Journal of Clinical & Experimental Dermatology Research

Aquino et al., J Clin Exp Dermatol Res 2014, 5:6
DOI: 10.4172/2155-9554.1000245

Case Report open access

First Case Report of Cutaneous Leishmaniasis Caused by *Leishmania (Leishmania) infantum* in a Brazilian Patient Treated with Adalimumab

Thaíssa Araújo Aquino[1], Sofia Sales Martins[1], Ciro Martins Gomes[1,2], Jorgeth de Oliveira Carneiro da Motta[1,3], Daniel Graziani[3], Amanda da Mota Silveira Rodrigues[4], Rayane Marques Cardoso[4], Beatriz Dolabela de Lima[5] and Raimunda Nonata Ribeiro Sampaio[1-3*]

[1]*Hospital University of Brasilia, University of Brasilia, Brasilia, DF, Brazil*
[2]*POS graduate of Medical Sciences, Laboratory of Dermatology, Faculty of Medicine, University of Brasília, Brasília, DF, Brazil*
[3]*POS graduate of the Faculty of Sciences, University of Brasília, Brasília Health, DF, Brazil*
[4]*Faculty of Medicine, University of Brasília, Brasília, DF, Brazil*
[5]*Laboratory of Gene Biology, Department of Cell Biology, Institute of Biological Sciences, University of Brasília, Brasília, DF, Brazil*

Received date: August 22, 2014, **Accepted date:** October 14, 2014, **Published date:** October 21, 2014

[*]**Corresponding author:** Raimunda Nonata Ribeiro Sampaio, Faculty of Medicine, University of Brasília, SHIS QI 25 Conj 2, Casa 1, Lago Sul, Brasília, DF, Brazil, Tel: +55618121 6100; E-mail: raimunda.sampaio@gmail.com

Abstract

Leishmania (Leishmania) infantum is the main etiologic agent of visceral leishmaniasis in American continent. We report a rare case of cutaneous leishmaniasis caused by viscerotropic specie in a patient with ankylosing spondylitis on treatment with adalimumabe and methotrexate. The patient presented no signs of visceral involvement. PCR-RFLP and genetic sequencing demonstrated *Leishmania (Leishmania) infantum*. The patient was treated with N-methyl-glucamine (20 mgSbV/kg/day) for 20 days. Despite of interruption of treatment due to elevation of transaminases (TGO 48 U/L and TGP 62 U/L) for a week, the lesions healed completely.

Leishmania infection in patients who are on anti-TNF alpha treatment has to be remembered as an opportunistic disease associated with immunosuppression caused by biological therapies, especially in endemic countries. We consider that the use of immunosuppressive drugs may lead to atypical cases of cutaneous leishmaniasis even by viscerotropic agents.

Keywords: Cutaneous leishmaniasis; Mucocutaneous leishmaniasis; *Leishmania (Leishmania) infantum*; Immunosuppressive agents; Tumor necrosis factor-alpha

Case Report

A 38-year-old male patient from Minas Gerais, Brazil, suffering from ankylosing spondylitis and psoriasis who was been treated with methotrexate (15 mg per week) and adalimumab (40 mg every other week) developed three ulcers on his left arm after two years of treatment (Figure 1).

No other symptoms such as fever or weight loss were reported. The physical examination revealed no mucous lesions or hepatosplenomegaly. The blood count, electrolytes, liver and kidney function tests were normal. The leishmanin skin test was positive (19×9 mm) and parasite culture in Novy-Mac Neal-Nicolle (NNN) medium was positive for *Leishmania.* Indirect immunofluorescence was negative. *Leishmania (Leishmania) infantum* was identified by PCR-RFLP from the patient's skin biopsy sample, which was confirmed by direct sequencing of the PCR product. HIV serology was negative. Histopathological examination showed lymphohistiocytic infiltrate with granulomas (Figure 2).

The patient was treated with N-methyl-glucamine (20 mgSbV/kg/day) for 20 days with interruption of adalimumab and methotrexate during therapy (Figure 3). Although the treatment was discontinued for a week, due to elevation of transaminases (TGO 48 U/L and TGP 62 U/L) the lesions presented clinical cure after the end of therapy.

Discussion

In the Northern region of Brazil more than 90% of the Cutaneous Leishmaniasis (CL) are caused by *Leishmania* (Viannia) *guyanensis* and in other regions 80% by *Leishmania* (Viannia) *braziliensis* and 20% by *Leishmania* (Leishmania) *amazonensis* [1,2]. The patient is from the northern region of the state of Minas Gerais where *Leishmania* (Viannia) *braziliensis* is the main causative agent of CL and it is also an endemic area of visceral leishmaniasis (VL) caused by *Leishmania* (Leishmania) *infantum*. In the Americas *Leishmania* (Leishmania) *infantum* also known as *Leishmania* (Leishmania) *chagasi* is the most commonly species involved in cases of VL and has been occasionally associated with manifestations of CL. These cases are classified as post-kala-azar dermal *leishmaniasis* that usually occurs after treatment of VL as non-ulcerated papular lesions all over the skin, and rarely as the first manifestation of VL. To date no Brazilian cases of isolated cutaneous lesions caused by viscerotropic *Leishmania* species had been reported.

The fact that *Leishmania* (Leishmania) *infantum* may cause isolated CL suggests that immune response is crucial to determine the course of infection [3]. Studies have demonstrated that viscerotropic species in Honduras and the Mediterranean region showed low sensitivity to the action of complement, high infectivity and survival in macrophages when compared to dermotrophic strains [4]. The size of the inoculum and the inoculation route also appear to be important in the clinical spectrum of the disease [4]. High levels of intravenously inoculum were associated with visceralization by *Leishmania* (Leishmania) *infantum* strains in BALB/c mice genetically susceptible [4].

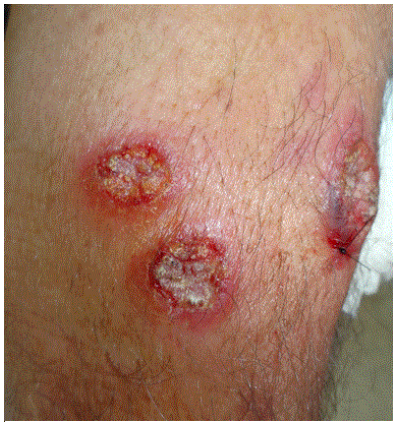

Figure 1: Ulcers caused by *L.* (L.) *infantum* before treatment with pentavalent antimony

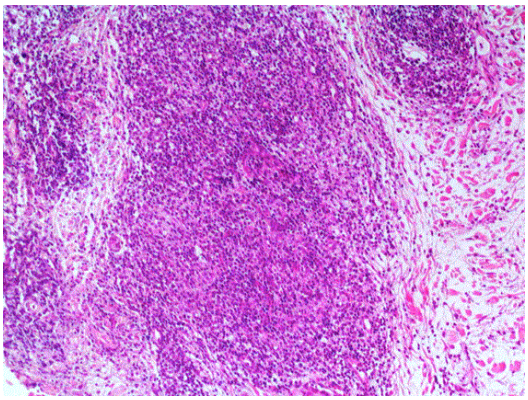

Figure 2: Histopathological examination showed lymphohistiocytic dermal infiltrate with granulomas

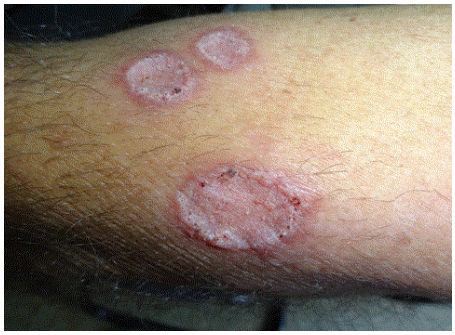

Figure 3: The ulcers caused by Leishmania (Leishmania) infantum during the treatment with pentavalent antimonal

The use of anti-TNF alpha to treat cutaneous disorders such as psoriasis has become increasingly common. The aim of this strategy is to reduce cutaneous immunologic response and heal inflammatory lesions. This kind of therapy is associated with opportunistic infections especially those where granuloma formation plays an important role in the host defense, such as cutaneous tuberculosis and leishmaniasis [4]. Cases reported in Spain of patients treated with adalimumab who developed CL and studies on the immunopathogenesis of the disease suggest that the formation of granulomas in these patients may be related to the induction of Th17 immune response and activation of Toll-like receptor-9 (TLR9) by Leishmania [5].

Despite the Th1 response is classically associated with protection against *Leishmania* recent studies showed that the production of cytokines related to Th17 lymphocyte activation also appears to be protective [6-8]. The Th17 cells are CD4+ T lymphocytes that produce pro-inflammatory IL-17 primarily by inducing the expression of several inflammatory mediators, and recruitment of neutrophils [9]. Experimental models have shown that a pro-inflammatory action is related to defence against a variety of infectious diseases [7,10,11]. Dendritic cell sand macrophages are capable of responding to IL-17 stimulation with increased production of IL-12, IFN-gamma and nitric oxide, leading to killing of intracellular pathogens [12].

Several aspects of the initial steps of the immune response after Leishmania infection are unknown. The signaling pathway of Toll-like receptors (TLRs) is one of the first systems of defense against *Leishmania* [13,14]. After the recognition of specific pathogen associated molecular patterns (PAMPs), TLRs trigger the NF-ΚB releasing which passes into the nucleus and promotes the transcription and synthesis of pro-inflammatory cytokines [13,14].

Recently, TLR9 has been described in a higher proportion in the granulomas produced by *Leishmania* (Viannia) *braziliensis* and it was concluded that TLR9 is important to develop and maintain the granulomas [5,13]. It is likely that *Leishmania* DNA fragments can bind to TLR9 in macrophages and dendritic cells, activating them and acting, as described in mycobacteria, causing pulmonary granulomatous response in rat models [5]. TLR9 could regulate Th17 activation and increase the secretion of IL-17A promoting the formation and maintenance of granulomas mediated by neutrophils [5].

We described a case of CL without visceral manifestation caused by *Leishmania* (Leishmania) *infantum* with formation of granulomas in a patient using anti-TNF alpha and methotrexate, both immunosuppressive drugs. In this case, the absence of visceralization could be explained by the presence of cellular immunity demonstrated by the positivity of leishmanin skin test, the granulomatous infiltrate in the histopathological examination and adequate response to the treatment [15]. Cases of CL worsened or triggered during the use of corticosteroids and immunosuppressive drugs such as methotrexate are frequent, however, in the present case the biological therapy may have been the main factor triggering the disease, since it is clearly associated with an increased risk of infections. We strongly believe that this patient was carrying on an unapparent infection by *Leishmania* (Leishmania) *infantum* and that anti-TNF alpha had been the trigger for the clinical manifestation of the disease.

To our knowledge this is the first report of human CL caused by Leishmania (Leishmania) infantum without visceral manifestation in Brazil, with only preceding canine VL-associated CL and atypical cases of CL by viscerotropic species [16].

Conclusion

Leishmania infection in patients treated with anti-TNF alpha has to be remembered as an opportunistic disease associated with biological therapies, especially in endemic countries. The role of anti-TNF alpha to CL by viscerotropic species is unclear.

References

1. Name RQ, Borges KT, Nogueira LSC, Sampaio JHD, Tauil PL, et al. (2005) Clinical, epidemiological and therapeuthic study of 402 patients with American cutaneous leishmaniasis seen at University Hospital of Brasilia, DF, Brazil. An Bras Dermatol 80: 249-254.
2. Department of Epidemiological Surveillance (2007) Manual for the Surveillance of American Cutaneous Leishmaniasis/ Ministry of Health. Secretariat of Health Surveillance. Department of Epidemiological Surveillance. (2nd Edn), Publishing House of the Ministry of Health, Brazil.
3. Belli A, García D, Palacios X, Rodriguez B, Valle S, et al. (1999) Widespread atypical cutaneous Leishmaniasis caused by Leishmania (L.) Chagasi in Nicaragua. Am J Trop Med Hyg 61: 380-385.
4. Campos-Ponce M, Ponce C, Ponce E, Maingon RDC (2005) Leishmania chagasi/infantum: further investigations on Leishmania tropisms in atypical cutaneous and visceral leishmaniasis foci in Central America. Exp Parasitol 109: 209-219.
5. Romero-Maté A, Martínez-Sánchez D, Tardío JC, Amalia Moreno-Torres A, García-Donoso C, et al. (2012) Cutaneous leishmaniasis with histopathologic pattern of on necrotizing granulomatous dermatitis in patients treated with adalimumab. Dermatol Online J 18: 7.
6. Liew FY, Parkinson C, Millott S, Severn A, Carrier M (1990) Tumor Necrosis factor (TNF alpha) in leishmaniasis. I. TNF alpha mediates host protection against cutaneous leishmaniasis. Immunol 69: 570-573.
7. Pitta MG, Romano A, Cabantous S, Henri S, Hammad A, et al. (2009) IL-17 and IL-22 are associated with protection against human kala azar caused by Leishmania donovani. Invest 119: 2379-2387.
8. Novoa R, Bacellar O, Nascimento M, Cardoso TM, Ramasawmy R, et al. (2011) IL-17 and Regulatory Cytokines (IL-10 and IL-27) in L. braziliensis Infection. Parasite Immunol 33: 132-136.
9. Kumar R, Nylén S (2012) Immunobiology of visceral leishmaniasis. Front Immunol 3: 251.
10. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, et al. (2009) Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med 206: 299-311.
11. da Matta Guedes PM, Gutierrez FR, Maia FL, Milanezi CM, Silva GK, et al. (2010) IL-17 produced during Trypanosoma cruzi infection plays a central role in regulating parasite-induced myocarditis. PLoS Negl Trop Dis 4: e604.
12. Cunha FQ, Assreuy J, Xu D, Charles I, Liew FY, et al. (1993) Repeated induction of nitric oxide synthase and leishmanicidal activity in murine macrophages. Eur J Immunol 23: 1385-1388.
13. Tuon FF, Fernandes ER, Pagliari C, Duarte MI, Amato VS (2010) The expression of TLR9 in human cutaneous leishmaniasis is associated with granuloma. Parasite Immunol 32: 769-772.
14. Tuon FF, Amato VS, Bacha HA, Almusawi T, Duarte MI, et al. (2008) Toll-like receptors and leishmaniasis. Infect Immun 76: 866-872.
15. Wilson ME, Jeronimo SM, Pearson RD (2005) Immunopathogenesis of infection with the visceralizing Leishmania species. Microb Pathog 38: 147-160.
16. Cavalcanti A, Lobo R, Elisa Cupolillo E, Bustamante F, Porrozzi R (2012) Canine cutaneous leishmaniasis caused by neotropical Leishmania infantum despite of systemic disease: a case report. Parasitol Int 61: 738-740.