Am. J. Trop. Med. Hyg., 99(2), 2018, pp. 327–330
doi:10.4269/ajtmh.17-0831

Case Report: Mucosal Leishmaniasis Presenting with Nasal Septum Perforation after Almost Thirty Years

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Abstract. Mucosal leishmaniasis (ML) is associated with progressive tissue destruction and granuloma formation, often after a considerable period of latency from an initial cutaneous infection. We report a case of recurrent epistaxis of 3 years duration and nasopharyngeal obstruction in a woman with treated cutaneous leishmaniasis nearly 30 years before and with no further exposure to Leishmania. Computed tomography revealed nasal septal perforation and histopathology demonstrated chronic inflammation. Microscopy was negative for amastigotes, but molecular testing of nasal mucosa biopsy detected *Leishmania (Viannia) braziliensis*. The patient underwent 28 days of treatment with IV sodium stibogluconate and her symptoms improved significantly. Sixteen months after treatment, she continues to have episodic epistaxis and detectable parasite load in her nasal lesion. Although ML is known to take years to decades to develop, there are few reported cases in the literature of such a long latency period. This report highlights the importance of considering ML in the differential diagnosis of chronic epistaxis in countries where leishmaniasis is endemic or in immigrants from these countries, even when presentation occurs decades after leaving an endemic region.

INTRODUCTION

Cutaneous leishmaniasis is considered an emerging and uncontrolled disease by the World Health Organization. It affects 12 million people in 88 countries, with 50,000 people dying from leishmaniasis each year.[1,2] In Peru, between 2008 and 2014 there were approximately 5,100–7,350 yearly cutaneous leishmaniasis cases.[3]

Leishmaniasis is characterized by broad clinical polymorphism: infection can be subclinical, cutaneous, mucocutaneous, or visceral.[4] Mucosal leishmaniasis (ML) indicates the development of a chronic, degenerative phase, usually following a cutaneous lesion. Most cases of ML develop within 2 years of onset of cutaneous disease.[5] Mucosal leishmaniasis can lead to disfiguring and life-threatening lesions, particularly in the nose, oropharynx, and nasopharynx.[2,6] Sequelae include septal perforations and vocal cord compromise. Disfiguration often results from a combination of the parasite's virulence and the patient's immune response.[7] Mucosal leishmaniasis is caused mainly by species in the *Vianna* subgenus, primarily *L.* (*V.*) *braziliensis*, but it has also been seen with *Leishmania* (*V.*) *panamensis*, *Leishmania* (*V.*) *guyanensis*, and *Leishmania amazonensis*.[8] Cases are mostly limited to Brazil, Peru, and Bolivia.[2]

CASE REPORT

A 42-year-old woman originally from the Huanuco region of Peru first presented to a health post in Lima with a 2-year history of episodic, small-volume epistaxis associated with blowing her nose. As informed by the patient, no workup or treatment was pursued then. Over the next year, the epistaxis became progressively more profuse and eventually the patient began breathing primarily through her mouth due to nasal obstruction. At this point she returned to the health post and was referred to a tertiary care hospital for an otolaryngologist consultation.

The patient was born and raised in Ambo Province in Huanuco, an endemic region for *L.* (*V.*) *braziliensis*. She reported a history of cutaneous leishmaniasis at an age of 12 years (28 years before presenting with epistaxis), with three lesions: a 4-cm ulcer on her right wrist (Figure 1), a 2-cm ulcer on her left hand, and a 7-cm ulcer on her left calf. She reported that diagnosis was made with a biopsy of one of the lesions and she received 20 days of treatment with intravenous sodium stibogluconate, after which her ulcers healed completely. When she was 25 years old, she moved to Lima (a non-endemic area for leishmaniasis) to work as a cleaning lady. She remained in Lima until the time of presentation with ML, save for one visit to her hometown at age 38. This visit lasted only 1 week, and she never left the urban area of the city. This was her only time back since moving to Lima and she reported no traveling to other leishmaniasis-endemic regions.

On examination, the otolaryngologist observed a septal perforation measuring 1.5 × 3 cm in Cottle's areas II and III. There was approximately 90% obstruction in both nasal fossae due to crusting, dark lesions. An additional lesion measuring 2 cm with a granulomatous appearance was observed on her hard palate. Thin-cut axial computed tomography of the face confirmed the perforation of the cartilaginous portion of the nasal septum and sinusitis of the right maxillary with signs of chronicity (Figure 2).

The patient underwent a right nasal cornet biopsy, and pathology revealed a dense, infiltrating lymphoplasmohistiocytosis in an area of chronic inflammation. Histiocytes comprised about 70% of the slide (Figure 3). Plasma cells were also observed. Periodic acid–Schiff (PAS) and bacillus of Koch staining demonstrated no fungi or mycobacteria, respectively. Staining of the biopsy sample failed to show visible amastigotes, although yeast was observed. Polymerase chain reaction (PCR) of kinetoplast DNA determined the presence of *Leishmania* (*Viannia*) DNA, and nested real-time PCR identified the *L.* (*V.*) *braziliensis* species.

The patient was treated with IV sodium stibogluconate at a daily dose of 20 mg/kg for 20 days, after which she presented

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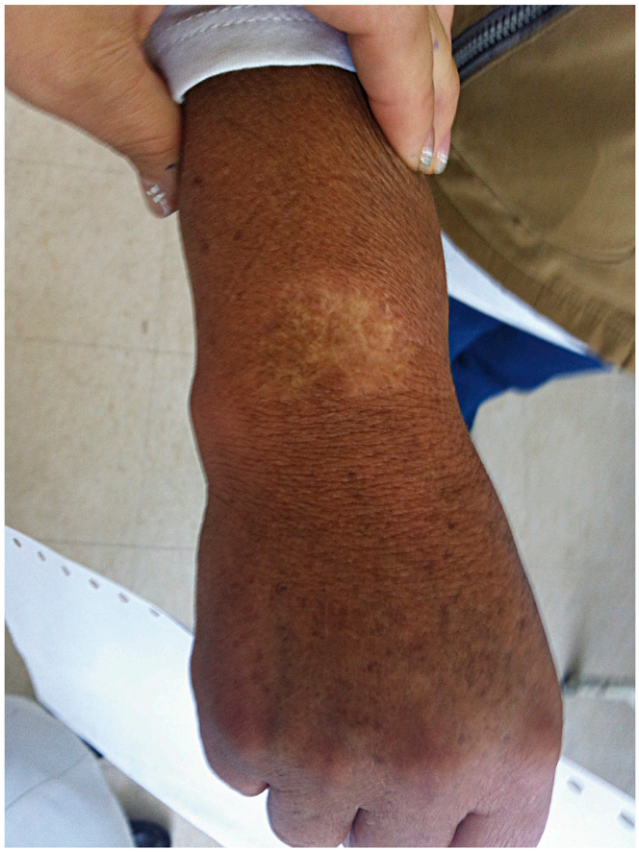

FIGURE 1. The 4-cm fully epithelized scar on the patient's right wrist, presenting the typical healing patterns of treated cutaneous leishmaniasis: a rugged, hypochromic, and slightly depressed scar. This figure appears in color at www.ajtmh.org.

with intense headaches, nausea, and asthenia. Treatment was interrupted and then resumed after 2 weeks for a total of 28 days of treatment.

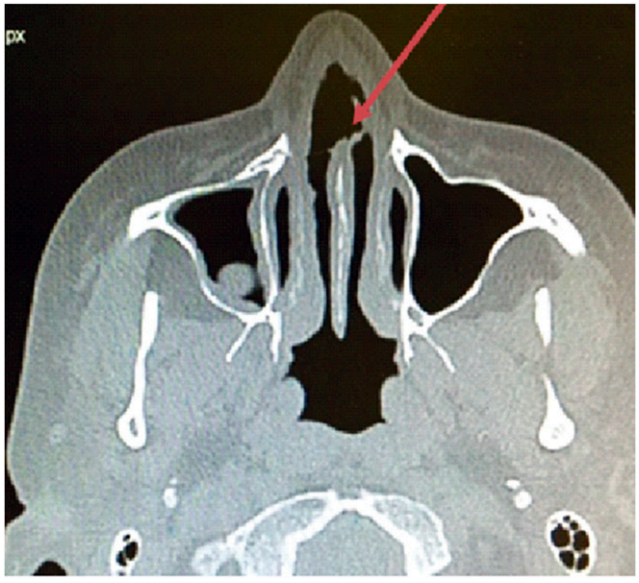

FIGURE 2. Head computed tomography from the patient, showing perforation of the cartilaginous part of nasal septum (red arrow). This figure appears in color at www.ajtmh.org.

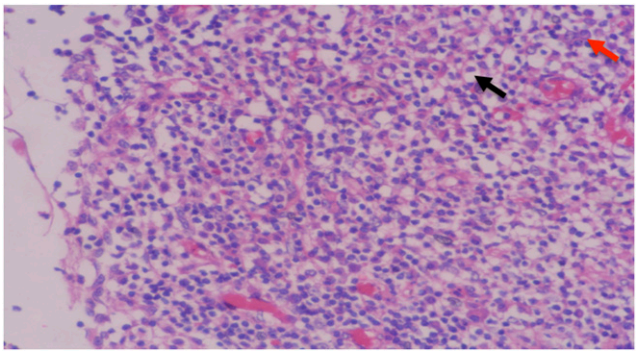

FIGURE 3. Histiocytes (black arrow) and lymphocytes (red arrow) are seen throughout the biopsy tissue, at 1,000× magnification with Giemsa stain. This figure appears in color at www.ajtmh.org.

Plasma immunoglobulin G against *Leishmania* spp. was measured by indirect immunofluorescence and was positive at a titer of 1:160 before treatment, compared with a titer of 1:80 posttreatment. Bleeding diminished significantly after antimonial treatment, although the patient required cauterization of bleeding vessels with the otolaryngologist shortly after her hospital discharge.

Sixteen months after her treatment, the patient presented with abundant nasopharyngeal secretions and was found to have a 1.3 cm hypertrophic septal perforation in Cottle's Area I–II with surrounding scarring.

The patient underwent a follow-up biopsy of her nasal septum lesion. Tissue was again positive for PCR-kinetoplast DNA of *Leishmania Viannia*. A third IFI was was carried out and was positive with a titer of 1/40. At this stage, the patient received conventional (nonliposomal) amphotericin B at a daily dose of 0.6 mg/kg. The drug was diluted in 500 mL of 5% dextrose. After 1 week, the patient reported an intense general malaise for which she requested her voluntary discharge. She has not returned to the hospital to date.

Written informed consent was obtained from the patient for the publication of this case report and all accompanying images.

DISCUSSION

We observed a case of ML 28 years after successful treatment, without recurrence of a cutaneous lesion nor further exposure to the parasite. Mucocutaneous lesions are known to take years to develop, but there are few reports in the literature to our knowledge with such a long latency period and with strong confirmatory evidence.

As far as the authors are aware, few reported cases of mucocutaneous leishmaniasis with a long latency period have been published. A Bolivian case noted a 14-year latency period[9]; one Venezuela report noted a 16-year latency period, with nasal destruction[10]; and one four-case report cites a latency range of 11–24 years.[11] The reports with longer latency periods, ranging from 30 to 70 years, suffer from lack of specific diagnostic information or verification. For example, a report from Panama mentions a latency period of 30 years, although it provides no evidence of diagnostic confirmation, nor that the recurrence was not in fact a second primary infection.[12] A much longer latency report of 70 years lacked diagnostic support for the initial lesion and was based solely on an initially overlooked scar found at the time of MCL diagnosis.[13]

In considering ML, health-care providers should consider risk factors such as time spent in areas where leishmaniasis is endemic, the patient's immunocompetence, and a personal history of cutaneous leishmaniasis. In the latter case, it is important to note whether a full treatment course was administered.[14–16]

Differential diagnosis of chronic epistaxis in adults includes mucosal irritation (from drug use such as nasal steroids, drug abuse such as cocaine, chemical exposure to dry air, or allergic rhinosinusitis); septal abnormalities; blood dyscrasias; uncontrolled hypertension; inflammatory autoimmune diseases (such as sarcoidosis or Wegener's granulomatosis); arteriosclerosis; neoplasia; and infection.[17] Infectious causes include ML, tuberculosis, blastomycosis, paracoccidioidomycosis, amebiasis, tertiary syphillis, and leprosy.[15] In our patient's case, her unusually long latency period of ML probably prevented earlier diagnosis, in addition to potential limitations in resources and training common in primary care facilities.

Mucosal leishmaniasis is challenging to manage not only because of complications from tissue damage, but also because of the difficulty in diagnosing it.[18,19] Because mucosal tissue is internal and not easily visible, diagnosis is often made years after the lesion first appears.[19,20] A biopsy is required for definitive diagnosis, carrying bleeding and infection risks and limiting prompt diagnosis in rural areas.[21] Finally, mucosal lesions tend to have lower levels of amastigotes than cutaneous lesions, rendering a diagnosis by culture or Giemsa stain less accurate than by PCR. Sensitivity is improved by 55–70% with PCR in ML when compared with conventional parasitological diagnosis.[22] Its use is still limited outside tertiary care hospitals, but it could substantially improve case management.[2,6] In our case, the PAS and Giemsa-stained tissue were negative for amastigotes, however PCR detected kDNA of *Leishmania* spp. In addition, we observed a decrease of IgG antibodies during the evolution of the patient, which could indicate a decrease of the parasitic load.

Parenteral treatment options for ML include pentavalent antimonials (i.e., sodium stibogluconate) and conventional and liposomal amphotericin B.[23] Oral treatments include miltefosine and tumor necrosis factor-alpha (TNF-a) inhibitors, used alone or in combination with antimonial treatment. Miltefosine's efficacy is highly dependent on the parasite species and previous studies on its cure rate have been discouraging. There is not much evidence for the use of liposomal amphotericin B in ML, but conventional amphotericin B may have upward of a 75% cure rate.[24–26] Both miltefosine and amphotericin B, however, have serious side effect profiles that limit their use, including teratogenicity in miltefosine's case.[27–29] They are also very costly in Peru. Finally, the combination of antimony and oral pentoxyfilline, a TNF-a inhibitor, has promising results for ML, with cure rates between 90 and 100%.[30–33] Nonetheless, this combination therapy is not yet approved in Peru.

Leishmaniasis is no longer exclusively a problem of countries in which it is endemic but may affect travelers and immigrants from these countries. Leishmaniasis should be considered in the diagnostic assessment of immigrants or travelers who may have been exposed to the parasite. Our report highlights the need for ongoing follow-up with thorough nasal and oral examinations in patients with a history of cutaneous leishmaniasis to promptly diagnose and treat any mucocutaneous recurrence.

Received October 24, 2017. Accepted for publication April 13, 2018.

Published online June 4, 2018.

Acknowledgments: We thank Victor Rojas Figueroa, otolaryngologist at the Hospital Guillermo Almenara Irigoyen, and resident clinician Lisbeth Meza from the same service. We also thank Maxy de los Santos from the U.S. Naval Medical Research Unit No. 6 (NAMRU-6) in Lima, Peru for diagnostic support. Andres G. Lescano is sponsored by the training grant D43 TW007393 awarded by the Fogarty International Center of the US National Institutes of Health awarded to Emerge, the Emerging Diseases and Climate Change Research Unit of the School and Public Health Administration at Universidad Peruana Cayetano Heredia.

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