Diagnosis and Management of Oral Leishmaniasis—Case Series and Literature Review

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The worldwide prevalence of leishmaniasis is increasing because of ecologic changes and increased medical profession awareness. Furthermore, solitary cases have been recently reported in Western countries. The authors describe the epidemiology, mode of transmission, and diagnosis of leishmaniasis and present 4 oral cases treated with systemic, localized, or combined therapy. The authors suggest that clinicians should maintain a high index of suspicion for atypical, resistant, oral and perioral lesions in individuals with a history of traveling in certain geographic regions. After diagnosis, treatment should be determined jointly by experts from the fields of oral and maxillofacial surgery, oral medicine, and dermatology based on leishmaniasis species and clinical presentation.

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Leishmaniasis is a group of diseases caused by protozoan parasites of the *Leishmania* genus.[1] The worldwide prevalence and incidence of leishmaniasis are estimated at 12 million and 1.5 to 2 million, respectively. The latter is rapidly increasing because of urbanization, climate change, migration and travel into endemic areas for tourism and economic and political reasons.[2-4] *Leishmania* species are usually separated into Old World and New World types according to their geographic location, with different vectors serving as reservoirs. Old World leishmaniasis is found in open semiarid areas or deserts in some parts of Asia, the Middle East, Africa (mostly in the northern and tropical regions), and southern Europe.[5] New World leishmaniasis is usually found in forests, specifically in some parts of Mexico and Central and South America.[5] Recently, sporadic cases of leishmaniasis have been reported in southern Europe.[6-8] Moreover, in the United States, cases have been seen in Texas and Oklahoma, showing the extent of the geographic expansion of leishmaniasis. It has been proposed that this spread could be the result of climate change, the creation of environmental conditions that drew the enzootic cycle into peri-domestic surroundings, and increased human contact. Clarke et al[9] suggested that leishmaniasis occurrence followed a northeastern trajectory. Nevertheless, cases in the United States are mostly associated with immigration, tourist excursions in Latin America, and military travel in Iraq and Afghanistan.[10,11]

Individuals at risk for infection are those living in endemic locations and regional travelers, such as ecotourists, missionaries, and soldiers. Recently, an increase in the incidence of *Leishmania* and human immunodeficiency virus (HIV) coinfection has been noted and partly attributed to the geographic overlap between the 2 diseases.[12] HIV infection may reactivate latent infection and increase transmission rates through sandflies or intravenous drug usage.[12] HIV-positive patients

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usually have greater parasite loads and atypical symptoms (eg, gastrointestinal), especially with low CD4 cell counts. This group of HIV-infected patients responds poorly to treatment and shows high relapse rates.[2] Transplant recipients (mostly after kidney transplantation) also are more susceptible to leishmaniasis infection. Indeed, Antinori et al[13] reported that since 1990 an increase in cases of leishmaniasis has been seen in transplant recipients. Thus, immunosuppression after HIV infection or organ transplantation seems to predispose patients to leishmaniasis.

Old World leishmaniasis are caused primarily by *Leishmania major*, *Leishmania tropica*, and *Leishmania aethiopica*, whereas New World leishmaniasis are caused by *Leishmania mexicana*, *Leishmania venezuelensis*, *Leishmania amazonensis*, or the *Viannia* complex such as *Leishmania brasiliensis*, *Leishmania panamensis*, *Leishmania guyanensis*, and *Leishmania peruviana*. Sandflies serve as vectors for *Leishmania* transmission and are widely scattered throughout the tropics, subtropics, and temperate regions, including deserts, rain forests, savannahs, and highlands. They are more active from dusk to dawn, and their relatively small size (2 to 3 mm) allows them to pass through ordinary mosquito nets.[11] Fortunately, they are extremely sensitive to insecticides.[5] In each ecologic setting, specific parasite species and sandflies maintain the transmission cycle.[14] Leishmaniasis transmission occurs among wild animals, such as rodents, hyraxes, and marsupials, or peri-domestic animals, such as dogs.[5,15] *Leishmania* species exist in 2 basic forms, promastigotes (flagellated extracellular forms, found in sandflies) and amastigotes (nonflagellated and obligate intracellular forms, found in vertebral hosts). Female sandflies become infected after a blood meal of an infected human being or terrestrial mammals. Subsequently, the amastigotes differentiate in the gut of the sandfly and replicate as extracellular promastigotes (3 to 4 days).[1] Five to 7 days after infection, the parasites differentiate into the virulent promastigote, adapted for life in the mammalian host. Furthermore, impairment of the sandfly's feeding process usually promotes it to probe repeatedly and for longer periods, thus facilitating parasite transmission.[16,17]

The clinical manifestations of leishmaniasis, usually divided into cutaneous (CL), mucocutaneous (MCL), and visceral leishmaniasis, are determined by the parasite species and host immune response. In MCL, the primary cutaneous lesions are similar to the CL lesions; however, after various time frames, mucosal involvement may occur because of hematologic or lymphatic dissemination.[18] In New World leishmaniasis, the CL form may coincide with or develop into MCL.[18,19] Moreover, there may be cases in which the MCL would be seen without cutaneous lesions. In fact, in 30% of MCL cases, patients do not recall the presence of a primary cutaneous lesion. MCL is rare and often resolves spontaneously. However, in a minority of cases, MCL may result in major deformities or, rarely, death.[19-21]

Oral and perioral involvement can be nonspecific and remains a diagnostic challenge for the clinician.[3,18,21-24] Unfortunately, delayed diagnosis and the lack of consensus on optimal treatment[25] can frequently lead to inappropriate management of the disease.[2] This report describes 4 cases that show the diagnosis and various treatment options for oral and perioral leishmaniasis.

Report of Cases

Patients were treated for oral and perioral leishmaniasis in the Hadassah-Hebrew University Medical Center (Jerusalem, Israel). Three patients also were treated for associated skin lesions in the department of dermatology. The clinical presentation and therapeutic regiments are presented in Table 1.

PATIENT 1—PARENTERAL TREATMENT OF CL

A 14-year-old, generally healthy girl, residing in an endemic area, complained of persistent lip enlargement and sores that appeared after several days of fever and had been present for 3 months. The patient had been receiving treatment for chronic asthma with montelukast sodium 5 mg/day (Singulair, Merck, Sharp & Dohme B.V., Holland). At examination, the upper lip appeared swollen with crusts and scales, with no accompanying lymphadenopathy (Fig 1). Blood count was normal except for mild eosinophilia (0.76 K/μL; range, 0.04 to 0.4 K/μL). Skin smears stained with Giemsa showed Leishman Donovan bodies (amastigotes) and polymerized chain reaction (PCR) was positive for *L major*. The clinical presentation and histologic findings supported the diagnosis of CL. Treatment with parenteral antimonial sodium stibogluconate (SSG; Pentostam, GlaxoSmithKline, Barnard Castle UK) at a dose of 750 mg/day (20 mg/kg/day) was initiated. After 5 days, the patient and her family traveled abroad and treatment was halted for 10 days. Subsequent attempts to resume treatment were unsuccessful because of adverse drug reactions. These included facial and upper limb erythema, diaphoresis, and dyspnea, which required administration of hydrocortisone (100 mg) and promethazine (12.5 mg). Despite the risk of lip deformation, the patient was noncompliant for additional treatment. Complete healing with no residual scarring was seen after 4 months (Fig 2).

PATIENT 2—PARENTERAL TREATMENT OF MCL

A 65-year-old man, residing in an endemic area, presented with oral lesions of 2 months' duration. Eighteen