Imported Mucosal Leishmaniasis in a Traveler

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We report a case of mucosal leishmaniasis in a traveler returning from South America. The traveler developed nasal symptoms 2 months after the appearance of cutaneous ulcers. Diagnosis of mucosal *Leishmania viannia braziliensis* infection was made 5 years later. The clinical presentation and diagnosis for the patient are reported, and previous cases in travelers are reviewed. We recommend that mucosal examination should be part of follow-up for *L. viannia braziliensis* infection in travelers. Mucosal leishmaniasis should be part of the differential diagnosis of mucosal lesions in patients with a history of travel to South America, however remote the likelihood of infection.

In the past decade, travel to South and Central America has increased among young adults, causing potential exposure to tropical diseases, including leishmaniasis. New World cutaneous leishmaniasis, endemic in some parts of the Americas, is caused by *Leishmania viannia* and *Leishmania mexicana* species complexes. Infection with *L. viannia* species, particularly *Leishmania viannia braziliensis*, results in skin lesions that tend to be persistent and may be further complicated by mucocutaneous involvement [1]. Mucosal leishmaniasis probably results from early hematogenous or lymphatic spread from cutaneous lesions. It causes destruction of the facial structure that may lead to aspiration, infection, and even death. Mucosal leishmaniasis may appear at any time from the first months after infection to decades afterward [1, 2]. Risk factors include large or multiple cutaneous lesions, male sex, and long-standing skin lesions for which adequate systemic treatment has not been administered [3]. Therefore, the treatment of cutaneous *L. vian-nia braziliensis* infection with systemic pentavalent antimonial compounds is aimed at reducing the risk of mucosal leishmaniasis [2, 3].

**Case report.** A 26-year-old male student presented to the Center for Geographic Medicine at The Chaim Sheba Medical Center (Jerusalem, Israel) with progressive ulceration in the nasal and oral mucosa of 5 years’ duration. The patient reported having traveled to South America 6 years before presentation. A month after visiting the Bolivian Amazon jungle, he noted 12 skin ulcers, most of which were on the trunk and upper extremities. On his return to Israel 2 weeks later, he sought medical consultation, and a diagnosis of cutaneous leishmaniasis was made. He was treated with topical paromomycin, with gradual resolution of the ulcers over the subsequent 3 months. The patient recalled experiencing nasal congestion that began ~2 months after the ulcers appeared. He went to an ear, nose, and throat specialist and was given decongestants. During the subsequent 5 years, he was not under any medical surveillance, but he noted progressive ulceration of the oral and nasal mucosa and chronic blood-tinged rhinorrhea.

At presentation, the patient had a hoarse voice with a nasal quality. His left nostril was red and edematous (figure 1), and the upper lip was thickened. The nasal mucosa was ulcerated with seropurulent discharge. Ulcerated plaques covered the hard and soft palate (figure 2), and the uvula was extremely thickened. Twelve old scars were noted on his trunk and limbs. There was no palpable lymphadenopathy, and the rest of the findings of the physical examination were normal. Histopathological examination of specimens from the palatine mucosa revealed granulomatous inflammation with giant cells. The results of histochemical stains for acid-fast bacteria and fungi were negative. Leishmania tissue amastigotes were neither seen in the palatine biopsy specimen nor detected by PCR analysis. However, culture of mucosal tissue specimens, the results of which became positive after 3 weeks, revealed *Leishmania* parasites identified as *L. viannia braziliensis* by species-specific PCR [4].

CT of the head and neck revealed infiltrative soft-tissue thickening of the upper airways from the oropharynx to the vocal cords (figure 3A, 3C, and 3E). Enlarged lymph nodes were observed in the jugular and posterior cervical chains. The findings of a complete blood cell count and chemistry analyses were unremarkable, and the results of serological tests for HIV
were negative. The results of serological tests for *Leishmania* were strongly positive.

The patient was treated with intravenous sodium stibogluconate at a dosage of 20 mg/kg for 28 days, and there were no significant complications or clinical or laboratory abnormalities. At the completion of the treatment, there was notable clinical improvement. CT of the head and neck at this stage revealed a reduction of ~50% in soft-tissue thickening throughout the upper airway (figure 3B, 3D, and 3F). Further clinical improvement was observed during the following year, although the mucosa of the palate and uvula was still slightly edematous.

**Discussion.** *L. viannia braziliensis* is the most prevalent species of *Leishmania* in the rain forest areas of South America [1]. This pathogen has complex interactions with the host’s immune system that can lead to 3 clinical outcomes [2]. First, in most cases, there is a cellular immune reaction in the inoculation site that eventually leads to the elimination of the parasites and to acquisition of immunity to *L. viannia braziliensis*. Clinically, this reaction results in localized cutaneous leishmaniasis characterized by skin ulcers, nodules, and, sometimes, regional lymphadenopathy. Secondly, cutaneous dissemination of the parasite can occur if cellular immune response is inadequate. Patients with disseminated leishmaniasis have lower levels of IFN-γ and TNF-α production than do patients with localized cutaneous leishmaniasis [5]. These cytokines are markers of macrophage activation. Finally, in a subset of patients, the parasites spread via hematogenous or lymphatic routes and invade the oropharyngeal mucosa, leading to mucosal leishmaniasis [1, 2]. Granulomatous reaction in the mucosal tissue causes thickening of the upper airway walls that may lead to obstruction. An exaggerated hypersensitivity reaction to the parasite in mucosal leishmaniasis is suggested by the paucity of amastigotes in the granulomas, the strongly positive *Leishmania* test result, and the high level of circulating TNF-α [6, 7].

Clinically, mucosal leishmaniasis is a progressive disease that destroys facial and upper airway structures. Without treatment, the outcome may be fatal because of the aforementioned airway compromise. The time lag between the appearance of skin lesions and mucosal disease ranges from simultaneous appearance to as much as 35 years [2]. Among the population of areas of endemicity in South America, mucosal leishmaniasis is estimated to occur in 3% of patients infected with *L. viannia braziliensis*. Risk factors include lesions above the waist, large or multiple cutaneous lesions, male sex, and long-standing skin lesions for which adequate systemic treatment has not been administered [3]. In addition, it has long been suspected that the risk of developing mucosal leishmaniasis has a genetic component. Recently, an association between HLA and the presence of mucosal leishmaniasis has been demonstrated. In a study in Brazil that compared 43 patients who had mucosal leishmaniasis with 111 matched control subjects, there was found to be a significant decrease in the frequency of HLA-DR2 and a significant increase in HLA-DQw3 among patients, compared...
Diagnosis of mucosal leishmaniasis can be obtained by examination of biopsy specimens or culture or PCR of specimens from the affected mucosa; these methods are routinely used in cases of cutaneous lesions. Comparative studies of their sensivities for diagnosis of cutaneous lesions associated with *L. viannia braziliensis* show that PCR has a much higher sensitivity (80%–98%) than does culture (42%–46%) [10–12]. In mucosal leishmaniasis, because of the minute parasite load in the mucosal lesion, definitive determination of the pathogen may be difficult. In previous studies, PCR showed a striking diagnostic sensitivity for mucosal leishmaniasis, compared with other methods: PCR results were positive for 71% of 24 patients with mucosal leishmaniasis, whereas other methods, including histopathological examination, culture, and smear, were positive for only 17% [13]. However, in our patient, the results of examination of the biopsy specimen and PCR of samples from the mucosal lesions were negative, but culture became positive for leishmaniasis after 3 weeks. The species-specific PCR performed with the culture revealed *L. viannia braziliensis*.

The differential diagnosis of mucosal leishmaniasis includes Wegener granulomatosis, midline granuloma, lymphoproliferative disease, sarcoidosis, relapsing polychondritis, and non-keratinizing squamous cell carcinomas. Additional differential diagnoses of infectious diseases that may involve facial structures include tuberculosis, syphilis, rhinoscleroma, actinomycosis, leprosy, blastomycosis, histoplasmosis, and coccidiomycosis.

Systemic treatment with intravenous sodium stibogluconate (20 mg/kg for 20 days) is recommended for the initial skin infection, to decrease the risk of mucosal invasion [2]. The recommended treatment regimen for mucosal leishmaniasis is intravenous sodium stibogluconate (20 mg/kg for 28 days) [14].

Mucosal leishmaniasis is rare in Western travelers returning from areas of endemicity. There are 3 previously published reports about this complication. The first report described a female Swiss traveler to Bolivia who developed a cutaneous lesion on the arm that was initially misdiagnosed [15]. Cosmetically disturbing mucosal lesions developed 6 months later, and, after the diagnosis of South American leishmaniasis was made, treatment with parenteral antimonials was given, with a good response. The second report described a male traveler who returned to the United Kingdom from South America with nearly concurrent appearances of mucosal and cutaneous disease [16]. The third patient was a Dutch cameraman who periodically visited South America. He acquired cutaneous *L. viannia braziliensis* infection of the neck and face that was treated with intramuscular sodium stibogluconate (10 mg/kg), followed by pentamidine because of the initial persistence of the ulcers [17]. Five years later, he presented with mucosal leishmaniasis of the nasal septum. The authors suspected that the trigger for the appearance of mucosal leishmaniasis was...
surgery for septal deviation and that the initial lack of response to treatment indicates that he was infected with a more resistant strain of *Leishmania*. This patient’s mucosal disease was treated effectively with intravenous amphotericin B at a total dose of 2 g [17].

Of note, our patient had several of the clinical risk factors previously mentioned. He was a young, male traveler with multiple cutaneous lesions, most of which were above the waist. He received only topical therapy and began to develop mucosal disease within 6 months after infection. Although no controlled studies have been published, many authors believe that systemic treatment with sodium stibogluconate at a dose of 20 mg/kg for 20 days significantly decreases the risk of mucosal disease [2]. The Dutch patient did receive sodium stibogluconate for his cutaneous disease, but perhaps the dose of 10 mg/kg was inadequate, as suggested by the resistance of his cutaneous lesions to this treatment regimen.

In our patient, mucosal leishmaniasis was initially overlooked when the patient presented with nasal congestion. With the increase in travel to areas were leishmaniasis is endemic, such as South America, physicians in countries where it is not endemic may encounter patients with imported leishmaniasis. They must be aware of mucosal leishmaniasis. Because the mucosal involvement may occur years after infection, physicians must inquire about travel history. Old dermal scars may point to mucosal leishmaniasis in the differential diagnosis. Parasitological diagnosis is not easy to obtain, because direct smear, culture, and even PCR results may be negative. Several concurrent diagnostic methods may be necessary to increase diagnostic sensitivity. CT is a useful tool for assessing initial airway involvement and for follow-up observations of the response to treatment.

In conclusion, because *L. viannia braziliensis* might cause mucosal involvement, if a cutaneous leishmaniasis lesion is acquired in the parts of the Americas where *L. viannia braziliensis* is endemic, the organism should be identified to the species level. In patients with *L. viannia braziliensis* infection, systemic treatment is recommended, and screening for mucosal involvement should be undertaken. This examination should be performed at baseline and at follow-up intervals several years later.

**References**