Visceral leishmaniasis and anti-TNF-α therapy: case report and review of the literature

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ABSTRACT

Objectives. *Visceral leishmaniasis (VL) is an extremely rare example of opportunistic infection in patients treated with TNF-α antagonists and only a few cases have been described. In this paper risk factors, clinical features, diagnostic work-up and outcome of patients developing VL under biologic therapy are described.*

Methods. *Case report and review of the published cases of VL in patients under biologic treatment.*

Results. *We retrieved six patients, including ours, all of whom presented anarchic fever and pancytopenia. In 5 cases, splenomegaly was detected. The same number of patients came from endemic areas for VL. In the majority of the cases a bone marrow examination was not diagnostic, requiring the performance of a second one and/or the execution of other diagnostic tests. One fatal outcome was observed.*

Conclusion. *Even if VL represents a sporadic complication of biologic treatments, its presence should always be suspected in patients developing a triad of signs and symptoms constituted by fluctuant fever, pancytopenia and splenomegaly, especially if coming from endemic areas. In these cases an extensive diagnostic work-up must be warranted. Atypical and confusing features may resemble autoimmune diseases at presentation and during the course of the illness.*

Introduction

Tumour necrosis factor α (TNF-α) is a pro-inflammatory cytokine playing a pivotal role in the pathogenesis of many chronic autoimmune diseases such as rheumatoid arthritis (RA) and seronegative spondyloarthritides. TNF-α is also crucial for the control of several infectious diseases caused by intracellular microorganisms via its action in promoting cytokine-induced macrophage activation and granuloma formation.

The introduction of TNF-α inhibitors has dramatically changed the course of several chronic autoimmune conditions. Despite their striking effectiveness, their use is clearly linked to an increased risk of serious infections due to both opportunistic and routinary microorganisms (1-3).

Visceral leishmaniasis (VL) may represent a rare complication of biologic therapies. In this paper we present the case of a man with psoriatic arthritis (PsA) who developed VL while he was receiving treatment with infliximab. Following this, we present a review and discussion of analogous reports from the literature.

Methods

Case report

In May 2006, a 63-year-old man with a 16-year history of PsA was hospitalized because of the appearance of fluctuant fever and asthenia. Since 2003 he had been receiving a combination therapy with intramuscular methotrexate (7.5 mg/week) and infliximab (3 mg/kg every 8 weeks) with benefit. On admission, both the drugs were discontinued. Laboratory tests showed a leukocyte count of 1900/mmc with neutropenia (5.8%), lymphocytosis (64%) and monocytosis (26%), mild anemia (hemoglobin: 10.5 mg /dL; normal range (nr): 11.5-16.5), low platelets count (142,000/mmc; nr: 150,000-450,000), high CRP (3.59 mg/dL; nr: 0-0.6) and ESR (81 mm; nr: 0-29; Test-1 method), hypertransaminasemia (alanine aminotransferase: 287 U/l; nr: 7-40. Aspartate aminotransferase: 177 U/l; nr: 7-35) and hypergammaglobulinemia (35.2%) with oligoclonal bands (IgG κ, IgG λ). Several microbiologic tests for viral, bacterial and protozoan infections, including the antibodies against Leishmania, were negative. Tests for autoimmunity showed positivity of ANA (1:320), rheumatoid factor (241 IU/dl), anti-cardiolipin IgM (33 U/ml), anti-β2 glicoprotein IgM (31 U/ml) and anti-smooth muscle antibodies. A total-body TC scan was negative apart from the presence of hepato-splenomegaly. A bone marrow aspiration revealed a non-specific reactive hyperplasia while a liver biopsy was compatible with autoimmune hepatitis (autoimmune hepatitis score: 11). A diagnosis of lupus-like syndrome induced by infliximab with associated autoimmune hepatitis was made. The patient underwent treatment with azathioprine 50 mg/day and

oral prednisone 35 mg/day gradually tapered, with an improvement of symptoms and normalization of cell blood count and liver tests. After 2 months he reported the acute reappraisal of persistent high-grade fever, severe pancytopenia and asthenia. Hepato-splenomegaly was still present. Azathioprine and corticosteroids were promptly discontinued. The examination of a new bone marrow aspiration showed numerous intracellular leishmania parasites. The patient was treated with intravenous liposomal amphotericin B at the standard doses with resolution of the clinical picture within a further 3 weeks. No adverse event was observed during the antibiotic therapy. To date, he has not reported any signs or symptoms suggesting a relapse of the infection.

Review of the literature

A research on MEDLINE was made using the entry-terms "infliximab", adalimumab" and "etanercept" coupled by the boolean operator "OR". The retrieved citations were subsequently coupled with the entry-term "visceral leishmaniasis" by the boolean operator "AND". No limit was used for the research strategy. Finally, we selected 5 articles about patients who developed VL under treatment with anti-TNF-α therapy. All of them were descriptions of single cases in the form of case-report or letter to the Editor (4-8).

Data analysis

We considered all the described patients as a unique group. Due to the very small sample size, no statistical test was performed. Results are shown as number of observations compared to the total.

Results

The demographic and relevant clinical features and the available follow-up data of the presented series are summarized in Table I.

The median age at onset of symptoms due to VL was 57.5 years (range 45-69) while the median age of the underlying rheumatic disease was 12 years (range 5-30).

Clinically, all the patients presented fluctuant/anarchic fever, pancytopenia and very high markers of inflammation. In 5 cases splenomegaly was present. Other notable features were, in order of frequency, asthenia, hepatomegaly, hypergammaglobulinemia, hepatitis, nocturnal sweats, paroxysmal atrial fibrillation and rigor (4-8).

Only in 1 report was diagnosis immediately reached by the execution of a bone marrow aspiration (8). In the remaining cases, a second bone marrow examination and/or the execution of other tests including ELISA, polymerase chain reaction and immunofluorescence was required (4-7).

Discussion

Leishmaniasis represents a striking public health problem with a reported

Table I. Demographic characteristics, clinical features and follow-up data of the described cases (available data).

Study	De Leonardis *et al.*	Tektonidou *et al.*	Bassetti *et al.*	Bagalas *et al.*	Fabre *et al.*	Romanì-Costa *et al.*
Sex	Male	Male	Female	Female	Female	Male
Age (years)	63	45	69	60	53	55
Underlying rheumatic disease	Psoriatic arthritis	Psoriatic arthritis	Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis	Psoriatic arthritis
Anti-TNF-α	Infliximab 3mg/kg	Infliximab 3-5 mg/kg	Adalimumab 40 mg every other week	Etanercept since 18 months Previous treatment with Anakinra	Infliximab 3 mg/kg	Infliximab 3 mg/kg
Concomitant DMARDs	MTX and AZA in different times	MTX	MTX	CSA	AZA	Not reported
Risk factors for VL	Endemic area	Endemic area Previous contact with infected dog	Endemic area	Not recognized	Endemic area	Endemic area Previous contact with infected dog
Salient clinical features						
Pancytopenia	+	+	+	+	+	+
Fever	+	+	+	+	+	+
High inflammation markers	+	+	+	+	+	+
Splenomegaly	+	+	–	+	+	+
Therapy	Liposomal amphotericin B	Liposomal amphotericin B	Liposomal amphotericin B	Liposomal amphotericin B	Liposomal amphotericin B	Meglumine antimoniate
Outcome	Recovery Articular and cutaneous pictures still in remission	Recovery MTX 12.5 mg weekly reintroduced 40 days after the first amphotericin infusion with no reported problem during the following 10 months	Recovery	Fatal outcome due to lung superinfection and multiple organ dysfunction syndrome.	Recovery Reintroduction of anti-TNF-α therapy (etanercept 25 mg x2/week) after 5 months from recovery	Recovery

PDN: prednisone; MTX: methotrexate; CSA: cyclosporine A; AZA: azathioprine.

prevalence of about 12 million cases worldwide (including both the visceral and cutaneous diseases) and an estimated yearly incidence of 500 000 new cases for the visceral form. The infection is a zoonosis, with transmission of the parasite by sandflies to rodents and canines. Humans are usually incidental hosts (9). VL (also known as *kala azar*, "black-fever") is invariably lethal if left untreated. The typical clinical picture includes hepato-splenomegaly, lynphadenopathy, irregular fever, substantial weight loss and bone marrow failure.

In Europe, the disease is seen exclusively in the area of the Mediterranean basin, where the dog represents the main source of protozoa for the vector. Notably, all the described patients came from this area. In Mediterranean countries, leishmania is widespread but, at the same time, leishmaniasis shows a low prevalence in humans infecting almost exclusively HIV-positive patients (10). Until 2003 a total of 1911 cases of HIV/leishmania co-infection had been registered in Italy, France, Spain and Portugal (9). Apart from these data, the exact magnitude of leishmaniasis in south-western Europe remains unknown.

Since their introduction into clinical practice, anti-TNF-α agents have been successfully used for treating several autoimmune diseases in more than 1 million patients worldwide (3). On this background VL seems an extremely rare example of opportunistic infection under biologic therapy. Apart from the 5 cases retrieved from the literature, we found only another similar report described: it is the case of a 9-year-old French girl affected by juvenile idiopathic arthritis, who developed VL after a 6-month treatment with anakinra (11). In our experience, we observed only one case on a total of 440 patients treated with anti-TNF-α drugs in our Center. However, following the rapidly expanding use of biologic therapies and the increasing interface between leishmaniasis and the new world, a growing incidence in endemic countries might be expected in next years.

It is known that the risk of granulomatous infections is higher in patients receiving a monoclonal antibody rather than the soluble receptor. The important differences between the 2 classes of TNF-α antagonists, both in terms of kinetics and mechanisms of action (12, 13), may help to explain the apparent higher incidence of VL (5 out 6 cases) among the patients receiving a monoclonal antibody (infliximab in particular).

The clinical manifestations of VL largely depend on the immune response of the host. In immunocompetent subjects, an effective leishmania-specific Th1-response makes the infection asymptomatic or subclinical in most of the cases. The immunosuppressive activities of anti-TNF-α drugs include downregulation of local and systemic proinflammatory cytokine production and reduction in number of recruited lymphocytes and macrophages via a switch of the cytokine profile in favour of Th2 cell-associated molecules (such as IL-10, IL-13, IL-14 and TGF-β), that are able to inhibit the immune response against intracellular pathogens (4).

An open question concerns the possibility of distinguishing cases of new parasite infestation from those caused by reactivation of a latent infection. It is difficult to decide which of the two possibilities verified in the reported cases, apart from the patients with positive history for direct exposure to the protozoa (previous contact with infected animals) for whom the hypothesis of a reactivation of a latent infection is plausible.

Our case-report emphasizes the possibility of atypical presentations of VL in patients treated with biologic agents. Fever, pancytopenia and systemic inflammatory state in any combination may be frequently observed during flares of connective tissue diseases and VL is known to be able to mimic these conditions very well (14). Moreover, splenomegaly and leukopenia in association with severe longstanding (rheumatoid) arthritis are typical of Felty's syndrome. In our patient, the high transaminases values, a florid autoimmune panel, the liver histology, the negativity for antibodies against leishmania and the absence of parasites in the first bone marrow examination contributed to a misleading diagnosis at presentation, making the hypothesis of a iatrogenic lupus-like syndrome in association with autoimmune hepatitis plausible. Anti-TNF-α agents are known to be responsible for induction of both asymptomatic positivity for auto-antibodies and full-blown autoimmune syndromes (15), and several cases of autoimmune hepatitis induced by infliximab had been described (16-18).

The difficulties in the diagnostic work-up were confirmed by our review: in 5 out 6 cases, the correct diagnosis was formulated with the execution of 2 or more diagnostic tests in different combinations and times; in 4 cases (including ours) a second bone marrow examination was required (5-7). Thus, we suggest that, if the clinical suspicion of VL is high, the physician should continue the search for protozoa even in the presence of one or two negative tests. Some Authors proposed the execution of serologic screening for leishmania in all the candidates to anti-TNF-α agents presenting at least one risk factor (7). We believe that due to the low incidence rate of the disease, it is more important to stress the significance of a careful and detailed medical history. We also agree with Fabre and colleagues about the necessity for correct information about the existent risk for medical teams operating in endemic areas (7).

In conclusion, we have reported a case that emphasizes the possibility of atypical presentations of opportunistic infections in patients treated with anti-TNF-α agents. In addition, our review suggests that, even if VL represents a sporadic complication of biologic treatments, its presence should always be suspected in patients developing a triad of signs and symptoms characterized by fluctuant anarchic fever, pancytopenia and splenomegaly, and especially in those coming from endemic areas.

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