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Intestinal helminth coinfection is associated with mucosal lesions and poor response to therapy in American tegumentary leishmaniasis

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ABSTRACT

The most severe clinical form of American tegumentary leishmaniasis (ATL) due to *Leishmania braziliensis* is mucosal leishmaniasis (ML), characterized by destructive lesions in the facial mucosa. We performed a retrospective cohort study of 109 ATL patients from Rio de Janeiro State, Brazil, where ATL is caused by *L. braziliensis*, to evaluate the influence of intestinal parasite coinfections in the clinical course of ATL. Parasitological stool examination (PSE) was performed with samples from all patients by the sedimentation, Kato-Katz and Baermann-Moraes methods. The diagnosis of ATL was made from lesion biopsies by direct observation of amastigotes in Giemsa-stained imprints, isolation of *Leishmania* promastigotes or histopathological examination. All patients were treated with meglumine antimoniate. Patients with positive PSE had a frequency of mucosal lesions significantly higher than those with negative PSE ($p < 0.005$). The same was observed for infections with helminths in general ($p < 0.05$), with nematodes ($p < 0.05$) and with *Ascaris lumbricoides* ($p < 0.05$), but not for protozoan infections. Patients with intestinal parasites had poor response to therapy (therapeutic failure or relapse) significantly more frequently than the patients with negative stool examination ($p < 0.005$). A similar difference ($p < 0.005$) was observed between patients with positive and negative results for intestinal helminths, but not for intestinal protozoa. Patients with positive PSE took significantly longer to heal than those with negative PSE ($p < 0.005$). A similar difference was observed for intestinal helminth infections ($p < 0.005$), but not for protozoan infections. Our results indicate a deleterious influence of intestinal helminth infections in the clinical course of ATL and evidence for the first time an association between ML and these coinfections, particularly with nematodes and *A. lumbricoides*.

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1. Introduction

The HIV pandemic has taught us that concomitant infection with a different pathogen may alter dramatically the clinical expression of leishmaniasis, both visceral (Peters et al., 1990) and cutaneous (Coura et al., 1987). Differences in clinical and immunological features have been reported between patients with malaria-associated visceral leishmaniasis and those without this coinfection (van den Bogaart et al., 2013, 2014). Clinical and immunological characteristics of cutaneous and mucosal leishmaniasis patients coinfected with pathogenic mycobacteria have also been described (Delobel et al., 2003; Matos et al., 2005). However, little is still known about the effect that intestinal parasite coinfections may have on leishmaniasis.

Leishmania (Viannia) braziliensis is the main causative species of American tegumentary leishmaniasis (ATL) in Brazil (Leite et al., 2012) and is virtually the only causative agent of ATL in the state of Rio de Janeiro (Vieira-Gonçalves et al., 2008), where this study was conducted. In fact, there is only one report of another dermotropic *Leishmania* species (*Leishmania amazonensis*) causing human dis-

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ease in Rio de Janeiro state, in Paraty, very close to the border of the state of São Paulo (Azeredo-Coutinho et al., 2007). The human infection with *Leishmania braziliensis* may result in cutaneous and mucosal lesions (Gomes-Silva et al., 2007). The majority of *L. braziliensis*-infected patients present cutaneous leishmaniasis (CL), with lesions restricted to the skin. Lesions in nasal and/or oral mucosa may develop in a small proportion of patients (Jirmanus et al., 2012), characterizing the severe clinical form termed mucosal leishmaniasis (ML). ML, also known as mucocutaneous leishmaniasis, because one or more cutaneous lesions usually precede or may be still present during the development of this clinical form, is defined by destructive lesions of nasal, oral and pharyngeal mucosa, which, in the absence of adequate treatment, may progress to a mutilating and disabling disease (Goto and Lindoso, 2010). In Brazil, leishmaniasis is a compulsory notification disease. According to the Information System (Sinan) of the Brazilian Ministry of Health, ML accounted for 15.6% of ATL cases notified in Rio de Janeiro state during the period of 1999–2013. A proportion of 12.7% of mucosal leishmaniasis was reported among a series of patients studied at INI-Fiocruz (de Oliveira-Neto et al., 2000).

L. braziliensis infection in humans is characterized by a proinflammatory cytokine response, with high production of T helper (Th) 1 cytokines (Silveira et al., 2009; Souza et al., 2012). Although an exacerbated Th1 response may lead to tissue damage and be associated with to the immunopathogenesis of ML (Bacellar et al., 2002), Th1 cytokines, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, are indispensable for the control of Leishmania infection in macrophages (Green et al., 1990), the major host cells for this parasite in their mammalian hosts (Naderer and McConville, 2011). On the other hand, infections with intestinal helminths are associated with type 2 responses (Pulendran and Artis, 2012), which are able to inhibit Th1 responses and IFN-γ production (Del Prete, 1998).

This retrospective study aimed at evaluating the influence of intestinal parasites in the clinical course of ATL and its putative association with ML.

2. Materials and methods

2.1. Patients

We performed a retrospective study based on records of the Instituto Nacional de Infectologia Evandro Chagas (INI), Fundação Oswaldo Cruz (Fiocruz). The Laboratory of Leishmaniasis Surveillance of INI-Fiocruz is a referral center for the investigation of patients with suspected leishmaniasis and treatment of diagnosed cases, located in the city of Rio de Janeiro, Brazil. More than 90% of ATL cases in the municipality of Rio de Janeiro and at least 50% of the cases in the state of Rio de Janeiro are diagnosed and treated at INI-Fiocruz.

All American tegumentary patients from Rio de Janeiro State, treated in INI-Fiocruz with the antimonial schedule described below during the period of November 11, 2004, to November 22, 2006, were studied. The main demographic and clinical data of those patients are shown in Table 1.

The transmission of cutaneous leishmaniasis in Rio de Janeiro State is domestic and peridomestic (Souza et al., 1992). Occupations are not a risk factor in this context. The most frequent occupations of the patients were: student (23.9%), housewife (13.8%), brick mason (8.3%) and farmer (6.4%). Each of the other occupations accounted for less than 3.7% of the cases.

2.2. Diagnosis of American tegumentary leishmaniasis

The epidemiological history of the patients was investigated, and clinical, dermatological and otorhinolaryngological examinations were performed as previously described (Oliveira-Neto et al., 2000; Schubach et al., 2005). All cases were parasitologically diagnosed. The diagnosis of ATL was made by isolation of promastigote forms of *Leishmania* from lesion biopsies, or by observation of amastigote forms in histopathological sections, in tissue samples obtained through biopsy of the lesions, performed in all patients. The biopsy specimen was divided into several fragments. One of them was used to make Giemsa-stained imprints and was then fixed in 10% buffered formalin, embedded in paraffin and stained with haematoxylin-eosin, PAS, Grocott and Ziehl–Neelsen for histopathological examination. Another fragment was cultured in enriched blood agar medium (NNN) for the isolation of promastigote forms of *Leishmania* (Fagundes et al., 2010). *Leishmania* parasites were isolated from 88 patients (80.7%), amastigotes were seen by direct examination of Giemsa-stained material from lesion biopsies from 39 patients (35.8%) and by histopathological examination in 43 cases (39.4% of the patients). Forty-seven of the isolates were submitted to species characterization by multilocus enzyme electrophoresis (MLEE), performed according to previously described procedures (Cupolillo et al., 1994). Five enzyme systems were used: glucose-6-phosphate dehydrogenase (G6PDH, EC.1.1.1.49), 6-phosphogluconate dehydrogenase (6PGDH, EC.1.1.1.43), glucose phosphate isomerase (GPI, EC.5.3.1.9), nucleoside hydrolase (NH, 2 loci, EC. 3.2.2.1) and malic enzyme (ME, EC.1.1.1.40). All the samples analyzed by MLEE in this study were identified as *L. braziliensis* as they showed electromorphic profiles similar to the *L. braziliensis* reference strain MHOM/BR/75/M2903 (Ferreira et al., 2015). No isoenzymatic variants were observed. Among these isolates, 42 were from CL cases and five from ML cases.

2.3. Parasitological stool examination and treatment of intestinal parasites

Parasitological stool examination was routinely performed in all ATL patients attended at the leishmaniasis outpatient unit of INI/Fiocruz during the study period using the sedimentation, Kato-Katz and Baermann-Moraes methods. The presence of eggs in stool samples was determined with a thick smear technique using the Kato-Katz method (Katz et al., 1972; Peters et al., 1980). For detection of *Strongyloides stercoralis*, 25 g of fresh stool were examined using the Bearmann-Moraes technique (Carvalho et al., 2012). The presence of protozoa was verified by a modified Hoffmann (Hoffmann et al., 1934) consisting in the centrifugation of 5 g of stool diluted in water and examination of the sediment by light microscopy.

The patients were treated for the pathogenic intestinal parasites found before the onset of specific therapy for leishmaniasis. The therapeutic schemes used were those recommended by the Brazilian Ministry of Health: for Ancylostomidae, *Ascaris lumbricoides, Trichuris trichiura*, *Enterobius vermicularis,* albendazole 400 mg, single dose; for *S. stercoralis*, albendazole 400 mg/day for 3 consecutive days; for *Schistosoma mansoni*, praziquantel 50 mg/kg, single dose; for *Entamoeba histolytica* and *Giardia lamblia*, secnidazol 2 g, single dose. All treatments were given by oral route. The infections with *Blastocystis hominis*, *Entamoeba coli* and *Endolimax nana* were asymptomatic and were not treated.

2.4. Leishmaniasis treatment and follow-up

All patients were treated with meglumine antimoniate, 5 mg Sb/kg/day for 30 days (Oliveira-Neto et al., 1997), administered intramuscularly, at the leishmaniasis outpatient unit of INI-Fiocruz, and all of them completed the 30 day schedule. Concerning the outcome of antimonial therapy, cure was defined as complete epithelialization of the lesions without any sign of inflammation including nodules, papules, erythema, edema, itching or scale. In

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