Unexpected outcome (positive or negative) including adverse drug reactions

Let off the leash: kala-azar following the use of tumour necrosis factor antibodies

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Summary

A 74-year-old woman with a history of psoriatic arthritis was referred to the Hospital for Tropical Diseases following investigation of a skin lesion that had failed to heal after a visit to Malta 2 years previously. Skin biopsy had revealed invasion of *Leishmania* amastigotes. She reported a recent history of weight loss, dry cough and dyspnoea, and was investigated for pancytopenia and hepatosplenomegaly.

Bone marrow biopsy confirmed the diagnosis of visceral leishmaniasis and she responded well to treatment with intravenous liposomal amphotericin B. Recent rheumatological treatment with adalimumab, a monoclonal antibody to tumour necrosis factor α , was thought to be the factor responsible for causing the cutaneous lesion to become disseminated. This case highlights an unexpected adverse effect of novel immunosuppressants. As the use of biologics becomes widespread, there is an increasing need for clinical surveillance.

BACKGROUND

As international travel becomes increasingly widespread and affordable, the numbers of people exposed to previously unknown disease vectors will increase. This is particularly relevant in an era where a range of novel immunosuppressants are being used to treat illnesses ranging from inflammatory bowel disease to Alzheimer's disease.

A range of adverse associations has been reported with the tumour necrosis factor (TNF α) inhibitors from the development of lymphoma to demyelinating nervous system disorders and tuberculosis.¹ Associations with aspergillosis, histoplasmosis, coccidioidomycosis, nocardiosis, listeriosis and hepatitis B reactivation have been reported; however, there are few reports discussing the risk of kala-azar. This disease is widespread in temperate countries, including the Mediterranean, and physician awareness of the clinical presentation is important for reducing mortality and morbidity.²

Furthermore, this patient lacked classical risk factors and had only limited exposure to the vector. Her presentation was non-specific and delay in diagnosis might well have proven fatal given the pancytopenia on presentation.

CASE PRESENTATION

A 74-year-old UK-born woman was referred to the Hospital for Tropical Diseases, London. She had developed a skin lesion on her ankle after a trip to Malta 2 years previously.

She reported a dry cough, dyspnoea, anorexia and marked weight loss. Her past medical history included psoriatic arthritis treated with adalimumab (Humira; Abbott Laboratories, Abbott Park, Illinois, USA) 40 mg fortnightly for 21 months until 4 months previously in addition to methotrexate. There was evidence of a healing

ankle ulcer on examination in addition to significant hepatosplenomegaly.

INVESTIGATIONS

Skin biopsy revealed a florid histiocytic infiltrate with abundant intracellular *Leishmania* amastigotes. *L. donovani* complex DNA was detected by PCR on paraffin sections from the biopsy. Abdominal CT showed marked hepatosplenomegaly with discrete splenic lesions (figure 1A). Leishmania ELISA serology was strongly positive at 1:102 400 and anti-K39 antibodies were present in serum. Full blood count revealed pancytopenia consistent with bone marrow invasion and bone marrow biopsy showed *Leishmania* amastigotes, confirming the diagnosis of visceral leishmaniasis (figure 1B). HIV serology was negative.

DIFFERENTIAL DIAGNOSIS

Tuberculosis, lymphoma, leukaemia and carcinomatosis.

TREATMENT

The cutaneous lesion was infiltrated with sodium stibogluconate. She was treated with intravenous liposomal amphotericin (ambisome) at a dose of 3 mg/kg on days 1–5, 10 and then weekly for 4 weeks.

OUTCOME AND FOLLOW-UP

Her symptoms improved rapidly and haematological parameters normalised over 4 weeks. Subsequently, her psoriatic arthropathy flared badly. After a full discussion of the risks of re-activation of leishmaniasis, she elected to re-start anti-TNF treatment with close monitoring of full blood counts and temperature to assess for the presence of persisting intracellular forms. After more than 12 months of

Figure 1 (A) Histological image. Bone marrow biopsy; arrow demonstrating leishmania amastigotes ($\times 100$ magnification). (B) Radiological image. Coronal CT demonstrating marked hepatosplenomegaly with splenic lesions.

treatment, there has been no subsequent relapse. A further relapse would probably indicate a need for prophylaxis in the form of intravenous pentamidine, which has proven effective in the HIV co-infection cohort.

DISCUSSION

We propose that our patient was bitten by a sandfly in Malta and injected with *Leishmania* promastigotes. She initially developed localised disease, modified by ongoing immunosuppression, resulting in loss of immune control and then progressed to visceral infection. This is an unusual sequence of events in that patients usually develop either cutaneous leishmaniasis or visceral leishmaniasis depending on the infecting strain and host immunity. *L. donovani* can cause both cutaneous and visceral disease.

Leishmaniasis is endemic in 88 countries and infects 12 million people worldwide causing 57 000 deaths every year.² Geographical distribution is expanding under the twin pressures of urbanisation and migration. Cutaneous leishmaniasis causes 75% of the 2 million new cases annually; however, visceral leishmaniasis is far more severe with an untreated mortality of almost 100%. *L. donovani* (Asia and Africa) and *L. infantum* (Southern Europe and South America) cause 500 000 cases of visceral leishmaniasis annually.

The infecting vector is the female phlebotomus sandfly and features include fever, cough, hepatosplenomegaly and lymphadenopathy. Recognised risk factors include HIV, malnutrition, transplantation and haematological neoplasia. Liposomal amphotericin is the gold standard for treatment of visceral leishmaniasis and cure rates of 98% have been demonstrated in immunocompetent patients.³ Visceral leishmaniasis has been reported in three other cases involving adalimumab all in rheumatoid arthritis patients.^{4–6}

The organism is an obligate intracellular protozoan, which replicates in macrophages. Adalimumab is a humanised IgG1 monoclonal antibody directed against the cytokine TNF α . Its action directly impairs the T helper type one response needed to control the disease as supported by the association of infliximab with a variety of opportunistic infections ranging from leprosy to *Pneumocystis jirovecii*.⁷

The role of TNF α has been well-established in controlling tissue granuloma formation and cytokine-induced mac-

rophage activation.⁸ Patients with active leishmaniasis exhibit a lower frequency of TNF α monocytes, associated with higher levels of IL-10, suggesting a mechanism for individual susceptibility.⁹ TNF-deficient mice exhibit absent early granulomatous reactions with widespread tissue inflammation and hepatic necrosis.¹⁰ Key features in mice with persistent tuberculosis are the lack of an organised granulomatous response suggesting TNF α has a key role in signalling appropriate immune cells and maintaining granuloma structure.¹¹

Monoclonal antibody treatment against TNF α is successfully used in disorders ranging from psoriasis to rheumatoid arthritis. Over 27 000 patients worldwide have been treated with adalimumab. Use will only increase and the need for informed clinical surveillance among a wide variety of physicians will need to be enhanced accordingly. The risks associated with these drugs require careful assessment prior to use, advice to the patient on avoiding vector exposure and close clinical follow-up of the patient with a high index of suspicion for reported symptoms.

Learning points

- Increasing use of biologics in a variety of specialties is likely to lead to a rise in the number of hitherto unusual opportunistic infections.
- Monoclonal antibodies to TNF α abrogate the normal T cell response to a wide variety of pathogens.
- With particular reference to diseases not normally associated with developed nations, a careful travel history and liaison with infectious diseases is important.
- Patients in living in endemic areas are at particular risk; however, this case highlights the limited nature of exposure sufficient to cause infection.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumour necrosis factor alpha neutralizing agent. *N Engl J Med*. 2001;**345**:1098–104.

2. World Health Organization, 2010. http://www.who.int/leishmaniasis/burden/magnitude/burden_magnitude/en/index.html (Accessed 16 August 2010).
3. **Gradoni L**, Gramiccia M, Scalone A. Change in human visceral leishmaniasis treatment in Italy. *Parassitologia*. 2004;**46**:199–201.
4. **Pizzorni C**, Secchi ME, Cutolo M. [Leishmaniasis in rheumatoid arthritis]. *Rheumatismo* 2007;**59**:235–9.
5. **Bassetti M**, Pizzorni C, Gradoni L, *et al*. Visceral leishmaniasis infection in a rheumatoid arthritis patient treated with adalimumab: a case description and literature review]. *Enferm Infecc Microbiol Clin* 2010;**28**:261–2.
6. **Moreno D**, Martínez P, Berbegal J, *et al*. [Visceral leishmaniasis infection in a rheumatoid arthritis patient treated with adalimumab: a case description and literature review]. *Enferm Infecc Microbiol Clin* 2010;**28**:261–2.
7. **Rychly DJ**, DiPiro JT. Infections associated with tumor necrosis factor-alpha antagonists. *Pharmacotherapy* 2005;**25**:1181–92.
8. **Allenbach C**, Launois P, Mueller C, *et al*. An essential role for transmembrane TNF in the resolution of the inflammatory lesion induced by Leishmania major infection. *Eur J Immunol* 2008;**38**:720–31.
9. **Peruhype-Magalhães V**, Martins-Filho OA, Prata A, *et al*. Mixed inflammatory/regulatory cytokine profile marked by simultaneous raise of interferon-gamma and interleukin-10 and low frequency of tumour necrosis factor-alpha (+) monocytes are hallmarks of active human visceral Leishmaniasis due to Leishmania chagasi infection. *Clin Exp Immunol* 2006;**146**:124–32.
10. **Murray HW**, Jungbluth A, Ritter E, *et al*. Visceral leishmaniasis in mice devoid of tumor necrosis factor and response to treatment. *Infect Immun* 2000;**68**:6289–93.
11. **Bean AG**, Roach DR, Briscoe H, *et al*. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol Mycobacterium tuberculosis infection, which is not compensated for by lymphotoxin. *J Immunol* 1999;**162**:3504–11.

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Khan A, Coakley G, Cosgrove C, Lockwood D. Let off the leash: kala-azar following the use of tumour necrosis factor antibodies. *BMJ Case Reports* 2010; 10.1136/bcr.04.2010.2878, date of publication

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