

Case Report

Good response to pentamidine isethionate in a case of Mucosal Leishmaniasis caused by *Leishmania (Viannia) braziliensis* that was difficult to treat: Case Report

Benivaldo Ramos Ferreira Terceiro^[1], Tania Salgado de Souza Torraca^[2], Frederico Pereira Bom Braga^[1], Ana Cristina da Costa Martins^[1], Lucia Regina Brahim^[1], Mauricio Naoto Saheki^[1], Luciana de Freitas Campos Miranda^[1], Armando de Oliveira Schubach^[1] and Cláudia Maria Valete-Rosalino^{[1],[2]}

[1]. Instituto Nacional de Infectologia, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brasil.

[2]. Departamento de Otorrinolaringologia e Oftalmologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil.

Abstract

In Brazil, meglumine antimoniate is the first drug of choice for mucosal leishmaniasis treatment followed by amphotericin B and pentamidine isethionate. We report the case of a patient with severe mucosal lesions caused by *Leishmania (Viannia) braziliensis* that were difficult to treat. Over a 14-year period, the patient showed low adherence and three treatment attempts with meglumine antimoniate failed. Additionally, there was an unsatisfactory response to liposomal amphotericin B and nephrotoxicity when using amphotericin B deoxycholate that persisted after new treatment attempt with liposomal amphotericin B. Finally, healing was achieved with pentamidine isethionate and maintained during nine months of monitoring.

Keywords: Mucosal leishmaniasis. Therapy. Pentamidine isethionate.

INTRODUCTION

American tegumentary leishmaniasis (ATL) can affect the skin and/or mucosa of the upper aerodigestive tract. In Rio de Janeiro, Brazil, ATL is caused by *Leishmania (Viannia) braziliensis*, the main etiological agent of mucosal leishmaniasis (ML)¹. The nasal mucosa is involved in more than 90% cases, followed by the oral, pharyngeal and laryngeal mucosae^{1,2}.

Until 2016, in Brazil, the Ministry of Health recommended treating ML patients with 20 mg Sb⁵⁺/kg/day of meglumine antimoniate (MA) over 30 days¹. In Rio de Janeiro, MA is used in doses of 5 mg Sb⁵⁺/kg/day intramuscularly administered, without interruption, until epithelialization of the mucosa, which generally occurs between 30 and 90 days^{3,4,5}. In case

of unsatisfactory responses, the treatment can be repeated¹. If the second treatment fails, amphotericin B or pentamidine isethionate are indicated^{1,5}. Treatment must be monitored, due to the risk of adverse effects that may demand its interruption¹.

We report the case of a patient with ML caused by *L. (V.) braziliensis* that was difficult to treat, followed in Rio de Janeiro, between 1998 and 2012. The patient agreed to have his case published and signed an informed consent form; this was approved by the research ethics committee.

CASE REPORT

A 50-year-old male patient, born in Rio de Janeiro, was examined in March 1998 at the Evandro Chagas National Institute of Infectious Diseases (INI) with complaints of rhinorrhea, nasal obstruction and dysphonia for 10 months, without active skin lesions or scars suggestive of cutaneous leishmaniasis. He presented infiltrative mucosal lesions in the nasal septum, palate, uvula, and larynx, which were observed by nasal video endoscopy and video laryngoscopy with the aid of a 30- or 70-degree rigid endoscope (Karl Storz SE,

Corresponding author: Dra. Cláudia Maria Valete Rosalino. ORCID: 0000-0003-3110-9271

e-mail: claudia.valete@ini.fiocruz.br

Received 16 June 2018

Accepted 7 August 2018

Germany). Histopathological examination of the nasal mucosa revealed chronic a granulomatous inflammatory process with the presence of amastigote forms. *Leishmania (Viannia) braziliensis* was isolated in biphasic medium Novy, MacNeal, and Nicolle (NNN) plus Schneider's *Drosophila* medium (Sigma-Aldrich) supplemented with 10% fetal bovine serum. Identification of species was carried out by multilocus enzyme electrophoresis^{6,7}. Serology results for HIV, and cultures for fungi and mycobacteria were negative. The purified protein derivative test and chest x-ray were normal. Differential diagnostic examinations were repeated before each subsequent treatment and remained negative. The patient was hospitalized to start treatment with 5 mg Sb⁵⁺/kg/day of MA with 100 mg hydrocortisone intravenously administered. He presented laryngeal edema that regressed within 72 h, and was discharged without corticotherapy and oriented to maintain MA until his return in one week.

However, he returned only in May 2005 (**Figure 1**), without having concluded the treatment, with worsening of the lesion, and partial destruction of the nasal septum and inferior nasal conchae, collapse of the tip of the nose, uvular lesions, and extensive involvement of the laryngeal mucosa. After restarting

5 mg Sb⁵⁺/kg/day MA, there was a slight improvement of the lesions, but treatment was again abandoned after the 50th dose. Eight months later, he returned with worsening of the lesions and underwent another nasal biopsy, with the isolation of *L. (V.) braziliensis* in culture, but he did not return to resume treatment. In April 2007, there was no improvement after treatment with 3000 mg of liposomal amphotericin B. Over the next four years, he returned three times for examination with persistent lesions, but he did not appear for the scheduled appointments to restart treatment.

In January 2011, he underwent another nasal and oral biopsy with positive polymerase chain reaction assay for *Leishmania*. Ambulatory treatment was resumed with 5 mg Sb⁵⁺/kg/day MA in series of 10 days interspersed with 10-day intervals without medication totaling 100 doses, with the healing of laryngeal lesions but the persistence of oral and nasal lesions. In September 2011, histopathological examination of the oral mucosa showed amastigote forms. In November 2011, he was successively treated with amphotericin B deoxycholate (50 mg total dose) and liposomal amphotericin B (200 mg total dose), both interrupted due to nephrotoxicity. In January 2012, he returned with nasal and oral lesions and intramuscular pentamidine isethionate

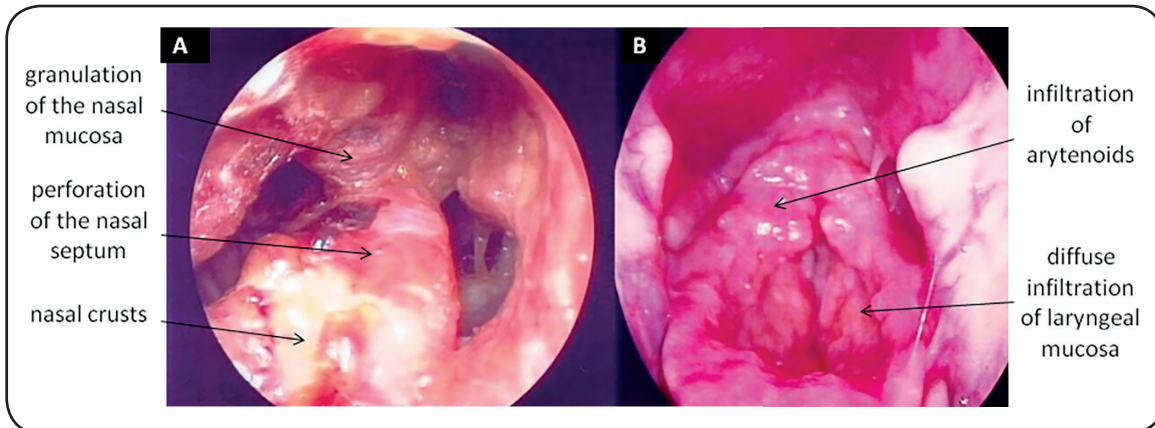


FIGURE 1: Extensive lesions in the nasal and laryngeal mucosa, May 2005.

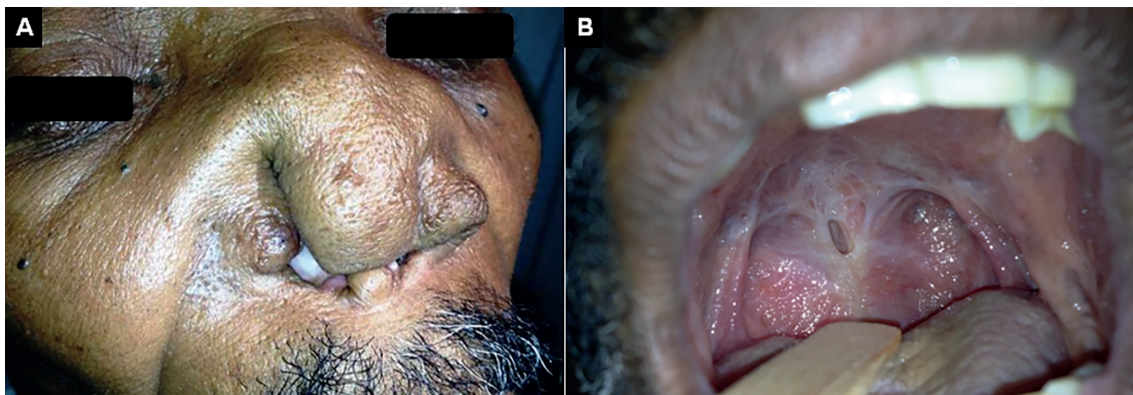


FIGURE 2: A: Anatomical sequelae with nasal tip drop - "Tapir Nose". B: Anatomical sequelae with uvula amputation and fibrosis on the palate mucosa, November 2012.

(4 mg/kg) was introduced every four days with complete healing of the lesions from the seventh of ten doses (2200 mg total dose). After 9 months of post-cure monitoring, the lesions remained healed and the patient presented with anatomical sequelae: uvula amputation, septal perforation and collapse of the tip of the nose (**Figure 2**). **Figure 3** represents the timeline from the first treatment until the last examination.

DISCUSSION

In this study we described a case of ML caused by *L. (V.) braziliensis* acquired in Rio de Janeiro with low adherence and poor response to MA, failure and intolerance to amphotericin B, and lesion healing after using pentamidine isethionate.

A possible cause of the poor response to treatment, in this case, was the marked treatment irregularity. In this case, the patient started treatment with the alternative dose of 5 mg Sb⁵⁺/kg/day MA with successive dropouts. Several factors may influence the therapeutic response, including the presence of oral lesions, doses, regularity of administration, immune status of the host and parasite resistance to the drugs employed^{2,8,9,10}. *L. (V.) braziliensis* promastigote forms from Rio de Janeiro were more sensitive, *in vitro* than strains of other origins, which could explain the good response of ATL to low doses of MA in Rio de Janeiro⁸. Therapeutic responses to MA may vary according to the region or species that causes ATL⁸. However, no genotypic differences were observed among *Leishmania* samples isolated from responders or non-responders to MA treatment regardless

of the geographical area where the infection was acquired⁶. In a study, the sensitivity of *L. (V.) braziliensis* samples isolated from patients with therapeutic failure or relapse was smaller than that of samples with good therapeutic response⁸. On the other hand, another *in vitro* sensitivity study with *L. (V.) braziliensis* isolates obtained before treatment with 5 mg Sb⁵⁺/kg/day MA and after therapeutic failure does not support the hypothesis that the use of a small dose induces the selection of resistant parasites *in vitro* and suggests that other factors may influence the therapeutic outcome⁷.

Regardless of the origin of the patients and the severity of the disease, the standard dose of MA 20 mg Sb⁵⁺/kg/day is practically not used in INI, both for the treatment of CL and ML patients. Between 2001 and 2013, 777 ATL patients were followed up at INI, Rio de Janeiro, with 13% coming from other Brazilian states. Some patients had to receive 1–3 additional treatments because of unsatisfactory initial response or relapse, totaling 997 treatments. Alternative schemes with MA were used in 85.3% of cases, 73.1% with 5 mg Sb⁵⁺/kg/day and 12.2% intralesionally administered. Relapse and late ML incidences were 5.8% and 0.25%, respectively. As an outcome of all 777 patients, 95.9% were cured, 0.1% died (one patient treated with MA 20 mg Sb⁵⁺/kg/day) and 4% abandoned follow-up. Such results are promising when compared with other Brazilian regions that do not use alternative therapeutic schemes for ATL treatment⁵. The use of alternative schemes should be attempted in other regions outside Rio de Janeiro when the use of the standard scheme is risky for patients¹¹.

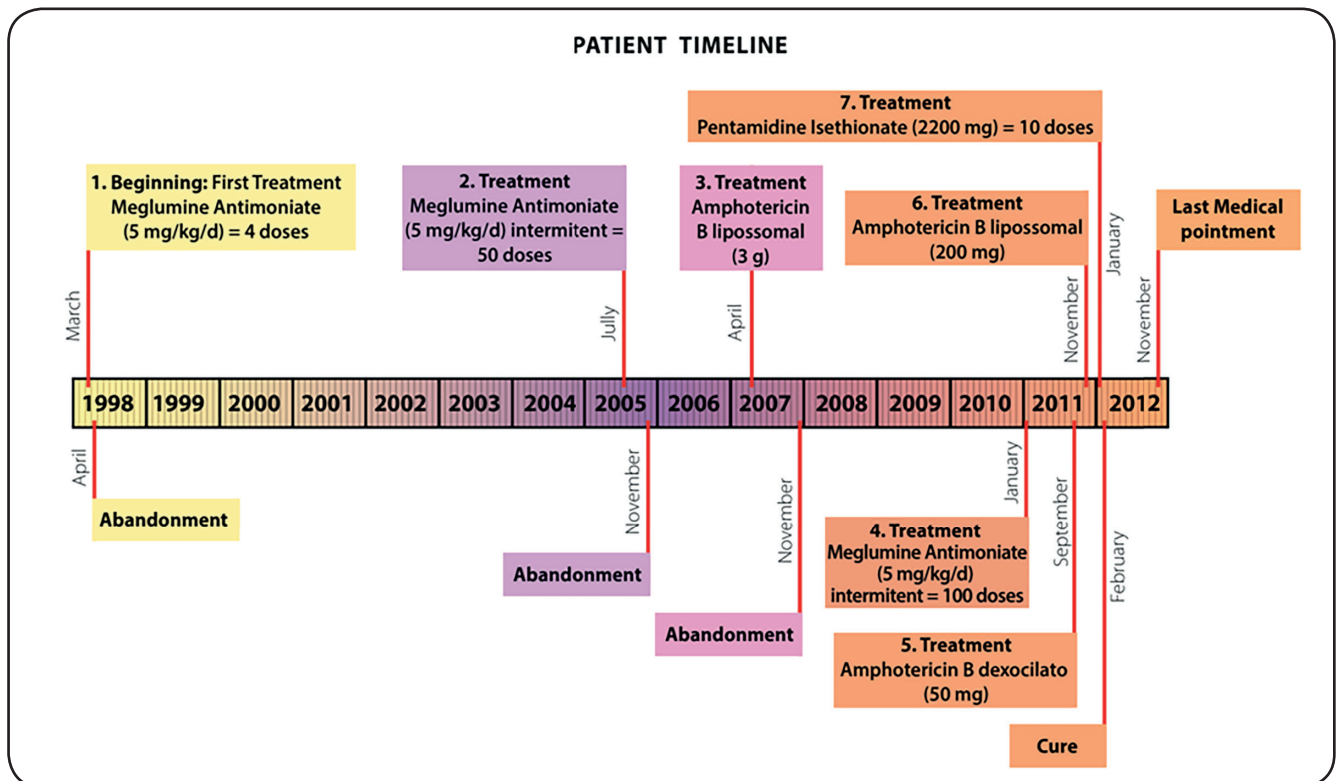


FIGURE 3: Timeline during patient follow-up and treatment, March 1998 - November 2012.

In addition to poor response to MA, the patient did not respond adequately to liposomal amphotericin B. This unsatisfactory response was unexpected because amphotericin B is considered efficient in ATL treatment, and has been indicated, in Brazil, as a second-line drug in cases of therapeutic failure or contraindication to the use of MA¹. Because of its efficiency, short treatment time and good tolerability, liposomal amphotericin B has been indicated as the first drug of choice for ATL patients older than 50 years¹. However, the reported patient did not tolerate a second treatment with amphotericin B (deoxycholate and liposomal) due to nephrotoxicity. At INI, between 2001 and 2013, amphotericin B (deoxycholate or liposomal forms) was the drug of choice for the initial treatment of 17 (2.2%) patients with contraindication to MA. However, in patients with therapeutic failure or relapse after MA, 42.1% (8/19) presented healing with amphotericin B (deoxycholate and liposomal forms)⁵.

Pentamidine isethionate was well tolerated by the patient and the final result was satisfactory, with lesion healing kept up to nine months of monitoring. Similar response to pentamidine isethionate had already been reported for a patient with cutaneous leishmaniasis with poor response to MA and intolerance to amphotericin B¹². In Brazil, pentamidine isethionate is indicated as the first drug of choice in the treatment of ATL caused by *L. (V.) guyanensis* and considered a therapeutic option in cases of therapeutic failure or contraindication to the use of MA¹. As pentamidine isethionate might have acute toxic action on beta-pancreatic cells, hypoglycemia may occur during treatment and diabetes mellitus at a later stage¹, which did not occur in this case. Between 2001 and 2013, pentamidine isethionate was the drug chosen for the initial treatment of 3 (0.4%) patients managed at INI with contraindication for MA or amphotericin B. In addition, it was successfully used in 2 (10.5%) of 19 patients who did not respond to different treatments with MA or amphotericin B⁵.

Pentamidine isethionate was well tolerated and effective in the treatment of this ML case that was difficult to control over 14 years, due to low adherence to treatment, lack of response to MA, in addition to intolerance and unresponsiveness to amphotericin B. This report suggests that pentamidine isethionate might be a good therapeutic option in ML caused by *L. (V.) braziliensis*, in cases of difficult treatment, including the elderly.

Acknowledgments: We offer our deepest thanks to the institutions that provided technical support for the development and implementation of this study and we wish to thank the patient and the following research staff: Maria Helena de Araújo Melo, Mateus Pereira Bom Braga, Maria Inês Fernandes Pimentel, Marcelo Rosandiski Lyra, Ananda Dutra da Costa, Marcia Lucena, Leonardo Pereira Quintella, Aline Fagundes and Rosana Blois da Silva.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Support: This study was supported by the *Secretaria Municipal de Saúde do Rio de Janeiro* (convênio RJ/FIOCRUZ), FIOCRUZ, FAPERJ (E-26/102.183/2013), *Projeto FAPERJ Apoio Emergencial BBP/PPP- processo E-26/200.839/2017*, CNPq, and PAPES4/FIOCRUZ.

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