing. The case presented here may be used to alert clinicians to the unusual clinical manifestations of delayed onset of secondary eruptions in a rare variant of PR, PRV. The knowledge of these unusual clinical findings may avoid misdiagnosis by clinicians.
Bilateral Scaly Plaques in Axillae

Figure 1. Right axilla showing multiple, oval sharply defined, coalescent scaly annular plaques surrounded by erythema.

Figure 2. Similar eruptions in left axilla.

Figure 3. Close view of right axillary lesions demonstrating central clearing and typical collarette scales.

Figure 4. Skin biopsy revealed parakeratosis, epidermal spongiosis, dermal inflammatory cells, and extravasated red blood cells.

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To the Editor:

A case recently observed in our department captured our attention. A 42-year-old man presented to our clinic for basal cell carcinoma; however, at the time of medical examination, we noticed the presence of many freckles solely on his right arm. After assessing his case history, we learned about a birth trauma that caused a palsy of his right brachial plexus. Freckles appeared about 5 years before but neither his working environment nor his daily life had been the cause of prolonged and localized sun exposure. Since the dimension and the one-sided location were unusual, we performed punch biopsy. Results showed a slight hyperplasia of epidermis, an increase of melanin with normal number of melanocytes, and some macrophages in papillary dermis; therefore, the diagnosis of ephelides (or freckles) was confirmed.

DISCUSSION

This prompted us to search for the potential connection between the appearance of localized skin lesions and the nerve injury. Several cases associated with this have been reported, including a case of papillomatosis cutis due to paraplegia,1 a case of acne limited to an area of post-traumatic neuralgia,2 several cases of malignancy localized on amputation stumps,3 and many more linked with herpes virus infections.3 The common feature in all of these conditions, whatever the cause, was the damage of peripheral nerve fibres. This leads to a condition of vulnerability of these regions, called “immunocompromised district.” These sites become permissive for a subsequent development of heterogeneous skin disorders, in particular malignancies, further infections, or dis-immune reactions. The nerve injury entails the onset of different diseases because of the impairment of the immune response (either defective or excessive) as a result of an altered signaling of neuromediators. It is known that immune response is the result of a complex set of cellular interactions, each with multiple regulatory points based on the normal trafficking of immunocompetent cells through lymphatic channels and on the signals that the neuropeptides and neurotransmitters released by peripheral nerves send to cell membrane receptors of immune cells. Neuropeptides released by cutaneous neurons such as substance P (SP), vasointestinal peptide, calcitonine gene-regulated peptide, proopiomelanocortin (POMC) peptides, and others, modulate the function of immunocompetent and inflammatory cells as well as epithelial and endothelial cells.4 Neuropeptides have been found to function as mediators of cell proliferation, cytokine and growth factor production, and adhesion molecule and cell surface receptor expression. In addition, many cells including keratinocytes, fibroblasts, endothelial cells, and inflammatory cells have been shown to release several neuropeptides and express their corresponding receptors.

These findings indicate that neuropeptides participate in the complex network of mediators that regulate cutaneous inflammation and immune response.4 An imbalance of these functions is obviously present in all of the conditions mentioned above. Post-traumatic neuralgia, paraplegia, herpes virus infections, and amputation are all conditions of clear nerve injury and, therefore, of impaired neuroimmune cross-talking. In post-neuralgia acne, the therapeutic effectiveness of capsaicin treatment supports the pathogenic role of SP. Moreover, the role of POMC and its derivatives (α, β, and γ-MSH) as melanocyte-stimulating hormones is well known and there is a link between immunomodulating neuropeptides and photosensitivity.5

CONCLUSIONS

In light of this, we think that the appearance of freckles on only the right arm of our patient might be related to the nerve fibres damage through an altered melanocyte response to sun exposure. This patient could be an example of an immunocompromised district.

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REFERENCES


**Figure.** Freckles found solely on the right arm of our patient.
A 32-year-old woman presented with an intensely pruritic eruption on the dorsa of the hands for the past 2 weeks. She belonged to a low-socioeconomic stratum and lived in unhygienic conditions among pets. The lesion progressed daily despite multiple application of an unknown product recommended by an unreputable source. Serpiginous, transluscent, erythematous raised tracts approximately 4 cm long and 1 to 2 mm wide was prominent, diagnostic of cutaneous larva migrans (Figure). Two doses of ivermectin 200 μg/kg of body weight given a week apart resulted in complete regression of the lesions during a period of 2 weeks.

Hookworm-related cutaneous larva migrans (HrCLM) is a parasitic skin disease caused by the migration of animal hookworm larvae in the epidermis. HrCLM is a self-limiting disease because the parasite is unable to invade the dermis in humans and hence unable to complete a life cycle. Occasionally, untreated cases may persist for longer periods.

Bacterial superinfection may occur as a result of scratching. HrCLM is endemic in the developing world; however, sporadic cases and small pockets of epidemics occur in developed nations, where travellers account for the majority of cases. Direct contact of skin with contaminated soil is the usual mode of transmission in humans. Larvae may be transmitted through fomites. The lesion starts as a small reddish papule. Subsequently, the diagnostic serpiginous, slightly elevated, erythematous track eventuates. Itching is typically very intense and can prevent patients from sleeping. The diagnosis is clinical and is supported by a recent travel history and the possibility of exposure. Ivermectin in a single dose (200 μg/kg of bodyweight) or repeated treatments with albendazole (400 mg daily) are effective therapies with cure rates of 92% to 100%.

Topical thiabendazole is an alternative in localized lesions. Regular treatment of dogs and cats with anthelmintic drugs is needed to control community outbreaks. Contact with contaminated soil should be avoided.
Sorilux™ (calcipotriene) Foam, 0.005%

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

INDICATIONS AND USAGE
Sorilux Foam is indicated for the topical treatment of plaque psoriasis in patients aged 18 years and older.

CONTRAINDICATIONS
Sorilux Foam should not be used by patients with known hypercalcemia.

WARNINGS AND PRECAUTIONS

Flammability
The propellant in Sorilux is flammable. Instruct the patient to avoid fire, flame, and/or smoking during and immediately following application.

Effects on Calcium Metabolism
Transient, rapidly reversible elevation of serum calcium has occurred with use of calcipotriene. If elevation in serum calcium outside the normal range should occur, discontinue treatment until normal calcium levels are restored.

Ultraviolet Light Exposure
Instruct the patient to avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use Sorilux Foam. [See Nonclinical Toxicology (13.1).]

Unevaluated Uses
Sorilux Foam has not been evaluated in patients with erythrodermic, exfoliative, or pustular psoriasis.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Sorilux Foam was studied in three-vehicle controlled trials. Seven hundred and thirty one subjects with plaque psoriasis, including 473 exposed to Sorilux Foam were treated twice daily for 8 weeks.

Adverse events reported in greater than 1% of subjects and in a hundred and thirty one subjects with plaque psoriasis, including 473 exposed to Sorilux Foam were treated twice daily for 8 weeks.

DRUG INTERACTIONS
No drug interaction studies were conducted with Sorilux Foam.

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects, Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. Therefore, Sorilux Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies of teratogenicity were done by the oral route where bioavailability is expected to be approximately 40-60% of the administered dose. Increased rabbit maternal and fetal toxicity was noted at 12 mcg/kg/day (132 mcg/m²/day). Rabbits administered 36 mcg/kg/day (396 mcg/m²/day) resulted in fetuses with a significant increase in the incidences of incomplete ossification of pubic bones and forelimb phalanges. In a rat study, doses of 54 mcg/kg/day (318 mcg/m²/day) resulted in a significantly higher incidence of skeletal abnormalities consisting primarily of enlarged fontanelles and extra ribs. The enlarged fontanelles are most likely due to calcipotriene’s effect upon calcium metabolism. The maternal and fetal no-effect exposures in the rat (43.2 mcg/m²/day) and rabbit (17.6 mcg/m²/day) studies are approximately equal to the expected human systemic exposure level (18.5 mcg/m²/day) from dermal application.

Nursing Mothers
It is not known whether calcipotriene is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sorilux Foam is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of Sorilux Foam in pediatric patients less than 18 years of age have not been established.

Geriatric Use
Clinical studies of Sorilux Foam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

Topically applied calcipotriene can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with use of topical calcipotriene. [See Warnings and Precautions (5.2).]

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 mcg/kg/day (corresponding to 9, 30, or 90 mcg/m²/day) showed no significant changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors. [See Warnings and Precautions (5.3).]

The genotoxic potential of calcipotriene was evaluated in an Ames assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, and a mouse micronucleus assay. All assay results were negative.

Studies in rats at doses up to 54 mcg/kg/day (318 mcg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling in full Prescribing Information].

The patient should be instructed as follows:

• Do not place Sorilux Foam in the refrigerator or freezer.
• Avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps.
• If Sorilux Foam gets in or near their eyes, to rinse thoroughly with water.
• Talk to their doctor if their skin does not improve after treatment with Sorilux Foam for 8 weeks.
• Wash their hands after applying Sorilux Foam unless their hands are the affected site
• Avoid fire, flame, or smoking during and immediately following application since Sorilux Foam is flammable.

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Stiefel a GSK company
Indicated for the topical treatment of plaque psoriasis in patients aged 18 years or older

My doctor has prescribed SORILUX Foam for my plaque psoriasis...

The only vitamin D₃ analog treatment in a topical foam formulation

VersaFoam®-AEF: Aqueous-based Emulsion Formulation
- Free of ethanol, preservatives, parabens, and fragrance
- SORILUX Foam, with VersaFoam technology, penetrates the skin barrier to deliver the molecule into the epidermis and dermis

Important Safety Information for SORILUX Foam
- SORILUX Foam should not be used by patients with known hypercalcemia
- The propellant in SORILUX Foam is flammable. Instruct the patient to avoid fire, flame, and/or smoking during and immediately following application
- Transient, rapidly reversible elevation of serum calcium has occurred with use of calcipotriene. If elevation in serum calcium outside the normal range should occur, discontinue treatment until normal calcium levels are restored
- Instruct the patient to avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use SORILUX Foam
- SORILUX Foam has not been evaluated in patients with erythrodermic, exfoliative, or pustular psoriasis
- Adverse events reported in greater than 1% of subjects and in a higher rate in subjects treated with SORILUX Foam compared with vehicle were limited to erythema
- SORILUX Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- It is not known whether calcipotriene is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORILUX Foam is administered to a nursing woman
- Safety and effectiveness of SORILUX Foam in pediatric patients less than 18 years of age have not been established
- SORILUX Foam is not for oral, ophthalmic, or intravaginal use

Please see Brief Summary of Prescribing Information on the next page.

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