Case Report

First report of treatment failure in a patient with cutaneous leishmaniasis infected by *Leishmania (Viannia) naiffi* carrying *Leishmania* RNA virus: a fortuitous combination?

Ricardo Vieira-Gonçalves[1]#, Giselle Aparecida Fagundes-Silva[1]#, Júlia Furtado Heringer[1], Maria Fantinatti[1], Alda Maria Da-Cruz[1], Manoel Paes Oliveira-Neto[2], Jorge Augusto Oliveira Guerra[3] and Adriano Gomes-Silva[1],[4]

[1]. Laboratório Interdisciplinar de Pesquisas Médicas, Instituto Oswaldo Cruz, FIOCRUZ, Rio de Janeiro, RJ, Brasil.
[3]. Gerência de Leishmaniose, Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, Manaus, AM, Brasil.
[4]. Laboratório de Pesquisa Clínica em Microbioterrorism, Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ, Rio de Janeiro, RJ, Brasil.

Abstract

We report the case of a 32-year-old man from Rio de Janeiro, who was infected in the Amazon region of Brazil by *Leishmania (Viannia) naiffi*. Generally, patients with *L. naiffi* cutaneous leishmaniasis exhibit a good therapeutic response to either pentavalent antimonials or pentamidine. However, after pentamidine treatment, this patient’s infection evolved to therapeutic failure. To understand this clinical outcome, we investigated the presence of the *Leishmania* RNA virus (LRV) in parasites isolated from the cutaneous lesion; herein, we discuss the possible association between a poor response to pentamidine therapy and the presence of the LRV.

Keywords: *Leishmania (Viannia) naiffi*. Therapeutic failure. *Leishmania* RNA virus.

INTRODUCTION

*Leishmania (Viannia) naiffi* was first isolated in the armadillo (*Dasypus novemcinctus*) in 1989 by Lainson and Shaw in the Brazilian Amazon[1]. Soon after, this species was detected in a patient with human cutaneous leishmaniasis (CL). Other cases were reported in Latin America[2], most of which involved military personnel or tourists[1]. However, *L. naiffi* is still considered an unusual parasite species. In Brazil, these cases occur mainly in the Amazon region, where frequencies of 4%, 20%, or even 26.7%[4] have been reported.

*L. naiffi* CL lesions are usually ulcerated, unique, and small, located on the hands, arms, or legs. They usually develop with a favorable prognosis and even spontaneous healing[3], and mucosal leishmaniasis has not yet been reported. Commonly, patients with *L. naiffi* CL exhibit a good therapeutic response to either pentavalent antimonials or pentamidine[3]. In addition, experimental studies have shown that *L. naiffi* causes discrete or even unapparent infections on the skin of hamsters[1].

We describe an unusual *L. naiffi* CL case that evolved with pentamidine resistance, and we also discuss the possible association between poor therapy response and the presence of the LRV.

CASE REPORT

A 32-year-old man from Rio de Janeiro state, Brazil, was infected in September 2009 during his military training in the Amazon region (Manaus, AM). A papular lesion approximately 0.5 cm in diameter was noted on his left hand 30 days later. No lymphadenopathy was noted. The patient was treated with a three-day course of pentamidine (4 mg/kg). The treatment was unsuccessful, and an active lesion persisted (Figure 1A). In March 2010, the patient underwent surgical removal of the entire lesion. Pseudo-epitheliomatous squamous hyperplasia and chronic granulomatous dermatitis were observed on
histopathological analysis. No amastigotes were found. Leishmania spp. was isolated and characterized as L. naiffi based on isoenzyme electrophoresis. One month after the surgical procedure and without undergoing another round of therapy, no signs of active disease were detected. The scar remained completely healed until three years after surgery (Figure 1B and 1C), at which time clinical follow-up was discontinued.

Anti-Leishmania immunoglobulin G (IgG), IgG1, and IgG3 were measured using the enzyme-linked immunosorbent assay method. Despite therapeutic failure, immunoglobulin levels remained negative up to two years after treatment. The LRV was detected in the sample using a sequencing technique (Figure 1D). The LRV from L. naiffi showed 91% identity with LRV1 sequences from GenBank.

**DISCUSSION**

This case involved therapeutic pentamidine failure in CL caused by L. naiffi, and it is intriguing that complete cure was achieved after surgical removal of the lesion. Two possible hypotheses to explain this therapeutic failure occurrence are as follows: 1) therapeutic failure in L. naiffi CL is a more common phenomenon than previously reported and 2) the presence of the LRV contributed to increased parasite virulence.

The frequency of human L. naiffi infection is likely underreported due to the failure of health systems to isolate and identify Leishmania species. Recent reports suggest that transmission of L. naiffi in the Amazon region may be more common than expected. Furthermore, we described another two of eight cases of L. naiffi infection that evolved with therapeutic failure post-pentamidine or -antimony treatment. However, the mechanisms associated with L. naiffi resistance to these drugs are unknown.

The LRV has primarily been detected in two Viannia subgenera (L. braziliensis and L. guyanensis species), and its role as a virulence factor remains controversial. Indeed, studies have suggested that the LRV reduces sensitivity to oxidative stress, which may contribute to the decreased effectiveness of drugs. Furthermore, this double-stranded RNA virus is known to increase the transcription of proinflammatory cytokines, which in turn promotes tissue damage and poor prognosis. Remarkably, we first evidenced the presence of the LRV in L. naiffi species, raising the possibility that the presence of this virus could increase Leishmania spp. virulence and thereby influence therapeutic failure. Case studies of CL caused by L. braziliensis or L. guyanensis revealed that treatment failure with antimonial therapy or pentamidine, respectively, was significantly higher when an isolated parasite presents with the LRV infection. Further studies are needed to confirm its role in the dynamics of Leishmania spp. infection.

This study reinforces the importance of defining the true epidemiological importance of L. naiffi as an etiological agent of CL in South America, especially in the Amazon region. Thus, the identification of possible factors associated with treatment failure should allow for better clinical monitoring of patients.

**Acknowledgments:** The authors thank the technical team from “Gerência de Leishmaniose – Fundação de Medicina Tropical Heitor Vieira Dourado.” We also thank the “Laboratório de Referência Nacional para Tipagem de Leishmaniose” (IOC), FIOCruz, and the sequencing platform (IOC).

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

**Financial Support:** This work was funded by Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ-APQ1) (grant number E-26/110.497/2012) (www.faperj.br), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (number 458858/2014-5). AMDC is a CNPq and FAPERJ (CNE) research fellow. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**REFERENCES**
