CASE REPORT

Tuberculosis and TNF-inhibitors: history of exposure should outweigh investigations

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Accepted 3 April 2014

SUMMARY

A 39-year-old Indian man was diagnosed with ulcerative colitis on colonic biopsy and started on mesalazine, prednisolone and azathioprine. However, the colitis remained active and required antitumour necrosis factor (TNF) treatment with infliximab. Prior to starting infliximab, his chest X-ray was normal and QuantiFERON interferon γ release assay for tuberculosis (TB) was negative. However, his wife had been treated for pulmonary TB 11 years previously when they were cohabiting. On attending for his third dose of infliximab, he was feverish and tachycardic, and was admitted for investigation. Chest X-ray on admission showed changes consistent with miliary TB, and thoracic CT confirmed extensive miliary nodules with supraclavicular and mediastinal lymphadenopathy. Abdominal CT showed multiple mesenteric lymph nodes. Subsequent bronchoalveolar lavage, neck lymph node aspirate and colonic biopsies all cultured *Mycobacterium tuberculosis*. In retrospect, a clear history of close household TB exposure should have precipitated consideration of TB chemoprophylaxis prior to anti-TNF treatment.

BACKGROUND

Tuberculosis (TB) continues to be a global health concern with 8 million new cases of TB being reported worldwide each year¹ and annual mortality of over 1.5 million deaths.² Antitumour necrosis factor (TNF) treatment for inflammatory diseases greatly increases the risk of TB reactivation.³ Interferon γ release assays are often used to exclude the presence of latent TB prior to starting anti-TNF therapy. However, there is a significant false-negative rate, with QuantiFERON sensitivity reported as low as 73%,⁴ and so a negative result does not rule out latent TB.

CASE PRESENTATION

A 39-year-old man presented with a 6-week history of increasing bowel frequency and rectal bleeding. Subsequent colonic biopsy confirmed ulcerative colitis with typical appearances of this condition. Mesalazine, prednisolone and azathioprine were then started. Remission was achieved temporarily before active colitis returned 10 months later. Despite azathioprine and prednisolone, bowel symptoms continued. Consequently, infliximab 5 mg/kg was started. This man was born in the Indian subcontinent. His wife received treatment for 6 months without complication for smear positive pulmonary TB 11 years prior to his acute presentation, when they had lived together.

When attending for his third dose of infliximab, the patient was found to be feverish and tachycardic and was admitted for investigation. There were no specific respiratory symptoms. A right supraclavicular lymph node was palpated but examination was otherwise unremarkable.

INVESTIGATIONS

Initial blood investigations found his C reactive protein raised at 318 mg/L, a mild lymphopenia $1.1 \times 10^9/L$ and a normocytic anaemia with haemoglobin 113 g/L. HIV serology was negative. His chest X-ray on presentation showed fine nodular shadowing throughout both lung fields (figure 1). High-resolution CT of his chest showed extensive centrilobular nodularity throughout both lungs and right mediastinal and supraclavicular lymph nodes (figure 2). Ultrasound of his neck found a 16×10 mm right supraclavicular lymph node which was aspirated. The aspirate showed macrophages and lymphocytes with no granulomata or acid-fast bacilli. Bronchoscopy with wash was performed, and in view of the persistent gastrointestinal symptoms, a colonic biopsy was taken.

DIFFERENTIAL DIAGNOSIS

Appearances were typical of miliary TB and therefore TB treatment was started. Other differentials for miliary shadowing, such as disseminated malignancy, were dismissed clinically.

TREATMENT

On the basis of a clinical diagnosis of miliary TB, quadruple therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) was started after bronchoscopy. Subsequently, fully sensitive *Mycobacterium*

Figure 1 Chest X-ray on presentation showing fine nodularity in both lung fields.

To cite: Reichmann MT, Marshall BG, Cummings F, et al. *BMJ Case Rep*. Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202127

Figure 2 Chest CT showing miliary nodules throughout both lung fields.

tuberculosis was cultured from the lymph node aspirate, the bronchial washings and the colonic biopsy.

OUTCOME AND FOLLOW-UP

After 2 months of TB treatment, the patient was very well, with resolution of the febrile symptoms and a normal chest X-ray, and he was stepped down to continuation phase treatment with rifampicin and isoniazid. Treatment for miliary TB was completed at 6 months without complication. Once the TB was treated, and the colitis treated, the colitis was much improved.

DISCUSSION

TB spreads via aerosol transmission, penetrating the alveoli of the lower lobes and causing an inflammatory reaction and development of a Ghon focus. Although active TB develops in approximately 10% of those exposed over a lifetime, in 90% of people, *M tuberculosis* remains controlled by the host immune response, termed latent disease. TNF- α plays an important role in the host immune response.^{5 6} Anti-TNF treatment can greatly increase the risk of TB reactivation, and so current guidelines recommend screening for latent TB prior to administering TB chemoprophylaxis.⁷ If latent TB is identified, then guidelines recommend either 6 months isoniazid chemoprophylaxis or 3 months dual therapy consisting of isoniazid and rifampicin to eradicate mycobacteria prior to starting anti-TNF treatment.⁷

Here, we present a case of miliary TB developing in a patient with ulcerative colitis treated with infliximab with a negative screening QuantiFERON blood test. The absolute value of QuantiFERON was just below what would have been positive but was not totally non-responsive, and was potentially due to immunosuppression. After reviewing the history, the patient's very close contact with his wife when she had pulmonary TB should have outweighed the negative QuantiFERON test and

led to consideration of prophylactic TB treatment therapy or a T spot test, which has a higher sensitivity.^{4 8} TB developing after anti-TNF treatment is well described³ and other cases of TB with negative QuantiFERON have been reported.⁹ A repeat QuantiFERON was not repeated because it was not clinically indicated and would not change management. Careful history taking and clinical risk evaluation should take priority over laboratory analyses.

Learning points

- ▶ Disseminated tuberculosis (TB) can develop despite a negative QuantiFERON.
- ▶ Immunosuppression can reduce the sensitivity of tests for latent TB.
- ▶ Careful evaluation of TB exposure history should be undertaken in all cases.
- ▶ If a clear history of exposure is obtained, either further investigation with an ELISPOT should be performed or chemoprophylaxis should be prescribed.

Acknowledgements The authors would like to thank the tuberculosis specialist nurses for their expert case management and ongoing support of the tuberculosis service.

Contributors All authors agreed with the final submitted version of the manuscript. BGM, FC and PTE treated the patient in clinic, and MTR reviewed all clinical records and wrote the first draft of the manuscript with subsequent input from all authors.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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