An unexpected case of disseminated tuberculosis from tumour necrosis factor inhibition

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The risk of latent tuberculosis (TB) infection (LTBI) reactivation is increased with the use of tumour necrosis factor inhibition (TNFi) and often presents with extrapulmonary infection. Although uncommon, false-negative LTBI screening with interferon gamma release assay (IGRA) does occur and can mislead clinicians to delaying a diagnosis of LTBI reactivation, especially given the systemic nature of active TB with often unusual presentations. A high index of suspicion of TB is thus needed when patients present with a systemic febrile illness and extensive testing should be undertaken to localise disease and direct therapy.

We report a 26-year-old South Korean-born, Australian man (migrated at age seven) who presented with a two-week febrile illness associated with dyspnoea, palpitations, night sweats, weight loss, myalgia and a non-productive cough. Nine months prior, he had the unusual diagnosis of posterior uveitis secondary to retinal vasculitis for which he was treated with and responded to adalimumab 40mg fortnightly, oral methotrexate 20mg weekly and tapering prednisolone. Prior to treatment, his pre-biologic screening with chest x-ray and IGRA (QuantiferonFERON-TB Gold) had been negative for LTBI. His posterior uveitis had responded to treatment and resolved seven months prior. He worked as a carpenter and had no known TB contacts or recent travel.

Initial evaluation revealed raised inflammatory markers (ESR 92mm/hr, CRP 122mg/L), hypervolemic hyponatremia (sodium 124mmol/L) and a transaminitis without cholestasis (ALT 231IU/L) and negative blood cultures. Chest x-ray revealed a pleuro-pericardial effusion with globular cardiomegaly, as well as right middle lobe consolidation which was confirmed on CT. An urgent pericardiocentesis produced 680mL of blood-stained exudate (lactate dehydrogenase 510units/L, protein 54g/L) that had benign cytology and was negative for bacteria on Gram and acid-fast stains. Transthoracic echocardiography revealed moderate biventricular dysfunction without thrombus or vegetation. A differential diagnosis of a systemic rheumatological condition, either related to the known posterior uveitis, or in relation to autoantibody formation from anti-TNF therapy, was considered, however extensive autoimmune panel revealed only a low-positive ANA with nucleolar staining pattern and positive anti-smooth muscle antibody. Colchicine was commenced for a presumed viral pleuro-pericarditis although serology was negative for causes such as adenovirus and HIV.

Two days later, he demonstrated new confusion and ongoing pyrexia. Broad spectrum antibiotics were started. Magnetic resonance imaging of the brain confirmed two cerebral abscesses (Figure 1) although cerebrospinal fluid analysis was unremarkable (glucose 3.0mmol/L, protein 0.26g/L, 0×10^6 polymorphs). Due to the low sensitivity of acid-fast staining, additional nucleic acid amplification testing of the initial pericardial fluid sample was performed for Mycobacterium tuberculosis (GeneXpert® Ultra, Cepheid, Sunnyvale CA, US) and confirmed pericardial tuberculosis. Repeat pleural drainage and subsequent onset of productive cough allowed additional pleural fluid and sputum testing, which confirmed both pleural and pulmonary tuberculosis, although
insufficient volume precluded testing on CSF. A final diagnosis of disseminated TB with pericardial, pleural, pulmonary and (presumed) central nervous system involvement was made and treatment was commenced with rifampicin, isoniazid, pyrazinamide, moxifloxacin (for central nervous system penetration) and prednisolone (for pericardial involvement), with symptoms resolving over two weeks.

We postulate that this man likely had LTBI acquired in South Korea, which has a high incidence, and that his initial IGRA testing was likely a false-negative. It remains a further possibility that this man’s initial diagnosis of posterior uveitis was actually TB uveitis rather than retinal vasculitis. The sensitivity of a test is defined as the proportion of patients with a disease that tests positive, which has been reported to be 63-90% for IGRA. When the disease is common (or when the patient has a high pre-test probability of the disease), even a modest sensitivity will translate to a high false-negative rate. It is therefore vital for clinicians to understand the diagnostic accuracy of all medical investigations and the expected interplay with clinical suspicion. In this case, despite a high pre-test probability for TB due to his known risk factors (birth in a high incidence country and significant immunosuppression), the index of suspicion remained falsely low and led to a delay in testing and diagnosis, due only to the single negative IGRA test nine months prior. Moreover,

Figure 1: Magnetic resonance imaging of the brain demonstrating 3mm left frontal lobe abscess with surrounding cerebritis and associated early osteomyelitis of the abutting frontal bone, as well as a 6mm left posterior lobe abscess with minimal oedema.
intraocular TB infections are thought to be a paucibilliary immune-mediated process, suggesting that this man’s initial improvement with immunosuppression may not be entirely unexpected.7,8 A positive IGRA relies on the host immune response, and therefore false-negatives may occur with immunosuppression that commonly occurs in patients with rheumatological conditions, 5, 6 and decreases to as low as 9% in immunocompromised individuals.3,9 Therefore, sequential IGRA testing to improve sensitivity prior to biologics may have been necessary to rule out LTBI.1 This case highlights the importance of maintaining a high index of suspicion for an atypical infection in a patient treated with immunosuppressive therapy despite negative screening, especially when a confluence of systemic symptoms can present as diagnostic challenges, to facilitate early management before multiple organ involvement ensues.

Competing interests:
Nil.

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