Cutaneous leishmaniasis associated with TNF- α blockers: a case report

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ABSTRACT

Leishmaniasis is a chronic protozoan disease that is found in diverse geographical areas of the world. *Leishmania* spp. are endemic in the Mediterranean coasts of southern Europe. Tumour necrosis factor alpha (TNF- α) plays an important role in the defence of the host against infection by *Leishmania* spp. In this case report we describe *Leishmania* infection caused by a monoclonal antibody against TNF- α : infliximab. A 51-year-old patient with psoriatic arthritis treated with infliximab, 5 mg/kg every 6 weeks as immunomodulatory treatment and methotrexate 10 mg weekly as a conventional disease-modifying antirheumatic drug, visited his otorhinolaryngologist owing to a lesion in his left nostril. The lesion was diagnosed as cutaneous leishmaniasis so treatment with infliximab was suspended. The patient was then treated with liposomal amphotericin B and showed a total recovery of the lesion; liposomal amphotericin B was maintained at 5 mg/kg monthly.

BACKGROUND

Leishmaniasis is a chronic protozoan disease of the mononuclear phagocytic system found in diverse geographical areas of the world. *Leishmania* spp. are endemic to the Mediterranean coasts of southern Europe.¹ *Leishmania* infection can be localised in the skin (cutaneous leishmaniasis) and mucous membranes (mucosal leishmaniasis) or spread in the reticuloendothelial system (visceral leishmaniasis).² Tumour necrosis factor alpha (TNF- α) plays an important role in the defence of the host against infection by *Leishmania* spp.^{3,4} Biological agents that inhibit tumour necrosis factor (anti-TNF) are effective treatments for diseases in which the immune system is involved; however, they may increase the risk of reactivation or dissemination of granulomatous infections.⁵ Although it is known that anti-TNF agents may increase the risk of developing infections such as tuberculosis, there is little literature on *Leishmania* infections in patients treated with these drugs. We report a case of cutaneous leishmaniasis in a patient with psoriatic arthritis treated with an anti-TNF drug: infliximab.

CASE PRESENTATION

A 51-year-old male patient with psoriatic arthritis treated with infliximab, 5 mg/kg every 6 weeks as immunomodulatory treatment and methotrexate 10 mg weekly as a conventional disease-modifying antirheumatic drug, visited his otorhinolaryngologist owing to a lesion in his left nostril.

INVESTIGATIONS

When a biopsy was carried out, leishmaniasis (identified with a Giemsa stain) was found in pseudopolypoid granulation tissue with focal ulceration of the surface epithelium. The patient mentioned having a cat and also resides in an area endemic for *Leishmania* spp.

On examination, the patient was afebrile, without splenomegaly and without relevant haematological or biochemical alterations (haemoglobin 14.5 g/dL, lymphocytes 26.9%, neutrophils 62.2%, alanine aminotransferase 15 U/L) so the infectious diseases department was contacted. Antibody titration was performed by indirect immunofluorescence and a positive result was obtained, corroborating a diagnosis of cutaneous leishmaniasis.

TREATMENT

Treatment with infliximab was suspended and the patient was referred to his reference hospital for the treatment of cutaneous leishmaniasis with liposomal amphotericin B at 5 mg/kg on days 0, 5 and 10. After this, the patient showed clinical improvement with total disappearance of the lesion. A new treatment with etanercept was then started, maintaining liposomal amphotericin B at 5 mg/kg monthly.

OUTCOME AND FOLLOW-UP

After several months of treatment with etanercept, the patient's psoriatic arthritis worsened and it was agreed to restart infliximab, maintaining liposomal amphotericin B at 5 mg/kg monthly as prophylaxis to prevent a possible reactivation. Currently, the patient is being followed up by the rheumatology and infectious diseases services.

DISCUSSION

In the scientific literature, several cases are reported of the reactivation of latent diseases such as hepatitis B and tuberculosis after the administration of anti-TNF treatment. However, there are few reports of the reactivation of leishmaniasis after the use of this type of treatment.⁶ Traditionally, leishmaniasis affects the poorest populations as it is associated with malnutrition, population displacements, poor housing conditions, weakness of the immune system and lack of resources. However, recently there has been a slight increase in the number of cases of infection caused by *Leishmania* spp. in developed countries. This increase seems to be related to the greater use of anti-TNF agents for the treatment of autoimmune diseases (rheumatoid arthritis, psoriasis, psoriatic arthritis) increasingly

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common in our community.⁷ This biological treatment leads to immunosuppression, which makes the reactivation of leishmaniasis more plausible, as reflected in the case described.

The role of TNF- α in the immune response to infections by intracellular parasites is widely described in the literature.⁸ In particular, TNF- α increases the expression of monocyte chemoattractant protein 1, intercellular adhesion molecule 1, E-selectin and vascular cell adhesion molecule, essential cytokines in the formation of granuloma and migration of monocytes that leads to the eradication of *Leishmania* spp.⁹ The use of infliximab and other anti-TNF agents may reduce this process, which would lead to a greater probability of reactivations or primary infections in these patients.¹⁰ In view of this, serological detection may be indicated to diagnose possible latent *Leishmania* infection before the prescription of TNF inhibitors in countries with a high incidence of infection by aggressive *Leishmania* spp.

As hospital pharmacists, our role is crucial to ensure a pre-dispensation screening of possible latent infections which might be reactivated owing to immunosuppressive therapy. Hospital pharmacists have collaborated in developing screening protocols for other latent infectious diseases. Thus, a screening protocol should be set by the department of pharmacy in association with both the department of infectious diseases and the department of microbiology to guarantee that no TNF- α blocker is dispensed without examining the possibility of latent *Leishmania* infection, at least, in patients who live in areas endemic for *Leishmania* spp. The hospital pharmacist has an important role when checking the diagnosis, treatment, dose, posology and

the immunocompetent state of outpatients before dispensation of this type of drug. If latent *Leishmania* infection is diagnosed, antiprotozoal prophylaxis should be used, which is a possible option as reported in this case.

To conclude, it should be noted that the current technical specifications of the various anti-TNF treatments do not mention the possible reactivation of leishmaniasis that may occur after its administration, unlike the reactivation of hepatitis B and tuberculosis, which is specifically described. Therefore, we believe that communication to the pharmacovigilance centres of different countries and regions of possible reactivation of leishmaniasis caused by these drugs is essential, and should be included in technical documents describing adverse events.

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Learning points

- TNF α blockers may lead to a reactivation of *Leishmania* infections.
- *Leishmania* infections in immunosuppressed patients are an emerging health problem in southern Europe that should be assessed with the proper pharmacovigilance and preventive diagnosis.
- Liposomal amphotericin B may be a possible prophylaxis in patients who need to start a treatment with an anti-TNF drug.