

What's Eating You? Phlebotomine Sandflies and *Leishmania* Parasites

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PRACTICE POINTS

- The *Phlebotomus* and *Lutzomyia* genera of sandflies are vectors of *Leishmania* parasites, which can result in an array of clinical findings associated with leishmaniasis.
- Treatment options for leishmaniasis differ based on whether the infection is considered uncomplicated or complicated, which depends on the species of *Leishmania*; the number, size, and location of the lesion(s); and host immune status.
- All US practitioners should be aware of this pathogen, especially with regard to patients who have a history of travel to other countries. Health care professionals in states such as Texas and Oklahoma should be especially cognizant because these constitute one of the few areas in the United States where locally acquired cases of leishmaniasis have been reported.

Phlebotomine sandflies of the *Phlebotomus* and *Lutzomyia* genera are vectors for the spread of *Leishmania* parasites. Leishmaniasis is a parasitic infection most common in the Middle East and Central and South America. Few cases have been reported in the United States, with most patients presenting after returning from travel to other countries; however, the parasite has been locally acquired in Texas and Oklahoma. Clinical presentation varies depending on the species of *Leishmania*. There are 4 general clinical classifications

of leishmaniasis: cutaneous, diffuse cutaneous, mucocutaneous, and visceral.

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The genus *Leishmania* comprises protozoan parasites that cause approximately 2 million new cases of leishmaniasis each year across 98 countries.¹ These protozoa are obligate intracellular parasites of phlebotomine sandfly species that transmit leishmaniasis and result in a considerable parasitic cause of fatalities globally, second only to malaria.^{2,3}

Phlebotomine sandflies primarily live in tropical and subtropical regions and function as vectors for many pathogens in addition to *Leishmania* species, such as *Bartonella* species and arboviruses.³ In 2004, it was noted that the majority of leishmaniasis cases affected developing countries: 90% of visceral leishmaniasis cases occurred in Bangladesh, India, Nepal, Sudan, and Brazil, and 90% of cutaneous leishmaniasis cases occurred in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Syria.⁴ Of note, with recent environmental changes, phlebotomine sandflies have gradually migrated to more northerly latitudes, extending into Europe.⁵

Twenty *Leishmania* species and 30 sandfly species have been identified as causes of leishmaniasis.⁴ *Leishmania* infection occurs when an infected sandfly bites a mammalian host and transmits the parasite's flagellated form,

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known as a promastigote. Host inflammatory cells, such as monocytes and dendritic cells, phagocytize parasites that enter the skin. The interaction between parasites and dendritic cells become an important factor in the outcome of *Leishmania* infection in the host because dendritic cells promote development of CD4 and CD8 T lymphocytes with specificity to target *Leishmania* parasites and protect the host.¹

The number of cases of leishmaniasis has increased worldwide, most likely due to changes in the environment and human behaviors such as urbanization, the creation of new settlements, and migration from rural to urban areas.^{3,5} Important risk factors in individual patients include malnutrition; low-quality housing and sanitation; a history of migration or travel; and immunosuppression, such as that caused by HIV co-infection.^{2,5}

Case Report

An otherwise healthy 25-year-old Bangladeshi man presented to our community hospital for evaluation of a painful leg ulcer of 1 month's duration. The patient had migrated from Bangladesh to Panama, then to Costa Rica, followed by Guatemala, Honduras, Mexico, and, last, Texas. In Texas, he was identified by the US Immigration and Customs Enforcement, transported to a detention facility, and transferred to this hospital shortly afterward.

The patient reported that, during his extensive migration, he had lived in the jungle and reported what he described as mosquito bites on the legs. He subsequently developed a 3-cm ulcerated and crusted plaque with rolled borders on the right medial ankle (Figure 1). In addition, he had a palpable nodular cord on the medial leg from the ankle lesion to the mid thigh that was consistent with lymphocutaneous spread. Ultrasonography was negative for deep-vein thrombosis.

Because the patient's recent migration from Central America was highly concerning for microbial infection, vancomycin and piperacillin-tazobactam were started empirically on admission. A punch biopsy from the right medial ankle was nondiagnostic, showing acute and chronic necrotizing inflammation along with numerous epithelioid histiocytes with a vaguely granulomatous appearance (Figure 2). A specimen from the right medial ankle that had already been taken by an astute border patrol medical provider was sent to the Centers for Disease Control and Prevention (CDC) for polymerase chain reaction analysis following admission and was found to be positive for *Leishmania panamensis*.

Given the concern for mucocutaneous leishmaniasis with this particular species, otolaryngology was consulted; however, the patient did not demonstrate mucocutaneous disease. Because of the elevated risk for persistent disease with *L panamensis*, systemic therapy was indicated and administered: IV amphotericin B 200 mg on days 1 through 5 and again on day 10. Improvement in the ulcer was seen after the 10-day regimen was completed.

Comment

Leishmaniasis can be broadly classified by geographic region or clinical presentation. Under the geographic region system, leishmaniasis can be categorized as Old World or New World. Old World leishmaniasis primarily is transmitted by *Phlebotomus* sandflies and carries the parasites *Leishmania major* and *Leishmania tropica*, among others. New World leishmaniasis is caused by *Lutzomyia* sandflies, which carry *Leishmania mexicana*, *Leishmania braziliensis*, *Leishmania amazonensis*, and others.⁶

Our patient presented with cutaneous leishmaniasis, one of 4 primary clinical disease forms of leishmaniasis; the other 3 forms under this classification system are diffuse cutaneous, mucocutaneous, and visceral leishmaniasis, also known as kala-azar.^{3,6} Cutaneous leishmaniasis is limited to the skin, particularly the face and extremities. This form is more common with Old World vectors, with most cases occurring in Peru, Brazil, and the Middle East. In Old World cutaneous leishmaniasis, the disease begins with a solitary nodule at the site of the bite that ulcerates and can continue to spread in a sporotrichoid pattern. This cutaneous form tends to heal slowly over months to years with residual scarring. New World cutaneous leishmaniasis can present with a variety of clinical manifestations, including ulcerative, sarcoidlike, miliary, and nodular lesions.^{6,7}



FIGURE 1. A and B, A single, 3-cm, ulcerated and crusted plaque with rolled borders on the right medial ankle.

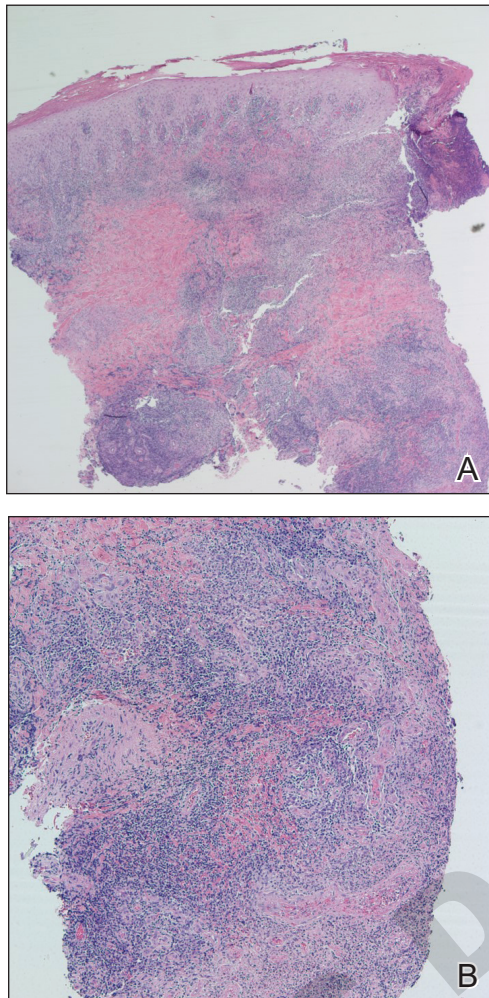


FIGURE 2. A and B, In addition to acute and chronic necrotizing inflammation, numerous histiocytes have a vaguely granulomatous appearance (H&E, original magnifications $\times 4$ and $\times 10$).

The diffuse form of cutaneous leishmaniasis begins in a similar manner to the Old World cutaneous form: a single nodule spreads widely over the body, especially the nose, and covers the patient's skin with keloidal or verrucous lesions that do not ulcerate. These nodules contain large groupings of *Leishmania*-filled foamy macrophages. Often, patients with diffuse cutaneous leishmaniasis are immunosuppressed and are unable to develop an immune response to leishmanin and other skin antigens.^{6,7}

Mucocutaneous leishmaniasis predominantly is caused by the New World species *L braziliensis* but also has been attributed to *L amazonensis*, *L panamensis*, and *L guyanensis*. This form manifests as mucosal lesions that can develop simultaneously with cutaneous lesions but more commonly appear months to years after resolution of the skin infection. Patients often present with ulceration of the lip, nose, and oropharynx, and destruction of the nasopharynx can result in severe consequences such

as obstruction of the airway and perforation of the nasal septum (also known as espondia).^{6,7}

The most severe presentation of leishmaniasis is the visceral form (kala-azar), which presents with parasitic infection of the liver, spleen, and bone marrow. Most commonly caused by *Leishmania donovani*, *Leishmania infantum*, and *Leishmania chagasi*, this form has a long incubation period spanning months to years before presenting with diarrhea, hepatomegaly, splenomegaly, darkening of the skin (in Hindi, kala-azar means "black fever"), pancytopenia, lymphadenopathy, nephritis, and intestinal hemorrhage, among other severe manifestations. Visceral leishmaniasis has a poor prognosis: patients succumb to disease within 2 years if not treated.^{6,7}

Diagnosis—Diagnosing leishmaniasis starts with a complete personal and medical history, paying close attention to travel and exposures. Diagnosis is most successfully performed by polymerase chain reaction analysis, which is both highly sensitive and specific but also can be determined by culture using Novy-McNeal-Nicolle medium or by light microscopy. Histologic findings include the marquee sign, which describes an array of amastigotes (promastigotes that have developed into the intracellular tissue-stage form) with kinetoplasts surrounding the periphery of parasitized histiocytes. Giemsa staining can be helpful in identifying organisms.^{2,6,7}

The diagnosis in our case was challenging, as none of the above findings were seen in our patient. The specimen taken by the border patrol medical provider was negative on Gram, Giemsa, and Grocott-Gömöri methenamine silver staining; no amastigotes were identified. Another diagnostic modality (not performed in our patient) is the Montenegro delayed skin-reaction test, which often is positive in patients with cutaneous leishmaniasis but also yields a positive result in patients who have been cured of *Leishmania* infection.⁶

An important consideration in the diagnostic workup of leishmaniasis is that collaboration with the CDC can be helpful, such as in our case, as they provide clear guidance for specimen collection and processing.²

Treatment—Treating leishmaniasis is challenging and complex. Even the initial decision to treat depends on several factors, including the form of infection. Most visceral and mucocutaneous infections should be treated due to both the lack of self-resolution of these forms and the higher risk for a potentially life-threatening disease course; in contrast, cutaneous forms require further consideration before initiating treatment. Some indicators for treating cutaneous leishmaniasis include widespread infection, intention to decrease scarring, and lesions with the potential to cause further complications (eg, on the face or ears or close to joints).⁶⁻⁸

The treatment of choice for cutaneous and mucocutaneous leishmaniasis is pentavalent antimony; however, this drug can only be obtained in the United States for investigational use, requiring approval by the CDC.

A 20-day intravenous or intramuscular course of 20 mg/kg per day typically is used for cutaneous cases; a 28-day course typically is used for mucosal forms.

Amphotericin B is not only the treatment of choice for visceral leishmaniasis but also is an important alternative therapy for patients with mucosal leishmaniasis or who are co-infected with HIV. Patients with visceral infection also should receive supportive care for any concomitant afflictions, such as malnutrition or other infections. Although different regimens have been described, the US Food and Drug Administration has created outlines of specific intravenous infusion schedules for liposomal amphotericin B in immunocompetent and immunosuppressed patients.⁸ Liposomal amphotericin B also has a more favorable toxicity profile than conventional amphotericin B deoxycholate, which is otherwise effective in combating visceral leishmaniasis.⁶⁻⁸

Other treatments that have been attempted include pentamidine, miltefosine, thermotherapy, oral itraconazole and fluconazole, rifampicin, metronidazole and cotrimoxazole, dapsone, photodynamic therapy, thermotherapy, topical paromomycin formulations, intralesional pentavalent antimony, and laser cryotherapy. Notable among these other agents is miltefosine, a US Food and Drug Administration–approved oral medication for adults and adolescents (used off-label for patients younger than 12 years) with cutaneous leishmaniasis caused by *L. braziliensis*, *L. panamensis*, or *L. guyanensis*. Other oral options mentioned include the so-called azole antifungal medications, which historically have produced variable results. From the CDC's reports, ketoconazole was moderately effective in Guatemala and Panama,⁸ whereas itraconazole did not demonstrate efficacy in Colombia, and the efficacy of fluconazole was inconsistent in different countries.⁸ When considering one of the local (as opposed to oral and parenteral) therapies mentioned, the extent of cutaneous findings as well as the risk of mucosal spread should be factored in.⁶⁻⁸

Understandably, a number of considerations can come into play in determining the appropriate treatment modality, including body region affected, clinical form, severity, and *Leishmania* species.⁶⁻⁸ Our case is of particular interest because it demonstrates the complexities behind the diagnosis and treatment of cutaneous leishmaniasis, with careful consideration geared toward the species; for example, because our patient was infected with *L. panamensis*, which is known to cause mucocutaneous disease, the infectious disease service decided to pursue systemic therapy with amphotericin B rather than topical treatment.

Prevention—Vector control is the primary means of preventing leishmaniasis under 2 umbrellas: environmental management and synthetic insecticides. The goal of environmental management is to eliminate the phlebotomine sandfly habitat; this was the primary method of vector control until 1940. Until that time, tree stumps

were removed, indoor cracks and crevices were filled to prevent sandfly emergence, and areas around animal shelters were cleaned. These methods were highly dependent on community awareness and involvement; today, they can be combined with synthetic insecticides to offer maximum protection.

Synthetic insecticides include indoor sprays, treated nets, repellents, and impregnated dog collars, all of which control sandflies. However, the use of these insecticides in endemic areas, such as India, has driven development of insecticide resistance in many sandfly vector species.³

As of 2020, 5 vaccines against *Leishmania* have been created. Two are approved—one in Brazil and one in Uzbekistan—for human use as immunotherapy, while the other 3 have been developed to immunize dogs in Brazil. However, the effectiveness of these vaccines is under debate. First, one of the vaccines used as immunotherapy for cutaneous leishmaniasis must be used in combination with conventional chemotherapy; second, long-term effects of the canine vaccine are unknown.¹ A preventive vaccine for humans is under development.^{1,3}

Final Thoughts

Leishmaniasis remains a notable parasitic disease that is increasing in prevalence worldwide. Clinicians should be aware of this disease because early detection and treatment are essential to control infection.³ Health care providers in the United States should be especially aware of this condition among patients who have a history of travel or migration; those in Texas should recognize the current endemic status of leishmaniasis there.^{4,6}

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