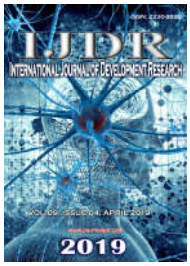
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 04, pp. 27225-27228, April, 2019



RESEARCH ARTICLE OPEN ACCESS

SUCCESSFUL TREATMENT OF MUCOCUTANEOUS *LEISHMANIA*SIS WITH LIPOSOMAL AMPHOTERICIN B IN A PATIENT WITH HIV

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ARTICLE INFO

Article History:
Received 27th January, 2019
Received in revised form
16th February, 2019
Accepted 20th March, 2019
Published online 30th April, 2019

Key Words:
Mucocutaneous Leishmaniasis; Hiv;
Liposomal Amphotericin B;
Leishmaniasis-Hiv Coinfection.

ABSTRACT

*Leishmania*sis is a non-contagious infectious-parasitic disease caused by an etiological agent of the genus *Leishmania*. *Leishmania* braziliensis is the main species that causes the disease in Brazil, which is transmitted through the bite of phlebotomid mosquitoes. In this report, a case of localized tegumentary *Leishmania*sis with important mucocutaneous involvement is presented in a patient diagnosed concurrently with acquired human immunodeficiency syndrome (AIDS). Despite the aggravating factors, this patient presented excellent therapeutic response after a single cycle of amphotericin B with complete resolution of the lesion.

Citation: Daniela Zonin, Francine Zanella Miotto, Sylka Rebelato Toppan, Eduardo Scardazzi Silva Ragni, Günter Hans Filho and Luiz Carlos Takita. 2019. "Successful treatment of mucocutaneous leishmaniasis with liposomal amphotericin b in a patient with HIV", *International Journal of Development Research*, 09, (04), 27225-27228.

INTRODUCTION

*Leishmania*sis is a non-contagious infectious-parasitic disease caused by an etiological agent of the genus *Leishmania*. To date, more than 20 species have been recorded as pathogenic to humans. In Asia, Africa and the Mediterranean region, the main species found are: *Leishmania tropica*, *Leishmania major*, *Leishmania aethiopica*, and *Leishmania donovani*. In Central and South America, along with southern Texas, *Leishmania mexicana*, *Leishmania braziliensis*, and *Leishmania guyanensis* are more common. Specifically in Brazil, *Leishmania braziliensis*, *Leishmania amazonensis* and *Leishmania* guyanensis are the main etiological agents (MOTA LAA *et al*., 2011; HANDLER MZ *et al.,* 2015). It is an endemic disease in more than 70 countries, and 90% of cases occur in Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia and Syria (REITHINGER R *et al.*, 2007). It is a public health problem on four continents, with an annual record of 0.7 to 1.3 million new cases.

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In Brazil between 1995 and 2014, there was an annual average of 25,763 new cases of *leishmania*sis. It predominates in children and young adult males. (MINISTÉRIO DA SAÚDE, 2017). The transmission of *Leishmania*sis occurs through the bite of phlebotomid mosquitoes. The genus *Phlebotomusspp* is more common in North America, Europe, Asia and Africa. The mosquito of the genus *Lutzomyia spp* is more frequent in the countries of Central and South America (REITHINGER R*et al.*, 2007). It is popularly known in Brazil as mosquito-palha, tatuquira or birigui. Through the bite, the vector inoculates the promastigote *Leishmania* flagellate form, which will be phagocytosed by the macrophages in the skin of the host, remaining in the amastigote form. The main hosts are human beings, domestic animals and rarely possums, rodents and anteaters. The clinical manifestations depend on the species of *Leishmania* and the immunological characteristics of the host (ALMEIDA OLS *et al.,* 2011; CAMPOS TM *et al.*, 2017). There are two clinical forms of presentation: visceral *Leishmania*sis (VL), tegumentary *Leishmania*sis (TL): cutaneous, mucosal or mucocutaneous, in localized or disseminated form. In South America, mucocutaneous involvement is more closely related to *Leishmania*

braziliensis. The first clinical sign of TL is erythema at the site of the vector's bite, progressing to nodule and ulceration (ALMEIDA OLS *et al.,* 2011). Diagnosis can be performed by parasitological tests: amastigote screening on lesion smears or patient tissue fragments imprinting, histopathology and immunohistochemistry; Immunological tests: Montenegro skin test, indirect immunofluorescence test and enzyme-linked immunosorbent assay (ELISA); polymerase chain reaction (PCR) test; culture in Novy-MacNeal-Nicolle medium (MINISTÉRIO DA SAÚDE, 2017). The sensitivity of each method is variable, and influenced by the host's immunological conditions. Typically, the parasite is identified in 70% of the cases in the cutaneous form and 50% in the mucocutaneous form, with lower rates in patients infected with human immunodeficiency virus (HIV). (HANDLER MZ*et al.*, 2015;FONTENELE E SILVA JS *et al.,* 2013)

The first reported coinfection case of *Leishmania*sis and HIV in the world was in 1985 in Europe. In Brazil, the first case is dated back to 1987, in Rio de Janeiro. Since the 1980, as the number of new cases of HIV rise so do the number of coinfected *Leishmania*sis/HIV patients (SAMPAIORNR *et al.*, 2002). Due to specific immunological changes in HIV patients, such as the poor performance of the Th1 response and the predominance of Th2 response, the parasites spread easily and the cases tend to be more severe, with more atypical clinical features, a higher rate of therapeutic failure, and a higher probability of recurrence (ALMEIDA OLS *et al.,* 2011; SAMPAIO RNR, 2002; ZIJLSTRA EE, 2014). Regarding the treatment, for the population in general the drugs of choice are pentavalent antimonials, drugs that are contraindicated in children, pregnant women, patients with certain chronic diseases, the elderly and immunocompromised. In these special cases, the main medication is amphotericin B (deoxycholate, liposomal or lipid complex) due to its lower toxicity. Second-line options are pentamidine isethionate and miltefosine, but both are contraindicated during pregnancy (ALMEIDA OLS *et al.,* 2011; FONTENELE E SILVA JS *et al.,* 2013). This case report aims to address the effectiveness of treatment with a short cycle of liposomal complex amphotericin B in a patient with *Leishmania*sis and HIV coinfection. In addition, it intends to emphasize that every patient diagnosed with *Leishmania*sis should be investigated for HIV, in order to determine the appropriate choice of treatment.

Case Report

Male patient, 44 years old, 95,7 kg, farmer, from the State of Mato Grosso do Sul, Brazil. He was admitted to a public dermatology service with nasolabial ulceration, claiming he had had the lesion for over a year (Fig. 1). He denied previous comorbidities or trauma at the site of the ulcer. In laboratory research, direct examination and cultures were negative for fungi, mycobacteria and *Leishmania*sis. The Montenegro skin test was not carried out. Chest x-ray and abdominal ultrasonography were normal. The anatomopathological examination of the borders of the lesion revealed an ulcerated epidermis with pseudoepitheliomatous hyperplasia; dermis with dense, granulomatous, loose inflammatory lymphohistiocytic infiltrate (Fig. 2), with foci of coagulative necrosis; negative research for fungi and acid-fast bacilli (AFB); absence of morphological evidence of malignancy; observing corpuscular structures compatible with amastigote forms (Fig. 3). Through histopathologic examination, the hypothesis of mucocutaneous *Leishmania*sis was proposed. Due to the significant mucosal involvement, the presence of candidiasis in oral mucosa and feeding difficulty, the patient was hospitalized for a better therapeutic approach. During routine exams, positive HIV serologic test was detected, with a viral load of 101,724 copies/ ml and 102 CD4 cells / mm^3, establishing acquired immunodeficiency syndrome (AIDS). Tests for hepatitis and syphilis were negative.

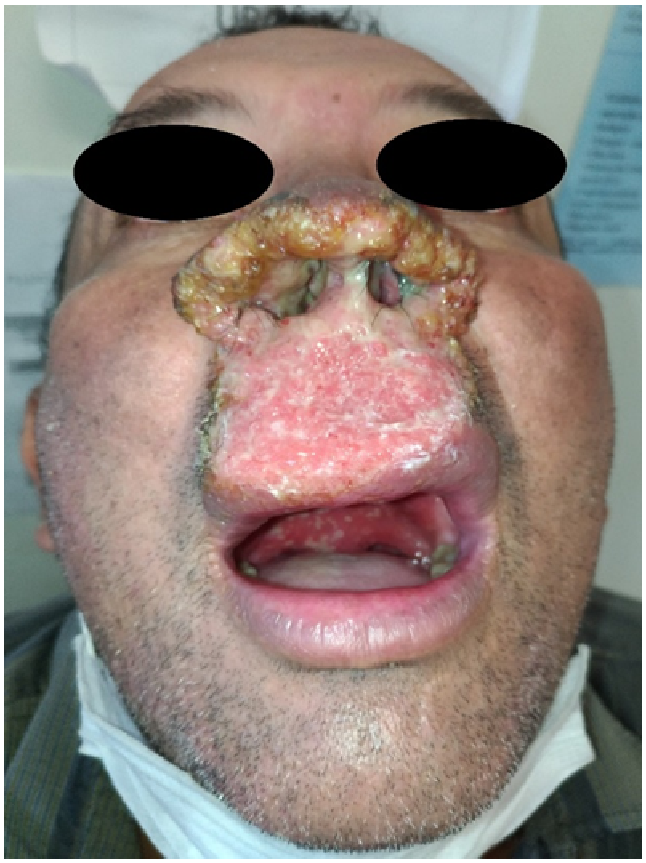

Fig. 1. Ulcer due to mucocutaneous tegumentary *Leishmania*sis, before treatment

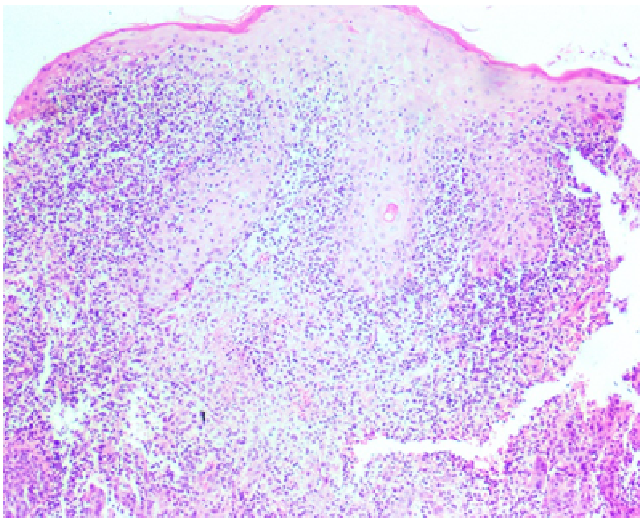

Fig. 2. Pseudoepitheliomatous hyperplasia with lymphohystiocytic infiltrate in the dermis (Hematoxylin & eosin, 100x)

Antiretroviral therapy (ART) was started with tenofovir, lamivudine and dolutegravir along with the treatment of mucocutaneous *Leishmania*sis with amphotericin B deoxycholate, 50mg/day.

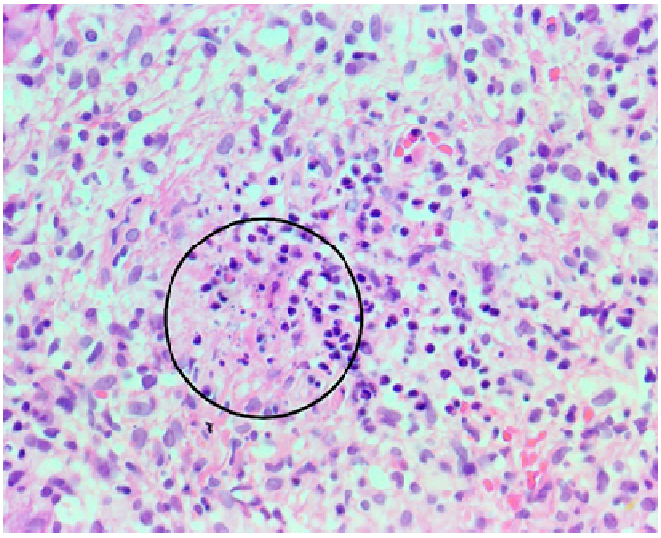

Fig. 3. Amastigote forms of the protozoan *Leishmania spp* (Hematoxylin & eosin, 400x)

After four days of treatment, due to chest pain and elevated serum creatinine levels, amphotericin B deoxycholate was replaced with liposomal amphotericin B 300mg/day. Tenofovir was replaced by abacavir, and the prophylaxis regimen of azithromycin 500mg 3x/week and sulfamethoxazole-trimetropim 400mg/80mg 1 tablet every 12 hours was started. The patient completed a total dose of 3.8 grams (40mg/kg) of amphotericin B (4 days of deoxycholate and 12 days of liposomal). There was complete resolution of the ulceration, without relapse after one year of treatment (Fig. 4).

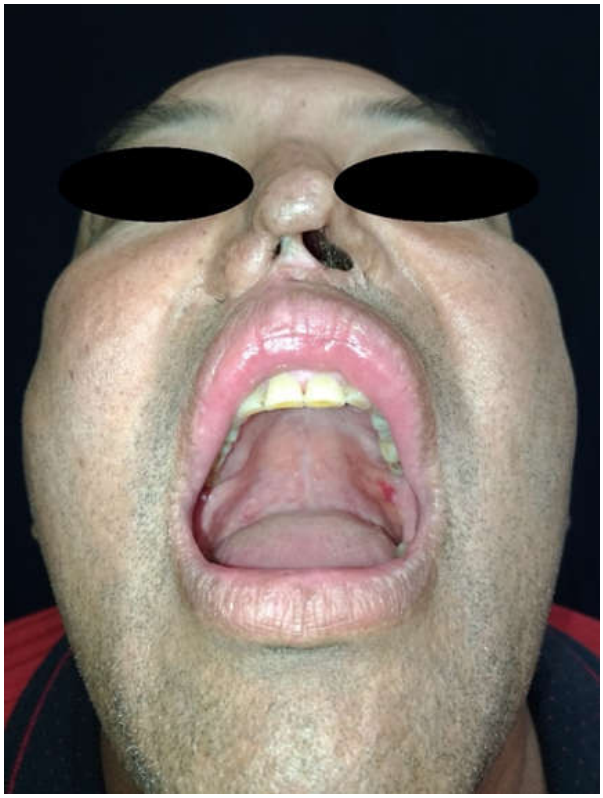

Fig. 4. One year after the end of liposomal amphotericin B therapy

DISCUSSION

This report presents a case of localized tegumentary *leishmania*sis with important mucocutaneous involvement in a patient diagnosed concomitantly with AIDS. In HIV-infected people, the most common form of *Leishmania*sis is visceral (VL), followed by the disseminated cutaneous form and in rare cases the mucocutaneous form. In 2006 the Brazilian Ministry of Health did a survey and identified between 2001 and 2005, in Brazil, 176 cases of VL/AIDS coinfection and 150 cases of TL/AIDS coinfection (MINISTÉRIO DA SAÚDE BR, 2011). In Brazil, by June 2003, 100 cases of *Leishmania*sis/HIV coinfection were reported, of which 63% had TL: 43% with associated mucosal involvement and 20% with cutaneous involvement only (RABELLO A *et al.*, 2002). This patient had a high viral load (101,724 copies / ml) and low CD4 (102 cells / mm³) at the time of diagnosis. It is known that the immune response against *Leishmania* depends on the innate immune system, through natural killer cells (NK), CD4 and CD8 T lymphocytes, as well as the cytotoxic action of IFN-γ and TNF-α. Changes in immunological mechanisms by HIV, such as CD4 T lymphocyte deficiency, contribute to the development of more severe mucocutaneous forms, with a higher treatment resistance (CAMPOS TM *et al.*, 2017; CASTELLANO LR *et al.*, 2011; SAMPAIO RNR *et al.,* 2002). In spite of the potentially aggravating factors, the patient presented excellent therapeutic response in a single cycle of liposomal amphotericin B, completing 16 days of treatment and complete resolution of the lesion.

In a Brazilian study of a series of 15 cases with TL associated with HIV-AIDS, 13 were treated with pentavalent antimonials and 1 with pentamidine. One patient was not treated due to a current pregnancy. Seven patients did not respond to the first treatment regimen and required a new treatment. Out of the 13 patients, 8 had recurrence within five years (GUERRA JAO *et al.*, 2011). Another Brazilian study with 23 HIV-infected patients showed that 60% of cases presented *Leishmania*sis as the first opportunistic infection, and 12 out of 17 cases initiated treatments with pentavalent antimonial was altered to amphotericin B due to side effects. However, there was relapse in 56% of the cases (FONTENELE E SILVA JS *et al*., 2013). According to Amato VS *et al*., in Brazil, the first report of the use of liposomal amphotericin B in mucocutaneous *Leishmania*sis/HIV with therapeutic success was in the year 2000. In view of the high rate of therapeutic failure with pentavalent antimonial in immunocompromised patients, it is of utmost importance to screen patients for HIV in any case suspected or diagnosed with *Leishmania*sis. Currently, the best results for cutaneous and mucosal *Leishmania*sis treatment are seen with liposomal amphotericin B and miltefosine (FONTENELE E SILVA J S *et al*., 2013; MOSIMANNA V*et al.,* 2018). However, controlled and randomized clinical trials are needed to prove the efficiency of therapeutic options in TL and to review the optimal doses in order to establish treatment protocols. At the moment, the patient awaits surgical reconstruction of the nasal septum and follows regular treatment with ART, without recurrence of *Leishmania*sis.

Acknowledgements

Special thanks to the infectology team fromuniversitary hospital Maria Aparecida Pedrossian - UFMS, for helping in the treatment of this patient.

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