

Cutaneous and mucocutaneous leishmaniasis

CONSUELO V. DAVID*† & NOAH CRAFT*‡

**Divisions of Dermatology and Adult Infectious Disease, Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, †University of Maryland School of Medicine, Baltimore, Maryland, and ‡David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California*

ABSTRACT: Leishmaniasis is a cluster of diseases caused by protozoa in the genus *Leishmania*. There are three basic clinical forms: cutaneous, mucocutaneous, and visceral leishmaniasis. The present review focuses on the diagnosis and treatment of cutaneous and mucocutaneous leishmaniasis. Characteristics of both the human host and the parasite species influence the clinical disease manifestations that range from asymptomatic exposure, to self-healing skin ulcers, to life-threatening widespread destructive ulcerations. Whether through medical treatment or through spontaneous resolution, skin ulcerations generally result in disfiguring scars with significant social and economic impact. Tests to confirm the diagnosis should be performed on patients who have recently visited endemic areas and have skin or mucosal manifestations consistent with leishmaniasis. Treatment depends on the species of *Leishmania* and the risk of widespread or disfiguring disease. Because of increasing trends in global travel, educating health care providers to recognize and treat leishmaniasis in both endemic and non-endemic countries is imperative.

KEYWORDS: cutaneous leishmaniasis, *Leishmania* therapy, protozoa, tropical dermatology

Introduction

The term “leishmaniasis” describes a range of diseases resulting from infection with any of the protozoan parasites in the genus *Leishmania*. Depending on species type and host immune response, three general forms of clinical disease can arise: cutaneous, mucocutaneous, and visceral leishmaniasis. The present review will focus on the diagnosis and treatment of cutaneous and mucocutaneous disease.

Epidemiology and transmission

Over 350 million people reside in areas of active parasite transmission (1). Annually, an estimated

1.5–2 million children and adults develop symptomatic disease (2); subclinical infection adds to this significant disease burden (1). Leishmaniasis is associated with 2–4 million disability-adjusted life years and 70,000 deaths per year (2). It is a neglected disease embedded in poverty (1).

Leishmaniasis is endemic in 88 countries in Southern Europe, Central and South America, Africa, the Middle East, and South Asia (3). Seventy-two of these countries are developing nations, and 13 are among the least-developed nations (4). Ninety percent of cutaneous leishmaniasis (CL) cases are contracted in Afghanistan, Pakistan, Syria, Saudi Arabia, Algeria, Iran, Brazil, and Peru (2,5). Recognition and diagnosis of leishmaniasis are of growing importance even in countries where the disease is not endemic because of increased military appointment and voluntary travel to endemic countries. Although leishmaniasis is not endemic in the United States, members of the US military and other travelers not uncommonly return to the United States with infections.

Address correspondence and reprint requests to: Noah Craft, MD, PhD, DTM&H, Divisions of Dermatology and Adult Infectious Disease, Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Room 207, Hanley Hardison Building, 1124 W. Carson Street, Torrance, CA 90502, or email: ncraft@ucla.edu.

Leishmaniasis has traditionally been separated into two groups: Old World and New World leishmaniasis. These categories refer to the geographic region the infection is acquired. "Old World" leishmaniasis refers to the disease caused by species found in the Mediterranean basin, the Middle East, and Africa. "New World" leishmaniasis refers to the infection by the species found in Mexico, Central America, and South America. Virulence, pathogenicity, and clinical manifestations are species dependent. Understanding the geographic distribution of *Leishmania* can often narrow infection down to a specific group of *Leishmania* species and dictates treatment regimens, anticipation of clinical prognosis, and progression of disease.

Leishmaniasis is transmitted through the bite of an infected female sand fly that typically seeks blood meals at dusk (1) and is least active during the hottest parts of the day (6). After a sand fly feeds on the blood of an infected human or animal, the parasite replicates within the gut of the sand fly and then is injected into the skin during a subsequent blood meal (7). The prevalence of sand flies can vary with seasons in some geographic regions.

Leishmania is an intracellular parasite that targets and multiplies within phagocytic cells of the innate immune system such as the macrophage, dendritic cell, and neutrophil (8,9). Brisk replication can result in cell lysis followed by infection of surrounding macrophages. In a typical situation, infection and detection result in recruitment of inflammatory cells that in turn stimulate members of the adaptive immune response.

There are at least 21 species of *Leishmania* that can cause human disease. The range of interspecies variability in infectivity and virulence is wide. In humans, clinical symptoms are influenced by the type of immune response that the host mounts (10,11). Other influential human host properties include age and nutritional state (1). There is substantial evidence to suggest that *Leishmania* parasites can persist at both the primary infection site and/or the draining lymph nodes after healing (regardless of the use of medical therapy); many scientists believe that parasite persistence is required for long-term adaptive immunity to future infection (12). Although this provides protection against reinfection, there is an underlying risk of relapse if host immunity falters.

CL

CL is most commonly caused by the species *Leishmania mexicana*, *Leishmania (Viannia) braziliensis*,

or *Leishmania panamensis* in the Americas, and *Leishmania major* or *Leishmania tropica* in all other countries. *L. major* and *L. tropica* tend to be less severe, heal more quickly, and therefore, take on a relatively benign course. Regardless of species, CL is not life threatening. However, lesions can lead to significant disfigurement and social stigmatization. In a small percentage of cases, inadequate treatment of a primary CL lesion may leave an individual at risk for later development of mucocutaneous leishmaniasis.

History and clinical presentation

If practicing in a non-endemic country, both medical and travel histories are key elements to diagnosing leishmaniasis. Cutaneous lesions may develop anywhere from a few weeks to months after the sand fly bite, and the lack of travel in the immediate past does not rule out infection. The patient's immune status should be noted. CL lesions are usually found on exposed parts of the body such as the face, arms, and legs (13). Patients may have one or more lesions; in strict CL, each lesion represents an independent sand fly bite. In rare cases, CL can manifest as a disseminated disease (diffuse CL (DCL)). Lesions are often chronic and unresponsive to attempts at using antibiotics or steroids (6). Lesions are often pruritic and are not as painful as they may appear. In most cases, systemic symptoms are absent. However, some systemic symptoms such as lymphadenopathy, fever, and hepatomegaly have been reported to precede *L. braziliensis* ulcerative lesions (14,15).

Lesions may begin as small red papules (5–10 mm initially). Depending on the species of *Leishmania*, over 1–3 months, they can progress into erythematous nodules, indurated plaques, scaly plaques (FIG. 1A), or ulcers with raised, rolled dusky borders (FIG. 1B) (16–18). Lesions may be dry and crusted or accompanied by exudates (4). Satellite lesions and local lymphadenopathy are sometimes present. Lesions may leave depigmented retracted scars (4). Acutely, lesions of CL often are mistaken for furuncles and methicillin-resistant *Staphylococcus aureus* infections. The differential diagnosis for patients with chronic lesions like these and a travel history to endemic areas includes deep fungal infections (paracoccidioidomycosis and histoplasmosis), mycobacterial infections (*Mycobacterium marinum*, cutaneous tuberculosis, and other atypical mycobacteria), syphilis, tertiary yaws, leprosy, sarcoidosis, and cutaneous neoplasms.



FIG. 1. Cutaneous leishmaniasis lesions. (A) Scaly raised plaques caused by infection with *Leishmania major*. (B) Crusted ulcer with rolled indurated borders caused by infection with *Leishmania mexicana*.

Efforts have been made to classify the various cutaneous manifestations of different *Leishmania* species in the Old World and New World groupings, but these are not particularly useful clinically as there is so much overlap in presentations between species. The *Leishmania* species causing mucocutaneous leishmaniasis are most commonly found in the Americas, and progression to mucocutaneous disease is a small, but real, risk.

Diagnosis

Leishmania species have a complex life cycle and exist in two main morphologies. Within the sand fly, the parasites have flagella and are termed promastigotes. Within an infected cell, *Leishmania* species take on an ovoid morphology and are known as amastigotes (no flagella). This is the only clinically relevant form. Presence of amastigotes on touch preparation or histopathology is diagnostic.

Tissue scrapings are typically the first diagnostic step for ulcerative lesions. This can be performed in the office if the clinician is capable of staining the specimen with Giemsa stain. To perform a tissue scraping, the lesions must be cleaned and any eschars or exudates must be removed. Use of 1% lidocaine is helpful to decrease bleeding, optimize debridement, and obtain and improve tissue scraping quality (18). For tissue scrapings, a no. 10 or no. 15 scalpel blade may be scraped along the base of an active ulcer. Scraping should be performed with a pressure that is adequate to obtain exudates, without eliciting bleeding (18). On a glass slide, a circular motion should be used to spread the dermal tissue in a 2–3-cm diameter (19). The slide can be fixed briefly with methanol, Giemsa stained, and examined by a qualified provider for the presence of amastigotes.

If tissue scraping does not reveal amastigotes, but clinical suspicion remains high or if the lesion is nodular, a 4-mm punch biopsy should be performed at the edge of the lesion or ulcer in question (4,18). Half of the specimen can be used to make impression smears on a glass slide in the office. The punch specimen, simply, should be bisected, and then, the specimen should be grasped firmly with forceps to sequentially blot the flat edge onto a dry glass slide. It should be stained and examined as above. With the remaining tissue, pathologists can cut the tissue into 3–4- μ m sections and stain separate slides with hematoxylin and eosin or Giemsa (4,18). Brown-Hopps, Gram, or Leishman stains may also be utilized (4).

If positive, amastigotes are visualized within macrophages on touch preparation or histopathology. A helpful histopathologic clue is the rod-shaped kinetoplast (extranuclear structure containing mitochondrial DNA) next to the amastigote nucleus that stains intensely purple with hematoxylin (18). Typical infections have a mixed cell granulomatous inflammatory response in the dermis containing numerous parasitized macrophages, mononuclear cells, eosinophils, and lymphocytes (13).

If possible, culture and identification of *Leishmania* species can provide useful information for treatment and prognosis. Most laboratories are not prepared to assist with speciation of *Leishmania*. Thus, in the United States, it is recommended to send a fresh 4-mm punch biopsy specimen to the Centers for Disease Control and Prevention (CDC) in Atlanta. Specific culture media (Novy-MacNeal-Nicolle medium) and detailed instructions for sending the specimen can be obtained by calling (770) 488-4475. The CDC can determine the *Leish-*

mania species using both polymerase chain reaction and/or isoenzyme analysis.

The Montenegro or leishmanin skin test (LST) is occasionally utilized in endemic countries. The test is based on similar principles as purified protein derivative to detect exposure to tuberculosis, and as the LST detects a delayed-type hypersensitivity response, it cannot distinguish between prior infection and active infection. To perform the LST, a “phenol-treated *Leishmania* antigens” preparation is injected intradermally into the forearm. A diameter greater than 5 mm in 48–72 hours is considered positive (World Health Organization protocol). The LST is not available in the United States or Canada. Serologic tests are not sensitive for the diagnosis of CL (18).

Treatment indications

In an immunocompetent host, most lesions, particularly those under 10 mm, will self-resolve. Currently, medications used to treat leishmaniasis are expensive, difficult to obtain in the United States, and somewhat toxic. If culture and speciation are available, depending on the species of *Leishmania*, the stage, and anatomic location of the lesion, some medical providers may opt not to treat. For example, if a patient presents with small, late-stage lesions and because of *L. major* (species not associated with the Americas and has a less severe clinical course), a physician may forgo treatment to avoid exposing the patient to the toxicities of parenteral antimony.

However, untreated lesions can leave disfiguring scars that may affect activities of daily living and have social consequences. Without treatment, self-cure may take anywhere from 2 to 15 months, depending on the *Leishmania* species (20–23). Most lesions are treated to expedite healing, reduce scarring, prevent dissemination, and reduce chance of relapse (1). Treatment is also encouraged if there are multiple (>5–10) or large (>4–5 cm) lesions, if the lesion has been present for more than 6 months, or if the lesions are located in a cosmetically sensitive area (i.e., face) or is located over joints (19).

Depending on the species and treatment regimen, a clinician can anticipate a reduction in lesion size by two-thirds within the sixth week of treatment. Consider an alternate regimen if reduction falls between 1/3 and 2/3 of the original size. Definitely seek an alternate regimen if lesion reduction is less than one-third (1). Superficial bacterial infections may complicate ulcerated leishmaniasis lesions and can be treated with antibiotics appropriate for skin flora.

Treatment regimens

There are effective treatments for CL, however, associated toxicities make them suboptimal (Table 1). Currently, there is no medication that is both perfectly safe and completely efficacious. Many drugs used to treat leishmaniasis must be obtained directly from the manufacturer, are not available commercially, or must be obtained through compounding pharmacies. Because leishmaniasis is not a common disease in the United States, there are very few agents approved to treat leishmaniasis. There are no Food and Drug Administration-approved intralesional therapy protocols.

Pentavalent antimony

Pentavalent antimony (PA) is the most common form of treatment to date. The two forms of PA used are sodium stibogluconate (SSB) (8.5% antimony, Pentostam, GlaxoSmithKline, UK) and meglumine antimoniate (MA, 10% antimony). One meta-analysis reported that in the treatment of American CL, PA was superior to all other forms of therapy except pentamidine (24). The mechanism of action of antimonials against leishmaniasis involves both host factors and parasite factors. Trivalent antimony directly inhibits trypanothione reductase (25), but many of the mechanistic details remain unclear, and a thorough discussion is outside the scope of the present paper (reviewed by Ashutosh et al. (26)). In the United States, Pentostam must be obtained through the CDC and administered under a compassionate use protocol that is Institutional Review Board approved at a local institution. The CDC drug service can be reached at 404-639-3670 to obtain the details of how to initiate this process.

PA is highly effective and is the first-line treatment in most patients, especially those without comorbidities. PA is a particularly recommended treatment for American CL because of the potential risk of mucosal progression. For CL, the recommended dose is 20 mg/kg/day intravenous (IV) or intramuscular (IM) for 20 days. SSB is administered intravenously; MA can be administered IV or IM. In regions where PA is not commercially developed, it can be formulated in compound pharmacies (27).

Primary resistance to antimony is reported in up to 15% of patients treated with antimonial therapy (24). Both species and region affect treatment response. For example, the same *Leishmania* species may have different medication responses depending on the country of origin (24), and many *Leishmania* species are more commonly acquiring resistance to antimony as well. Treatment response

Table 1. Cutaneous, diffuse cutaneous, and mucosal leishmaniasis treatment regimens (1,27,97–99)

Disease type	Medication	Adult and pediatric doses	Adverse events	Notes
Cutaneous	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 20 days	*>50%: elevated LFTs, amylase/lipase (asymptomatic pancreatitis); 25–50%: myalgias, arthralgias; abdominal pain, nausea, thrombocytopenia; <25%: ECG changes and cardiotoxicity	Avoid in patients with cardiac abnormalities and prolonged QT, or monitor ECG closely
	Meglumine antimoniate	20 mg Sb/kg/day IV or IM × 20 days		
	Intralesional antimony	50 mg/0.5 mL every 2–3 weeks for 12 weeks	Pain during injection	Non-American cutaneous leishmaniasis only; consider in patients where parenteral therapy is contraindicated
	Miltefosine	2.5 mg/kg/day PO (maximum 150 mg/day) × 28 days	25–50%: nausea, vomiting, diarrhea, elevated creatinine; <25%: elevated LFTs; teratogenic in animals.	Consider in cases of resistance to PA or amphotericin B
	Pentamidine	2–3 mg/kg/day IV or IM daily or every other day × 4–7 doses	50%: nausea, vomiting (>50%)	Few side effects, consider in cases where PA is contraindicated
Diffuse cutaneous leishmaniasis	Sodium stibogluconate	20 mg/kg/day IV or IM × 20 days	*See above ADRs for parenteral antimony	
Mucosal	Meglumine antimoniate	20 mg/kg/day IV or IM × 28 days	*See above ADRs for parenteral antimony.	
	Amphotericin B	2–3 mg/kg/day IV daily or every other day until lesion healing	>50%: infusion-related reactions; 25–50%: azotemia; <25%: anemia, hypokalemia	Liposomal formulation associated with less renal toxicity compared with deoxycholate
	Pentamidine	2–4 mg/kg/day every other day until lesion healing	*See above	

ADRs, adverse drug reactions; ECG, electrocardiogram; IM, intramuscular; IV, intravenous; LFTs, liver function tests; PA, pentavalent antimony; PO, oral; Sb, antimony.

may also be explained by variations in renal clearance of antimony (28). Dosage can be increased above the standard guidelines if necessary. Therapeutic failure is often attributed subtherapeutic dosing (<10 mg/kg/day), course duration, or

underdosing because of obesity (24,29). The generic formula of SSB is as effective as branded PA (24,30–33).

PA has some known toxicities. Common side effects include myalgia, joint stiffness, abdominal

pains, and anorexia (30,34). Electrocardiogram changes including prolonged QT interval, ST depression, ST elevation, and bradycardia have been noted and may continue up to 1 month following drug cessation (34). Serious, but rare, side effects include hepatotoxicity, pancreatitis, hemolytic anemia, nephrotoxicity, and anaphylaxis (34–36). If possible, baseline and weekly electrocardiograms should be monitored in patients with cardiovascular disease or QT prolongation (34).

Intralesional PA

Intralesional PA is usually only used to treat non-American CL. The risk of mucosal dissemination precludes its use in American CL (37). This therapy is most effective in lesions less than 3 months old and less than 3 cm in diameter. Using a 27–30-gauge needle, the medication should be injected in several points around the lesion until there is complete blanching (38). One 50 mg PA/0.5 mL every 2–3 weeks for 12 weeks should be administered. An average of three injections is required for healing. Side effects include pain during injection and erythema (39). Systemic side effects are less common. Thus, this may be an option for patients with non-American CL and concomitant cardiac, hepatic, and renal comorbidities.

Pentamidine

Pentamidine is an effective alternate to PA and can be used as a first-line agent (24). It is frequently the second-line agent following PA treatment failure. As a primary treatment, the standard recommended dose is 4 mg/kg/day for 7 consecutive days IM or IV. If there is no improvement after 1 week, another three injections should be administered every other day (40). As a second-line agent, 4 mg/kg/day should be administered for 3–4 days total daily or on alternate days. Possible mechanisms include interference with DNA synthesis, modification of kinetoplast morphology, and mitochondria fragmentation (41). Common side effects are pain at injection site, metallic taste in mouth, headache, congestion, dyspnea, and hypnea (40). Uncommon side effects include fever, facial paresthesias, burning eyes, perspiration, dizziness, and fatigue (40). Patients should be monitored for hypotension and hypoglycemia (41).

Miltefosine

Miltefosine (Aeterna Zentaris) is a hexadecylphosphocholine. When used to treat American CL, milte-

fosine has exhibited cure rates equivalent to PA in some countries, but overall, the clinical response rate has been quite variable, and care should be taken when considering this agent for CL acquired in the Americas. Cure is achieved at a slower rate than PA (42,43). Miltefosine is administered at an oral dose of 2.5 mg/kg/day for 28 days. Advantages of miltefosine over PA include oral administration and less severe side effects (nausea, vomiting, diarrhea, and elevated creatinine) (42,44–46). Miltefosine is an option for individuals who are resistant to PA or exhibit cross-resistance to amphotericin B (47). Miltefosine is not Food and Drug Administration approved in the United States and is only available by direct importation from the manufacturer.

Paromomycin

Paromomycin, an aminoglycoside, is prepared as both parenteral and topical formulations. Although the idea of a topical formulation is an exciting alternate to parenteral and intralesional treatments, topical paromomycin alone is considered an insufficient treatment for any form of CL. However, parenteral administration of paromomycin is as effective as antimonials (48). A meta-analysis reports that topical paromomycin plus methylbenzethonium chloride twice a day for 10–20 days may be a possible alternate to intralesional PA for non-American CL (48).

Amphotericin B

Liposomal amphotericin B can be administered at 3 mg/kg/day IV for 5 consecutive days, followed by a sixth and final dose on Day 10 for *L. braziliensis* leishmaniasis (35). Liposomal amphotericin B is considered less toxic than the deoxycholate form because it specifically targets the macrophage (49). Infusion-related side effects of dyspnea and flushing can be treated with IV hydrocortisone and avoided by slow infusion rate (49).

Others

Cryotherapy (50,51), imiquimod (Graceway Pharmaceuticals) (20,52), photodynamic therapy (53), allopurinol (54,55), and azoles (38) both alone and in combination with PA have been evaluated. Results are variable, and outcomes are often not as effective as the standard treatment course of PA. Examples of combination therapies include intralesional and parenteral SSB (56) and combination of PA and omeprazole (57). Thermotherapy using a single application of a radio-frequency device appears to be a safe alternate for non-American CL (58).

DCL

DCL is rare even in countries where *Leishmania* is endemic (59). It is most commonly caused by *L. mexicana* in the Americas, and *Leishmania aethiopic*a in the Mediterranean basin, the Middle East, and Africa (60–62). Patients exhibit specific anergy to *Leishmania* antigens, although lymphocyte proliferation and response to other intracellular microbes remain intact (63,64). DCL can clinically resemble lepromatous leprosy.

Clinical presentation

Disease typically begins with an initial, painless papule or nodule at the site of inoculation and progresses to diffuse, non-ulcerating, erythematous to violaceous macules, nodules, and plaques heavily infiltrated with amastigotes (59,65). The face, upper and lower extremities, and buttocks are most commonly affected (66,67). There is occasional involvement of the trunk and genitalia, whereas the scalp and axillae are usually spared (61,63). Sensation is unaffected (68). A sporotrichoid morphology may be observed because of the lymphatic spread of parasites (69,70).

Diagnosis

Specimens should be obtained via dermal scrapings, needle aspirate, or punch biopsy (as above). DCL patients are anergic to *Leishmania*, therefore, the LST, which examines cell-mediated immune response to *Leishmania* antigen, will be negative in DCL and immunosuppressed patients. However, a conversion from negative to positive skin test during treatment implies an improved prognosis (71).

Awareness of *Leishmania* and human immunodeficiency virus (HIV) coinfection is an important new disease pattern with increasing prevalence. Host cell-mediated immune deficiency is compounded by HIV and *Leishmania* coinfection, resulting in a loss of primary protection against infection, recurrences, and systemic spread of parasites (72). DCL without visceral involvement has been reported as the first manifestation of HIV (72). A patient coinfecting with HIV and *Leishmania* may exhibit a severe presentation of CL (>200 lesions), or present with lesions in atypical anatomic sites or with multiple atypical morphologies (72).

Treatment indications and response

All patients with DCL should be treated. PA is the primary form of treatment. Treatment should

begin with the standard dose of 20–25 mg/kg/day × 20 days. If treatment fails, the patient should rest for 1 week and then a full course treatment should be administered again. Case reports describe mixed results from treatment of DCL with miltefosine (73,74). DCL is inherently difficult to treat; relapse and recurrence are common. Following successful treatment, secondary prophylaxis should be continued until CD4 count exceeds 200 cells/ μ L.

Mucocutaneous leishmaniasis

In contrast to CL, mucosal leishmaniasis (ML) is potentially life threatening and requires treatment (1). ML is a known risk from *Leishmania* species of the *Viannia* subgenus, typically found in the Americas (*L. (V) braziliensis*, *Leishmania (Viannia) amazonensis*, *L. (V) panamensis*, and *Leishmania (V) guyanensis*). Clinical progression to mucosal disease is dependent on a combination of host cell-mediated immunity and parasite virulence. Among a population of infected individuals, infection progresses to the mucosa in 1–10% of patients (75–78). The specific host factors that determine which patients will develop and will not develop ML are unclear.

History

The same social and travel history details important in diagnosing CL apply to ML diagnoses. Additionally, a prior history of CL is key. Patients may describe a history of CL with onset of mucosal involvement 1–5 years after the cutaneous lesion has healed (76). Primary lesions, which are typically ulcerative (versus the potentially non-ulcerative lesions associated with *Leishmania* species found outside of the Americas), may have been in singles or in multiples (76). Immunodeficiency does not necessarily predisposes an individual to ML. The most common presenting symptom is persistent nasal congestion (79). Erythema, erosions, and ulcers around the nares and lips are seen as the disease progresses (FIG. 2A). These findings are sometimes quite subtle and are mistaken commonly for impetigo contagiosum. Lesions of the oropharynx can be followed by a more widespread cutaneous disease as well (FIG. 2B). Destructive chronic ML is commonly misdiagnosed as rhinoscleroma or Wegener's granulomatosis, and these should be included in the differential diagnosis as listed above for CL.



FIG. 2. Mucocutaneous leishmaniasis lesions. (A) Crusted papules and plaques around the nose and lips caused by infection with *Leishmania (Viannia) braziliensis*. (B) Deeper, wet appearing ulcers on the legs of the same patient.

Clinical presentation

Ninety percent of patients have a scar from a prior episode of CL (76). Early ML can commence with erythema and ulceration of the nares. Anterior nasal septal granulomas can be appreciated using a light source and Thudicum's speculum (79). Nasoendoscopy will reveal posterior granulomas (79). Lymphadenopathy may be present and is a common finding in *L. braziliensis*-associated leishmaniasis (14,15,80). In this setting, lymphadenopathy typically precedes lesion ulceration and may be accompanied with systemic symptoms such as fever and hepatomegaly (14,15). Mid-to-late disease can present with erythema and edema of the nares, nasal septum perforation, palatal ulceration, gingival edema, and periodontitis. Eventually, there is progressive destruction of the oronasopharyngeal mucosa, and cartilaginous facial and upper airway structures, resulting in disfigurement, secondary infection, and airway obstruction (1,4,81,82).

Diagnosis

Biopsy and demonstration of intracellular amastigotes are required for diagnosis. Unlike CL and DCL, histopathology and touch preparations (Giemsa stain) of the nasal mucosa exhibit very few parasites, making it difficult to make a definitive diagnosis based on visualization of amastigotes. Following anesthesia, biopsies (2–4 mm) from mucosal lesions should be obtained; nasal turbinates should also be biopsied even if there is no overt disease (79). Specimens commonly reveal granulomas. If amastigotes are not visualized on touch preparation or histopathology, when clinical

suspicion is high, the most sensitive test to evaluate ML is identification of *Leishmania* DNA by polymerase chain reaction (80). Specimens can be sent to the CDC as explained above.

Treatment indications and response

PA is the most commonly used medication followed by amphotericin B (83). The World Health Organization recommends the use of PA to treat ML (84). There are no data that establish ML cure rates, however, there is evidence that MA (and not SSB), pentamidine, and amphotericin B may be equally effective at treating ML (83).

There is some bias in these studies. For example, all meglumine studies were performed in Brazil, whereas all stibogluconate studies were performed in Peru or Panama (83). However, given these findings, our recommended first-line treatments are MA 20 mg/kg/day for 28 days or more, pentamidine 4 mg/kg/day IV administered every 2 days until lesions heal (an average of 2–4 g total needed until cure) (41,85), or liposomal amphotericin B 2–3 mg/kg/day for 20 days or more (86,87). Studies in Rio de Janeiro have demonstrated drug sensitivity down to 5 mg/kg/day (88). Treatment regimens should be chosen based on patient comorbidities. The dose-limiting factor of pentamidine is pancreatotoxicity; liposomal amphotericin B has demonstrated less renal toxicity compared with deoxycholate amphotericin B (87,89).

Patients should be monitored for associated complications, particularly if disease is in the later stages. Patients are frequently resistant to antimonial therapy and may undergo multiple courses of treatment. Treatment failure and relapse are common (90,91).

Post-Kala-Azar dermal leishmaniasis

Post-kala-azar dermal leishmaniasis (PKDL) is a dermal manifestation of visceral leishmaniasis. It is frequently caused by the species *Leishmania donovani*. PKDL can present anywhere from weeks to years after remission from infection (92–94). The spectrum of PKDL dermal presentation ranges from hypopigmented macules to infiltrated papules or nodules (92). Eruptions may or may not ulcerate, depending on the species and geographic region the infection is acquired (92). PKDL lesions may act as a parasite reservoir. Diagnosis is based on epidemiological and clinical patterns. The tissue culture and slit smear are the gold standard diagnoses. However, serologic tests, microscopy, and detection of parasite in DNA tissue are also utilized to confirm diagnosis. Diagnosis can be difficult because of the low parasite burden within the lesions. Treatment is for visceral leishmaniasis, and discussion is beyond the scope of the present review.

Leishmaniasis preventive measures

For individuals residing or visiting *Leishmania*-endemic countries, the US Department of Defense, Deployment Health and Clinical Center recommends the following (6):

- Remain in well-screened or air-conditioned tents or accommodations from dusk until dawn.
- Wear long-sleeved shirts and pants when going outdoors; tuck shirts into pants. Apply insect repellent on uncovered areas.
- If sleeping in an area without adequate netting or air-conditioning, utilize a fine mesh bed net (minimum 18 holes per inch) and tuck under mattress. Soak or spray the net in permethrin; sand flies are small enough to pass through the holes.
- Avoid dogs or rodents near sleeping areas.

Leishmania and HIV coinfection

Although studies are limited, visceralization of cutaneous *Leishmania* in HIV coinfecting individuals remains a risk. Patients coinfecting with CL and HIV can also present with mucosal lesions because of parasite dissemination to nasal and oral mucosa (95,96). These, however, should not be categorized as mucocutaneous leishmaniasis. In endemic areas of leprosy, such as India, DCL may be mistaken as lepromatous leprosy. Absence of anesthesia can facilitate distinction between the two

processes. Therefore, in the context of HIV, it is important to maintain DCL within the differential. Conversely, if DCL is diagnosed, an HIV workup is appropriate.

Summary

Consider leishmaniasis in patients with a history of residence or travel to an endemic country, and a chronic cutaneous or mucocutaneous lesion unresponsive to standard therapies. Diagnosis is confirmed by visualization of amastigotes on touch preparation or histopathology. For health care providers practicing in the United States, free diagnostic guidance and speciation can be obtained by contacting the CDC. This can assist greatly in prognosticating. Pentostam is the standard first-line therapy, and this can also be obtained through the CDC.

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