Case Report: Cutaneous Leishmaniasis due to *Leishmania (Viannia) panamensis* in Two Travelers Successfully Treated with Miltefosine

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Abstract. We present two cases of *Leishmania (V) panamensis* in returning travelers from Central America successfully treated with miltefosine. The couple presented with ulcerative skin lesions nonresponsive to antibiotics. Skin biopsy with polymerase chain reaction (PCR) revealed *L. (V) panamensis*. To prevent the development of mucosal disease and avoid the inconvenience of parental therapy, we treated both patients with oral miltefosine. We suggest that miltefosine represents an important therapeutic alternative in the treatment of cutaneous lesions caused by *L. panamensis* and in preventing mucosal involvement.

A 31-old-man and a 30-year-old woman traveled to Costa Rica for their honeymoon. They visited many regions of this country and participated in hiking, rafting, and camping. They both reported insect bites.

The husband had a history of Hodgkin lymphoma treated 10 years ago and was in remission. Approximately 3 weeks after returning home, the husband noticed a dime-sized papule proximal to his first, right thumb. He also reported “enlarged nodes” on his right arm. He denied any other symptoms. The lesion continued to grow in size, despite a 7-day empiric course of cephalexin.

On examination, the husband had a 6-cm ulcer (1 cm deep) on the dorsal aspect of his right thenar eminence with surrounding erythema (Figure 1) along with three erythematous slightly tender sporotrichoid nodules along the volar forearm. In addition, he had right epitrochlear and axillary lymph nodes.

His wife denied any past medical history. Two weeks after returning from Costa Rica, she described a well-circumscribed asymptomatic erythematous plaque on her right chest that became scaly. She denied any fevers, abdominal pain, epistaxis, mouth lesions, or enlarged lymph nodes.

On examination, the wife had a 2-cm zosteriform-like plaque on her right chest (Figure 2). No lymphadenopathy was noted. Similar to her husband, she had no evidence of abdominal tenderness, hepatosplenomegaly, or lesions in the mouth or nose.

Skin biopsies in both cases demonstrated acute, chronic, and granulomatous dermatitis with intracellular amastigotes (Figure 3). Molecular testing of the skin biopsy specimen by PCR revealed the presence of *Leishmania panamensis* (Division of Parasitic Diseases and malaria, CDC, Atlanta GA). Systemic therapy with oral miltefosine (Impavido[®]) 50 mg three times daily was instituted for both patients, as it is more convenient and less toxic than parental therapy. Given that the husband had concern for lymphangitic spread to his right axilla, we recommended a 56-day course of miltefosine therapy. At follow-up, he had significant improvement of the lesion.

Because of the presence of a thick fibrous scar at the ulcerative lesion border, we recommended a short course of collagenase ointment (Santyl[®]), which promoted complete healing of the ulcer (Figure 4). After the wife had a negative pregnancy test and we provided contraceptive counseling, we treated her with a single course of 28-day miltefosine with substantial improvement of the cutaneous lesion (Figure 5). Both husband and wife reported nausea and mild abdominal pain with miltefosine which improved when ingested with food. No other side effects were reported.

DISCUSSION

Leishmaniasis refers collectively to a spectrum of clinical syndromes (cutaneous, mucocutaneous, and visceral) caused by infection with intracellular protozoa of the subgenera *Leishmania (Leishmania)*, *Leishmania (Viannia)*, or *Leishmania (Mundinia)* acquired by the bite of sand flies.¹ Cutaneous leishmaniasis (CL) is the most frequently reported form of the disease, and it is associated with more than 20 *Leishmania (L.)* species with different degrees of pathogenicity.² In addition to producing CL, some species may also produce nasopharyngeal and laryngeal mucosal involvement, causing additional morbidity and disfigurement. Mucosal leishmaniasis (ML) may occur concomitantly with the cutaneous lesion, or it may manifest a few months, or even years, after the cutaneous lesions have healed.^{3–5} In the New World (Americas), species of the subgenus *L. Viannia (V)* are associated with the mucosal forms of the disease, particularly *Leishmania (V) braziliensis*, *Leishmania (V) guyanensis*, and *L. (V) panamensis*.⁶ New evidence suggests that some of these *Leishmania* species are coinfecting with *Leishmania* RNA virus and that the immune response to this virus elicits an hyperinflammatory response through toll-like receptors, leading to mucosal damage.⁷ In addition, some *Leishmania* species, which are traditional causes of CL, may produce a mixed syndrome of cutaneous and visceral disease denominated viscerotropic disease caused predominantly by *Leishmania tropica* in the Old World and *Leishmania amazonensis* in the New World.⁸

Cutaneous leishmaniasis typically occurs at the site of the sand fly bite, starting as small papules which enlarge slowly over months eventually ulcerating with heaped up borders.⁴ The spectrum of cutaneous manifestations associated with

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FIGURE 1. Hand lesion on initial evaluation. This figure appears in color at www.ajtmh.org.

CL in the New World includes ulcerative, diffuse, disseminated, and atypical forms (psoriasiform, verrucous, zosteriform, or nodular).^{6,9}

The Pan American Health Organization recommends assessing the annual CL transmission index to identify the locations within the Americas with the highest risk of transmission. Used to prioritize and control interventions, this index is constituted by the annual incidence of CL and the density of transmission which is defined as the total annual number of CL cases in a defined geographic area by municipalities, regions, and subregions of countries with existing leishmaniasis transmission. Travel medicine practitioners can use this index to counsel travelers about high transmission areas and prevent phlebotomine sand fly bites.⁶

Cutaneous leishmaniasis occurring in an immune-competent individual with no evidence of mucosal involvement does not usually require treatment because it spontaneously resolves. However, local or systemic treatment is recommended for individuals with complex CL defined as the presence of subcutaneous nodules; area greater than 5 cm; regional adenopathy; lesions on the face, fingers, toes, or genitalia; location or size not amenable to localized treatment; immunocompromised host; previous clinical failure; infection due to a *Leishmania* species potentially associated with mucosal disease; or diffuse CL.^{9,10} In these clinical scenarios, treatment accelerates the healing process and reduces the chances of relapse and dissemination (mucosal or visceral).

Treatment options for CL acquired in the New World include either systemic or local therapy. Systemic therapies include parenteral or oral options. In the armamentarium of parenteral infusions, the most frequently used is pentavalent antimonial compounds (SbV), followed by amphotericin B (deoxycholate or liposomal formulations), and pentamidine. Oral options include azoles and the more recently approved antiparasitic drug miltefosine. Local treatment includes topical paromomycin, intralesional injections of antimonials, thermotherapy, and photo or laser treatment for clinically simple lesions not associated with ML.

FIGURE 2. Chest lesion on initial evaluation. This figure appears in color at www.ajtmh.org.

There is no ideal treatment regimen for leishmaniasis. Experts recommend individualizing therapy based on a patient's immune status, comorbid conditions, child-bearing plans, risk of mucocutaneous disease, extent of involvement, and published agent response rates of the therapy in the relevant geographic region.¹¹ A retrospective study of CL involving 43 European travelers demonstrated that the use of amphotericin B formulations was mostly effective against some of the Old World leishmaniasis: *Leishmania infantum* and *Leishmania tropica*.¹² However, for species of the subgenus *L. Viannia*, the use of amphotericin B was associated with high rates of treatment failure.¹²

Because our patients had confirmed *L. (V) panamensis*, we decided to institute systemic therapy. We chose miltefosine over pentavalent antimonials based on existing efficacy against *L. (V) panamensis*^{13,14} and for logistic reasons to avoid the need for parenteral administration. We also recommended wound care and applying emollients, such as petroleum jelly, to the wound.

Miltefosine, approved by the FDA in 2014 for CL caused by *L. panamensis*, *L. braziliensis*, and *L. guyanensis*, is a phosphocholine analogue that interferes with cell-signaling pathways and membrane synthesis.¹⁴ The major benefits of this treatment regimen are oral administration and a minimal side effect profile. Adverse effects include nausea and diarrhea, which can be ameliorated by ingesting the medication with food. Patients should also receive safe sex counseling, as the medication has teratogenic potential. Other rare side effects include hepatotoxicity and renal insufficiency. Additional disadvantages are the cost of the medication and the potential risk of relapse.

FIGURE 3. H&E images of cutaneous leishmaniasis at 100× (A/C) and 600× (B/D) magnification. (A/C) Prominent lymphoplasmacytic dermal inflammation with occasional granulomas. (B/D) Histiocytes with intracellular amastigotes [arrows]. This figure appears in color at www.ajtmh.org.

Although there are a limited number of clinical trials evaluating miltefosine, most of the studies have revealed that miltefosine is efficacious. A randomized open-label trial of 90 patients with *L. braziliensis* revealed a statistically significant cure rate of 75% in the miltefosine group compared with 53.3% in the pentavalent antimony group.¹⁵ Furthermore, a trial of miltefosine in pediatric children in Colombia with *L. panamensis* and *L. guyanensis* revealed that miltefosine was not inferior to meglumine antimoniate and had a lower toxicity profile.¹⁶ The use of miltefosine in CL from Columbia revealed cure rates > 80% for patients infected with *L. panamensis*.^{13,14} Other trials demonstrated a cure rate of < 70% that was attributed to higher proportions of *L. braziliensis* cases.¹⁷ This may be secondary to *L. braziliensis*' reduced capacity to internalize miltefosine.¹⁸

For treatment, a course of 28 days of miltefosine is preferred, but one may recommend extended courses for lymphangitic spread such as in our patient. Because leishmaniasis may recur, there is a need for intermittently monitoring patients after completing therapy. If treatment is successful, the lesion size

should decrease by greater than 50%, with no evidence of new lesions. In addition, ulcerative lesions should re-epithelialize and heal by 3 months.¹⁰ The wife had resolution of ulcerations with no new lesions (Figure 4), and the husband had re-epithelialization of his ulcer at our first 3-month follow-up (Figure 5). We also identified the potential benefit of collagenase ointment in patients with CL to improve residual scar accumulation at the prior ulcer border.

In summary, our cases contribute to the growing threat of CL in travelers.¹⁹ Travel health practitioners should advise travelers to avoid phlebotomine sand fly bites in regions with high leishmaniasis cutaneous indexes. Cutaneous leishmaniasis should always be on the differential diagnosis for a returning traveler with cutaneous lesions. Because of the risk of mucosal involvement with particular *Leishmania* species in returning travelers from the New World, it is highly recommended to identify the species involved to guide the preferred treatment regimen. Miltefosine is a convenient and well-tolerated oral alternative for the treatment of CL caused by *L. (V) panamensis*.

FIGURE 4. Hand lesion after therapy at 3-month follow-up. This figure appears in color at www.ajtmh.org.

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FIGURE 5. Chest lesion after therapy at 3-month follow-up. This figure appears in color at www.ajtmh.org.

REFERENCES

1. Espinosa OA, Serrano MG, Camargo EP, Teixeira MMG, Shaw JJ, 2018. An appraisal of the taxonomy and nomenclature of trypanosomatids presently classified as *Leishmania* and *Endotrypanum*. *Parasitology* 145: 430–442.
2. Aronson NE, Joya CA, 2019. Cutaneous leishmaniasis: updates in diagnosis and management. *Infect Dis Clin North Am* 33: 101–117.
3. Herwaldt BL, 1999. Leishmaniasis. *Lancet* 354: 1191–1199.
4. Berman JD, 1997. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. *Clin Infect Dis* 24: 684–703.
5. Walton BC, Chinel LV, Eguia y Eguia O, 1973. Onset of espundia after many years of occult infection with *Leishmania braziliensis*. *Am J Trop Med Hyg* 22: 696–698.
6. Organización Panamericana de la Salud, 2019. *Manual Para Vigilancia y Control de las Leishmaniasis en las Américas*. Available at: http://iris.paho.org/xmlui/bitstream/handle/123456789/50524/9789275320631_spa.pdf?sequence=1&isAllowed=y. Accessed December 20, 2019.
7. Hartley MA, Ronet C, Zangger H, Beverley SM, Fasel N, 2012. *Leishmania* RNA virus: when the host pays the toll. *Front Cell Infect Microbiol* 2: 99.
8. Weiss F, Vogenthaler N, Franco-Paredes C, Parker SR, 2009. *Leishmania tropica*-induced cutaneous and presumptive concomitant viscerotropic leishmaniasis with prolonged incubation. *Arch Dermatol* 145: 1023–1026.
9. Olivo Freitas C, Gundacker ND, Pascale JM, Saldaña A, Diaz-Suarez R, Jimenez G, Sosa N, García E, Jimenez A, Suarez JA, 2018. First case of diffuse leishmaniasis associated with *Leishmania panamensis*. *Open Forum Infect Dis* 5: ofy281.
10. Aronson N, Herwaldt BL, Libman M, Pearson R, Lopez-Velez R, Weina P, Carvalho EM, Ephros M, Jeronimo S, Magill A, 2016. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the infectious diseases society of America (IDSA) and the American society of tropical medicine and hygiene (ASTMH). *Clin Infect Dis* 63: e202–e264.
11. Barkati S, Ndao M, Libman M, 2019. Cutaneous leishmaniasis in the 21st century: from the laboratory to the bedside. *Curr Opin Infect Dis* 32: 419–425.
12. Guery R et al., 2017. Liposomal amphotericin B in travelers with cutaneous and muco-cutaneous leishmaniasis: not a panacea. *PLoS Negl Trop Dis* 11: e0006094.
13. Soto J et al., 2004. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 38: 1266–1272.
14. Soto J, Toledo J, Gutierrez P, Nicholls RS, Padilla J, Engel J, Fischer C, Voss A, Berman J, 2001. Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis* 33: E57–E61.
15. Machado PR, Ampuero J, Guimaraes LH, Villasboas L, Rocha AT, Schriefer A, Sousa RS, Talhari A, Penna G, Carvalho EM, 2010. Miltefosine in the treatment of cutaneous leishmaniasis caused by *Leishmania braziliensis* in Brazil: a randomized and controlled trial. *PLoS Negl Trop Dis* 4: e912.
16. Rubiano LC et al., 2012. Noninferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children. *J Infect Dis* 205: 684–692.
17. Velez I, Lopez L, Sanchez X, Mestra L, Rojas C, Rodriguez E, 2010. Efficacy of miltefosine for the treatment of American cutaneous leishmaniasis. *Am J Trop Med Hyg* 83: 351–356.
18. Sanchez-Canete MP, Carvalho L, Perez-Victoria FJ, Gamarro F, Castanys S, 2009. Low plasma membrane expression of the miltefosine transport complex renders *Leishmania braziliensis* refractory to the drug. *Antimicrob Agents Chemother* 53: 1305–1313.
19. Franco-Paredes C, 2014. The growing challenge of leishmaniasis in travelers. *Travel Med Infect Dis* 12: 559–560.