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CME CREDIT

The Clinical Picture

Multiple leg ulcers in a traveler

A PREVIOUSLY HEALTHY 52-year-old white man presents with two painful ulcerations and a nodule in the lower extremities. The lesions appeared 1 month after a trip to Belize, in Central America. The lesions started as small pustules that gradually increased in size and began to ulcerate (FIGURE 1).

He denies any history of trauma or constitutional symptoms. Multiple empiric courses of oral antibiotics and antifungals provided by his primary care physician were ineffective. Multiple biopsies performed at another institution yielded nonspecific findings. Previous bacterial cultures were negative. The ulcers continued to enlarge, a new nodule developed on his leg, and we were consulted.

Q: Based on the history and clinical presentation, which is the most likely diagnosis?

- ❑ Pyoderma gangrenosum
- ❑ Venous ulcers
- ❑ Ecthyma
- ❑ Sporotrichosis
- ❑ Cutaneous leishmaniasis

A: All of the above are diagnostic possibilities in a previously healthy patient presenting with multiple leg ulcerations. The differential diagnosis of leg ulcers is extensive and includes inflammatory, infectious, metabolic, neoplastic, traumatic, vascular, neuropathic, and idiopathic conditions, as well as infestations and bites.

Pyoderma gangrenosum is an inflammatory, idiopathic dermatosis. In its classic form, it produces painful ulcerations, frequently involving the lower extremities. Although it is associated with inflammatory bowel disease, collagen vascular disease, and myeloproliferative diseases, in up to 50% of cases it presents in previously healthy people. Because of the lack of specific serologic and histopathologic findings, it is considered a diagnosis of exclusion.

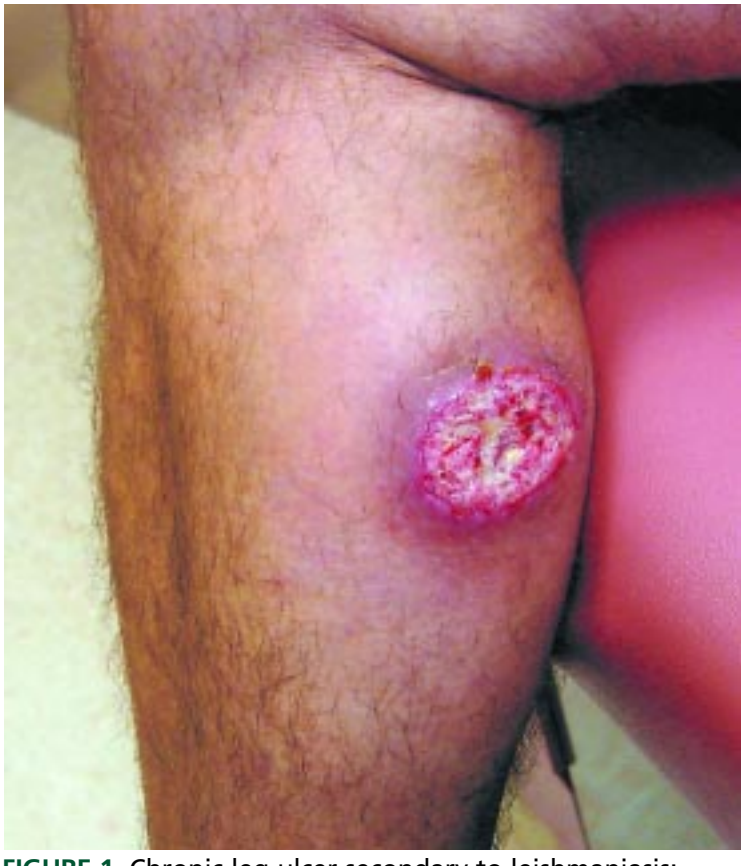

FIGURE 1. Chronic leg ulcer secondary to leishmaniasis: A deep ulceration with abdundant granulation tissue and a sharp, "rolled" border.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

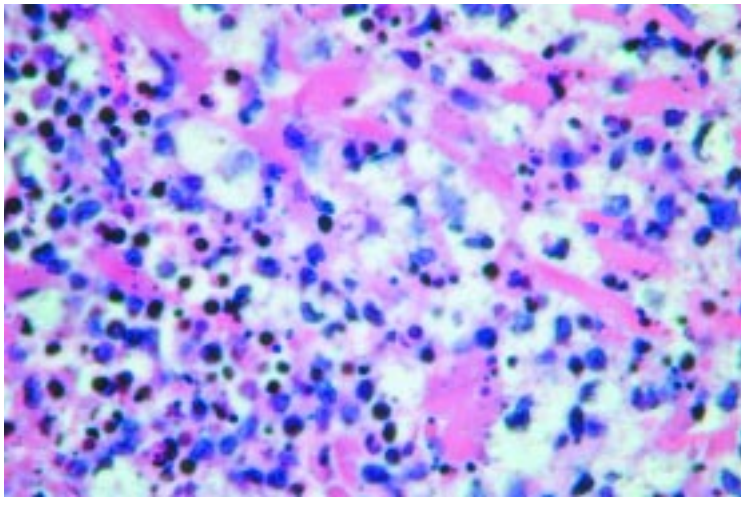

FIGURE 2. Abundant parasitized histiocytes in the dermis (hematoxylin and eosin, x 40).

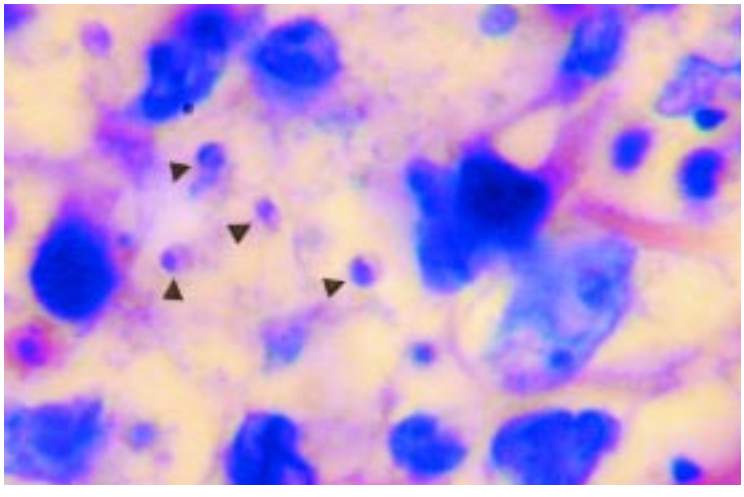

FIGURE 3. Leishmanial amastigotes (arrowheads) in a biopsy specimen (Giemsa, x 1000).

Venous ulcers account for up to 90% of all leg ulcers and develop in patients with chronic venous insufficiency. Classically, single or multiple ulcers are located on the lower medial aspects of the leg. Changes of stasis dermatitis and lipodermatosclerosis are found on the skin surrounding the ulcers. Varicose veins are usually present. In most cases, the diagnosis can be made on clinical grounds.

Ecthyma is a streptococcal or staphylococcal pyoderma. It can be considered a variant of impetigo. Children are most often affected, but it has been reported in adults. Ecthyma is common in tropical climates. It produces ulcerative lesions, mostly on the shin and the dorsum of the foot. The lesions begin as vesicopustules, which enlarge and become crusted. When the crust is removed, it leaves a punched-out ulceration with elevated edges.

Sporotrichosis is a deep mycosis caused by the dimorphic fungus *Sporothrix schenckii*, which is present worldwide. Most often, the disease affects the skin, subcutaneous tissue, and lymphatics; however, in very rare cases it may disseminate, particularly in immunocompromised patients. The initial lesion may begin as a tender nodule or ulcer at the site of primary cutaneous inoculation. Multiple lesions may appear along the lymphatic drainage after a few weeks. The diagnosis requires confirmation by isolation and culture of the organism.

Cutaneous leishmaniasis is a vector-borne zoonosis transmitted by sandflies. It is caused by different species of *Leishmania* (a protozoon), and it should be suspected in travelers to endemic areas who present with cutaneous ulcerations. The lesions are usually located in exposed areas of the body, including the lower extremities. Characteristically, the ulcers are painless unless secondary bacterial infection develops. The diagnosis is established by demonstration of the parasite in tissue specimens.

Case continued: Biopsy confirms diagnosis

The patient underwent punch biopsy of a new nodular lesion. Cultures for bacteria, mycobacteria, and fungi were negative. Skin stained with hematoxylin and eosin showed an acanthotic epidermis and a superficial and deep dermal granulomatous infiltrate with parasitized histiocytes (FIGURE 2). A Giemsa stain highlighted the intracellular leishmanial amastigotes (FIGURE 3). Special stains for fungi (periodic acid-Schiff and Gomori methenamine silver) were negative. A diagnosis of cutaneous leishmaniasis was made.

The patient refused antimonial therapy due to concerns about toxicity. He was started on pentamidine intramuscular injections, 300 mg/day (3 mg/kg) every other day with 3 days of rest after every fourth dose. This regimen was continued for 6 weeks, for a total of 15 doses. Oral ketoconazole was given at 400 mg/day for 8 weeks. After 8 weeks of therapy, his ulcers began to heal slowly.

MORE ABOUT CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis is a vector-borne zoonosis caused by an obligate intracellular protozoan parasite of the *Trypanosomatidae* family,[1] genus *Leishmania*. It is transmitted by the bite of an infective female sandfly. Other forms of leishmaniasis include a mucocutaneous form, a diffuse anergic form, and a visceral form.

Cutaneous leishmaniasis is endemic from Mexico southward, including all Central American countries and every South American country except Chile and Uruguay.[2]

Two million new cases per year are reported worldwide. Humans are "accidental" hosts, whereas rodents, dogs, and small mammals are reservoirs.[3]

Primary clinical and histologic features

Typically, cutaneous ulcers develop at the sites of sandfly bites on exposed areas such as legs, arms, and face. The lesions begin as erythematous papules. Multiple lesions may be present if multiple bites occurred or from secondary lympho-hematogenous spread from a bite site.

The histopathology of cutaneous leishmaniasis varies according to the age of the lesions and other host factors.[4] Initially, the parasite induces mixed inflammation with infiltration of histiocytes and variable amounts of lymphocytes, multinucleated giant cells, plasma cells, neutrophils, and eosinophils. In early lesions, parasite amastigotes are found within macrophages. In older lesions, granulomatous inflammation develops and fewer organisms are seen.

Not to be confused with histoplasmosis. A less-experienced pathologist may confuse the leishmanial amastigotes with another group of intracellular organisms, *Histoplasma* species, which are confirmed by the presence of internal organelles (nucleus and kinetoplast).

Furthermore, *Histoplasma* species can be demonstrated by special stains (periodic acid-Schiff, Gomori methenamine silver), but not with Giemsa stain.

Biopsy of fresh lesions, multiple lesions preferable

This case demonstrates the better yield when biopsy specimens are obtained from fresh nodules or early ulcerated lesions as compared with chronic long-standing ulcers. Definitive diagnosis requires laboratory confirmation, accomplished with histopathology, microbiology, serologic tests, or molecular techniques such as polymerase chain reaction assay. Multiple biopsy specimens should be obtained from the border of an active ulcer and should include some nonulcerated tissue.

Exclude other infections

One portion of the biopsy material should be submitted for culture to exclude bacterial, mycobacterial, and fungal infections. One portion must be submitted for hematoxylin-eosin staining and for special stains to rule out other infectious agents.

Request Giemsa stain

When leishmaniasis is suspected, the clinician should request Giemsa staining of a biopsy specimen (**FIGURE 3**). Leishmanial forms (amastigotes) may be easier to visualize in Giemsa-stained specimens than in specimens stained with hematoxylin-eosin. Giemsa staining may be obtained from methanol-fixed touch preparations (touch smears) or from paraffin-fixed specimens.[5]

Diagnostic yield is better with biopsy of fresh nodules or early lesions

Other tests

When routine tests are negative but cutaneous leishmaniasis is still considered likely, a biopsy specimen should be submitted for culture in the dimorphic NNN (Novy-McNeal-Nicolle) medium, available from the US Centers for Disease Control and Prevention (CDC).

Antibody analyses have low sensitivity and specificity for cutaneous leishmaniasis. The intradermal leishmanin (Montenegro) test is a screening tool that detects prior exposure to the parasite, but the test is not readily available in the United States. In situ hybridization[6] and polymerase chain reaction testing[7] are both sensitive and specific but are not required in most cases.

Treatment considerations

No current treatment for cutaneous leishmaniasis is ideal. The most efficacious treatments have known toxicities, and disease recurrence is not uncommon.

The decision on how and when to treat cutaneous leishmaniasis must take into account host factors and the location and bulk of the disease. Some lesions heal spontaneously. Local therapies for less virulent forms include local heat, cryotherapy, excision, intralesional antimonial agents, and paromomycin sulfate ointment.

Systemic therapy with intravenous or intramuscular antimonial compounds is the most effective and is the first-line treatment for cutaneous leishmaniasis.[8] The two available compounds are sodium stibogluconate and meglumine antimonate.

Pentamidine and amphotericin B have shown efficacy in some studies.[9,10] Other agents that have shown limited success or have not been studied enough to be recommended as first-line treatments include paromomycin, interferon gamma, oral azoles, dapsone, and allopurinol.

Prevention

Several vaccines are being developed.[11] In the meantime, preventive measures rely on sandfly and reservoir animal control to reduce transmission.[12,13] Travelers to endemic areas, including military personnel, should take measures such as the use of fine-mesh bed netting, insect repellents, and protective clothing, and should avoid outdoor activities in the evenings.

Further helpful information on leishmaniasis can be found at the CDC web site **www.cdc.gov/ncidod/dpd/parasites/leishmania/default.htm**.

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