Anti-Tumour Necrosis Factor-Induced Visceral and Cutaneous Leishmaniasis: Case Report and Review of the Literature

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**Key Words**
Cutaneous leishmaniasis · Leishmaniasis · Adalimumab · Anti-tumour necrosis factor · Tumour necrosis factor-α · Rheumatoid arthritis · Liposomal amphotericin · Pentavalent antimonials

**Abstract**

**Background:** Leishmaniasis is a chronic protozoan disease in which organisms are found within phagolysosomes of the mononuclear phagocyte system. There are three major forms: cutaneous, mucocutaneous and visceral. We report the first case of visceral leishmaniasis with cutaneous involvement in a patient with rheumatoid arthritis treated with the anti-tumour necrosis factor (anti-TNF) adalimumab. **Objective:** To highlight cutaneous leishmaniasis as the first indicator of a kala-azar disease in a patient treated with anti-TNF and to review the literature on leishmaniasis in the context of anti-TNF therapy.

**Case Report:** A 59-year-old woman was referred to our dermatology department for evaluation of a plaque on the right elbow of 1 year’s duration. She had rheumatoid arthritis, which had been treated with adalimumab (40 mg/15 days) for 34 months after the initiation of adalimumab. A cutaneous biopsy showed intracellular amastigotes. No Leishmania parasites were observed in a bone marrow aspirate, but laboratory tests showed anaemia and impaired liver function, abdominal ultrasonography showed hepatomegaly, and ELISA serology was strongly positive for Leishmania antibodies in serum and urine. Adalimumab was withdrawn and treatment combining intraleosional pentavalent antimonials and liposomal amphotericin was started. Eight weeks later, the leishmaniasis had resolved.

**Conclusion:** A skin biopsy disclosing leishmaniasis should prompt tests to rule out visceral leishmaniasis, especially in an area such as the Mediterranean where the prevalence of latent Leishmania infection is high.

**Introduction**

Leishmaniasis is a chronic protozoan disease of the mononuclear phagocytic system [1]. Leishmania spp. is endemic in southern Europe along the Mediterranean coasts. Leishmania infection can be localized to the skin (cutaneous leishmaniasis, CL) and mucous membranes (mucosal leishmaniasis, ML), or disseminated in the reticuloendothelial system (visceral leishmaniasis, VL) [2]. Tumour necrosis factor-α (TNF-α) has an important role in the host defence against infection by Leishmania spp. [3, 4]. Anti-tumour necrosis factor (anti-TNF) biologic agents are very effective treatments for several immune-mediated diseases and may increase the risk of reactivation or dissemination of granulomatous infections [5]. We report a case of VL with cutaneous involvement in a patient with rheumatoid arthritis treated with adalimumab and review previous reports of leishmaniasis in association with anti-TNF treatment.

**Case Report**

A 59-year-old woman was referred to our dermatology department for evaluation of a plaque on the right elbow of 1 year’s duration. She had rheumatoid arthritis, which had been treated with adalimumab (40 mg/15 days) for 34 months and previously with methotrexate for 1 year. She lived in an endemic area of leishmaniasis on the Catalan coast and explained that she had had a dog which had died of leishmaniasis 30 years earlier. Since then she had kept no pets and she had never travelled abroad. Skin examination revealed a well-circumscribed plaque with an erythematous border and a central crust on the right elbow (fig. 1). No other skin lesions could be seen. Physical examination showed no hepatosplenomegaly and the patient was afebrile.

A Giemsa-stained biopsy of the plaque showed intracellular amastigotes with peripheral nuclei. This histologic finding, together with the clinical picture, was con-
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Discontinued and the elbow plaque was initially treated with intralesional pentaximun. Upon making the diagnosis of VL, liposomal amphotericin B was started at a dose of 4 mg/kg for 7 days. The patient received additional doses of liposomal amphotericin B (4 mg/kg/week) for 4 weeks. This led to a rapid regression of the skin lesion within 8 weeks and resolution of alterations in laboratory parameters. Subsequently, a flare of rheumatoid arthritis occurred, and after full discussion with the patient about the risks of leishmaniasis reactivation, treatment with adalimumab was restarted. No relapse of either CL or VL has been observed after 24 months of follow-up.

Discussion

Leishmaniasis is a chronic disease of the mononuclear phagocytic system caused by more than 15 species of Leishmania. Leishmania spp. is endemic in several regions of the world, including the Mediterranean area. In the Alicante region in Spain, around 10% of children and 50% of adults have a positive leishmanin skin test [6], and 20% of these individuals are asymptomatic carriers with parasitaemia. There are three major forms of leishmaniasis: CL, which is restricted to the skin, ML, which affects both the skin and mucosal surfaces, and VL, which affects the organs of the mononuclear phagocyte system, e.g. the liver and spleen [7]. VL is a systemic disease characterized by hepatosplenomegaly, fever, cachexia, pancytopenia, hypergammaglobulinaemia and ultimately death if the disease goes untreated [8]. The diagnosis of VL is based on identification of the parasite in bone marrow or splenic aspirate smears, the detection of significant levels of anti-leishmanial antibodies by serological techniques [9] or the detection of Leishmania DNA by a polymerase chain reaction [10]. The incubation period is usually long, from 1 to 3 months, but it may be as short as 10–14 days. Under conditions of immunosuppression, however, there is evidence of activation of latent infection several years after exposure to the parasite [11, 12]. Nevertheless, asymptomatic leishmanial infection that is not well defined, but is usually ascertained by a positive serological test, polymerase chain reaction or leishmanin skin test, can be detected in individuals who are otherwise in a healthy condition [13].

TNF-α is a proinflammatory cytokine produced by macrophages, monocytes and T lymphocytes that is involved in both the pathogenesis of several inflammatory diseases and the immune-mediated response to several infections [3], including leishmaniasis [4]. Herein we report a case of VL triggered by anti-TNF therapy in a patient with rheumatoid arthritis. Anti-TNF biologic agents are indicated for the management of immune-mediated diseases such as rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease and moderate-to-severe psoriasis. Since anti-TNF biologic agents entered the market at the end of the 1990s their use has increased, but growing numbers of cases of opportunistic infections, including leishmaniasis, have been reported [5]. In a study with mice infected with Leishmania major, the presence of anti-TNF was related to both an important reduction in the leishmanicidal activity of macrophages and the development of larger cutaneous lesions [14].

The first instance suggestive of an association between anti-TNF agents and leishmaniasis was reported in 2004. Since then, 37 cases (including ours) of anti-TNF-induced leishmaniasis have been reported (online supplementary table 1, see www.karger.com/doi/10.1159/000370238) [15–45]. All patients were living in or had travelled to leishmaniasis-endemic areas. 14 (37.8%) patients were men and 23 (62.2%) were women. Their median age was 51.5 years (range 7–77 years). 20 patients developed VL (54.1%), 15 CL (40.5%) and 6 ML (16.2%). Only 2 patients (5.4%), including ours, developed VL and CL simultaneously. At the time the diagnosis of leishmaniasis was made, most patients had been treated or were treated with one or more standard immunosuppressive agents, including corticosteroids (24/37 [64.9%]), methotrexate (26/37 [70.3%]), cyclospo-
rine (3/37 [8.1%]) and azathioprine (1/37 [2.7%]). Two patients (2/37 [5.4%]) had been treated with a recombinant interleukin-1 receptor antagonist (anakinra) and one patient (1/37 [2.7%]) with leflunomide. 16 of 37 (43.2%) patients were taking or had taken adalimumab, 20 of 37 (54.1%) infliximab and 5 of 37 (13.5%) etanercept. In 4 patients of 37 (10.8%) biologic treatments had been discontinued before the diagnosis of leishmaniasis. The onset of anti-TNF-induced leishmaniasis varied from 15 days to 72 months after the start of immunosuppressive treatment.

Most patients with VL presented with the classic symptoms of fever, cachexia, splenomegaly, hypergammaglobulinemia and pancytopenia. A diagnosis was most often made by isolating amastigotes from bone marrow, but interestingly, some cases, such as our patient, required more than one bone marrow biopsy or the detection of significant levels of antileishmanial antibodies for a diagnosis of VL.

In patients diagnosed with VL or ML, 20 of 26 (76.9%) were treated with liposomal amphotericin B and 6 of 26 (23.1%) with pentavalent antimonials. Pentavalent antimonials were the mainstay of therapy in patients with CL. Only one patient died in the context of the treatment of leishmaniasis that had been diagnosed during treatment with anti-TNF [20]. Two patients (who were maintained on infliximab treatment) experienced recurrent ML [23, 29]. Anti-TNF treatment was restarted after successful treatment of leishmaniasis in 18 of 37 patients (48.6%): in 5 of 18 (27.8%) infliximab was switched to etanercept and to adalimumab in one (5.6%), 8 of 18 patients (44.4%) were retreated with adalimumab, and in 4 of 18 (22.2%) treatment with infliximab was restarted. All 18 patients remained free of disease. Only in one patient were results of tests for antibodies against Leishmania spp. available before immunosuppressive therapy was begun [23], and they were negative.

This review shows that patients receiving anti-TNF therapy in endemic areas might have an elevated risk not only for VL, but also for CL and ML. Our case shows that CL may occasionally be complicated by VL, thus exhaustive exploration is needed to rule out visceral involvement in the context of impaired immunity. Furthermore, this raises the issue of a possible atypical presentation in patients treated with anti-TNF, probably due to the lack of impairment of an effective inflammatory response.

From a biologic point of view, the risk of leishmaniasis by type of anti-TNF therapy might be explained by marked differences in the mode of action of the various biologic agents, even though relative incidence data are lacking. Our observation that the number of reports of opportunistic leishmaniasis in patients treated with etanercept is lower than with monoclonal antibodies parallels the registry-based evidence with other infectious complications and might be biologically plausible, since this compound primarily targets soluble TNF-α [46, 47], unlike adalimumab and infliximab, which target both soluble and transmembrane TNF-α.

Physicians should enquire into a possible antecedent of leishmaniasis in immunosuppressed patients with a high risk of exposure (having travelled to or living in an endemic area). Serological screening should also be considered to detect latent disease and prevent its reactivation, and patients should be closely monitored for signs and symptoms of a new infection acquired during biologic treatment.

The main limitation of this study is that cases of leishmaniasis associated with anti-TNF are probably underreported and thus our conclusions are likely to underestimate the true magnitude of this relationship. Furthermore, with the exception of one case, it is unclear whether leishmaniasis was a primary infection or reactivation of latent disease. Lastly, we cannot exclude a potential confounding effect of underlying disease-associated immunosuppression and exposure to other immunosuppressants that might obscure the relative risk of leishmaniasis associated with the different anti-TNF agents. The relative risk of leishmaniasis can only be ascertained by registry studies.

**Conclusion**

We report the first case of CL and VL appearing in the course of adalimumab treatment in a patient with rheumatoid arthritis. This case provides further evidence regarding an increased risk of patients receiving TNF-blocking agents, not only for VL, but also for CL and ML. Every effort should be made in immunosuppressed patients with CL to rule out visceral involvement, especially in areas with a high prevalence of latent leishmaniasis infection, such as the Mediterranean region.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

**References**


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