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Active tuberculosis (TB) with a negative interferon gamma release assay: failure of this test to rule out TB

Michael Maze, Lutz Beckert

Abstract

This report describes a patient with pulmonary tuberculosis in whom the interferon gamma release assay (IGRA) was negative at presentaion. It became positive following treatment. This illustrates that this test cannot be used to rule out tuberculosis, even in a low incidence country.

Tuberculosis (TB) notification rates in New Zealand are around 7/100,000 with highest rates in those of non-European ethnicity.[1] Primary pulmonary infection is often asymptomatic with conversion of a tuberculin skin test or interferon gamma release assay (IGRA) the only evidence of infection.

Active tuberculosis refers to patients with replicating organisms.[1] The diagnosis of active tuberculosis can be difficult because of the low sensitivity of sputum microscopy and the prolonged culture required.[2]

IGRAs are increasingly being used as a screening test to rule out TB infection. A positive IGRA result does not distinguish between latent and active disease and importantly false negative results can occur.[3–6]

We describe a case of active tuberculosis associated with a negative IGRA at presentation that seroconverted following treatment.

Case report

A 29-year-old man of Indian origin presented with 7 weeks of an unproductive cough, unexplained weight loss and supraclavicular lymphadenopathy. He was born in India, lived in New Zealand since 2006 and had frequent visits to India. His sister-in-law was being investigated for active TB. He had no significant past medical history and HIV serology was negative.

Examination was unremarkable besides small non-tender supraclavicular lymphadenopathy on the right. His chest radiograph showed a 30mm opacity in the right upper lobe. His interferon gamma release assay (QuantiFERON-TB Gold in-tube assay, Cellestis Ltd., Victoria, Australia) was negative with a value of 0.23 IU/ml.

A computed tomography scan of his chest showed low attenuation centre consolidation in the right upper lobe with some associated ground glass and lymph nodes at the right hilum extending up the mediastinum to the root of the neck on the right hand side. These nodes showed low attenuation centres. He then underwent bronchoscopy with right upper lobe lavage as well as a fine needle aspirate of a supraclavicular node. Both were negative for acid-fast bacilli on Ziehl-Neeson stain.

Nucleic acid amplification with the GeneXpert (Cepheid, California, USA) detected *Mycobacterium tuberculosis* DNA. The organism was subsequently cultured and proved to be fully sensitive. He was treated with six months of standard combination anti-tuberculous therapy. His symptoms resolved and his chest radiograph normalised. His repeat IGRA was positive with a value of 0.86 IU/ml.

Discussion

New Zealand's prevalence of TB is around 7-10/100,000; it is a low prevalence country but cases are concentrated in migrants.[1] A highly sensitivity test is required to rule out tuberculosis in a low prevalence setting. IGRAs indicate a cellular immune response to *Mycobacterium* tuberculosis antigens and therefore infection; they have been proposed as appropriate tests to rule out TB.[7]

One study has shown the T-spot.TB to be more sensitive than QuantiFERON-TB Gold in-tube assay, but a recent meta-analysis showed a sensitivity of approximately 80% for both the QuantiFERON-TB Gold in-tube assay (Cellestis Ltd., Carnegie, Australia) and the T-Spot.TB (Oxford Immunotec Ltd., Abingdon, UK).[3,8]

This may be due to a window period (up to 22 weeks) from infection to IGRA conversion, immunosupression such as HIV as well as impaired T cell activity from immune anergy caused by active TB infection.[39,10] The low sensitivity of IGRA results in a low negative predictive value in situations such as this case when there is a high clinical suspicion of tuberculosis.

This case serves as a reminder that even in low prevalence countries such as New Zealand, a negative IGRA does not rule out active tuberculosis when the clinical suspicion is high. Current guidelines conclude that IGRA should not be part of routine investigation for active tuberculosis but contribute only supplementary information .[1, 4,5]

Author information: Michael Maze, Advanced Trainee in Respiratory Medicine; Lutz Beckert, Respiratory Physician; Respiratory Medicine; Canterbury District Health Board, Christchurch

Correspondence: Lutz Beckert, Respiratory Medicine, Christchurch Hospital, PO Box 4345, Christchurch 8041, New Zealand. Email: Lutz.Beckert@cdhb.health.nz

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