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Case report

Microbial perils of the tropics: A case of cutaneous leishmaniasis in an immigrant from South America

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ABSTRACT

Cutaneous leishmaniasis is an important cause of nonhealing lesions in those recently immigrated to the United States from endemic areas. The lesions can present with various characteristics such as ulcerations, macules, or papules, and may be painful or painless. Several diagnostic modalities, including polymerase chain reaction testing, should be performed to identify the causative *Leishmania* species which is important in determining appropriate treatment. We describe a case of cutaneous leishmaniasis caused by *Leishmania panamensis* in a patient who recently traveled through South and Central America.

Introduction

Cutaneous leishmaniasis (CL) is a protozoan infection transmitted by the bite of a sand fly. While rarely encountered in the United States, leishmaniasis is endemic in many regions of the world, including North Africa, the Middle East, the Mediterranean, Central America, and northern parts of South America [1]. CL usually causes chronic non-healing ulcerative lesions on the skin. Almost all cases of leishmaniasis detected in the United States (U.S.) are amongst individuals who became infected while traveling through or living in an endemic region. In particular, travel through the Darién Gap in Colombia and Panama, a tropical terrain consisting of watershed, forest and mountains, and a common immigration route from South America, has been associated with cases of CL [2]. We present a case of CL caused by *Leishmania panamensis* in a person originally from Chile who traveled through the Darien Gap during his migration into the U.S. This case report demonstrates the need to include leishmaniasis in the differential diagnosis for patients presenting with chronic skin ulcers who have recently immigrated to the U.S., especially those who have a history of traveling through the tropical forests of South and Central America.

Case presentation

A 36-year-old man presented to the emergency department with nonhealing lesions on his left arm and forearm. The lesions first appeared about two months prior while the patient was migrating by foot from Chile to the United States. The patient recalled traveling through the forests between Colombia and Panama where he was bitten by numerous mosquitoes and possibly other insects. He denied prior injury to the site of his current wounds. The skin lesions began as a generalized papular rash which developed into vesicles draining clear fluid and eventually turned yellow in color. Many of the smaller lesions had since resolved leaving scars, but two large lesions remained that were intensely pruritic and painful on his left arm and forearm. In the past month, he sought treatment and was prescribed various antibiotics including cephalexin, clindamycin and piperacillin-tazobactam, none of which improved his symptoms. He also reported decreased appetite, fatigue, and headache over the past three days. He had never been affected by lesions like these before and denied fevers, chills, weight loss, joint pain, abdominal pain, nasal congestion, sore throat, or mucosal bleeding.

On admission, the patient's vitals were within normal limits. Skin exam showed a dry-appearing chronic ulcer with heaped-up borders and erythematous base measuring 4 cm by 3 cm on the ulnar aspect of the left forearm, and a similar lesion measuring 1 cm by 1 cm on the left bicep (Fig. 1). Surrounding skin was notably tender, and multiple 1–2 cm mobile lymph nodes were palpable proximal to the bicep lesion. No oral or nasal mucosal lesions were noted, and the rest of physical exam was otherwise normal.

Laboratory results, including a complete blood count, basic metabolic panel, sedimentation rate, c-reactive protein and procalcitonin were all within normal limits. Blood cultures revealed no growth of

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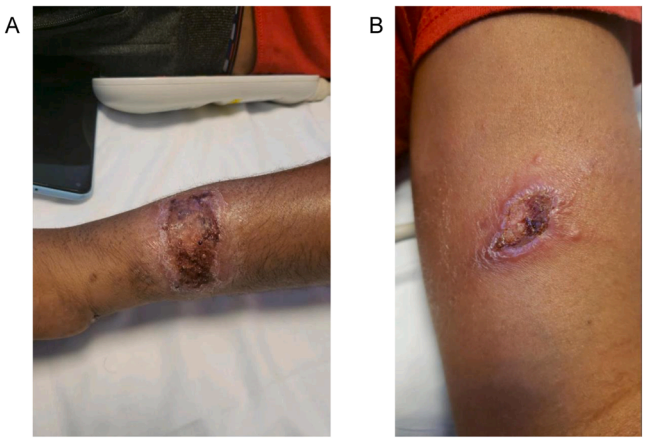

Fig. 1. A. Forearm lesion prior to treatment B. Bicep lesion prior to treatment.

microorganisms. A computed tomography scan of the humerus and forearm showed segmental regions of skin thickening and subcutaneous edema with no defined fluid collection or abscess. We obtained tissue biopsy samples for culture and histopathology, including molecular testing to be done by the Centers for Disease Control and Prevention (CDC). Given that the patient was clinically stable with low suspicion for superimposed bacterial infection, he was discharged without any treatment.

Routine, fungal, and mycobacterial cultures from biopsy samples did not reveal any growth. Pathology specimens later showed granulomatous inflammation, with sections of dermal inflammatory infiltrate of lymphocytes, epithelioid histiocytes, nuclear debris and Langerhans cells. Giemsa stain was negative for amastigotes. Acid-fast bacilli and Fite stains were negative for mycobacteria. Gomori methenamine silver stain was negative for fungal hyphae. Culture sample sent to the CDC did not yield any promastigotes or other parasites. Polymerase chain reaction (PCR) testing of the specimen by the CDC revealed the presence of *Leishmania panamensis.*

Initially, we started the patient on empiric treatment with oral fluconazole 200 mg once daily. The patient was seen in the clinic one week later and he had reported acute worsening of his forearm skin lesion with increased pain, and now with purulent, bloody discharge. By that time, our hospital pharmacy, through coordination with the manufacturer, received a shipment of miltefosine (Profounda Inc.); therefore, we discontinued fluconazole and transitioned his treatment to miltefosine 50 mg three times daily for 28 days. He presented to the clinic after completing the full course of treatment with marked healing of lesions which were nontender without discharge (Fig. 2).

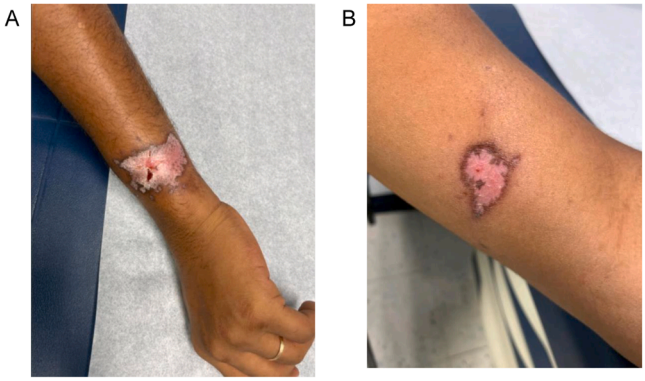

Fig. 2. A. Forearm lesion after treatment B. Bicep lesion after treatment.

Discussion

Leishmaniasis is a parasitic disease caused by a group of protozoa that are members of the *Trypanosomatidae* family and *Leishmania* genus. There are currently about 21 identified *Leishmania* species that are pathogenic in humans, including *L. tropica, L. major, L. aethiopica, L. donovani* complex species (*L. donovani, L. infantum)* - species found in the Eastern hemisphere, and *L. chagasi, L. mexicana* complex species (*L. mexicana*, *L. amazonensis*, *L. venezuelensis)* and the *Viannia* subgenus (*L. [V.] braziliensis*, *L. [V.] guyanensis*, *L. [V.] panamensis*, *L. [V.] peruviana)* - species found in the Western hemisphere [3].

Transmission is via the female phlebotomine sandfly vector. Leishmaniasis is found on every continent except for Australia and Antarctica. It is endemic in the tropical and subtropical regions, mainly in Latin America, Asia, the Middle East, Africa, and Southern Europe. The majority of cases (> 90 %) have been identified in Brazil, Peru, Syria, Afghanistan, Iran, and Saudi Arabia [3]. There are an estimated 0.7–1.2 million cases of leishmaniasis that occur each year [4]. In the United States, the majority of cases are related to individuals who are traveling or immigrating from other regions, especially Latin America.

Clinical manifestations of leishmaniasis range from cutaneous ulcers to systemic multiorgan disease and is typically categorized as either cutaneous, mucosal, or visceral. When symptomatic, the incubation period ranges from several weeks to months. About 10 % of individuals may have an asymptomatic infection [5]. The most common clinical presentation is localized CL, which typically presents as one to ten lesions that appear around the sandfly bite on exposed areas of the skin such as the face, neck, and extremities. Lesions typically start as red macules or papules, which over weeks to months may progress and increase in size to nodules with a central crust underneath; later, the nodules may ulcerate, and some can develop secondary bacterial infection. For patients who have been in endemic areas having developed non-resolving skin lesions not improved on antibiotics, such as the case with our patient, CL should be in the differential diagnosis.

CL lesions are usually known to be painless, although there is a growing body of evidence that many lesions are painful. In one study of 736 cases, 38 % of cutaneous lesions were painful which could not be entirely explained by secondary bacterial infection that occurred in 18 % of the cases [6]. Regional lymphadenopathy may also be present. CL may become diffuse or disseminated, presenting as multiple skin lesions of various morphology in two or more areas of the body. Mucosal leishmaniasis (ML) may also develop as a progression from CL, occurring at the same time, or developing years after the initial cutaneous infection. ML can presents as nasal stuffiness, discharge, epistaxis, and nasal septal ulceration; providers should evaluate for these clinical manifestations in a patient with suspected or confirmed CL.

Diagnosis of CL can be confirmed by direct visualization of amastigotes in skin smear or biopsy sample using light microscopy, sample culture showing promastigotes, immunochemistry for detection of *Leishmania* antigens, or PCR on lesion specimens. Several diagnostic tests should be performed to increase the likelihood of confirming leishmaniasis infection. In our patient case, culture and pathology did not reveal the *Leishmania* parasite, but PCR was able to detect it and identify the *Leishmania* species. This illustrates the value of PCR in obtaining diagnostic success and species identification, which impacts treatment decisions. Recently, advances in point-of-care DNA detection using loop mediated isothermal amplification assays has enabled rapid, highly-sensitive testing in resource-limited settings [7,8].

To prepare for sampling, the lesion is cleaned with soap and water, and exudate or hyperkeratotic eschar removed. The standard options for specimen collection include aspiration of samples from indurated margin, skin scraping of the base and margins of an ulcer, or brush cytology [1,9]. Full-thickness punch biopsy samples can also be obtained for simultaneous testing of other diagnoses [10]. The recommended site for biopsy is the raised border of an ulcerative lesion. In addition to leishmaniasis, the specimen that is submitted may also be

evaluated for mycobacteria and fungi [11]. In the United States, the CDC can provide guidance on testing.

The skin lesions associated with CL are usually self-limiting; however, the healing process may take months, or even years. CL can relapse, which may occur decades after the primary lesion has resolved. Mortality from CL is rare, but may occur in individuals with mucocutaneous infection, typically due to secondary infection.

Treatment for CL begins with determining the complexity of the lesion. Features of uncomplicated CL include infection with species not likely to be associated with mucosal leishmaniasis, no mucosal involvement, single or few lesions ($\leq$ 4 lesions), small lesion size (eg, $\leq$ 1 cm), and immunocompetent host. Features of complicated CL include infection with *Leishmania* species associated with mucosal leishmaniasis (mainly *Viannia* spp), more than four lesions of significant size (eg, $>$ 1 cm), individual lesion $\geq$ 5 cm, subcutaneous nodules, large regional adenopathy, size or location of lesions for which local treatment is not feasible, lesions on face, fingers, toes, or genitalia, immunosuppressed host, and clinical failure of local therapy after two to three months posttreatment [10].

For uncomplicated CL that is healing spontaneously, clinical observation without antimicrobial treatment is reasonable. Otherwise, uncomplicated lesions can be given local therapy [3,10]. Topical antiparasitic agents include paromomycin, intralesional antimonials, and imiquimod. Other local therapies includes cryotherapy and thermotherapy. For complicated CL, systemic antibiotics is warranted. Oral antiparasitic agents include miltefosine and azoles (ie. ketoconazole, fluconazole). Parenteral antiparasitic agents include pentavalent antimonial therapy, amphotericin B, and pentamidine isethionate [9]. Treatment options depend on infecting species, treatment availability, and local resistance patterns. For example, in a study of 26 patients treated with miltefosine, there was good efficacy to a number of *Leishmaniasis* species such as *L. panamensis* and *L. infantum*, but there were high failure rates for *L. braziliensis* and *L. aethiopica* [12]. The World Health Organization provides graded recommendations of treatment options depending on species [13]. During the first 2–3 weeks of therapy, there may be a paradoxical increase in inflammatory response, as in this case, and patients can develop new satellite lesions or more erythema and induration [10]. The full treatment course should be completed, and there should be appreciable improvement 4–6 weeks post-treatment [14]. Patients should be followed for 6–12 months to evaluate for relapse.

In conclusion, CL should be considered in the differential diagnosis of chronic skin lesions in patients who have traveled to endemic areas. They can present in various ways as macular, papular, nodular, psoriasiform, or ulcerative lesions that can be associated with or without pain. Several testing modalities, including PCR, should be performed to help with the parasitological diagnosis and identification of the causative *Leishmania* species, which is important for determining optimal treatment.

CRediT authorship contribution statement

Rachel Cowan: Care of patient, Writing – original draft, Writing – review & editing. **Shruti Varadarajan:** Writing – original draft, Writing – review & editing. **Abraham Wei:** Care of patient, Writing – review & editing and submission of manuscript. **Tanzila Salim:** Care of patient, Writing – review & editing. **Michelle Dalla Piazza:** Care of patient, Writing – review & editing, Supervision.

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Ethical approval

The patient agreed that his case can be published and contributed in the writing of the manuscript.

Consent

Patient consented for publication.

Conflict of interest statement

The authors report there are no competing interests to declare.

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