Case Report: Relapsing Cutaneous Leishmaniasis in a Patient with Ankylosing Spondylitis Treated with Infliximab

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Abstract. A 31-year-old man with ankylosing spondylitis, receiving treatment with infliximab, presented with a large progressive cutaneous ulcer at the right knee. Biopsies showed Leishmania amastigotes, and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis showed Leishmania infantum as the causative agent. After treatment with miltefosine, the ulcer resolved completely, and infliximab was reinstituted because of progression of spondylitis. After 1 year, there was a recurrent ulcer at the same site being positive for Leishmania DNA by PCR. Local treatment with sodium stibogluconate resulted in complete regression. Cutaneous leishmaniasis should be added to the list of opportunistic infections associated with anti-tumor necrosis factor (TNF) treatment. Despite recurrences, antileishmanial treatment may be effective in cases without alternatives to anti-TNF therapy.

INTRODUCTION

Since the commercialization of monoclonal tumor necrosis factor-α (TNF-α) antibodies in 1999, these biological drugs are a matter of growing interest for clinicians because of their clinical efficacy and their growing spectrum of indications.1 Not surprisingly, a number of opportunistic infections have been reported in association with the use of anti-TNF-α drugs, including among others tuberculosis, aspergillosis, coccidioidomycosis, and histoplasmosis.

To our knowledge, three cases have been published concerning visceral leishmaniasis associated with anti-TNF-α therapy.2–4 Here we report on relapsing cutaneous leishmaniasis (CL) in a patient with ankylosing spondylitis treated with infliximab.

CASE REPORT

A 31-year-old man presented with a cutaneous ulceration at the right knee (Figure 1A). Seven months earlier, the patient had spent his holidays in the mountains of Mallorca, one of the Balearic Islands of Spain in the Mediterranean Sea. The patient had no fever, weight loss, or other systemic symptoms. Local antymycotic and oral antibiotic treatment was without effect, and his rheumatologist referred him to a dermatology clinic. A skin biopsy was performed, but histopathologic examinations did not show a definite diagnosis. The patient was referred to the Department of Infectious Diseases and Tropical Medicine. Here, 3-mm punch biopsies were collected from the outside margin of the ulceration, and numerous intracellular Leishmania amastigotes could be detected in Giemsa-stained impression smears (Figure 1B). Polymerase chain reaction (PCR) of a biopsy specimen amplified a Leishmania-specific sequence of the internal transcribed spacer-1 gene,5 and subsequent restriction fragment length polymorphism (RFLP) analysis identified the species as Leishmania infantum. The strain could be isolated in culture and the zymodeme classified as MON-1.6 Immunoblot analysis of the patient’s serum showed specific IgG antibodies against 14- and 16-kd proteins of L. infantum.7

The patient had ankylosing spondylitis since 14 years of age, which also had affected his father. For 4 years, he had been successfully treated with the anti-TNF-α drug infliximab. Four months previously, the therapy had been interrupted because of the continuously growing ulceration at the right knee. Approximately 8 weeks after discontinuation, the patient had growing pain from spondylitis.

The patient was treated with miltefosine 50 mg twice a day for 6 weeks, which resulted in a complete resolution of the lesion. Afterward, the therapy for ankylosing spondylitis was resumed with infliximab.

After 1 year of therapy with infliximab, a new red swelling of 3 × 4 cm with a central lesion appeared in the location of the former lesion (Figure 1C). In multiple smears and biopsies, no Leishmania amastigotes could be found. However, in a biopsy, PCR was positive (RFLP: L. infantum), but histopathology and culture were negative.

Because the clinical appearance was suggestive of a relapse of CL, we offered the patient local treatment with sodium stibogluconate (Pentostam, GlaxoSmithKline UK, Uxbridge, UK). After two infiltrations with ~2 mL Pentostam, applied 1 week apart, the wound resolved completely within 5 months. Therapy with infliximab was continued and within the next 2 years of follow-up, there was no relapse of CL.

DISCUSSION

Leishmania organisms are flagellated protozoa that are usually transmitted by female phlebotomine sandflies to mammalian hosts, where they multiply as obligate intracellular parasites in the mononuclear phagocytic system. The wide spectrum of human infection as visceral, cutaneous, or mucosal/mucocutaneous leishmaniasis depends both on the Leishmania species involved and on the immune response of the host.

Leishmaniasis is endemic in 88 countries, with an estimated yearly incidence of 1–1.5 million cases of CL and 500,000 cases of visceral leishmaniasis (VL). More than 90% of the CL cases occur in six countries (i.e., Afghanistan, Iran, Saudi Arabia, Syria, Brazil, and Peru).8 L. infantum is endemic in all Mediterranean European countries and the predominant cause of both VL and CL. In addition, L. tropica has been
found to cause CL in Greece. Recently, phlebotomine vectors and leishmaniasis have spread northward, as shown by recent reports of indigenous VL cases in northern Italy and southern Germany. Approximately 700 new cases of leishmaniasis are reported per year in southern European countries, most of them as VL. However, CL is not notifiable in most European countries, and uncomplicated CL probably remains undiagnosed in the majority of cases.

It has been suggested that there are dermatotropic and viscerotropic strains of *L. infantum* causing predominately CL or VL, respectively. According to the current gold standard of typing *Leishmania* by multilocus isoenzyme analysis, there are zymodemes of *L. infantum* that are mostly dermatotropic. However, the most prevalent zymodeme MON-1 is both associated with CL and VL, and even further genetic subtyping has not shown a clear correlation between genotypes and clinical manifestation thus far.

Therefore, in addition to genomic polymorphisms of the parasite, host factors certainly play an important role. Innate and adaptive immune responses to *Leishmania* infection involve numerous immune cells (CD4+ and CD8+ T cells, macrophages, dendritic cells, and natural killer cells) and cytokines (interferon γ, interleukin 12, and TNF-α). Nitric oxide (NO) produced by inducible NO synthase (iNOS) and phagocyte NADPH oxidase (phox) have crucial roles as effector molecules against leishmanial amastigotes. TNF-α is a proinflammatory cytokine with numerous biologic effects including antiviral and antitumor activity and the mediation of systemic inflammatory responses to infection and sepsis. Fonseca and others showed that TNF-α mediates the induction of iNOS in macrophages. In *L. major*-infected C57BL/6 mice, anti-TNF-α treatment reduced the expression of iNOS in the macrophages, which led to an increase in the number of parasites and the size of lesion. Liese and others showed that, in CL caused by *L. major*, iNOS and phox complement each other in the skin, lymph node, and spleen. Whereas iNOS is most important for the control of *L. major* in the dermis and the draining lymph node, the function of phox is critical for preventing visceralization of the parasite. Similar to the situation observed in CL, TNF-α has a pivotal role in experimental VL. Most pathogens lead to a rapid induction of TNF secretion by macrophages within 1 or 2 hours of microbial exposure. In contrast, *L. donovani* amastigotes or promastigotes provoke only a limited initial TNF production. It has been proposed that those species of *Leishmania* that cause VL escape this initial proinflammatory host process. Treatment
with TNF-α antagonists may also impair this initial proinflammatory host reaction with the consequence of an elevated susceptibility of those patients for VL. Furthermore, patients treated with TNF-α antagonists may have a reduced ability for resolution of VL. In one study, mice deficient in TNF-α were unable to control parasite growth, had impaired hepatic granuloma formation, and finally died after 6 weeks of infection.16 Similarly, mice infected with L. donovani that received a neutralizing anti-TNF antibody were unable to resolve infection in their liver.17

We hypothesize that, in our patient, infliximab therapy led to a reduction of the expression of iNOS, which facilitated the dermal manifestation of L. infantum infection and promoted its progress to an unusually large cutaneous ulceration. After clinical cure of CL, a small number of viable parasites persist at the site of the former skin lesion and possibly also in regional lymph nodes.12 Under compromising conditions such as malnutrition and immunosuppression, reactivation of leishmaniasis can occur from persisting parasites.

In our case, the restart of the infliximab therapy after clinical resolution of the cutaneous lesion may have resulted in the impairment of local parasite control, which led to the relapse of the cutaneous leishmaniasis. In conclusion, patients under anti-TNF-α antagonist therapy might have an elevated risk not only for VL but also for CL. Moreover, our case shows that anti-TNF-α therapy can provoke a relapse of resolved CL. Patients with a history of Leishmaniasis receiving anti-TNF-α therapy should be subject to close monitoring.

Received January 16, 2009. Accepted for publication March 27, 2009.

Acknowledgments: The authors thank Dr. Francine Pratlong and Professor Jean-Pierre Dedet, Laboratoire de Parasitologie and Centre National de Référence des Leishmania, Centre Hospitalier Universitaire de Montpellier, for thezymodeme determination by multilocus isoenzyme analysis.

Disclaimers: Dr. Grünke has received consulting fees from Centocor. There are no conflicts of interests for the other authors.

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