Case Report: Progressive Perforation of the Nasal Septum due to *Leishmania major*: A Case of Mucosal Leishmaniasis in a Traveler

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Abstract. This report describes a case of mucosal leishmaniasis caused by *Leishmania major* with destructive perforation of the nasal septum illustrating the diagnostic challenges of a rare clinical presentation of *L. major* infection in a traveler. The atypical presentation may have been associated with the use of cortisone as a potential trigger for the progressive destruction of the nasal septum.

INTRODUCTION

Leishmaniasis typically manifests itself as one of three classical disease entities—visceral, cutaneous, and mucocutaneous leishmaniasis. So far about 20 different *Leishmania* species have been identified as human pathogens and are commonly divided into New World and Old World *Leishmania* spp. Mucocutaneous leishmaniasis is usually caused by *Leishmania* spp. of the New World, mainly by representatives of the *Leishmania braziliensis* complex, and less often by representatives of the *Leishmania guyanensis* complex, which are only endemic in South and Central America.

However, new terms are used to describe the different manifestations of leishmaniasis more accurately—mucosal leishmaniasis (ML) refers to an involvement of mucous membranes in the oral cavity or the upper respiratory tract.¹ Several case studies have shown that species of Old World leishmaniasis may also involve mucosal membranes. There are reports about ML caused by *Leishmania donovani*,² *Leishmania infantum*,³ *Leishmania tropica*, or *Leishmania major*.^{4–6} So far only few cases of ML caused by *L. major* have been reported. One report described a case of ML of the lips in a young boy from Iran.⁷ In a small case series from Tunisia, four cases with mucosal involvement of the lips and one with an endonasal manifestations were depicted.⁶ However, only in one case *L. major* was identified. It appears that ML caused by Old World species is less destructive and often follows a cutaneous facial lesion.

The case that led to this report is one of the first to describe ML caused by *L. major* with destructive perforation of the nasal septum and without prior cutaneous manifestations.

CASE PRESENTATION

A 41-year-old male suffered for 2 years of recurrent but self-limiting epistaxis and noted a first nodular and subsequently ulcerative lesion at the nasal septum. Six months prior to initial presentation symptoms had worsened and the patient had consulted several specialists for otorhinolaryngology. Local and systemic application of cortisone was recommended. The small ulcer of the nasal septum rapidly

progressed to a large perforation (about 1.5 cm in diameter), destroying a substantial part of the septum (Figure 1). Based on the suspicion of Wegener's granulomatosis, a biopsy of the nasal septum was performed. Histology revealed unspecific necrosis and inflammation without signs of vasculitis or malignancy.

For further management, the patient referred himself to the outpatient ward for tropical medicine at the Medical University of Vienna. He reported frequent travels to various countries including prolonged stays in South America and Spain. Based on the history and clinical development, several infectious etiologies including atypical mycobacteria, leprosy, syphilis, and mucocutaneous leishmaniasis were considered. Laboratory analysis showed an unremarkable blood count and normal inflammation markers. The interferon-gamma release assay for tuberculosis (QuantiFERON-TB Gold, Qiagen, Hilden, Germany) and serology for syphilis (VDRL antigen; Becton, Dickinson and Company, Sparks, MD; Serodia-TPPA; FUJIREBIO, Tokyo, Japan) were negative. *Leishmania* serology revealed a negative immunochromatographic test (Kalazar Detect, Rapid Test, InBiOS, Maam, the Netherlands), but a positive IgG Western Blot (*Leishmania* Western Blot IgG, LDBIO Diagnostics, Lyon, France). The previously obtained histological specimen was reexamined by polymerase chain reaction (PCR) using a commercial oligochromatographic test for the detection of all *Leishmania* species (*Leishmania* OligoC-Test, Coris BioConcept, Gembloux, Belgium) yielding a negative result.

For further diagnostic evaluation, a second biopsy of the nasal septum was obtained. In this specimen, intracellular microorganisms compatible with *Leishmania* amastigotes were detected in the histological examination and the commercial PCR assay was positive confirming *Leishmania* infection. Based on the travel history to South America and the destructive mucosal inflammation, a presumptive diagnosis of mucocutaneous leishmaniasis was established and treatment with intravenous liposomal amphotericin B was initiated (cumulative dose of 30 mg/kg body weight). No further progression of disease was noted in follow-up visits over 3 months.

For species identification, a second PCR was performed, targeting the internal transcribed spacer 1 (ITS-1) region with the LITSR/L5.8S primers⁸ and including as a negative control PCR mix plus ultra-pure water (Sigma-Aldrich, Vienna, Austria) instead of DNA. The amplicon was sequenced by direct sequencing using the BigDye sequencing kit and an

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FIGURE 1. Nasal septum perforation demonstrated in (A) computed tomography and (B) upon endoscopic nasal examination. (A) Arrow marks site of perforation. (B) + Marks perforated nasal septum (Supplemental Video), * marks inferior nasal conchae.

automatic 310 ABI PRISM sequencer (AB Applied Biosystems, Darmstadt, Germany). Sequences were obtained from both strands and sequence data were processed with the GeneDoc sequence editor to obtain a consensus sequence. Species designation was achieved by multiple alignments with reference sequences of all *Leishmania* species from the GenBank using ClustalX. Surprisingly, the identified causative agent was not of the *L. braziliensis* or *L. guyanensis* complex but rather *L. major*, an Old World *Leishmania* species typically causing ulcerative cutaneous lesions. A second multiple alignment including all *L. major* sequences available at GenBank revealed a 100% identity of our sequence with three other sequences of *L. major* originating from the Middle East and Central Asia (accession numbers: KJ194178, FN677357, and AY573187). Sequence data obtained in this study were deposited at GenBank and are available under the accession number KX821679.

DISCUSSION

It is unclear why *L. major* infection presented primarily at the nasal mucosa in an immunocompetent host. Considering the slow progression of disease, it is plausible that the intact immune system of the host was able to control and confine the infection to the nasal mucosa. The sudden progression of the disease and subsequent perforation of the nasal septum may have been caused by the use of cortisone, which was first applied locally to the nasal mucosa and subsequently administered systemically, suppressing the mucosal immune defense and allowing faster growth and replication of the parasite leading to tissue destruction. The association of leishmaniasis and systemic immunosuppression—caused by systemic conditions like human immunodeficiency virus infection, organ transplantation or hematological disorders⁹—is well established. However, there are only few case reports describing that systemic corticosteroid treatment may worsen mucocutaneous leishmaniasis or lead to a recurrence of the disease.^{10,11}

This is the first description of ML caused by *L. major* in a traveler as opposed to patients residing in endemic areas. The place of exposure in this patient was most likely North Africa, where he had traveled to Tunisia, Morocco, and Egypt 2 years before the occurrence of the disease. The treatment with liposomal amphotericin B was initiated

based on the assumption that this was a case of mucocutaneous leishmaniasis caused by the *L. braziliensis* or *L. guyanensis* complex. Systemic pentavalent antimonials and miltefosine are other potential therapeutic options for Old World leishmaniasis. However, to date, miltefosine has not been evaluated extensively in Old World leishmaniasis and systemic pentavalent antimonials are associated with important safety concerns.¹²

In conclusion, this case report illustrates the diagnostic challenges of a rare clinical presentation of *L. major* infection as ML in a traveler. The atypical presentation may have been associated with the use of cortisone as a potential trigger for the progressive destruction of the nasal septum.

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REFERENCES

1. Strazzulla A, Cocuzza S, Pinzone MR, Postorino MC, Cosentino S, Serra A, Cacopardo B, Nunnari G, 2013. Mucosal leishmaniasis: an underestimated presentation of a neglected disease. *BioMed Res Int* 2013: 805108.
2. Daulatabad D, Singal A, Dhawan A, Pandhi D, Sharma S, 2015. Mucocutaneous leishmaniasis caused by *Leishmania donovani* infection in an Indian man. *Int J Dermatol* 54: 680–684.
3. Aliaga L, Cobo F, Mediavilla JD, Bravo J, Osuna A, Amador JM, Martin-Sanchez J, Cordero E, Navarro JM, 2003. Localized mucosal leishmaniasis due to *Leishmania* (*Leishmania*)

- infantum: clinical and microbiologic findings in 31 patients. *Medicine (Baltimore)* 82: 147–158.
4. Shirian S, Oryan A, Hatam GR, Daneshbod Y, 2012. Mixed mucosal leishmaniasis infection caused by *Leishmania tropica* and *Leishmania major*. *J Clin Microbiol* 50: 3805–3808.
 5. Shirian S, Oryan A, Hatam GR, Daneshbod Y, 2013. Three *Leishmania/L. species*–*L. infantum*, *L. major*, *L. tropica*–as causative agents of mucosal leishmaniasis in Iran. *Pathog Glob Health* 107: 267–272.
 6. Kharfi M, Fazaa B, Chaker E, Kamoun MR, 2003. Mucosal localization of leishmaniasis in Tunisia: 5 cases [in French]. *Ann Dermatol Venereol* 130: 27–30.
 7. Alborzi A, Pouladfar GR, Ghadimi Moghadam A, Attar A, Drakhshan N, Khosravi Maharlooee M, Kalantari M, 2013. First molecular-based detection of mucocutaneous leishmaniasis caused by *Leishmania major* in Iran. *J Infect Dev Ctries* 7: 413–416.
 8. el Tai NO, Osman OF, el Fari M, Presber W, Schonian G, 2000. Genetic heterogeneity of ribosomal internal transcribed spacer in clinical samples of *Leishmania donovani* spotted on filter paper as revealed by single-strand conformation polymorphisms and sequencing. *Trans R Soc Trop Med Hyg* 94: 575–579.
 9. van Griensven J, Carrillo E, Lopez-Velez R, Lynen L, Moreno J, 2014. Leishmaniasis in immunosuppressed individuals. *Clin Microbiol Infect* 20: 286–299.
 10. Tuon FF, Sabbaga Amato V, Floeter-Winter LM, de Andrade Zampieri R, Amato Neto V, Siqueira Franca FO, Shikanai-Yasuda MA, 2007. Cutaneous leishmaniasis reactivation 2 years after treatment caused by systemic corticosteroids: first report. *Int J Dermatol* 46: 628–630.
 11. Motta AC, Arruda D, Souza CS, Foss NT, 2003. Disseminated mucocutaneous leishmaniasis resulting from chronic use of corticosteroid. *Int J Dermatol* 42: 703–706.
 12. Blum J, Buffet P, Visser L, Harms G, Bailey MS, Caumes E, Clerinx J, van Thiel PP, Morizot G, Hatz C, Dorlo TP, Lockwood DN, 2014. LeishMan recommendations for treatment of cutaneous and mucosal leishmaniasis in travelers, 2014. *J Travel Med* 21: 116–129.