Complex cutaneous infection by *Leishmania mexicana* treated with miltefosine

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Key words: cutaneous leishmaniasis; Leishmania mexicana; miltefosine; parasitic infections.

INTRODUCTION

Leishmaniasis is a parasitic disease caused by over 20 known *Leishmania* species worldwide and is transmitted by the bite of female sandflies.[1] Three main clinical syndromes manifest as cutaneous, mucocutaneous, or visceral disease. Cutaneous leishmaniasis (CL) is the most frequently reported clinical syndrome with an estimated number of 1 million annual cases worldwide.[2] Geographical distribution is used to classify *Leishmania* species as Old or New World CL, and definitive speciation is made by polymerase chain reaction (PCR) assay.[3] Old World species are endemic to the Middle East, the Mediterranean Basin, northeast Africa, and southeast Asia, while New World species are found in Central and South America.[1,3] While CL can spontaneously heal over a period of 2 to 15 m, systemic treatment may be necessary for complex lesions, cosmetic concerns, or patients with a high risk of disease progression.[4,5] Complex CL is broadly defined by either infection of an immunocompromised host, infection by a species known for mucocutaneous involvement, large or numerous lesions, lesions involving areas unsuitable for local treatment, or continued lesions after failure of local treatment.[1,3,4] Efforts to identify appropriate therapeutic regimens for complex CL have been complicated by significant toxicities and limited by variability in treatment efficacy among species.[4] We present a case of complex CL with initial treatment failure requiring the use of second-line oral therapy.

Abbreviations used:

CL: cutaneous leishmaniasis
PCR: polymerase chain reaction

CASE REPORT

A 65-year-old male with a history of hypertension, substance use disorder on buprenorphine, and cirrhosis from chronic hepatitis C presented with a 3-week history of enlarging left infraorbital erythema, swelling, and ulceration. Three months prior, the patient had traveled to Yucatán, Mexico, where he spent time cave diving in the jungle. He recalled an initial small papule in the affected region at the time of travel. Further travel history revealed visits to Costa Rica and the Dominican Republic within the last 7 years. He was initially treated with antibiotics without clinical improvement. Skin biopsy revealed ulcerated epidermis with marked dermal chronic histiocytes and amastigotes on Giemsa stain, consistent with CL. He received 6 doses of amphotericin B over 9 days, but the course was complicated by nephrotoxicity, with a creatinine elevation to 1.71 mg/dL. Amphotericin B was discontinued, and the patient's renal function returned to normal. He was then placed on oral fluconazole and completed 1 month of therapy without improvement in the lesion.

The patient presented to our dermatology clinic with worsening pain and ulceration, now 2 months after the initial onset of the lesion. He denied any

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Funding sources: None.
IRB approval status: Not applicable.
Consent: Patient consent forms are on the file.
Previous publications/postings/related manuscripts and reports: None.

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JAAD Case Reports 2022;29:18-20.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.08.036

fevers, abdominal pain, nausea, vomiting, nasal pain, or discharge. Physical examination revealed a 4.0 × 2.0 cm shallow ulceration in the left infraorbital region with surrounding erythematous, raised borders and a 2.0 × 2.0 cm nodular area at the superior edge (Fig 1). A 3-mm punch biopsy of the lesion was repeated, showing granulomatous inflammation and abundant lymphoplasmacytic infiltrate without visualization of amastigotes (Fig 2). PCR assay of the specimen using mini exon DNA identified the species as *Leishmania mexicana*. After consultation with the Centers for Disease Control and Prevention, he was started on oral miltefosine 50 mg 3 times daily for 28 days. The patient was referred to otolaryngology for diagnostic nasal endoscopy, which was negative for mucosal involvement of the oronasopharynx. After 4 weeks of miltefosine therapy, decreased swelling of the lesion was evident, along with epithelialization of the distal ulcer edge and eschar formation over the remainder of the ulcer (Fig 3). The patient reported mild nausea and emesis within several hours of miltefosine dosing, which was managed with pre-dose ondansetron.

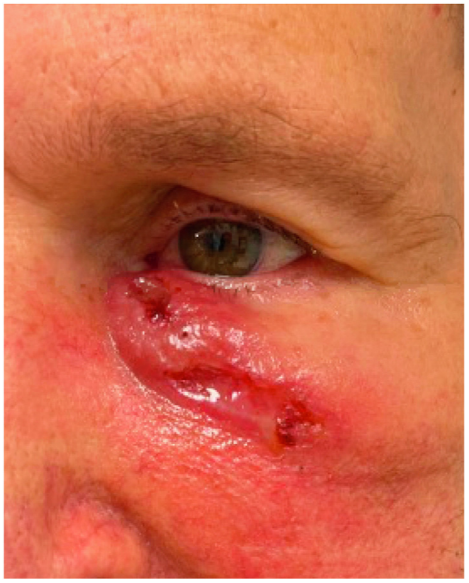

Fig 1. Infraorbital lesion on initial evaluation by dermatology 2 months after onset.

DISCUSSION

While uncommon, a few autochthonous cases of leishmaniasis have been reported in North America. The Pan American Health Organization recommends obtaining a detailed travel history when investigating suspected cases.[2] Given the patient's remote history of travel to Costa Rica, where *L panamensis* threatens mucocutaneous involvement, he underwent a negative nasal endoscopy. He also had recent travel to Mexico, where *L braziliensis* and *L mexicana* are the most common causes of CL in the country, and *L infantum* contributes to cases of visceral leishmaniasis.[2] The patient's travel history made PCR analysis critical in confirming *L mexicana* as the causative species, which is associated with cutaneous, diffuse cutaneous, and disseminated CL.[1]

Our patient exhibited the typical clinical manifestation of CL—initial small papular lesions followed by enlargement and ulceration over the course of several months.[6] Because many CL infections resolve clinically without treatment, decision on whom to treat is based on several factors, and the Infectious Diseases Society of America has published guidelines for treatment of CL with local or systemic therapy.[7] This case of complex CL warranted systemic treatment due to the facial lesion location, concern for progression and scarring, and previous treatment failure.

There is a relative paucity of *L mexicana* cases worldwide and no consensus on an ideal treatment regimen. Antimonials, such as sodium stibogluconate, have traditionally been used to treat leishmaniasis, but they are not currently approved by the Food and Drug Administration and are not commercially available in the United States.[7] While amphotericin B is frequently used, nephrotoxicity, which developed in our patient, is a well-documented adverse effect. Oral "azoles" have shown good cure rates for several Old and New World *Leishmania* species, including *L mexicana,* yet treatment failure remains common, and oral fluconazole yielded no clinical improvement in our patient.[4]

Miltefosine is an oral agent that is thought to disrupt membrane lipids and mitochondrial function in leishmanial species.[8] The drug was approved by the United States Food and Drug Administration in 2014 for treatment of New World CL caused by *L panamensis, L braziliensis,* and *L guayanensis*.[6] Minimal data exist in the literature regarding the use of miltefosine for *L mexicana*. One case series studying the use of miltefosine in 26 CL patients included 1 patient with local facial infection with *L mexicana*, whose clinical outcome met criteria for cure after 25 days of treatment with a cumulative dose of 3750 mg.[8] Larger randomized controlled trials have not yet investigated the use of miltefosine in cases of *L mexicana* CL.

This case offers an example of the successful use of miltefosine in a patient with proven *L mexicana* for whom initial therapies were inefficacious and with cosmetically sensitive facial subunit involvement

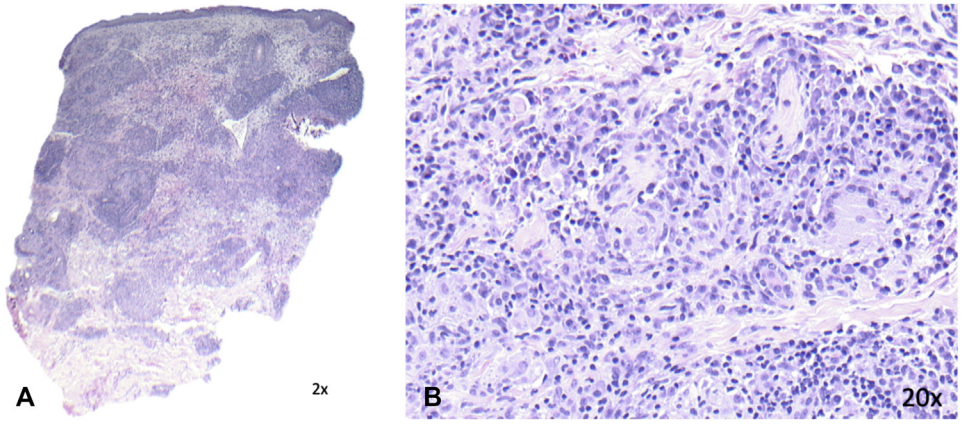

Fig 2. A, Skin with well-formed granulomas composed of epithelioid histiocytes and multinucleated giant cells, (2×). **B,** Abundant lymphoplasmacytic infiltrate in the surrounding dermis. This sample did not show any evidence of amastigotes, (20×).

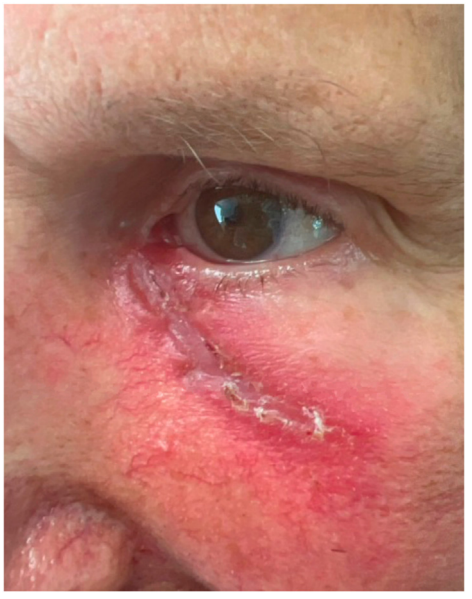

Fig 3. Status after oral miltefosine 50 mg 3 times daily for 28 days.

requiring more aggressive therapy. Further research of the therapeutic effect of miltefosine and other antileishmanial therapies against *L mexicana* and other New World *Leishmania* species is warranted.

Conflicts of interest

None disclosed.

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