Case Report: Coinfection of *Leishmania guyanensis* and Human Immunodeficiency Virus–Acquired Immune Deficiency Syndrome: Report of a Case of Disseminated Cutaneous Leishmaniasis in Ecuador

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Abstract. Reported herein is the first case of *Leishmania*–human immunodeficiency virus (HIV) coinfection in Ecuador. In Ecuador, HIV infections overlap endemic areas of leishmaniasis. Immunosuppression is a well-established risk factor for developing severe disease. This is a severe case of a 32-year-old man presenting with disseminated pleomorphic ulcers, papules, and cutaneous plaque-like lesions over his whole body. Numerous amastigotes were observed in both skin scrapings and biopsies. The sequence of the *cytochrome b* gene confirmed the presence of *Leishmania guyanensis*. The patient was treated but failed to respond to meglumine antimoniate and amphotericin B. Six months later, the patient died due to bacterial septic shock.

INTRODUCTION

Leishmaniasis are a group of vector-borne infectious diseases caused by several species of the genus *Leishmania*. American tegumentary leishmaniasis (ATL) can present in various clinical forms, including cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), and mucocutaneous leishmaniasis (MCL). CL includes ulcerative skin lesions (i.e., localized cutaneous leishmaniasis [LCL] and disseminated cutaneous leishmaniasis [DsCL]), as well as multiple nonulcerative nodules (i.e., diffuse cutaneous leishmaniasis [DCL]). In individuals with immunosuppression, CL can present with particular features, including parasite dissemination, clinical polymorphism with atypical and often more severe clinical forms.¹ Leishmaniasis is a rising opportunistic infection in human immunodeficiency virus (HIV)–positive individuals with *Leishmania*–HIV coinfection found more frequently in areas where both infections are endemic.² In South America, coinfection cases of ATL were reported in Argentina, Brazil, Colombia, French Guyana, Peru, and Venezuela, and were caused by *Leishmania guyanensis* and *Leishmania braziliensis*.^{2–5} Immunosuppression is one of the strongest risk factors for overt clinical disease, and can also alter the disease presentation and treatment response.¹ All antileishmanial drugs are less effective in HIV-positive patients. Pentavalent antimonials and amphotericin B (AMB) are more toxic to HIV patients, who require close monitoring for pancreatitis, cardiotoxicity, and nephrotoxicity.² In general, to reduce the probability of dissemination and relapse of CL in HIV-coinfected patients, systemic treatment is recommended over local treatment.¹ Usually, the same drugs used for immunocompetent individuals are offered to CL-HIV-coinfected individuals, namely pentavalent antimonials and AMB. However, in the latter group, there is a higher morbidity and mortality rate due to concurrent illness, complications, and drug toxicity.²

In Ecuador, ATL is endemic in 21 of the 24 provinces; CL is a public health problem because of its wide distribution, mainly in rural subtropical and tropical areas of the Pacific and Amazon regions, as well as in some inter-Andean valleys.^{6,7} Ecuador has one of the highest incidences of ATL in the Americas, with 11,983 cases documented from the years 2004–2010. The disease occurs in all of the recognized ATL forms: CL, MCL, and DCL, with CL the most widely distributed form in the country.⁷ Generally, CL lesions are ulcerative, but nonulcerated lesions such as papules, plaques, nodules, and erysipeloid forms are also seen. The sporotrichoid or “pian-bois,” the chiclero’s ulcer, cases of leishmaniasis recidiva cutis, a cutaneous variant characterized for reactivations in old scars, and two patients having dozens of cutaneous ulcers described as DsCL have also been reported.^{7,8} Currently, eight *Leishmania* spp. have been identified from human lesions, with the species *Leishmania panamensis* and *L. guyanensis*, being predominant in the subtropical and tropical lowlands of the Pacific coastal region.^{9–11}

Regarding HIV infection in Ecuador, data from the Ministry of Public Health (MSP), inform that since 1984, the year in which the first case of HIV was detected, until 2011, the mean prevalence of infection in the population was 0.24%; the registered number of HIV cases was 22,177, of which 9,911 are now acquired immune deficiency syndrome (AIDS) cases.¹² By 2014, MSP estimated that the number of people living with HIV was 33,000 (25,000–46,000). Most of the individuals who have HIV infection and AIDS in Ecuador are living in the provinces of the Pacific coastal region, mainly Guayas. The main change in recent years is the increase of reported HIV cases in other Pacific provinces, for example, Los Ríos and Esmeraldas.¹³

In this report, the first case described in Ecuador of a coinfection with HIV–AIDS and *L. guyanensis*, failed to respond to treatment with meglumine antimoniate (MA) and AMB.

CASE REPORT

The patient, a 32-year-old man, presented with multiple pleomorphic skin lesions over his entire body, upon admission to Hospital “Eugenio Espejo” in Quito. The patient had

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been living in Quito for the past 3 years, but was born and raised in the town of Ventanas, province of Los Ríos, located in the Pacific coastal region. He had a 5-year history of being infected by HIV, diagnosed in the year 2009 with a CD4 cell count of $102/\mu\text{L}$ and a viral load of 21 (log 10: 1.322), and treated with efavirenz, zidovudine, and lamivudine combination. Two years prior to admission he was diagnosed with CL presenting with a single cutaneous ulcer on his left leg. He was treated with MA (Glucantime®, Sanofi Aventis, Suzano, Brazil), using the dosage recommended by the MSP 20 mg/kg/day intramuscularly for 21 days. Because the ulceration persisted, the treatment regimen was repeated for another 21 days but without any improvement. The patient related that he had worked in the forest cutting trees for 2 months, in the year 2012, near the town of Pedro Vicente Maldonado, in the subtropical area of the Pacific coastal region.

The patient was hospitalized with an initial diagnosis of severe and generalized bacterial ecthyma. During the physical examination, numerous macular-papular-nodular-plaque-ulcerative and crusted skin lesions were observed on his face, ear lobes, neck, anterior and posterior trunk, abdomen, as well as the upper and lower extremities (Figures 1–3). Blood tests showed a white blood cell count of $12.5 \times 10^9/\text{L}$, with 78.7% neutrophils, 17.9% lymphocytes, and 3.4% monocytes. The erythrocyte sedimentation rate was 38 mm/hour, with hemoglobin of 10.2 g/dL, a hematocrit of 30.9%, and a platelet count of $542,000/\mu\text{L}$. Venereal Disease Research Laboratory test, Hepatitis B surface antigen, and fungal culture were all negative. Enzyme-linked immunosorbent assay and Western blot for HIV were both positive. The CD4 cell count was $71/\mu\text{L}$, with a viral load of 21 log(10) copies/mL. Serum urea and creatinine were 19.5 and 0.83 mg/dL, respectively. Serology, both IgG and IgM, was positive for toxoplasmosis. An ophthalmological examination showed retinochoroiditis in the left eye and uveitis in the right eye, compatible with toxoplasmosis. The patient did not have lymphadenopathy, hepatosplenomegaly, or fever, and was not tested for leishmanial visceralization. Combined anti-

FIGURE 2. Erythematous violaceous ulcerative lesions of different sizes with uneven borders covered with bloody purulent scabs located in the patient's lower limbs.

retroviral therapy regimen was changed to tenofovir, emtricitabine, lopinavir, and ritonavir.

Histopathology of biopsies taken from lesions on the abdomen showed an inflammatory infiltrate, characterized by leukocytes, neutrophils, and lymphocytes, with a large number of macrophages infected with numerous *Leishmania* spp. amastigotes (Figure 4). *Leishmania* amastigotes were also observed using Diff-Quik-stained slides of scrapings from lesions on the hand and right arm. *Leishmania* DNA was extracted from the tissue material spotted onto an FTA Classic Card (Whatman, Newton Center, MA). Leishmanial *cyt b* was amplified by polymerase chain reaction utilizing the DNA sequence of the parasite in a phylogenetic tree analysis; *L. guyanensis* was identified as the causative agent (Figure 5).

The patient received intravenous AMB therapy (50 mg every 48 hours). The treatment was halted at day 14 due to the development of acute renal failure with generalized edema and raising levels of urea and creatinine to 62 and 4.1 mg/dL, respectively. The renal impairment persisted for 2 weeks. The evolution of the cutaneous lesions was stationary, with active lesions persisting over all his body. One month after hospitalization, the patient was stabilized and

FIGURE 1. Erythematous, nonpainful, circumscribed, elevated plaque-like lesions with well-delineated borders located in the patient's upper limbs and hands.

FIGURE 3. Multiple elevated plaque-like lesions with active borders, some confluent and others as satellite papules scattered throughout the patient's abdomen.

FIGURE 4. Histopathology of a lesion from the patient's abdomen showing a massive inflammatory infiltrate with many leukocytes, neutrophils, lymphocytes, as well as a large number of macrophages infected with numerous *Leishmania* amastigotes.

discharged, but the skin lesions remained active and became more pronounced. Six months later, he returned to the hospital with fever and the leishmanial cutaneous lesions had worsened; 3 days later he died due to septic shock caused by a secondary bacterial infection. A written consent signed by his mother was obtained to publish the case with pictures of the lesions.

FIGURE 5. Phylogenetic tree of cytochrome *b* gene sequences from *Leishmania* species. The leishmanial *cyt b* genes were amplified from a cutaneous lesion of the patient (sample 8). Phylogenetic tree analysis with sequences obtained from the patient as well as those from 13 *Leishmania* spp. references strains was performed. Scale bar indicates 0.01% divergence.

DISCUSSION

This is the first report of a patient coinfecting with *Leishmania* and HIV in Ecuador. He presented with an unusual and severe form of CL with pleomorphic cutaneous lesions disseminated over his entire body. This clinical presentation was consistent with DsCL due to his severely immunocompromised condition with a CD4 cell counts of 71/ μ L. Several cases of *Leishmania*–HIV coinfection have been reported with atypical presentations including disseminated forms.^{3,4,14} Most immunocompetent individuals in Ecuador with CL present with a single ulcerative lesion.^{7,10} It is important to note that the patient described herein, had a single localized lesion on his left leg (LCL) for the first 2 years before the disease disseminated all over his body. This probably occurred, when the CD4 cell counts fell below 200/ μ L, even though the patient was under HIV treatment. *Leishmania* parasites tend to disseminate to different parts of the body in HIV-infected individuals, as has been reported in other coinfection cases in Latin America.² In HIV patients with low CD4+ T-cell count, one could expect even more atypical clinical features of CL to occur, such as visceralization, severe and disseminated cutaneous lesions which take longer to resolve, resistance to medications, and more severe side effects of drugs.²

Leishmania guyanensis was identified as the causative species, which he probably contracted while working in the endemic area for CL, where the dominant parasites are *L. guyanensis* and *L. panamensis*.^{9,11} In coinfecting individuals from Brazil, Bolivia, Argentina, and French Guyana, the infecting agents were identified as *L. guyanensis* and *L. braziliensis*; also, a viscerotropic variant of *Leishmania chagasi* was found in cutaneous lesions of an HIV-positive patient.^{2,3} The severity and characteristics of the lesions depend more on the degree of immunosuppression rather than the infecting *Leishmania* species. However, in immunocompetent individuals, the infecting species is the major determinant of the type of clinical presentation found.²

Although the patient received systemic treatment with two schemes of 21 days of MA, the only drug available and recommended by the MSP, the lesions failed to respond. Treatment failure and relapse rates are particularly high in cases of HIV coinfection, despite ongoing antiretroviral therapy.¹ The patient was given a combination of four antiretroviral drugs including tenofovir, emtricitabine, lopinavir, and ritonavir as recommended by the MSP in Ecuador. With MA, the expected clinical cure rate in immunocompetent individuals is 91.7%, as demonstrated in a study undertaken in the same geographical area where the patient became infected.¹⁵ Furthermore, most of the patients infected in the Pacific coastal region of Ecuador will self-cure after a *Leishmania* infection, as demonstrated in a study where a high number of patients were cured without drug treatment.¹⁶ It is well known that treatment response to antimonials in *Leishmania*–HIV coinfections tends to be poor (33–82%),^{2,17} with a relapse rate of 14–57%, and a high mortality.²

AMB, the second line of treatment as recommended by the MSP, was initiated in the patient, but he developed renal failure after the 14th dose. Because this side effect was life threatening, AMB was discontinued. However, the leishmanial lesions continued to persist. AMB has been

used in coinfecting patients with a cure rate ranging from 58% to 82%, but relapses often occur and up to 35% of treated cases suffer from nephrotoxicity.² Cases of CL and MCL have shown good results when treated with liposomal AMB.³ This drug is also recommended by the U.S. Centers for Disease Control and Prevention,¹⁸ but it is very costly and not readily available in Ecuador.

Because endemic areas of ATL and HIV infections overlap in Ecuador, and since there has been an increase in both infections in recent years, the occurrence of leishmaniasis in immunosuppressed patients will probably increase. The atypical clinical presentations of CL in immunosuppressed individuals can be easily misdiagnosed or mistaken as occurred in our case. To avoid misdiagnosis, awareness and enhanced surveillance systems should be implemented. It is also possible that more cases of coinfection are diagnosed but not reported. Education of physicians and health workers is important to ensure correct diagnosis and management of *Leishmania*-HIV-coinfecting individuals.

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