



Tuberculosis the great masquerader

Elizabeth Wenqian Wang^a, Christine N. Okwesili^a, James B. Doub^{b,*}

^a Division of Infectious Diseases, University of Maryland St. Joseph Medical Center, Towson, MD 21204, USA

^b Division of Clinical Care and Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD 21201, USA

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ABSTRACT

With increased use of disease-modifying antirheumatic drugs, screening for latent tuberculosis infection is more important than ever. However, even with appropriate screening, reactivation of tuberculosis can occur in patients who have had significant epidemiological exposures. Herein, we present a case of a seventy-four-year-old woman with severe rheumatoid arthritis on long-term disease-modifying antirheumatic drugs who developed cryptic miliary tuberculosis. Histopathological findings from an abdominal lymph node biopsy showed caseating granulomas which were initially attributed to her rheumatoid arthritis given screening tests and sputum acid-fast cultures were negative for tuberculosis. It was not until tuberculosis spondylitis developed that the diagnosis was finally elucidated. This case highlights the need for clinicians to be vigilant about discussing historical epidemiological exposures to tuberculosis instead of relying solely on screening testing.

Introduction

Cryptic miliary tuberculosis (TB) is a rare form of disseminated TB that occurs from lymphohematogenous spread after either primary infections or reactivation of latent TB [1]. Symptoms are often nonspecific despite numerous organ involvement [2]. Diagnosis can be arduous given limited deranged laboratory findings and screening testing (tuberculin skin testing and interferon gamma release assays) can be negative [3]. In addition, imaging modalities are often not diagnostic and the ability to culture *Mycobacterium tuberculosis* from various sites can be difficult [1,3]. Therefore, other underlying disease processes are commonly attributed to clinical and histological findings causing delayed diagnosis and consequently increased morbidity and mortality [4]. Herein we present a case of cryptic miliary TB that smoldered given negative tuberculosis screening testing and sputum acid-fast bacilli (AFB) cultures. Diagnosis of TB was not made until the patient presented with TB spondylitis causing destruction of thoracic vertebrae and cord compression.

Case presentation

Seventy-four-year-old woman, with kyphosis and severe rheumatoid arthritis (RA) presented with severe back pain. Historically, the patient was born in India and immigrated to the US in her twenties. The patient was a retired nurse and consequently had undergone numerous

tuberculin skin tests and interferon gamma release assays which were negative. A year before presentation with back pain, she had acute cholecystitis necessitating cholecystectomy. Surgical pathology of a lymph node adjacent to the gallbladder showed caseating granulomas however staining for AFB was negative. The specimen was not sent for AFB culture, but the histology was concerning for TB and subsequently three sputum AFB cultures were collected which were negative. Repeat interferon gamma release assay was also negative as was an AFB blood culture. Therefore, the caseating granulomas were thought to be from rheumatoid nodules and consequently no antimycobacterial agents were started. Rather to control her RA better, methotrexate was changed to tocilizumab with improvement in her RA joint symptoms. However, after one year of tocilizumab she presented with severe back pain.

Thoracic X-ray showed compression fracture of the 4th thoracic vertebrae. Given the negative tuberculosis testing, this was thought to be secondary to osteoporosis and she underwent spinal instrumentation to help alleviate pain. The back pain initially improved but recurred and MRI of the thoracic spine showed destruction of the T3-T5 vertebral bodies with bony retropulsion into the spinal canal at T3 and T4 causing compression of the adjacent spinal cord (Fig. 1). Surgical decompression was conducted with bone histology showing extensive granulomas but no AFB were seen on staining. In light of granulomas in the vertebral body, multiple risk factors for TB and tocilizumab use, she was started on empiric TB therapy with rifampin, isoniazid, ethambutol and pyrazinamide. AFB bone cultures ultimately grew *M. tuberculosis* with no

* Correspondence to: Division of Infectious Diseases, 725 West Lombard Street, Baltimore, MD 21201, USA.

E-mail address: jdoub@ihv.umaryland.edu (J.B. Doub).

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Fig. 1. MRI sagittal view of thoracic spine: Marked destruction of the T5 vertebral body (Red arrow) with bony retropulsion into the spinal canal at T3 and T4 causing significant cord flattening.

antimicrobial resistance observed.

After several months of therapy, the patient stopped TB therapy due to nausea and vomiting. Off antimycobacterial agents, her back pain intensified and was referred for further instrumentation. However, to ensure compliance with rifampin and isoniazid, definitive instrumentation was deferred for at least 3 months on antimycobacterial agents. After this time, she had C2-T8 posterior segmental instrumentation. Since this last procedure her pain has drastically improved, and she is compliant with rifampin and isoniazid.

Discussion

In this case, cryptic miliary TB was arduous to diagnose given her underlying RA confounded the diagnosis. The caseating granulomas observed with her cholecystectomy were thought to be from RA and not from TB given the lack of AFB on histological staining and her negative TB screening tests. These negative tests were misleading causing a false sense that the caseating granulomas were from RA. Although interferon gamma release assays have been demonstrated to have excellent sensitivity with active TB, it is important to recognize that a negative IGRA does not conclusively rule out the diagnosis of TB disease [3]. Therefore, clinicians need to be cognizant of this fact and interpreted results in context of other clinical data and potential epidemiological exposures. Here the historical exposures to TB correlated with the pathology should have caused heightened concern for TB initially.

Moreover, the intraabdominal lymph node at time of cholecystectomy was not sent for AFB culture and the negative AFB sputum cultures further mislead clinicians. Correlated with these negative tests, the initial surgical management of the patient's spinal compression fracture with instrumentation also missed the opportunity to obtain pathological evaluation and AFB bone cultures [5]. Therefore, instrumentation failed due to her unrealized and untreated TB infection (Fig. 1). It was not until she had worsening of symptoms of destructive TB spondylitis with cord compression that the diagnosis was finally made.

Cryptic miliary TB can have poor diagnostic yields with respect to

the ability to grow TB especially with sputum cultures [6]. Rather it has been shown the lymph node cultures have potentially the highest yield [6]. Consequently, the analysis of her intraabdominal lymph node, and initial thoracic spine fracture with AFB cultures or next generation genetic testing likely would have been able to determine the diagnosis sooner. As well, the early administration of antimycobacterial agents may have prevented her progression of spondylitis and the need for further instrumentation thereby reducing morbidity in this case. This can be seen in a retrospective review of 70 adults with thoracic spinal TB, in which medical therapy alone was successful in 69 out of 70 patients [7]. Unfortunately, without proper treatment, the destruction of this patient's vertebral bodies was so extensive that instrumentation was indicated to stabilize the spine.

In this case we also elected to ensure compliance, given her previous non-compliance, with TB medications to thereby thwart potential further instrumentation failure before definitive instrumentation was implanted. Unlike in pyogenic bacterial infections in which bacterial biofilm is a main cause of recurrence, in mycobacterial spinal infections there is a paucity of data with respect to need for suppression therapy to prevent recurrence. Therefore, further studies are needed to clarify the need for suppression therapy to prevent recurrences and hardware failure in mycobacterial spinal instrumentation cases.

In conclusion, this is a rare case of cryptic miliary TB that was not diagnosed until destructive TB spondylitis occurred. Lessons can be learned from this case in that reliance on laboratory testing should not be the sole determining factor in ruling out tuberculosis especially in patients with significant epidemiological exposures and on disease-modifying agents. Rather when diagnostic testing is suggestive of tuberculosis thorough evaluations should be conducted to initiate antimycobacterial agents to thereby thwart the morbidity and mortality associated with delayed diagnosis and treatment.

CRedit authorship contribution statement

E.W.W, C.N.O and J.B.D treated the patient. All authors wrote and edited the manuscript.

Ethical approval

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of Interest

No conflict of interest.

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