TREATMENT CUTANEOUS LEISHMANIASIS

Although lesions heal spontaneously in the majority of cases, their spread or persistence indicates that treatment may be needed. One or a few small lesions due to "self-healing species" can be treated with topical agents. Systemic treatment is required for lesions over the face, hands, or joints; multiple lesions; large ulcers; lymphatic spread; New World CL with the potential for development of ML; and CL in HIV co-infected patients.

A pentavalent antimonial is the first-line drug for all forms of CL and is used in a dose of 20 mg/kg for 20 days, as for VL. The exceptions to this rule are CL caused by *Leishmania (Viannia) guyanensis*, for which pentamidine isethionate is the drug of choice (two injections of 4 mg of salt/kg separated by a 48-h interval), and CL due to *L. aethiopica*, which responds to paromomycin (16 mg/kg daily) but not to antimonials. Relapses usually respond to a second course of treatment. In Peru, topical imiquimod (5–7.5%) plus parenteral antimonials have been shown to cure CL more rapidly than antimonials alone. Azoles and triazoles have been used with mixed responses in both Old and New World CL but have not been adequately assessed for this indication in clinical trials. In *L. major* infection, oral fluconazole (200 mg/d for 6 weeks) resulted in a higher rate of cure than placebo (79% vs 34%) and also cured infection faster. Adverse effects include gastrointestinal symptoms and hepatotoxicity. Ketoconazole (600 mg/d for 28 days) is 76–90% effective in CL due to *L. (V.) panamensis* and *L. mexicana* in Panama and Guatemala. Miltefosine has been used in CL in doses of 2.5 mg/kg for 28 days. This agent is effective against *L. major* infections. In Colombia, where CL is due to *L. (V.) panamensis*, miltefosine was also effective, with a cure rate of 91%. For *L. (V.) braziliensis* infections, however, the results with miltefosine are less consistent. In Brazil, miltefosine cured 71% of patients with *L. (V.) guyanensis* infection. Other drugs, such as dapsone, allopurinol, rifampin, azithromycin, and pentoxifylline, have been used either alone or in combinations, but most of the relevant studies have had design limitations that preclude meaningful conclusions.

Small lesions (≤3 cm in diameter) may conveniently be treated weekly until cure with an intralesional injection of a pentavalent antimonial at a dose adequate to blanch the lesion (0.2–2.0 mL). An ointment containing 15% paromomycin sulfate, either alone or with 0.5% gentamicin or 12% methylbenzonium chloride, cured 70–82% of lesions due to *L. major* in 20 days and may be suitable for lesions caused by other species. Heat therapy with an FDA-approved radiofrequency generator and cryotherapy with liquid nitrogen have also been used successfully.

Diffuse Cutaneous Leishmaniasis (DCL) DCL is a rare form of leishmaniasis caused by *L. amazonensis* and *L. mexicana* in South and Central America and by *L. aethiopica* in Ethiopia and Kenya. DCL is characterized by the lack of a cell-mediated immune response to the parasite, the uncontrolled multiplication of which thus continues unabated. The DTH response does not develop, and lymphocytes do not respond to leishmanial antigens in vitro. DCL patients have a polarized immune response with high levels of immunosuppressive cytokines, including IL-10, transforming growth factor (TGF) β, and IL-4, and low concentrations of IFN-γ. Profound immunosuppression leads to widespread cutaneous disease. Lesions may initially be confined to the face or a limb but spread over months or years to other areas of the skin. They may be symmetrically or asymmetrically distributed and include papules, nodules, plaques, and areas of diffuse infiltration. These lesions do not ulcerate. The overlying skin is usually erythematous in pale-skinned patients. The lesions are teeming with parasites, which are therefore easy to recover. DCL does not heal spontaneously and is difficult to treat. If relapse and drug resistance are to be prevented, treatment should be continued for some time after lesions have healed and parasites can no longer be isolated. In the New World, repeated 20-day courses of pentavalent antimonials are given, with an intervening drug-free period of 10 days. Miltefosine has been used for several months with a good initial response. Combinations should be tried. In Ethiopia, a combination of paromomycin (14 mg/kg per day) and sodium stibogluconate (10 mg/kg per day) is effective.

MUCOSAL LEISHMANIASIS

The subgenus *Viannia* is widespread from the Amazon basin to Paraguay and Costa Rica and is responsible for deep sores and for ML (Table 251-1). In *L. (V.) braziliensis* infections, cutaneous lesions may be simultaneously accompanied by mucosal spread of the disease or followed by spread years later. ML is typically caused by *L. (V.) braziliensis* and rarely by *L. amazonensis*, *L. (V.) guyanensis*, and *L. (V.) panamensis*. Young men with chronic lesions of CL are at particular risk. Overall, ~3% of infected persons develop ML. Not every patient with ML has a history of prior CL. ML is almost entirely confined to the Americas. In rare cases, ML may also be caused by Old World species like *L. major*, *L. infantum* (*L. chagasi*), or *L. donovani*.

Immunopathogenesis and Clinical Features The immune response is polarized toward a T_H1 response, with marked increases of IFN-γ and TNF-α and varying levels of T_H2 cytokines (IL-10 and TGF-β). Patients have a stronger DTH response with ML than with CL, and their peripheral-blood mononuclear cells respond strongly to leishmanial antigens. The parasite spreads via the lymphatics or the bloodstream to mucosal tissues of the upper respiratory tract. Intense inflammation leads to destruction, and severe disability ensues. Lesions in or around the nose or mouth (espundia; Fig. 251-6) are the typical presentation of ML. Patients usually provide a history of self-healed CL preceding ML by 1–5 years. Typically, ML presents as nasal stuffiness and bleeding followed by destruction of nasal cartilage, perforation of the nasal septum, and collapse of the nasal bridge. Subsequent involvement of the pharynx and larynx leads to difficulty in swallowing and phonation.

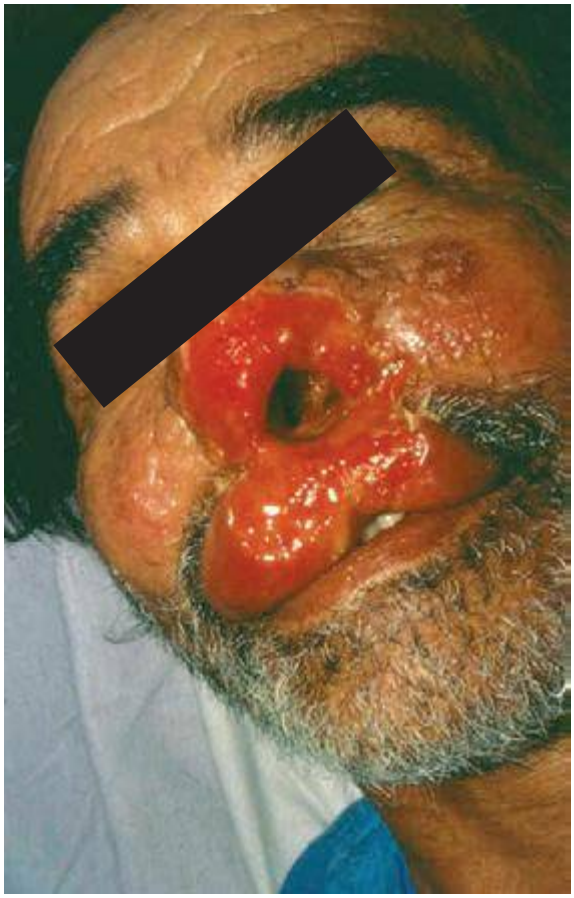

FIGURE 251-6 Mucosal leishmaniasis in a Brazilian patient. There is extensive inflammation around the nose and mouth, destruction of the nasal mucosa, ulceration of the upper lip and nose, and destruction of the nasal septum. *(Courtesy of R. Dietz, Universidade Federal do Espírito Santo, Vitória, Brazil.)*