BRITISH JOURNAL OF HOSPITAL MEDICINE

CASE REPORT

Where you least expect it: paradoxical tuberculosis-immune reconstitution inflammatory syndrome and wrist joint tuberculosis as the initial manifestation in a patient who is HIV-seronegative

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How to cite this article:
Ong Mingjing N, Casha R, Vella SM, Aquilina N, Fsadni C. Where you least expect it: paradoxical tuberculosis-immune reconstitution inflammatory syndrome and wrist joint tuberculosis as the initial manifestation in a patient who is HIV-seronegative. Br J Hosp Med. 2023. https://doi.org/10.12968/hmed.2022.0407

Introduction

Immune reconstitution inflammatory syndrome caused by tuberculosis is a diagnosis of exclusion that heavily relies on case definition with clinical data. Given that this can delay appropriate management and that there are limited treatment options, an in-depth

Case report

A 37-year-old Filipino, HIV-seronegative female was being investigated for lymphadenopathy, weight loss, persistent fever and mixed connective tissue disorder flare-up with right wrist synovitis. She was taking long-term corticosteroids for mixed connective tissue disorder and had no history of tuberculosis.

Investigations included an inpatient ultrasound-guided aspiration of the right wrist joint. The patient became septic post-procedure and developed constitutional symptoms with pleuritic chest pain and shortness of breath. An echocardiogram showed no cardiac pathology, but an electrocardiogram revealed Brugada changes secondary to ongoing sepsis. At the same time, a computed tomography pulmonary angiogram showed new enlarged supraclavicular and axillary lymph nodes with numerous pulmonary micronodules compared to a routine chest X-ray taken 1 month prior.

A right wrist washout was performed under teicoplanin and clindamycin cover, given the septic arthritis and Gram-positive growth culture from the right wrist. This culture later reported Gram-positive beaded rods, while the sample from the washout and sputum showed Grade 4+ and 1+ acid-fast bacilli on the Ziehl–Neelsen stain respectively. *Mycobacterium tuberculosis* complex cultivated showed no resistance to rifampicin or isoniazid. The standard anti-tuberculous treatment was started with rifampicin, isoniazid, ethambutol, pyrazinamide and pyridoxine dosed according to the patient's weight (44.6 kg).

She improved after starting anti-tuberculous treatment but deteriorated after 7 days, with 39.4°C fever, hypoxic with saturations of 90% on room air, constitutional symptoms, haemoptysis and dyspnoea at rest. Physical examination revealed bilateral lower limb pitting oedema and decreased air entry with fine crepitations in both lungs. Laboratory investigations revealed anaemia, dyselectrolytaemia and elevated levels of inflammatory markers. She was supplemented with electrolytes, oxygen and three units of red cells transfusion during this deterioration.

A repeat computed tomography pulmonary angiogram showed a new large pleural effusion bilaterally, pericardial effusion (Figures 1 and 2) and worsening lymphadenopathy, while another echocardiogram did not reveal any features of heart failure. Bumetanide and ertapenem were prescribed for lower limb oedema and *Klebsiella pneumoniae* extended spectrum beta-lactamase-positive urinary tract infection respectively. The dose of rifampicin, isoniazid, ethambutol, pyrazinamide was weight-adjusted during a 5 kg weight gain period secondary to the fluid retention from the hypoalbuminaemia.

In light of the new pleural effusions, worsening lymphadenopathy and symptoms following an initial response to treatment, a provisional diagnosis of tuberculosis-immune reconstitution inflammatory syndrome was made. She continued to improve with anti-tuberculous treatment and increased dose of corticosteroids. No further interventions or deterioration phases were made or observed. Treatment was continued for 12 months, and corticosteroids were reduced by 10 mg every 7 days for a month, then by 5 mg every 2 weeks.

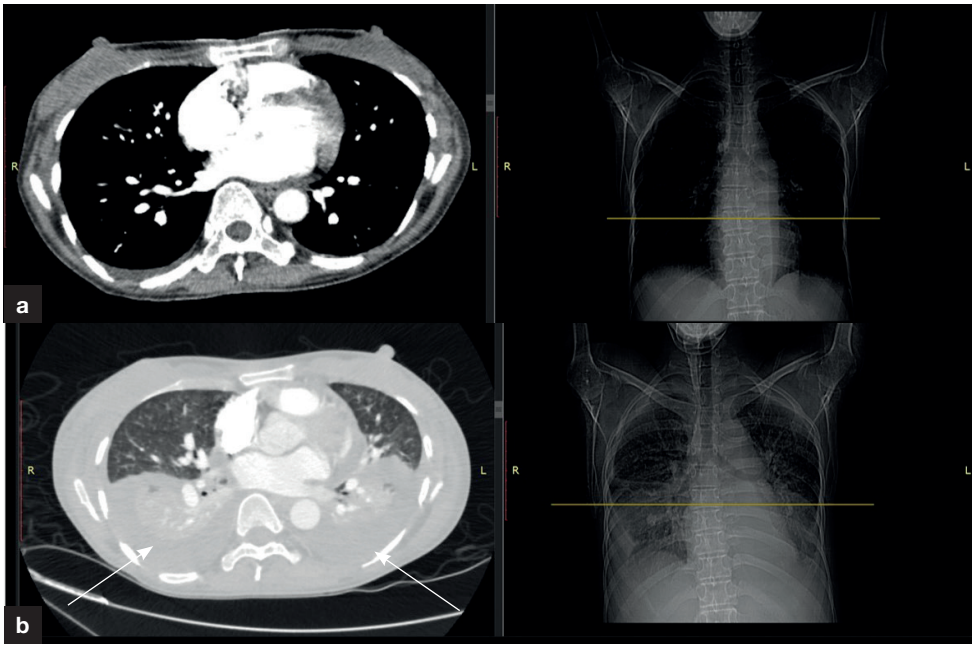

Figure 1. a. Computed tomography pulmonary angiogram taken just before starting treatment for tuberculosis. b. Large pleural effusion (arrows) on a computed tomography pulmonary angiogram taken 7 days later.

understanding of this phenomenon will increase clinician awareness and help with faster diagnosis and more effective management.

Immune reconstitution inflammatory syndrome and paradoxical reactions to tuberculosis are rarely linked in individuals who are not infected with human immunodeficiency virus (HIV). Tuberculosis involvement is also rarely seen in the wrist joint. This article highlights these uncommon occurrences in an individual who is immunosuppressed and HIV-seronegative.

Discussion

Diagnosis of tuberculosis in joints and bones and starting anti-tuberculous treatment are often delayed because of the low incidence in developed countries and the lengthy microbiological techniques or invasive biopsy practice that are needed despite medical advances (Malaviya, 2003; Sivasamy et al, 2019).

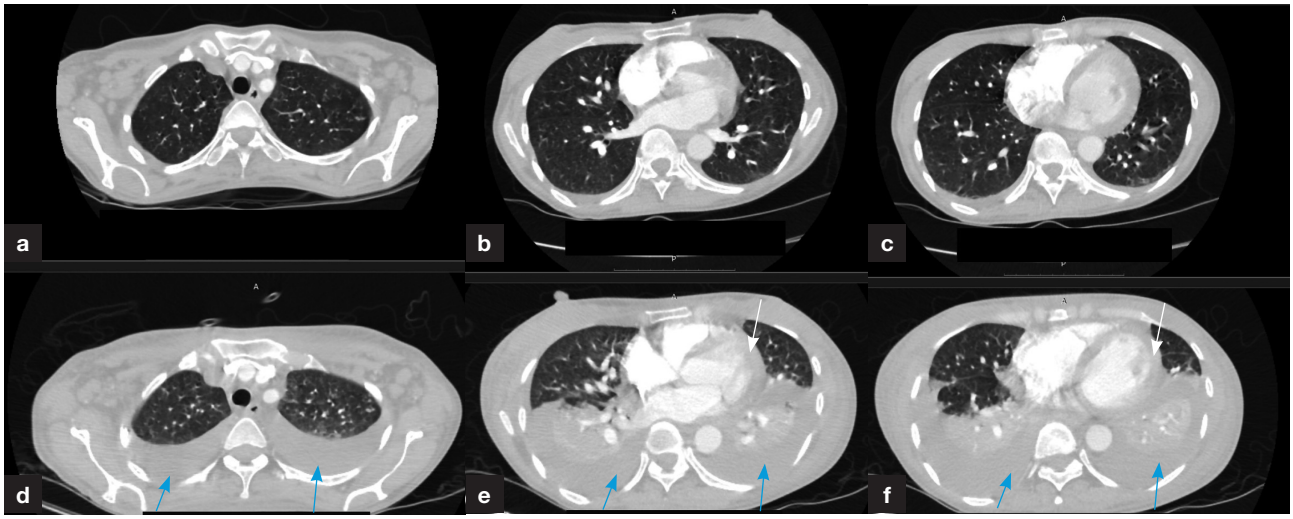

Figure 2. a–c. Three axial views of computed tomography pulmonary angiogram taken on day 0 of starting tuberculosis treatment compared to (d–f) views of the same site showing the extensive bilateral pleural effusion (blue arrows) and pericardial effusion (white arrows) taken on day 7.

Learning points

- Although the recorded mortality rate of paradoxical tuberculosis immune reconstitution inflammatory syndrome is relatively low, patients can deteriorate rapidly and become critically unwell.
- A delay in diagnosis can occur because of a low index of suspicion in HIV-seronegative patients.
- Better understanding of paradoxical tuberculosis-immune reconstitution inflammatory syndrome, increased clinician awareness and knowledge of associated risk factors could prevent unnecessary treatments, leading to faster diagnosis and effective patient management.

The immunopathogenesis of immune reconstitution inflammatory syndrome remains poorly understood with the involvement of T helper 1-driven immune responses in the presence of multibacillary disease and immunodeficiency (Lanzafame and Vento, 2016). High mycobacterial loads contribute to an increased risk of immune reconstitution inflammatory syndrome in people with disseminated and extrapulmonary tuberculosis (Cheng et al, 2007; Lanzafame and Vento, 2016).

Malnutrition, including anaemia, hypoalbuminaemia, baseline lymphopenia and lymphocytosis, are among the associated signs of paradoxical reactions in patients with tuberculosis who are HIV-negative (Cheng et al, 2007). Most paradoxical tuberculosis-immune reconstitution inflammatory syndrome in patients who do not have HIV has reported symptoms improving spontaneously following anti-tuberculous treatment initiation within 1–7 months and complete resolution within 18 months (Cheng et al, 2007; Wolfe, 2023).

There is currently no agreed standard treatment for tuberculosis-immune reconstitution inflammatory syndrome and limited evidence for its management (Quinn et al, 2020). However, it has been suggested that the length of antimicrobial therapy for bone involvement tuberculosis-immune reconstitution inflammatory syndrome should be at least 9 months, with a longer duration in those on adjuvant immunosuppressive therapies (Malaviya, 2003; Meintjes et al, 2010).

To date, corticosteroids remain the only first-line therapy proven by a randomised controlled trial to improve clinical symptoms, radiography results and quality of life (Meintjes et al, 2010). A tapering regimen has been suggested in the Médecins Sans Frontières medical guidelines, as abrupt cessation can lead to adrenal crisis and recrudescence of symptoms (Varaine and Rich, 2023). Despite clinical improvements being reported in patients with tuberculosis-immune reconstitution inflammatory syndrome using immunomodulators, such as tumour necrosis factor-alpha inhibitors, thalidomide, montelukast, pentoxifylline and vascular endothelial growth factor inhibitors, there is still inadequate evidence for their routine use (Quinn et al, 2020).

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References

Cheng S-L, Wang H-C, Yang P-C. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. Int J Tuberc Lung Dis. 2007;11(12):1290–1295

Lanzafame M, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. J Clin Tuberc Other Mycobact Dis. 2016;3:6–9. https://doi.org/10.1016/j.jctube.2016.03.002

Malaviya A. Arthritis associated with tuberculosis. Best Pract Res Clin Rheumatol. 2003;17(2):319–343. https://doi.org/10.1016/S1521-6942(02)00126-2

Meintjes G, Wilkinson RJ, Morroni C et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010;24(15):2381–2390. https://doi.org/10.1097/QAD.0b013e32833dfc68

Quinn CM, Poplin V, Kasibante J et al. Tuberculosis IRIS: pathogenesis, presentation, and management across the spectrum of disease. Life. 2020;10(11):262. https://doi.org/10.3390/life10110262

Sivasamy P, Bajuri MY, Ghani AW. Tuberculosis of the left wrist joint and spine. Cureus. 2019;11(11):e6203. https://doi.org/10.7759/cureus.6203

Varaine F, Rich ML. Tuberculosis. 2023. https://medicalguidelines.msf.org/sites/default/files/pdf/guideline-1063-en.pdf (accessed 23 November 2023)

Wolfe C. Immune reconstitution inflammatory syndrome. 2023. https://www.uptodate.com/contents/immune-reconstitution-inflammatory-syndrome#H2664891578 (accessed 21 November 2023)