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Case Report

Mucosal relapse of visceral leishmaniasis in a child treated with anti-TNFα

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SUMMARY

Visceral leishmaniasis is an enzootic parasitosis present across the Mediterranean Basin. Some consider it an opportunistic parasite. We report the case of a girl treated with anti-tumour necrosis factor alpha (anti-TNFα) for juvenile idiopathic arthritis who had previously presented with visceral leishmaniasis. Two and a half years later, she presented a tumour-like mass in the nasal mucous membrane caused by Leishmania parasites. *Leishmania infantum* is classically responsible for visceral leishmaniasis, but pure mucocutaneous leishmaniasis has also been described. To our knowledge, this is the first observation of a recurrence of visceral leishmaniasis in the mucocutaneous form. The occurrence of atypical forms and presentations in those on anti-TNF therapy should be considered.

1. Introduction

Visceral leishmaniasis (VL) is an endemic vector-borne and zoonotic–anthroponotic parasitosis found across the Mediterranean Basin. The causal agent is an obligate intracytomacrophagic protozoan, *Leishmania infantum*. VL is a life-threatening infection. Signs and symptoms include hectic fever, hepatosplenomegaly, and cytopenia. Sporadic cases with a cutaneous or mucous localization have been described. We report the first case of a child presenting both forms of the disease.

2. Case report

In 2001, a 4-year-old girl presented with mono-articular juvenile idiopathic arthritis (JIA) and bilateral uveitis. She was living in the Languedoc Roussillon area in the south of France, an area endemic for *L. infantum*, and had never travelled outside this area. In April 2002 she commenced treatment with prednisolone at a starting dose of 2 mg/kg, but relapses required the addition of anti-tumour necrosis factor alpha (anti-TNFα) therapy in February 2003. Etanercept was the anti-TNFα agent used until January 2004; following this infliximab was given at doses of 5 to 20 mg/kg every 6 weeks, leading to disease remission. The injections were then given every 8 weeks.

In January 2005, after seven infliximab treatments, the patient developed a fever lasting 15 days and was then admitted to hospital. Physical examination findings were asthenia, paleness, and hepatosplenomegaly. Laboratory test findings were the following: C-reactive protein 23 mg/l and bicytopenia (haemoglobin 11.4 g/dl, platelet count 76×10^9/l, white blood cell count 4.09×10^9/l). VL was confirmed by examination of bone marrow aspirate: direct examination of May–Grünwald–Giemsa-stained smears revealed Leishmania parasites. Serological tests were also positive: indirect fluorescent antibody test (IFAT) 1/5120 (cut-off 1/80), and ELISA 2.33 (cut-off 0.32). PCRs of whole blood and bone marrow aspirate were positive for *L. infantum*.

The patient was treated with intravenous liposomal amphotericin B 24 mg/kg in six doses. The outcome was favourable and the anti-TNFα treatment was maintained. After this curative treatment, the patient received prophylactic amphotericin B treatment

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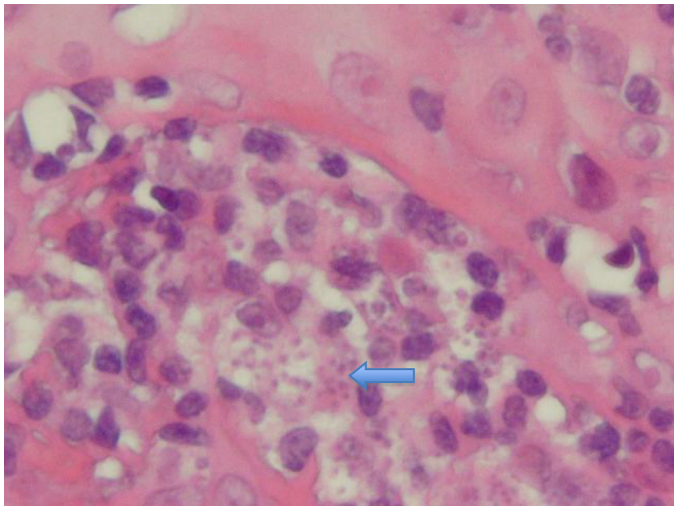

Figure 1. Granuloma with Leishmania inside macrophages (haematoxylin–eosin stain, ×60).

at 3 mg/kg/week because of the immunosuppression. This was stopped 4 months later due to non-tolerance (vomiting).

In July 2007, 26 months after amphotericin B therapy had ceased, she suffered recurrent epistaxis. An intra-nasal tumour was identified in November 2007. Clinical examination showed the tumour to be located in the median septum near the nasal opening. The patient presented no hepatosplenomegaly or fever. Magnetic resonance imaging (MRI) showed a paramedian tissue mass of 14 × 6.5 mm without osteo-cartilaginous invasion.

An excision biopsy was performed; pathological examination revealed a granuloma with macrophages containing *Leishmania* parasites (Figure 1). Positive PCR results confirmed the diagnosis of *L. infantum* in the mucosal lesion. Further investigations for extension, including bone marrow examination, specific PCR for *L. infantum* in blood, bone marrow aspiration, and gastro-oesophageal fibroscopy, were negative.

No other localizations or relapses occurred during the following 5-year period, hence no further medical treatment has been given for Leishmania. In light of the severity of the uveitis related to the JIA, the patient has continued to receive anti-TNFα therapy, steroids, and methotrexate since March 2008.

3. Discussion

L. infantum is classically responsible for VL or cutaneous leishmaniasis, but rare mucosal forms or lesions have been described. Nasal leishmaniasis is a rare mucosal form. A Spanish study has described five cases in a group of 31 patients with mucocutaneous leishmaniasis; in that study, the mucosal presentation was in the form of nodular swelling or pseudo-tumoural masses in 25 cases.[1]

Several clinical cases of VL occurring in patients on anti-TNFα therapy have been reported in the literature. For example, a 45-year-old Greek man with psoriatic arthritis, receiving treatment with infliximab, who was treated with amphotericin B with a good outcome.[2]

The leishmaniasis immune response has been studied extensively, but is not yet well understood. Furthermore, much progress has been made in recent years concerning the role of TNFα in experimental and clinical studies. Many experimental studies have shown the positive impact of TNF in the anti-Leishmania response: mortality rates are high without TNF production.[3] However other studies have suggested that the toxic action of high levels of TNF cause dysregulation of chemokines and of the immune response to leishmaniasis.[3] In human disease, elevated levels of TNFα in the blood have been shown to be associated with the visceral forms in cytokine studies. Moreover, human genetic studies have shown that certain TNF polymorphisms are more frequent in VL than in benign forms; these polymorphisms increase baseline TNF levels.[4]

Cutaneous leishmaniasis has a different pathway to VL. However, it has been shown that in cutaneous leishmaniasis, TNFα levels persist in tissues even after healing,[5] indicating that it has a role in preventing relapse by an immune-regulatory mechanism; this explains the occurrence of relapse under anti-TNFα therapy.

In conclusion, our case is interesting because it is the first to show recurrence of VL in the mucocutaneous form; it may also reflect the complex role of TNFα. The mucosal lesion was probably a relapse, but this is not certain because the strains were not characterized. The fact that this uncommon presentation occurred under anti-TNFα therapy suggests its role in this clinical case, which is supported by experimental data.

TNF has a variety of roles in experimental VL. Some benefit host resistance, while others mediate host pathology. More studies are required to clarify its role in human disease as it could have application in terms of diagnosis or therapy.

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