American Tegumentary Leishmaniasis and HIV-AIDS Association in a Tertiary Care Center in the Brazilian Amazon

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Abstract. American tegumentary leishmaniasis (ATL) and human immunodeficiency virus (HIV) are both common infectious diseases in the Brazilian Amazon with overlapping expansion areas, which leads to the occurrence of *Leishmania*/HIV coinfection. Most ATL/HIV-acquired immunodeficiency syndrome (AIDS) association cases have been reported from areas where *Leishmania* (*Viannia*) *braziliensis* is the main pathogen; this finding is in contrast with the Amazon region, where *L. (V.) guyanensis* is the most implicated agent, implying distinct clinical and therapeutic aspects. We describe 15 cases of ATL/HIV coinfection treated in a tertiary care center in the Brazilian Amazon between 1999 and 2008. Thirteen patients presented with diverse clinical manifestations of cutaneous leishmaniasis, and four of them had disseminated forms; two patients presented with mucosal leishmaniasis (ML). Seven patients required more than one course of treatment. The particularities of ATL/HIV-AIDS association in *L. (V.) guyanensis*-endemic areas require efforts for an increased understanding of its burden and subsequent improvements in case management.

INTRODUCTION

The Brazilian Amazon is an endemic region for American tegumentary leishmaniasis (ATL), with an approximate incidence of 53.9 cases/100,000 inhabitants in 2009.¹ In the Amazon region, ATL is mainly caused by the parasite *Leishmania* (*Viannia*) *guyanensis*,² and its occurrence is associated with poverty, unorganized occupation of cities' outskirts, and deforestation.^{3,4} ATL may present in different forms, including cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), and mucocutaneous leishmaniasis (MCL).

The human immunodeficiency virus (HIV) epidemic in Brazil (estimated to affect around 600,000 individuals) is displaying a trend of expansion to urban peripheries and rural areas, including an increasing incidence in the newly colonized areas in the northern region.^{5,6}

The superimposition of both epidemics in this region has led to the occurrence of ATL/HIV-acquired immunodeficiency syndrome (AIDS) association,^{7–9} a phenomenon that has increasingly been described in many other regions of the world. Although publications have mostly focused on the comparatively severe visceral leishmaniasis (VL),¹⁰ ATL/HIV-AIDS association has increasingly been described in Latin America.^{7,11} Leishmaniasis resolution requires an effective cellular immune response, and because immune function is particularly affected by HIV infection, it is not surprising that modifications in ATL presentation and response to treatment have been described.^{7,12,13}

The majority of reports of ATL/HIV-AIDS association have originated from areas of Latin America where *L. (V.) braziliensis* is the major causative parasite. It has been shown that the disease caused by *L. (V.) braziliensis* and *L. (V.) guyanensis* differs regarding clinical and therapeutic aspects.^{14,15} We,

therefore, report the clinical manifestations and treatment response in a series of 15 patients with ATL/HIV-AIDS association from an area of predominant *L. (V.) guyanensis* prevalence treated in a tertiary care center in the Brazilian Amazon.

PATIENTS AND METHODS

We retrospectively describe 15 HIV-positive patients diagnosed with ATL between 1999 and 2008 who were treated in the outpatient Clinic of the Tropical Medicine Foundation of Amazonas, a tertiary care center for infectious diseases in Manaus. The information regarding demographic data, clinical manifestations, biochemical and hematological markers, and assessment of immunological status was retrieved from medical records. The study was approved by the Tropical Medicine Foundation of Amazonas Ethics Committee.

The HIV serological status was assessed according to the Brazilian Ministry of Health guidelines using two distinct anti-HIV serological tests; initially, an enzyme-linked immunosorbent assay (ELISA) is performed, and subsequently, confirmation is made with an indirect immunofluorescence anti-HIV test. HIV viral load and the CD4⁺ T-cell count were requested at the moment of ATL diagnosis.

An initial diagnosis of leishmaniasis was made based on clinical presentation. CL was confirmed through direct observation of the *Leishmania* parasite in scarified samples of the lesion (using Giemsa staining technique) and/or histopathological analysis evidencing the presence of *Leishmania* amastigotes. The diagnosis of ML was based on the presence of mucosal lesions, histopathological analysis compatible with ML, previous history of CL, a positive delayed hypersensitivity skin test (Montenegro skin test), and analysis of the indirect immunofluorescence reaction test. In four cases, *Leishmania* species identification was performed using polymerase chain reaction (PCR) according to a previously described protocol.^{16,17}

In accordance with the Brazilian Ministry of Health recommendations for the management of ATL,¹⁸ initial treatment consisted of the administration of pentavalent antimonials (intravenous glucantime 15 mg/kg per day for 20 days for CL and 20 mg/kg per day for 30 days for MCL) or pentamidine (three doses of 4 mg/kg per day administered every other day).

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If relapse occurred, one of the following regimens was used: antimonials (intravenous glucantime 15 mg/kg per day for 30 days for CL and 20 mg/kg per day for 30 days for ML), pentamidine (three doses of 4 mg/kg per day administered every other day), and amphotericin B (0.5–0.7 mg/kg per day every other day in accordance with patient tolerance until a total received dose between 1 and 1.5 g is achieved). All patients were followed for a minimum of 90 days. Cure was determined based exclusively on clinical criteria and was applied to patients who exhibited healed lesions without any evidence of infiltration, ulcers, or lymphadenopathy during the post-treatment follow-up period. Relapse was defined as the occurrence of any sign of an active lesion (ulcer, infiltration, or lymphadenopathy) during follow-up.

RESULTS

Between 1998 and 2008, 15 patients with ATL/HIV-AIDS association were diagnosed and treated at our center. Thirteen patients were diagnosed with CL, and two were diagnosed with ML. All the patients were from the Amazon region. The clinical data of the reported patients are summarized in Table 1.

Among the 13 patients diagnosed with CL, 4 had disseminated disease (more than 20 lesions). All four patients had ulcerated lesions with an elevated rim, two patients had papular lesions, and one patient presented with tuberculous lesions. The remaining nine patients with exclusive CL each presented with an average of 3.5 lesions of typical characteristics. In 12 of the CL patients, the diagnosis was performed through direct observation of *Leishmania* amastigotes, whereas in the remaining patient, the diagnosis was based on histopathologi-

cal examination. The two patients with ML presented with nasal septum perforation, and the diagnosis was based on a previous history of CL and histological examination compatible with leishmaniasis.

Furthermore, *Leishmania* species characterization was performed in four patients using PCR, showing *L. (V.) guyanensis* in two patients with CL (patients 6 and 12) and one patient with ML (patient 14) and *L. (V.) braziliensis* in one patient with ML (patient 15).

One patient did not receive treatment, because she was pregnant, had only one mild lesion, and was receiving highly active antiretroviral therapy (HAART). During the third trimester, she experienced complete resolution of her lesion. Of the remaining 14 patients, 13 received antimonials as initial therapy, whereas 1 patient received pentamidine. Seven patients were successfully treated at the first attempt, whereas the remaining seven required more than one course of treatment. Patient follow-up ranged from at least 3 months to 5 years, with an average period of 2.73 years (follow-up was discontinued in five cases: three were lost to follow-up and there were two deaths). Eight patients experienced relapse and required additional courses of treatment. The average CD4⁺ cell count at the time of ATL diagnosis was 237 cells/mm³ (range = 35–612 cells/mm³), and seven patients were using HAART. Among the eight patients presenting with ATL relapse, only two were using HAART, whereas among the seven patients that were successfully treated at the first attempt, five were using HAART.

One patient with CL continued to experience active lesions, despite three courses of treatment with different drugs (two courses with antimonials and one course with amphotericin).

TABLE 1
Clinical characteristics and therapeutic responses of 15 patients with ATL/HIV-AIDS association

Patient	Gender	Age (years)	Number of lesions	Location of lesions	Duration of lesions	Treatment of leishmaniasis (no. of courses)	Duration of follow-up (months)	Leishmaniasis status	CD4 ⁺ count	HAART*	Associated illnesses
1	M	45	1	T	90 days	Pent (2×)	24	Cured	244	No	Seborrheic dermatitis, diarrhea
2	M	31	7	T	210 days	Antim (1×)	24	Cured	259	Yes	None
3	M	29	5	T, LLMM, UUMM	60 days	Antim (1×), Pent (1×), Ampho B (1×)	60	Cured	117	No	Diarrhea, weight loss, herpes zoster, genital condiloma
4	F	32	1	LM	35 days	None†	60	Cured	317	Yes	None
5	M	28	> 20	UUMM, N	60 days	Antim (1×), Pent (1×), Ampho B (1×)	60	Cured	336	No	Prurigo, scabies, weight loss
6	M	31	> 20	T, F, N, LLMM, UUMM	90 days	Antim (2×), Ampho B (1×)	60	Not cured	91	No	Cerebral toxoplasmosis, candidiasis, weight loss
7	M	49	> 20	LM, UM	N/A	Antim (1×)	3	Cured	76	No	Weight loss
8	M	23	1	LM	30 days	Antim (1×)	60	Cured	612	Yes	None
9	M	31	2	UUMM	14 days	Antim (1×)	12	Cured	35	Yes	Genital condiloma, cryptococcosis, herpes zoster
10	M	42	2	UUMM	120 days	Antim (1×), Pent (1×)	3	Cured	293	No	Generalized lymphadenopathy
11	M	42	8	F, LLMM, UUMM	30 days	Antim (1×), Ampho B (1×)	12	Cured	119	Yes	Cerebral toxoplasmosis, candidiasis
12	M	47	> 20	F, LLMM, UUMM	120 days	Antim (1×), Ampho B (1×)	36	Cured	59	No	Candidiasis, genital herpes, weight loss, prurigo
13	M	26	5	LLMM	210 days	Antim (1×)	36	Cured	440	No	None
14	M	58	Mucosal	Nasal septa	28 years	Antim (1×)	36	Not cured	400	Yes	None
15	M	30	Mucosal	Nasal septa	1 year	Antim (1×)	7	Not cured	151	Yes	Herpes zoster

M = male; F = female; UUMM = upper limbs; UM = upper limb; LLMM = lower limbs; LM = lower limb; T = trunk; N = neck; F = face; Pent = pentamidine; Antim = antimonials; Ampho B = amphotericin B; N/A = not available; HAART = highly active antiretroviral therapy.

* In the moment of ATL diagnosis.

† Pregnant.

This patient had severe immunosuppression and resistance to many antivirals along with several other opportunistic infections. No patient showed clinical or laboratorial evidence of visceral dissemination of leishmaniasis.

DISCUSSION

This report reinforces current knowledge that the superimposition of high-risk areas for both infections causes a predictable increase in the occurrence of ATL/HIV-AIDS association, which leads to diagnostic and therapeutic challenges for clinicians in tropical areas of Latin America.^{8,10,19}

According to Rabello and others,⁸ 100 cases of HIV and leishmaniasis coinfection had been reported in Brazil between 1982 and 2003, of which 63% were caused by ATL (68% ML and 32% CL). This situation differs widely from what is seen in the general population, where the proportion of ML and MCL cases is around 1.5%, clearly showing the relationship between this form of the disease and the immune status of the individual. The first reported case of ATL/HIV-AIDS association in Amazonas was in a patient infected with *L. (V.) guyanensis*.²⁰ The Brazilian Manual of *Leishmania*/HIV coinfection recommends that ATL patients with difficult to cure or disseminated lesions should be tested for HIV infection.⁵ In this series, the diagnosis of HIV was influenced by the unusual clinical presentation or treatment failure of ATL in 46.7% of the patients, similar to what was reported by Rabello and others,⁸ and this finding further emphasizes the importance of this recommendation.

As observed with other infections, the immunosuppression caused by HIV modifies both the clinical and therapeutic course of ATL. Several atypical forms and lesions of CL have been described in patients with HIV/AIDS, including polymorphic lesions, involvement of the genitourinary tract,⁷ and visceralization of otherwise strictly tegumentary-related pathogens²¹ among others. The treatment is another challenging issue in the management of coinfecting patients who, compared with immunocompetent patients, experience higher rates of treatment failure, drug toxicity, and case fatality.^{10,21} In the specific case of ML, HIV was independently associated with treatment failure.²²

Previous studies have clearly characterized the marked clinical, diagnostic, and therapeutic distinction between the disease caused by *L. (V.) braziliensis* and that caused by *L. (V.) guyanensis*; the latter typically presents with a higher frequency of lesions that are smaller and have a significantly lower response rate to antimonials.^{14,15} In a case-control study conducted in French Guyana where all 10 coinfecting patients had CD4⁺ counts above 200 cells/mm³ and a confirmed diagnosis of *L. (V.) guyanensis*, HIV-infected patients presented a significantly lower cure rate and higher recurrence rate compared with non-HIV infected patients.²¹

Our case series included patients from an area where *L. (V.) guyanensis* is the predominant cause of ATL, with a relatively low prevalence of *L. (V.) braziliensis* that ranges from 2.8% to 14%.^{2,17} The retrospective nature and lack of a control group means that we are unable to further explore the influence of CD4 cell count and the use of HAART on the presentation of ATL and response to treatment. Furthermore, it was only possible to ascertain the *Leishmania* species in four cases, and although previous data support the predominance of *L. (V.) guyanensis* in our region, accurate identification of the infecting species in future prospective studies will allow the formation

of more robust conclusions. Our patients received antimonials as first-line therapy, which is recommended by the Brazilian Ministry of Health guidelines,^{5,18} and the rate of treatment failure observed is in accordance with the already reported lower efficacy of this class of drugs against *L. (V.) guyanensis*,¹⁵ although a recent metaanalysis could not identify difference in the therapeutic response to pentavalent antimonials amongst CL patients infected with *L. (V.) braziliensis*, *L. (V.) guyanensis*, or *L. (L.) amazonensis*.²³ The lack of robust evidence highlights the need for more clinical trials to determine the best treatment of *L. (V.) guyanensis*-infected CL patients, allowing for a better decision on whether to modify the recommendations for first-line therapy in the Amazon region.

To achieve a better understanding of the complex interplay between HIV and leishmaniasis, additional clinical and immunological studies are required; these studies should explore factors related to the clinical manifestations and treatment response, especially the influence of CD4 cell count and the use of HAART, which may have a considerable impact on patient management. Our recent observation that *L. (V.) guyanensis* can cause ML²⁴ supports the need to further explore the distinct epidemiological and clinical features of the disease caused by this species. Furthermore, the increasing overlap between HIV- and ATL-endemic areas in the Amazon region will likely lead to more cases of coinfection. Physicians working in such areas must be alert to better diagnose and treat these patients.

Received February 4, 2011. Accepted for publication June 1, 2011.

Acknowledgments: Our sincere thanks to Christopher R. Jones for the revision and translation of this text.

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