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Visceral leishmaniasis infection in a rheumatoid arthritis patient treated with infliximab

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ABSTRACT

Anti-TNFα strategies can result in significant clinical benefits in rheumatoid arthritis (RA), but with an increased rate of opportunistic infections. Visceral leishmaniasis (VL) is a severe disease that can develop in immunocompromised hosts, principally in HIV patients. VL in RA patients treated with TNFα antagonists is an extremely rare event, and only one case has been described. Here we report a case of VL, occurring after 9 infusions of infliximab in association with azathioprine, in a patient who developed blood cytopenia, fluctuant fever, and splenomegaly.

Introduction

Anti-TNFα strategies have had a marked impact in the treatment of RA, demonstrating efficacy in reducing disease activity and in retarding radiographic progression. In general, the benefit/risk ratio is quite favourable, however higher incidence of serious adverse events has been described. Infections, particularly tuberculosis and opportunistic infections, are among the most serious adverse events, especially given delays in diagnosis due to subtle or atypical presentation (1-3). Visceral leishmaniasis (VL) is a severe disease that can develop in immunocompromised hosts, principally in HIV patients (4). VL is an extremely rare event in RA patients treated with TNFα antagonists, and only one case has been described (5, 6). Here we report a case of VL, occurring after the 9th infusion of infliximab in association with azathioprine, in a patient who developed blood cytopenia, fluctuant fever, and splenomegaly

Case report

A 53-year-old Caucasian woman, living in the Cevennes area (south of France), with RA (diagnosed in 1999) was treated with infliximab (3mg/Kg) for one year along with azathioprine (100mg/day) and corticosteroids. The RA disease was no longer active once the anti-TNFα treatment was started, however, after the 9th infusion of infliximab she had night sweats and moderate asthenia.

Laboratory test analysis showed a C-reactive-protein of 51, an erythrocyte sedimentation rate of 59, and a pancytopenia (haemoglobin: 10g/dl, WBCs: 2,400, and PLTs:114,000). During hospitalisation she presented a fluctuant fever with several peaks at 40°C. Physical examination revealed a splenomegaly with no hepatomegaly. Bone marrow examination (smear and core biopsy) revealed a non-specific reactive lymphoid infiltration with no myelodysplasia. A CT scan revealed a heterogeneous splenomegaly with infarcts.

Finally, after a second bone marrow aspiration, the direct examination of May-Grunwald-Giemsa stained smears detected *Leishmania* parasites, and serology was positive [IFAT: 1/5120 (cut off: 1/80); ELISA: 2.33 (cut off: 0.32)]. The positive polymerase chain reaction of blood and bone marrow confirmed diagnosis. Cultures on Novy, MacNeal, and Nicolle medium (NNN) and biochemical characterization of the *Leishmania* isolates by isoenzymatic electrophoresis identified *Leishmania infantum* MON-1. Infliximab and azathioprine treatments were withdrawn.

The patient was treated intravenously with amphotericin B, first 0.7 mg/kg/day for 15 days, then 0.7mg/kg every 15 days for four months (cumulative dose of 15.4mg/kg). She did not develop any adverse events and after 15 days of treatment, the PCR of blood and bone marrow no longer revealed parasites; bone marrow cultures were negative 2.5 months later. Five months after infliximab was stopped, we started etanercept (25mg x 2/week) because of important polarthritis' symptoms. Currently, no further clinical or biological symptoms of leishmaniasis were detected.

Discussion

Leishmaniasis is a parasitic disease caused by the transmission, in endemic areas, of the promastigote stage of the protozoan *Leishmania* from wild or domestic reservoirs (usually canine in the Mediterranean basin) to other mammals by sandfly bites. *Leishmania* spp. are obligate intraphagocytic micro organisms of the mononuclear phagocytic system. Unless the micro organ-

ism is eliminated by immune mechanisms, the parasite multiplication within the phagolysosome gives rise to clinical symptoms. Experimentally, the protozoan parasite *Leishmania major* infects the mononuclear phagocytes, and infection control depends on adequate activation of the infected macrophages to kill parasites and inhibit their replication (7). *In vitro* studies with murine macrophages revealed that soluble factors secreted by activated T cells mediate the activation of macrophages to produce nitric oxide (NO), resulting in killing or controling *L. major* parasites (8). Macrophage activation by soluble factors (cytokines) depends on gamma interferon (IFN-γ) as well as tumor necrosis factor (TNF) (9, 10).

In humans, the *leishmania* disease includes visceral, cutaneous, and mucocutaneous forms. Usually parasites of *L. infantum* complex are prone to induce a visceral form of the disease, and less frequently, cutaneous forms. Immunosuppression facilitates the diffusion of the parasite, and the clinical picture is worsened (11). Diagnosis relies on the detection of the parasite in bone marrow smears, in the culture of blood or bone marrow on NNN medium, and with the polymerase chain reaction of blood and bone marrow. *Leishmania* is characterized by isoenzymatic electrophoresis.

Only one case of VL has been reported in RA patients treated with TNFα antagonists (infliximab) (5, 14). In our case, the clinical picture was characterized by fever, asthenia, splenomegaly, and pancytopenia. Also, inflammatory markers were increased. Corticosteroids, azathioprine along with infliximab, may have played a permissive role. With an appropriate treatment the *Leishmania* infection was controlled (12). Four months following infection clearance, TNFα antagonists (etanercept) was started with clinical and biological follow-up. The patient was treated for one year with etanercept and no signs of VL had been detected.

The Cevennes area, where she lived, is a well known focus of VL (11, 13). Due to the low incidence rate of this disease it is difficult to propose a screening for leishmaniasis before treating with biologics. However, for patients with a high risk of exposure (living in an endemic area) we should screen the patient with serology. Indeed, the disease could be due to the reactivation of a latent infection induced by immunosuppressive drugs or to a recent infection. Moreover, in these areas medical teams should be informed of this risk.

Conclusion

To our knowledge, this is the second case of VL reported in a patient treated with TNFα antagonist. This confirms the risk of opportunistic infections and the difficulties of diagnosis in these immunosuppresed patients. Although pancytonia or thrombocytopenia could be due to a haematological form of lupus or rheumatoid arthritis, dysplasia and lymphoma, or side effects of methotrexate or other drugs, the association of fever, asthenia, hepatosplenomegaly, and pancytopenia should prompt the search for *Leishmania* in patients living in endemic leishmaniasis areas and treated with TNFα antagonists.

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