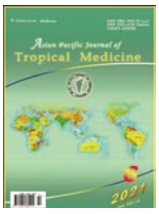

Case Report

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Disseminated cutaneous leishmaniasis due to *Leishmania (Leishmania) amazonensis* in human immunodeficiency virus (HIV)-infected patients: A report of two cases

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ABSTRACT

Rationale: Co-infection of human immunodeficiency virus (HIV) and *Leishmania* spp. has impact on clinical and therapeutic outcomes of leishmaniases. Most studies do not present the identification of *Leishmania* species causing American tegumentary leishmaniasis in co-infections. In the Americas, *Leishmania (L.) Viannia (V.) braziliensis* and *L. (V.) guyanensis* have been identified.

Patient concerns: In this study, two cases of American tegumentary leishmaniasis in patients infected with HIV are described. Patients presented several lesions with rapid dissemination and mucosal involvement.

Diagnosis: Disseminated cutaneous leishmaniasis caused by *L. amazonensis* was identified by molecular test.

Interventions: The patients were treated with conventional therapies for HIV infection and American tegumentary leishmaniasis.

Outcomes: In co-infection, the clinical manifestations are atypical and the treatment response can be impaired.

Lessons: These cases show that HIV infection impacts *L. amazonensis* infection and point to the relevance of identifying *Leishmania* species, which can lead to a better patient management.

KEYWORDS: *Leishmania amazonensis*; HIV; Disseminated cutaneous leishmaniasis; Case report

1. Introduction

Leishmania (L.) amazonensis protozoan is associated with localized cutaneous leishmaniasis, disseminated cutaneous leishmaniasis (DL), and diffuse cutaneous leishmaniasis (DCL). Whereas DL patients present cellular immunity and therapeutic response, DCL represents an anergic pole of immune response and there is no effective treatment[1]. The co-infection with *Leishmania*/human immunodeficiency virus (HIV) is a public health problem and represents 8.5% of all patients with American tegumentary leishmaniasis in Brazil. These two infectious agents act synergistically, facilitating their own replication and survival[2].

Co-infection with HIV/*Leishmania* has increased in Latin America. Most of the studies do not present the identification of *Leishmania* species causing American tegumentary leishmaniasis. In the Americas, few studies of co-infection reported *L. braziliensis*[3,4] and *L. guyanensis*[5] as causal agents in co-infections. Recently, *L. amazonensis* was reported causing DCL[6]. Here, we described two cases of DL in patients infected with HIV caused by *L. amazonensis*.

This study was approved by the local Ethics Committee (CAAE82524717.1.0000.5078), and patients signed the consent to participate in the research and publication.

2. Case reports

2.1. Case 1

In February 2019, an ulcerated lesion appeared on the scrotal region of a Brazilian 50-year-old male patient from Goiás, Midwestern region. After one month, ulcerated lesions spread for

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the trunk, face, nasal mucosa, and upper limbs. Lower limbs were affected presenting bleeding and papular lesions. Histopathological analysis suggested *Leishmania* infection and the patient was tested HIV positive by enzymatic immune assay (ELISA) and polymerase chain reaction (PCR). In Figure 1, the inflammatory process showed several macrophages with large vacuoles containing rounded structures, which were confirmed as *Leishmania* by immunohistochemistry. High number of $CD68^+$ macrophages as well as $CD3^+$ T lymphocytes was presented (Figure 1). The isolated parasite was characterized as *L. amazonensis* by PCR[7]. Reactive serology and computed tomography of the chest suggested paracoccidioidomycosis. The indirect immunofluorescence test (IFT) for American tegumentary leishmaniasis was positive (1/40), $CD4^+$ T lymphocyte count was 69 cells/mm^3, and the viral load was 143 993.

The antiretroviral tenofovir + lamivudine + dolutegravir and prophylactic antibiotic (sulfamethoxazole-trimethoprim) treatments were started for HIV infection. The meglumine antimoniate (Glucantime®) was used for American tegumentary leishmaniasis, but it was suspended on the 9th day due to alterations in the electrocardiogram. Then, liposomal amphotericin B was used for 12 days. The schedules are presented in Table 1. The patient has ended American tegumentary leishmaniasis treatment when itraconazole was prescribed for paracoccidioidomycosis. All American tegumentary leishmaniasis lesions were healed. His viral load became undetectable, $CD4^+$ T lymphocyte count was still low (77 cells/mm^3), but American tegumentary leishmaniasis lesions remained healed. He is still under follow up (Table 1).

2.2. Case 2

In Mato Grosso (Midwestern region), in June 2017, a Brazilian 52-year-old male patient was diagnosed with HIV (ELISA/PCR) and started the treatment with tenofovir + lamivudine + dolutegravir. In

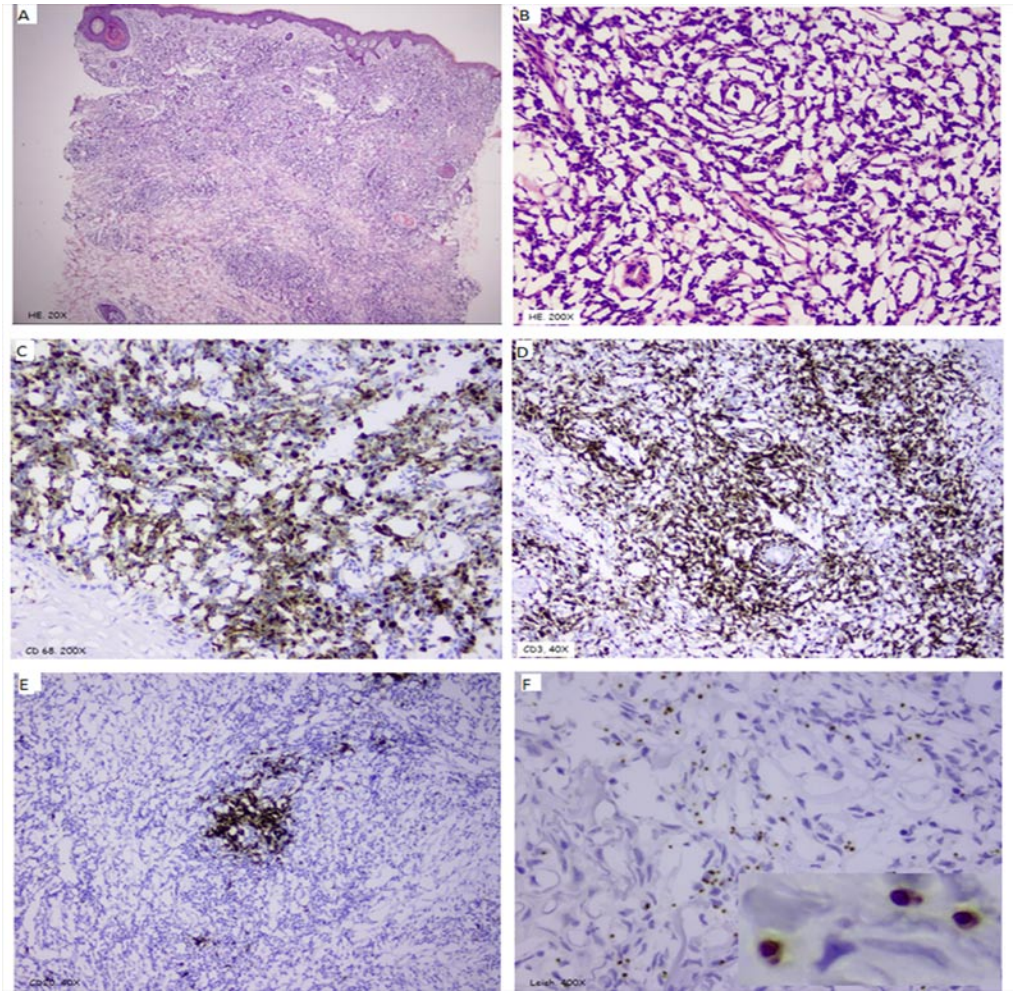

Figure 1. An ulcerated lesion appeared on the scrotal region of a Brazilian 50-year-old male patient from Goiás, Midwestern region. After one month, ulcerated lesions spread to the trunk, face, nasal mucosa, and upper limbs. Lower limbs were affected presenting bleeding and papular lesions. Histopathological analysis suggested *Leishmania* infection and the patient was tested HIV positive. Biopsy fragment from one cutaneous lesion was used to perform H&E and immunohistochemistry (IHC) stainings. (A) Panoramic view of the lesion, showing severe inflammatory process with mononuclear cells in upper and lower layers of the dermis (H&E, 200×). (B) Parasitophorous vacuoles in macrophages with rounded structures, suggestive of amastigotes, adhered to the membranes (H&E, 200×). (C) IHC detection of $CD68^+$ macrophages (IHC, 200×). (D) $CD3^+$ T lymphocytes (IHC, 40×). (E) $CD20^+$ B lymphocytes (IHC, 40×). (F) Amastigotes (IHC, 400×). The inset presents amastigote in detail showing nucleus and kinetoplast (1 000×).

Table 1. Clinical evolution of *Leishmania (Leishmania) amazonensis*/HIV co-infected patients.

Cases	Period (year/month)	Clinical evolution	$CD4^+$ T cells (cells/mm^3)[#]	Viral load (copies/mL)[*]	Treatment
Case 1	2019/November	ATL diagnosis	-	-	-
	2019/December	HIV and paracoccidioidomycosis diagnosis. Active ATL lesions with secondary infection.	69	143 993	TDF+3TC+DTG+Bactrim (400/80 mg, 2 capsules/day)-Glucantime®[a]; Liposomal amphotericin[b]
	2020/February	Fully healed lesions	-	-	TDF+3TC+DTG+Bactrim+ Itraconazole (200 mg/day)
	2020/August	Fully healed lesions	77	ND	TDF+3TC+DTG+Bactrim+ Itraconazole
Case 2	2017/June	HIV infection diagnosis	-	-	TDF+3TC+DTG
	2017/November	End of tuberculosis treatment	-	-	TDF+3TC+DTG
	2017/December	ATL diagnosis	-	-	TDF+3TC+DTG-Liposomal amphotericin[c]
	2018/January	ATL with no response to treatment	278	ND	TDF+3TC+DTG-Amphotericin B deoxycholate[d]-Liposomal amphotericin[e]
	2018/March	Tuberculosis relapsed	-	-	TDF+3TC+RAL
	2018/April	Return to the clinic	-	-	Liposomal amphotericin (250 mg/day) for 10 days + Glucantime®[f]
	2018/November	Secondary skin infection. Partially healed ATL lesions	-	-	TDF+3TC +RAL+Cephalothin[g]
	2019/March	Activity in the lower limbs and in the nasal mucosa	-	-	TDF+3TC+RAL+ Fluconazole®[h]
	2019/June	Fully healed skin lesions with no active lesions on the nasal mucosa-Cure for tuberculosis	-[i]	ND	TDF+3TC+RAL

-: No information; ND: not detectable; TDF: Tenofovir; 3TC: Lamivudine; DTG: Dolutegravir, RAL: Raltegravir; ATL: American tegumentary leishmaniasis. [a](20 mg Sb^{5+}\kg\day) for nine days, due to altered renal function; [b](250 mg/day), replaced for 250 mg/day for 12 days; [c]200 mg/day for seven days; [d]50 mg/day for 10 days; [e]200 mg/day for eight days; [f](20 mg Sb^{5+}\kg\day, 15 mL or 3 ampoules/day) weekly, ending in July 2018; [g]for seven days due secondary infection; [h](6 mg/kg/day: 3 capsules/day or 450 mg/day); [i]patient did not return; [#]by flow cytometry, reference values by Brazilian Ministry of Health: < 50 cells/mm^3: severe immunodeficiency; 50-200 cells/mm^3: high risk to opportunistic disease; 200-500 cells/mm^3: moderate risk to opportunistic disease; > 500 cells/mm^3: low risk to disease; [*]by real-time PCR, reference values by Ministry of Health: < 10 000 copies/mL: low risk to disease progression; 10 000-100 000 copies/mL: moderate risk to disease progression; > 100 000 copies/mL: high risk to disease progression.

November, he finished the treatment for tuberculosis. In December, he presented several cutaneous papular and ulcerated lesions on the lower limbs and feet, besides mucosal lesion when he arrived at Hospital de Doenças Tropicais (HDT, in Goiás). From a lesion fragment, *L. amazonensis* was identified by PCR[7] confirming American tegumentary leishmaniasis. Initially, he was treated with liposomal amphotericin for 7 days, but the lesions relapsed. He underwent amphotericin B deoxycholate for 10 days and subsequently, a second cycle of liposomal amphotericin for 8 days, with partial improvement. At the beginning of American tegumentary leishmaniasis treatment, $CD4^+$ T lymphocyte count was 278 cells/mm^3 and the viral load was undetectable. In April 2018, he was treated again with liposomal amphotericin for 10 days, followed by weekly prophylactic Glucantime®, ending in July 2018. The tuberculosis relapsed and treatment was changed (Table 1). In November, the lesions were partially healed, presented pruritus, and some of them showed serous secretion due to secondary skin infection. The patient received cephalothin for seven days with clinical improvement. In March 2019, the IFT for American tegumentary leishmaniasis was positive (1/160), with active lesions on the lower limbs and nasal mucosa. Then, fluconazole was prescribed for 30 days. In June 2019, the cutaneous lesions were fully healed, there were no active lesions on the nasal mucosa, IFT was negative, and tuberculosis was cured. Although the patient did not continue under follow up in Goiás, his viral load was required in Mato Grosso in October 2019, and it was undetectable. He was considered clinically cured for American tegumentary leishmaniasis (Table 1).

3. Discussion

The current co-infected patients presented several atypical, papular and inflammatory cutaneous lesions with ulceration, besides nasal mucosa involvement; the histophatological findings showed low amounts of amastigote forms and predominance of macrophages, but also B lymphocytes and high numbers of T lymphocytes. Both patients presented clinical cure with regular treatments for American tegumentary leishmaniasis and were infected with *L. amazonensis*. Although the cellular immune response was not evaluated, all the aspects above, in accordance with previous studies on American tegumentary leishmaniasis[8,9], suggested the diagnosis of DL instead of DCL caused by *L. amazonensis*[6].

In case 1, the pleomorphic and fast disseminated lesions outlined an aggressive DL. This outcome was expected due to the immunodeficiency caused by the reduced $CD4^+$ T lymphocyte count, which can lead to a deficiency in containing the parasite. Although case 2 presented a better immune status compared to case 1, he also had multiple papular and ulcerative cutaneous lesions. In both patients, the treatment was difficult, requiring different drugs to obtain success. As in this study, different schedules of treatments have been described for HIV-infected patients with American tegumentary leishmaniasis, which lead to an increase in side effects of the drugs[2,3].

The two cases here indicate that HIV infection can impact *L. amazonensis* infection leading to the spread of the parasite and make the American tegumentary leishmaniasis therapy difficult. Differences in response to American tegumentary leishmaniasis treatments have been described when comparing patients infected with different *Leishmania* spp[10]. Moreover, pentavalent antimonial fails to treat most of co-infected patients and causes increased side effects[3,5] as shown here. Remarkably, studies comparing the therapeutic outcome of American tegumentary leishmaniasis caused by different *Leishmania* spp. in HIV-infected patients are missing.

Our study described two cases of co-infected patients with *L. amazonensis* and HIV and indicates the necessity of *Leishmania* species identification to improve the management of co-infected patients.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

C.F.A. contributed to data acquisition and manuscript preparation. I.B.N.O. contributed to data acquisition and manuscript preparation as well as edition and revision. M.B.S. performed the *Leishmania* species identification. F.R-D. revised and edited the manuscript. Both I.B.N.O and F.R-D contributed equally to the final version of the manuscript. F.R-D. was responsible for conception and supervision of the research project and the manuscript.

References

[1] Goto H, Lindoso JAL. Cutaneous and mucocutaneous leishmaniasis. *Infect Dis Clin North Am* 2012; **26**: 293-307.

[2] Alvar J, Aparicio P, Aseffa A, Boer M, Cañavate C, Dedet J, et al. The relationship between leishmaniasis and AIDS: The decond 10 years. *Clin Microbiol Rev* 2008; **21**: 334-359.

[3] Sampaio R, Salaro C, Resende P, De Paula C. American cutaneous leishmaniasis associated with HIV/AIDS: Report of four clinical cases. *Rev Soc Bras Med Trop* 2002; **35**: 651-654.

[4] Silva G, Sugui D, Nunes R, Azevedo K, Azevedo M, Marques A, et al. Mucocutaneous leishmaniasis/HIV coinfection presented as a diffuse desquamative rash. *Case Rep Infect Dis* 2014; **2014**: 293761. doi: 10.1155/2014/293761.

[5] Guerra J, Coelho L, Pereira F, Siqueira A, Ribeiro R, Almeida T, et al. American tegumentary leishmaniasis and HIV-AIDS association in a tertiary care center in the Brazilian Amazon. *Am J Trop Med Hyg* 2011; **85**: 524-527.

[6] Corrêa Soares GH, Silva ABSD, Ferreira LSS, Ithamar JS, Medeiros GA, Pereira SRF, et al. Case report: Coinfection by *Leishmania amazonensis* and HIV in a Brazilian diffuse dutaneous leishmaniasis patient. *Am J Trop Med Hyg* 2020; **103**(3): 1076-1080.

[7] Volpini A, Passos V, Oliveira G, Romanha A. PCR-RFLP to identify *Leishmania(Viannia) braziliensis* and *L. (Leishmania) amazonensis* causing American cutaneous leishmaniasis. *Acta Trop* 2004; **90**: 31-37.

[8] Pereira LIA, Dorta ML, Pereira AJCS, Bastos RP, Oliveira MAP, Pinto, AS, et al. Case report: Increase of NK cells and proinflammatory monocytes are associated with the clinical improvement of diffuse cutaneous leishmaniasis after immunochemotherapy with BCG/ *Leishmania* antigens. *Am J Trop Med Hyg* 2009; **81**: 378-383.

[9] Machado GU, Prates FV, Machado PRL. Disseminated leishmaniasis: Clinical, pathogenic, and therapeutic aspects. *An Bras Dermatol* 2019; **94**: 9-16.

[10]Romero GAS, Guerra MVF, Paes MG, Macedo VO. Comparison of cutaneous leishmaniasis due to *Leishmania (Viannia) braziliensis* and *L. (V.) guyanensis* in Brazil: Therapeutic response to meglumine antimoniate. *Am J Trop Med Hyg* 2001; **65**: 456-465.