CASE REPORT

Atypical cutaneous leishmaniasis in the immunosuppressed

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SUMMARY

A 45-year-old woman, known case of seronegative arthritis and on immunosuppressive therapy, presented with a 2-week history of a macular lesion on the left calf that became papular and eventually ulcerated. The rest of the history was otherwise unremarkable and systemic examination did not reveal any abnormalities. The lesion was repeatedly biopsied but failed to reveal *Leishmania donovani* bodies. Concurrent *Leishmania* IgG was positive but IgM was negative. *Leishmania* IgG confirmatory testing by ELISA was negative. A biopsy from the lesion eventually tested positive for *L. donovani* through PCR. The patient was treated with sodium stibogluconate together with intravenous ciprofloxacin and amoxicillin to cover the secondary cutaneous bacterial infection. This led to complete resolution of the lesion.

BACKGROUND

This case highlights several important and clinically relevant learning points:

1. Mode of presentation of cutaneous leishmaniasis (CL) in patients on antitumour necrosis factor (TNF) anti-inflammatory drugs.
2. *Travel*: *Leishmania* is endemic in the Mediterranean basin. Such places are popular tourist destinations. Returning travellers who may have been exposed can present a diagnostic challenge.
3. *Importance of PCR*: this case highlights the importance of PCR in the diagnosis of CL in the immunosuppressed.

CASE PRESENTATION

A 45-year-old woman, known case of seronegative arthritis, presented with a 2-week history of a painful lesion on her left calf. This started out as a macular lesion progressing to a papular lesion and

eventually ulcerating into a 3 cm diameter ulcer, covered in golden-yellow crusts, with regular margins. A surrounding 2 cm area of hyperaemia was also noted (figure 1).

During her presentation the patient was on adalimumab, anti-TNF, twice weekly and methotrexate once weekly as treatment for her seronegative arthritis.

The patient denied any contact with animals.

INVESTIGATIONS

Baseline blood investigations including a full blood count, a renal profile, liver function tests, protein levels, albumin levels and random blood glucose were all normal. The erythrocyte sedimentation rate was found to be 35 mm/h but C reactive protein was within normal limits.

Leishmania IgG antibodies through immunofluorescence were positive, however confirmatory testing by ELISA was negative.

Repeated skin scrapings from the lesion were sent for fungal stains and culture both of which proved negative (figure 2).

A skin biopsy was also taken and sent for Gram stain, culture and sensitivity testing and histology. Gram stain showed abundant red blood cells and polymorphs accompanied by Gram-positive cocci and Gram-negative rods.

Cultures grew *Pseudomonas aeruginosa* and *Enterococcus faecalis*. The *Pseudomonas* was found to be sensitive to aztreonam, ciprofloxacin, gentamicin and piperacillin/tazobactam while the *Enterococcus* was sensitive to amoxicillin, ampicillin/sulbactam, gentamicin, teicoplanin and vancomycin.

The skin biopsy was also sent for Ziehl-Neelsen staining and mycobacterial cultures but proved negative.

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Figure 1 The initial presentation of the lesion showing exact location (left side) and a close-up view (right side).

Figure 2 The lesion after taking a skin biopsy 1 month after initial presentation, showing early signs of ulceration with a rim of golden-yellow crust.

Histology of the incisional skin biopsy showed a diffuse inflammatory infiltrate of the dermis composed of lymphocytes, numerous plasmacytes and occasional giant cells but no granulomata were seen. Focal areas of necrosis with neutrophils were seen predominantly at the skin surface. However no *Leishmania donovani* bodies (LDB) were found.

PCR testing on the biopsy confirmed the diagnosis of histology-negative atypical CL.

DIFFERENTIAL DIAGNOSIS

PCR-positive CL with negative histology and negative LDB staining in an immunosuppressed patient on anti-TNF.

TREATMENT

The patient was given sodium stibogluconate 850 mg intravenous daily for 21 days.

In addition, the patient was also started on intravenous ciprofloxacin 500 mg twice daily and 1 g amoxicillin six hourly for 2 days. These were switched to oral for another 10 days.

Adalimumab and methotrexate were temporarily stopped in view of their immunosuppressive action.

OUTCOME AND FOLLOW-UP

On this treatment the lesion improved as depicted in the accompanying photographs achieving complete resolution within 8 months. The patient was eventually restarted on her normal dose of anti-TNF that is, 1 month after stopping it, without any clinical evidence of a relapse of CL.

The patient was given a 21-day course of sodium stibogluconate followed by a monthly dose of the same drug as secondary prophylaxis for six consecutive months (figures 3–5).

DISCUSSION

CL is a dermatological condition caused by a flagellated protozoan and transmitted by the sandfly which results in a papule that progresses to a nodule and eventually ulcerates. Around 12 million people are infected worldwide with most cases occurring in southern Europe, the tropics and the subtropics.¹

A literature review in 2009 yielded 15 cases of leishmaniasis in Europe in patients who had been on one or more immunosuppressive agent for autoimmune rheumatic diseases. Of the 15 cases only 2 cases presented as CL and only 1 of them was on anti-TNFs.²

The case was of a 55-year-old man being treated with infliximab and methotrexate for ankylosing spondylitis who presented with painless but mildly pruritic vesicular lesions on the face. The patient lived in a *Leishmania* endemic area in Athens and scrapings of the lesion showed intracellular amastigotes. Infliximab and methotrexate were stopped and the patient was treated with liposomal amphotericin. However he did not receive secondary prophylaxis. Eighteen months later the patient was switched to etanercept.²

All the above patients, similar to our case, were living in a *Leishmania* endemic area within Europe. Interestingly, all 15 cases were published after 1998, the year in which anti-TNF

Figure 3 The lesion 2 months after initial presentation on the way to healing with healthy granulation tissue at the base.

Figure 4 The lesions 3 months after initial presentation showing drying up and crusting.

Figure 5 The lesion 10 months after initial presentation and around 8 months after initiating therapy showing full resolution.

drugs were introduced. Of the 15 cases 7 had received anti-TNF as part of their treatment regimen.

In 2011, an outbreak of CL was seen in Fuenlabrada, Spain. Two patients were on the anti-TNF adalimumab. The characteristic histology of CL shows intracellular non-flagellated amastigotes with a granulomatous inflammatory response.³ In both these cases histology failed to identify *Leishmania* parasites, however both were characterised by non-necrotising granulomas.⁴ As such PCR was used to nail the diagnosis.

While the cases described above showed either typical histology with positive staining for LDBs or granuloma formation, our case showed neither of these characteristics. This led to a diagnosis of CL through PCR. Antibody detection gave a false-positive result. This test has poor sensitivity in CL due to reduced antibody production.⁵ A possible explanation for the false-positive immunofluorescence result in this case is due to cross-reactivity with the adalimumab itself—a monoclonal IgG.

PCR for CL seems to have high sensitivity when compared with serological, histological and microbiological investigations.⁶ This sensitivity was found to be around 92%⁷ compared with the 69.5% of direct microscopy smear and 69.2% of in vitro culture.⁸

Lyons *et al*² conclude that there is an increasing number of leishmaniasis cases in patients who had received anti-TNFs. This increase in opportunistic leishmaniasis is thought to be around eightfold.⁹ TNF- α is a known important mediator needed to mount a defense against leishmaniasis. This chemical is vital to provide an adequate local environment where dendritic cells can move from skin to lymph nodes and also aids in granuloma formation.⁴

Owing to the small number of cases it is still unclear as to whether these were actually primary infections or reactivation of a latent parasite. Moreover, even though six of the nine cases of leishmaniasis presenting in patients with autoimmune disease between 2003 and 2009, had been receiving anti-TNFs, it is not known for certain whether the anti-TNF or the concomitant immunosuppressive drugs were to blame.² In addition, present data suggest that the risk of developing opportunistic leishmaniasis is smaller with etanercept than that with infliximab or adalimumab. As such this might be the drug of choice in patients inhabiting or visiting endemic areas for leishmaniasis.⁹

Another literature review shows that between 2004 and 2011 there were 19 cases in Europe of patients on anti-TNFs who acquired *Leishmania*, including also the visceral cases. Since information about these occurrences is limited to case reports it is still uncertain as to whether anti-TNFs should be continued or interrupted during the treatment of CL.¹⁰ In both cases reported by Romero-Maté *et al*, neither methotrexate nor adalimumab were discontinued with both having a favourable outcome.⁴ Moreover, it is most likely that an initial episode of opportunistic leishmaniasis does not warrant long-term antiparasitic secondary prophylaxis.¹⁰

Learning points

- An apparent increase and therefore a need of increasing awareness of cutaneous leishmaniasis (CL) in patients receiving immunosuppressive therapy.
- The atypical presentation of *Leishmania donovani* bodies (LDB)-negative CL on biopsy.
- The importance of PCR testing especially in biopsy LDB-negative cases.
- The need to consider this diagnosis in patients who return from *Leishmania* endemic areas.
- The need for further research as to which antitumour necrosis factor are ideal in *Leishmania* endemic regions, and whether there is an indication to start secondary prophylaxis in cutaneous opportunistic leishmaniasis.

Contributors CM had been involved in the acquisition of the necessary information to write up the case and had also conducted the literature review. He is the guarantor of the case. CMA had been responsible for the conception of the work, for critical revision and for the final approval of the version to be published.

Competing interests None.

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