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Leishmaniasis during anti-tumor necrosis factor therapy: Report of 4 cases and review of the literature (additional 28 cases)

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ABSTRACT

Objective: To describe the development of 4 new cases of leishmaniasis in patients receiving anti-tumor necrosis factor-α (anti-TNF) agents and review the pertinent literature.
Methods: Chart review of the 4 cases and MEDLINE search for additional reported cases.
Results: All reported cases, including ours, came from endemic areas. The infection was detected on an average of 23.5 months after the initiation of anti-TNF therapy. The majority of cases had the classical clinical presentation. The biological therapy was suspended in 21 cases. The results were successful for leishmaniasis therapy in all cases. In 10 cases it was possible to reintroduce anti-TNF agents. On follow-up it was observed that there was an infection relapse in 3 cases.
Conclusions: The present study shows that leishmaniasis, in its several clinical forms, should be included in the differential diagnosis of possible infections involving patients under use of aTNF therapy. Endemic disease under geographic expansion, easy international displacement and intense human migratory flows certainly represents a risk of this infection in an increasing universe of people which includes the immunosuppressed patients. Cutaneous lesions, prolonged fever, splenomegaly, and pancytopenias, the main clinical-laboratory findings of leishmaniasis, can also be present in auto-immune rheumatic disease, thus leading to delayed diagnosis and treatment of the parasitic disease. The diagnosis depends basically on a high suspicion index, being confirmed with the identification of the protozoan. The classic treatment of the infection when instituted is associated with complete recovery. It is important to point out that all cases reported so far had either originated from or been recently in regions regarded as endemic of leishmaniasis.

Introduction

The use of anti-TNF agents, since 1998, represented a turning point in the treatment of inflammatory arthritis, especially rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. However, this pharmacological blockade has been related to a series of adverse events, among which opportunistic infections with intracellular pathogens are prevalent. Mycobacteriosis, deep fungi, viruses and protozoa were described [1,2]. Among the latter, leishmaniasis was initially reported in 2004, and since then has been described in a limited number of cases [3–29]. In our Midwest part of Brazil, 4 new cases were identified within the past 2 years. We describe these cases and extensively review the current literature.

Case reports

Case 1

A 62-year-old man, with rheumatoid arthritis since 05/2006, had been regularly taking prednisone at a dose of 7.5 mg/day, methotrexate at 15 mg/week, and hydroxychloroquine at 400 mg/day. In 05/2007, due to an unsatisfactory clinical response, infliximab was added to the therapeutic regimen, with 3 mg/kg infusions every 2 months, with a rapid control of the articular

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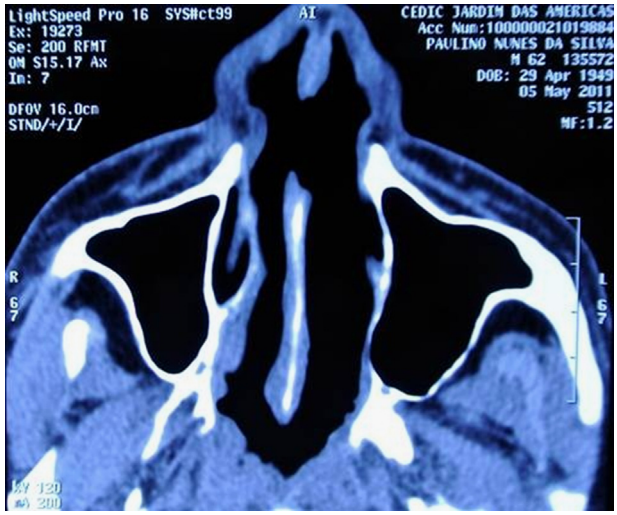

Fig. 1. Nasal septum perforation caused by leishmania in a patient with RA under aTNFa treatment.

inflammatory process. In 05/2011, he presented with nasal obstruction with purulent hemorrhagic discharge, painful swallowing, low fever, anorexia and loss of weight. The physical examination showed no signs of hepatosplenomegaly. At first, only infliximab was suspended. A video nasopharyngoscopy revealed a congested, hyperemic mucosa, with presence of purulent secretion, and perforation of the nasal septum (Fig. 1).

Laboratory workup showed: negative results for nasal secretion smears and cultures for bacteria, fungi and mycobacteria; negative results for Ziehl–Neelsen lymph smears; histopathological examination of nasal septum biopsy revealing dense lymphoplasmocitary infiltrate with lack of parasites; specific intradermal reaction test (Montenegro's intradermal reaction) was positive (10×14 mm); and polymerase chain reaction (PCR) on fragments of nasal septum biopsy was positive for the detection of *Leishmania* genome. The patient lives in a rural area, in the District of Santo Antonio de Leverger, near Cuiaba, State of Mato Grosso, Brazil, an endemic region for leishmaniasis. In 05/2011, after defining the diagnosis of mucocutaneous leishmaniasis, all drugs were suspended, and Glucantime (meglumine antimonate) at a dose of 20 mg/kg/day was begun, for 4 weeks. There was quick recovery in his clinical status, being asymptomatic 6 weeks later. In 08/2011, by reactivation of the articular inflammatory process, all antirheumatic medication was reintroduced (infiximab 3 mg/kg/infusion, methotrexate at 15 mg/week and prednisone at 5 mg/day). In 03/2012, during routine appointment, the patient displayed good general status, asymptomatic, and no recurrence of the parasitic disease.

Case 2

A 29-year-old man with ankylosing spondylitis since 1997, was under regular use of indomethacin at a dose of 50 mg/day, prednisone at 10 mg/day, sulfasalazine at 1.5 g/day and methotrexate at 17.5 mg/week. In 06/2009, as his clinical status worsened, infliximab was added to the therapeutic regimen, at 5.0 mg/kg/infusion every 2 months, obtaining a quick and long-lasting improvement. In 05/2011 he gradually developed fever, myalgias, headache and weight loss. Laboratory examinations showed: pancytopenia (hemoglobin 9.3 g/dL, hematocrit 28%, white cells 2.450/mm^3 with lymphopenia 808/mm^3 and thrombocytopenia 61.000/mm^3), urea (40 mg/mL), creatinine (1.4 mg/dL), alanine aminotransferase (44 U/L), aspartate aminotransferase (63 U/L), alkaline phosphatase (40 U/L), gamma glutamyl transpeptidase (32 U/L), normal total bilirubin, total proteins (8.8 g/dL), albumin (3.3 g/dL) and globulin (5.5 g/dL), C-reactive protein 165.53 mg/L, and erythrocyte sedimentation rate 78 mm/1st hour. Abdominal ultrasound showed splenomegaly (vol. 1467 cm^3). Rapid immunochromatographic test for leishmaniasis was positive. In 06/2011, after defining the diagnosis of visceral leishmaniasis, all antirheumatic drugs were suspended and he was treated with liposomal amphotericin B at 4 mg/day for 5 days, followed by monthly infusions at 4 mg/kg for 3 months. There was a good response to the treatment, and he was asymptomatic after 6 weeks. On 09/2011, the treatment against spondylitis was resumed (prednisone 5.0 mg/day) and adalimumab was introduced (40 mg every 2 weeks). In 03/2012, the patient displayed a good general state, asymptomatic, and was using all the medication prescribed.

Case 3

A 39-year-old man with psoriatic arthritis since 02/2010, was under regular use of prednisone at a dose of 10 mg/day and methotrexate at 25 mg/week. In 07/2010, adalimumab at 40 mg sc every 2 weeks was added to the therapeutic regimen. In 02/2011, after 7 months of regular use, he developed dysphagia, fatigue, nasal secretion and ulcers that, on biopsy, defined the diagnosis of mucocutaneous leishmaniasis. He began Glucantime (meglumine antimonate) at a dose of 20 mg/kg/day for 4 weeks, with clinical improvement and complete recovery. It was elected not to discontinue the aTNF therapy and after 1 year the patient is doing well.

Case 4

A 50-year-old man with psoriatic arthritis since 2002 was submitted to several treatments with little clinical response. In 12/2010 infliximab was started with good response for 6 months. In 06/2011, due to poor clinical response it was switched to adalimumab. In 02/2012, he developed skin lesions on left arm and the diagnosis workup (skin biopsy, Montenegro reaction of 9×19 mm, fragment culture positive for *Leishmania* sp) defined cutaneous leishmaniasis. Anti-TNFa was suspended and Glutantime (meglumine antimonate) was started at a dose of 20 mg/kg/day for 4 weeks, with a rapid clinical recovery. Adalimumab was reintroduced and the patient is doing fine after 12 months.

Literature review

PubMed research was carried out: ((“leishmaniasis, visceral” [MeSH Terms] OR (“leishmaniasis”[All Fields] AND “visceral”[All Fields]) OR “visceral leishmaniasis”[All Fields] OR (“visceral”[All Fields] AND “leishmaniasis”[All Fields])) OR (“leishmaniasis, cutaneous”[MeSH Terms] OR (“leishmaniasis”[All Fields] AND “cutaneous”[All Fields]) OR “cutaneous leishmaniasis”[All Fields] OR (“cutaneous”[All Fields] AND “leishmaniasis”[All Fields])) OR (“leishmaniasis, mucocutaneous”[MeSH Terms] OR (“leishmaniasis”[All Fields] AND “mucocutaneous”[All Fields]) OR “mucocutaneous leishmaniasis”[All Fields] OR (“mucocutaneous”[All Fields] AND “leishmaniasis”[All Fields]))) AND ((“infliximab”[Supplementary Concept] OR “infliximab”[All Fields]) OR (“adalimumab”[Supplementary Concept] OR “adalimumab”[All Fields]) OR (“TNFR-Fc fusion protein”[Supplementary Concept] OR “TNFR-Fc fusion protein”[All Fields] OR “etanercept”[All Fields]) OR (“golimumab”[Supplementary Concept] OR “golimumab”[All Fields]) OR (“certolizumab pegol”[Supplementary Concept] OR “certolizumab pegol”[All Fields] OR “certolizumab”[All Fields])).