

# Cutaneous leishmaniasis in a patient with ankylosing spondylitis using adalimumab

Kirla Wagner Poti Gomes<sup>1</sup>, André Nunes Benevides<sup>2</sup>, Francisco José Fernandes Vieira<sup>1</sup>,  
Maggy Poti de Moraes Burlamaqui<sup>3</sup>, Marcos de Almeida e Pontes Vieira<sup>4</sup>, Lysiane Maria Adeodato Ramos Fontenelle<sup>4</sup>

## ABSTRACT

Leishmaniasis is an anthroponosis caused by species of *Leishmania* and can have different clinical presentations, depending on the parasite-host relationship. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a cytokine essential to infection control, especially against intracellular parasites such as *Leishmania*. Anti-TNF- $\alpha$  strategies have had a marked impact on the treatment of rheumatic diseases, but the clinical use of those antagonists has been accompanied by an increased report of infections. We report the first case of cutaneous leishmaniasis in a patient with ankylosing spondylitis treated with adalimumab and methotrexate in Brazil. We believe that, in this case, there was no association between the anti-TNF- $\alpha$  treatment and cutaneous leishmaniasis, because the disease was limited to only one ulcer that healed completely after treatment. More studies, however, are necessary to better understand the possible relationship between anti-TNF- $\alpha$  agents and leishmaniasis.

**Keywords:** ankylosing spondylitis, tumor necrosis factor- $\alpha$ , cutaneous leishmaniasis, methotrexate.

© 2012 Elsevier Editora Ltda. All rights reserved.

## INTRODUCTION

Leishmaniasis is an anthroponosis that can be caused by several flagellated protozoa species of the *Leishmania* genus, transmitted by insects of the *Lutzomyia* genus. Those protozoa are obligate intracellular parasites of mononuclear phagocytic system cells.<sup>1,2</sup> The disease is considered a public health problem in 88 countries, with 1–1.5 million new cases of American tegumentary leishmaniasis (ATL) registered every year.<sup>1</sup> More than 90% of the cases of ATL occur in six countries, including Brazil.<sup>2</sup> The clinical manifestation of the disease depends not only on the *Leishmania* species involved, but also on the patient's immune status, a wide spectrum of clinical forms existing depending on the host's cellular immune response.<sup>1</sup>

The tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a pro-inflammatory cytokine produced by macrophages, involved in both the pathogenesis of several inflammatory diseases and the

immune-mediated response to several infections, especially that against intracellular pathogens.<sup>3</sup> The TNF- $\alpha$  is essential in the resistance to several microorganisms, such as the infectious species of *Leishmania*.<sup>1–4</sup>

Since the beginning of the commercialization of the anti-TNF- $\alpha$  biologics, at the end of the 1990s, the use of those drugs has become increasingly frequent. Their efficacy in the management of several immune diseases, such as rheumatoid arthritis, spondyloarthritides, Crohn disease and psoriasis, has confirmed their use.<sup>2,5,6</sup> The anti-TNF- $\alpha$  therapy, however, is affected by the increasing number of opportunistic infections, such as *Pneumocystis jirovecii* pneumonia, histoplasmosis, cytomegalovirus, aspergillosis, cryptococcal meningitis, leishmaniasis, and mainly tuberculosis.<sup>3,5</sup> We report one case of ATL in a female patient with ankylosing spondylitis and receiving the anti-TNF- $\alpha$  therapy with adalimumab (ADA).

Received on 02/20/2011. Approved on 03/05/2012. The authors declare no conflict of interest. Rheumatology Service of the Hospital Geral de Fortaleza – HGF.

1. Preceptor of the Residency in Rheumatology, Hospital Geral de Fortaleza – HGF

2. Medical Student, Universidade Federal do Ceará – UFCE

3. Preceptor of the Residency in Dermatology, Centro Dona Libânia

4. Resident of Rheumatology, HGF

Correspondence to: Kirla Wagner Poti Gomes. Rua Ávila Goulart, 900 – Papicu. CEP: 60175-295. Fortaleza, CE, Brasil. E-mail: nunes@hotmail.com

## CASE REPORT

The patient is a 36-year-old female complaining of an ulcerated, painless, and non-pruriginous lesion on her right leg for two months, which appeared after a trip to Timon, an important endemic area of tegumentary leishmaniasis in the state of Maranhão, Brazil. She had no other clinical complaints. The patient had ankylosing spondylitis and had been on ADA, 40 mg every 21 days, and methotrexate (MTX), 10 mg/week, for one year. On physical examination, an ulcer was observed on the lateral face of her right leg, with erythematous, elevated and well-defined margins, granulomatous base, and measuring 1.5 cm of diameter (Figure 1). The rest of her physical examination showed no other changes.

Her tuberculin skin test showed non-reactive purified protein derivative, and the Montenegro test evidenced a 12-mm reaction (reactions greater than 5 mm are considered positive). The direct search for Koch's bacillus and *Leishmania*, as well as the cultures for mycobacteria and fungi, were negative. The histopathology of the lesion showed exuberant granulation tissue. The other exams, such as electrocardiography, echocardiography, blood cell count, and renal and hepatic functions, showed no changes.

Based on the epidemiology, the aspect of the ulcer and the positive Montenegro test, the diagnosis of ATL was established. The use of ADA and MTX was suspended, and pentavalent antimony (Glucantime®) started. After 30 days of use, complete regression of the lesion occurred, leaving an atrophic scar on the site.



**Figure 1**  
Chronic ulcer in the right leg, diagnosed as American tegumentary leishmaniasis.

## DISCUSSION

TNF- $\alpha$  is a cytokine with an important role in the host defense against *Leishmania* species infection. Those protozoa are obligate intracellular parasites of macrophages, and the infection control requires the activation of those cells and formation of granulomas.<sup>1,2,7,8</sup> Most pathogens induce a rapid increase in the production of the cytokine in a host's attempt to control infection. The anti-TNF therapy impairs that initial response, increasing susceptibility and reducing the ability to fight infections such as leishmaniasis.<sup>2</sup> In a study with mice infected with *Leishmania major*, the presence of anti-TNF antibodies was related to both an important reduction in the leishmanicidal activity of macrophages, and the development of larger cutaneous lesions.<sup>7</sup> TNF is implicated not only in inducing the formation of granulomas, but also in maintaining them, which can explain the participation of the anti-TNF- $\alpha$  therapy in the reactivation of granulomatous diseases.<sup>8</sup>

The cases of cutaneous leishmaniasis in patients on biologics reported in the literature are few. A search in the PubMed/MEDLINE database evidenced six cases of ATL related to that therapy: three patients were on infliximab (IFX)<sup>2,4,6</sup> and the other three were on ADA.<sup>8-10</sup> No article relating etanercepte (ETN) to that clinical presentation of leishmaniasis has been found. The association with the visceral form, however, has been more widely reported.<sup>4</sup>

Considering the important role of TNF- $\alpha$  in the body's defenses, the major adverse effects expected in patients receiving anti-TNF therapy are infections.<sup>6</sup> Several randomized clinical trials have concluded that the use of agents such as IFX and ADA results in an increased risk for infections.<sup>5</sup> The risk of developing opportunistic infections seems to be greater in the first year of treatment, especially in the first months,<sup>3,5</sup> with a tendency towards more infectious complications in patients using IFX as compared with those on either ADA or ETN.<sup>5</sup> Atypical manifestations, disseminated forms and paradoxical reactions to treatment are the most common clinical presentations of opportunistic infections in those patients.<sup>3</sup>

Despite the use of those drugs, our patient developed response to the Montenegro test and responded well to the treatment with Glucantime®, having neither disseminated nor relapsing cutaneous lesions – that is, apparently, those drugs have not changed the natural course of the disease. Healthy individuals can also develop ATL when traveling to endemic areas. Thus, we believe that, in the present case, there was no association between the use of the anti-TNF therapy and the appearance of the ulcer. New studies, however, are required to better clarify the existence of that relationship.

Unfortunately, the vaccination against leishmaniasis is not systematic, although effective vaccines have been reported.<sup>11-13</sup> Thus, general measures are recommended when traveling to endemic areas, such as the use of repellents and clothes covering larger areas of skin, avoiding exposure during the times of the vector's activity (twilight and night).<sup>1</sup>

Although a positive epidemiology does not contraindicate the use of drugs such as ADA, a strict follow-up should be maintained in those cases. So far, there has not been enough evidence to support the search for leishmaniasis in the screening for the treatment with biologics.

## REFERENCES

1. Ministério da Saúde. Manual de vigilância da leishmaniose tegumentar americana. Brasília, DF, Brasil. 2007. [Accessed at: 05/02/2011]. Available from: [http://portal2.saude.gov.br/portal/arquivos/pdf/manual\\_Ita\\_2ed.pdf](http://portal2.saude.gov.br/portal/arquivos/pdf/manual_Ita_2ed.pdf).
2. Mueller MC, Fleischmann E, Grunke M, Schewe S, Bogner JR, Löscher T. Relapsing cutaneous leishmaniasis in a patient with ankylosing spondylitis treated with infliximab. *Am J Trop Med Hyg* 2009; 81(1):52–4.
3. Garcia-Vidal C, Rodríguez-Fernández S, Teijón S, Esteve M, Rodríguez-Carballeira M, Lacasa JM *et al.* Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. *Eur J Clin Microbiol Infect Dis* 2009; 28(4):331–7.
4. Xynos ID, Tektonidou MG, Pikazis D, Sipsas NV. Leishmaniasis, autoimmune rheumatic disease, and anti-tumor necrosis factor therapy, Europe. *Emerg Infect Dis* 2009; 15(6):959–9.
5. Martin-Mola E, Balsa A. Infectious complications of biologic agents. *Rheum Dis Clin North Am* 2009; 35(1):183–99.
6. Hakimi S, Rivière S, Del Giudice P, Dereure J, Le Quellec A. Localized Cutaneous Leishmaniasis due to *Leishmania infantum* in a patient Treated with Infliximab. *Dermatology* 2010; 220(1):63–5.
7. Liew FY, Parkinson C, Millott S, Severn A, Carrier M. Tumour necrosis factor (TNF $\alpha$ ) in leishmaniasis. I. TNF  $\alpha$  mediates host protection against cutaneous leishmaniasis. *Immunology* 1990; 69(4):570–3.
8. Franklin G, Greenspan J, Chen S. Anti-tumor necrosis factor- $\alpha$  therapy provokes latent leishmaniasis in a patient with rheumatoid arthritis. *Ann Clin Lab Sci* 2009; 39(2):192–5.
9. Baltà-Cruz S, Alsina-Gibert M, Mozos-Rocafort A, Cervera C, Colomo-Saperas L, Del Río A *et al.* Pseudolymphomatoid cutaneous leishmaniasis in a patient treated with adalimumab for rheumatoid arthritis. *Acta Derm Venereol* 2009; 89(4):432–3.
10. Schneider P, Bouaziz JD, Foulet F, Duong TA, Allanore LV, Bagot M. Multifocal cutaneous leishmaniasis due to *Leishmania infantum* under adalimumab therapy. *Ann Dermatol Venereol*. 2009; 136(11):815–6.
11. Llanos-Cuentas A, Calderón W, Cruz M, Ashman JA, Alves FP, Coler RN *et al.* A clinical trial to evaluate the safety and immunogenicity of the LEISH-F1+MPL-SE vaccine when used in combination with sodium stibogluconate for the treatment of mucosal leishmaniasis. *Vaccine* 2010; 28(46):7427–35.
12. Sukumaran B, Madhubala R. Leishmaniasis: current status of vaccine development. *Curr Mol Med* 2004; 4(6):667–79.
13. Mayrink W, Williams P, da Costa CA, Magalhães PA, Melo MN, Dias M *et al.* An experimental vaccine against American dermal leishmaniasis: experience in the State of Espírito Santo, Brazil. *Ann Trop Med Parasitol* 1985; 79(3):259–69.