Tegumentary Leishmaniasis as a Manifestation of Immune Reconstitution Inflammatory Syndrome in 2 Patients with AIDS

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Immune reconstitution inflammatory syndromes (IRISs) have been reported in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (AIDS) since the introduction of highly active antiretroviral therapy (HAART). This syndrome is characterized by clinical manifestations of opportunistic infections when signs of immune reconstitution are observed during therapy. We report on leishmaniasis, suggestive of HAART-induced IRIS, in 2 patients with AIDS. After beginning HAART, 1 patient presented with disseminated tegumentary lesions, whereas the other patient’s preexisting lesions worsened and became more extensive; however, at the same time, their CD4+ T cell counts were recovering and their virus loads were decreasing significantly. The lesions healed with anti-Leishmania therapy.

According to the World Health Organization, coinfection with HIV and Leishmania species is a high-priority emergent disease appearing throughout the world [1]. In the Mediterranean basin, visceral leishmaniasis is considered to be an opportunistic infection in patients with AIDS [2]. In Brazil, both HIV and Leishmania infections are highly prevalent; the target populations, which were previously geographically separated, now overlap because of the expansion of leishmaniasis into urban areas and of HIV infection into rural areas. Approximately 100 cases of coinfection with HIV and Leishmania species were reported in Brazil up to 2003 [3]. Since the advent of highly active antiretroviral therapy (HAART), to which Brazilian HIV-1-seropositive patients have had free access since November 1996, there has been a dramatic decrease in AIDS-associated mortality and morbidity worldwide. However, manifestations associated with either the adverse effects of HAART itself or with prolonged evolution of the disease have been reported (reviewed in [4]). In this context, a paradoxical deterioration in clinical status together with recovery of the immune response under HAART has been described. This phenomenon has been attributed to a strong inflammatory response and humoral or cellular immune responses against antigens of a defined or undefined nature and has been named immune reconstitution inflammatory syndrome (IRIS) [5]. IRIS has been reported to be associated with Mycobacterium tuberculosis, Mycobacterium avium complex, Cryptococcus neoformans, cytomegalovirus, herpes zoster and herpes simplex viruses, Pneumocystis jiroveci (carinii), hepatitis C and B viruses, and JC virus, as well as AIDS-related Kaposi sarcoma and autoimmune diseases [5]. With regard to parasite infection, 2 cases of visceral leishmaniasis [6] and uveitis due to Leishmania major in patients with AIDS with characteristics of IRIS [7] have been described. Given the apparent lack of clinical data on manifestations of cutaneous leishmaniasis as IRIS, we report on 2 cases of disseminated tegumentary leishmaniasis suggestive of manifestations of IRIS.

Case 1. A 52-year-old man who emigrated from an area in which leishmaniasis was endemic 15 years previously presented with severe weight loss, and HIV infection was diagnosed. His CD4+ T cell count was 38 cells/mm³, and his plasma virus load was above the maximum quantifiable level (>750,000 copies/mL). Combination therapy with the antiretrovirals zidovudine, lamivudine, and efavirenz was begun. After treatment for 1 month, the patient presented with a genital ulcer, erythematoviolaceous plaques, and papular lesions disseminated on the arms (figure 1A). After 3 months, worsening of the lesions occurred, and the patient reported ulcers in the oral and nasal mucosa, including nostrils, and erythematous and infiltrative plaques and macules on his face (figure 1B). Clinical
manifestations worsened, with odynophagia and dysphagia; fluconazole was prescribed on the basis of a presumptive diagnosis of mycosis, although only a slight improvement in the lesions was observed. Four months after the lesions appeared, additional clinical analyses were done. These revealed positive results of serological testing for leishmaniasis as established by an anti-Leishmania ELISA (titer, 1:320). Leishmaniasis was further confirmed by the presence of Leishmania species on immunohistopathological examination (performed according to [8]) of skin and nasal mucosa. The patient’s CD4+ T cell count was >65 cells/mm³ (9% of normal value) at that time. On the basis of the diagnosis of tegumentary leishmaniasis, the patient received intravenous amphotericin B (total dose, 1750 mg). The cutaneous and mucosal wounds healed and the patient was clinically cured after 1 month. The patient was stable and presented with a CD4+ T cell count of 240 cells/mm³ at the latest evaluation, 24 months after beginning HAART.

**Case 2.** A 46-year-old man had lived outside areas in which leishmaniasis was endemic for 33 years; 5 years before visiting the clinic, he traveled to areas of endemicity on a number of occasions during the course of his work as a truck driver. On his first visit to the clinic, the patient presented with erythem-
atoviolaceous plaques and papular wounds on his face, with erythematous plaques on the arms, legs, and feet (figure 1C) that resembled tuberculoid leprosy. He reported weight loss of 25 kg in 1 year, and HIV infection was diagnosed. His CD4+ T cell count was 23 cells/mm³ (7.9% of normal value), and therapy with zidovudine, lamivudine, and efavirenz was begun. One month later he developed progressive dysphagia and dyspnea; the cutaneous lesions worsened, with a disseminated, macular infiltration in the skin. Results of histopathological examination of the skin, lips, and palate were compatible with histoplasmosis. After treatment with amphotericin B (total dose, 580 mg) was begun, the lesions showed improvement. The patient was discharged under treatment with itraconazole. One month later, the skin and mucosal lesions worsened, with the appearance of ulcers on the legs and feet (figure 1D), oral mucosa, lips, and nose; papules and ulcers on the penis and scrotum; odynophagia; nasal bleeding; intense pain; and cellulites on the legs. Results of histopathological examination of the subsequent skin sample were compatible with histoplasmosis. After amphotericin B (total dose, 210 mg) was prescribed, a subtle improvement was seen in the lesions. However, serological testing for histoplasmosis yielded negative results, whereas results of serological testing were positive for leishmaniasis by ELISA (titer, 1:640). Leishmania infection was detected by immunohistochemical analysis in the skin and mucosal lesions, and Leishmania species were recovered from the culture of a biopsy specimen. The parasite was further identified as Leishmania braziliensis by polymerase chain reaction with primers described by Harris et al. [9] (LU-5A from a conserved region in the Leishmania genus and LC-3L from a specific region of L. braziliensis). At that time, 3 months after beginning HAART, the patient’s CD4+ T cell count was 93 cells/mm³. Pentavalent antimony treatment was begun, and a dramatic improvement was seen, together with the disappearance of the cutaneous (figure 1E) and mucocutaneous lesions after 28 days of treatment. Despite a rapid increase in CD4+ T cell count to 283 cells/mm³ and a virus load near the lower limit of detection (400 copies/mL), 3 months later, the patient presented with 2 ulcers on the scrotum (figure 1F) and 1 on the penis, and Leishmania was found in a biopsy specimen. Pentavalent antimony treatment was restarted, with an improvement in the lesions after 20 days of treatment. At the latest evaluation, the patient was stable, with a CD4+ T cell count of 328 cells/mm³ (19% of normal value) and a virus load below the lower limit of detection (400 copies/mL)

Discussion. HAART has been shown to reconstitute immune functions. The major finding is that by reducing virus load and viral replication, reconstitution of the T cell pool occurs [10]. Although such reconstitution may lead to clinical improvement, it can also lead to the activation of latent diseases, as described here, in which a previously exposed and infected person harboring a controlled disease suddenly develops its clinical symptoms. The explanation for this apparent dichotomy remains unclear.

It is known that HIV-1 affects macrophage/monocyte functions [11] and that it increases replication of Leishmania donovani in monocyte-derived cells [12]. Leishmaniasis in HIV-infected patients may thus be a consequence of these alterations in the immune response, which leads to the establishment and progression of infection. In the cases reported here, the presence of latent Leishmania infection was likely because the patients came from areas in which leishmaniasis was endemic. Progression of leishmaniasis may have occurred because of HIV infection, which was silent in patient 1 and with some cutaneous lesions in patient 2 before HAART was begun. Further, progressive, disseminated, forthcoming manifestations suggest that this spreading had occurred before full manifestation of IRIS. However, in these cases, the proximity in time from the beginning of HAART to the onset of leishmaniasis in 1 patient and the worsening of clinical features in the other suggest leishmaniasis as a manifestation of IRIS. In these cases, the onset or deterioration of clinical manifestations appeared when an increase in the initially low CD4+ T cell count and a decrease in the initially very high virus load were noticed after HAART was begun. The increase in CD4+ T cell count was small but would be sufficient to mount an inflammatory response with redistribution of memory T cell populations [10]. The dramatic improvement in the lesions and the complete healing observed when treatment specific for leishmaniasis was introduced further substantiate leishmaniasis as a manifestation of IRIS in these cases. In addition, in experimental murine cutaneous leishmaniasis, the presence of CD4+ T cells is a prerequisite for development of lesions [13, 14], and an immune response to pathoantigens of Leishmania species may be involved in lesion development [15]. In conclusion, we have presented 2 cases of suspected HAART-induced IRIS caused by Leishmania species. We suggest that the clinical evaluation and follow-up of patients undergoing HAART who previously have had leishmaniasis or of asymptomatic patients with previous exposure (i.e., time spent in areas of endemicity for leishmaniasis) should include tests to detect this infection.

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References


