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An Elusive Diagnosis: Miliary Tuberculosis With Initially Negative Diagnostic Tests

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Abstract

Miliary tuberculosis is a potentially life-threatening manifestation of *Mycobacterium tuberculosis* infection and occurs mainly due to the haematogenous dissemination of the pathogen. It can have various non-specific clinical manifestations, and with the possibility of false-negative respiratory samples and immunological tests, the diagnosis can be quite challenging. Here, we present the case of a 34-year-old female who presented with persistent fever, non-specific respiratory symptoms, and a history of travel to an endemic tuberculosis (TB) region. The patient was commenced on empirical therapy for pyrexia of unknown origin when all the initial investigations, including sputum acid-fast bacilli (AFB) smears, MTB PCR (*Mycobacterium tuberculosis* polymerase chain reaction), and interferon-gamma release assay (IGRA), came back negative. The treatment, however, did not result in substantial improvement. CT chest subsequently demonstrated bilateral pulmonary nodules and hilar lymphadenopathy, supporting the diagnosis of tuberculosis. With little improvement and progressive deterioration of the patient leading to respiratory failure and admission to intensive care for nasal high-flow oxygen therapy, empirical anti-tubercular therapy (ATT) was initiated and resulted in rapid and remarkable improvement of the patient. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed, and mediastinal lymph node culture ultimately confirmed *Mycobacterium tuberculosis*. This case highlights the diagnostic difficulty of miliary tuberculosis, especially in patients with atypical presentations and false-negative initial rapid diagnostic tests. The role of invasive modalities like EBUS is also worth mentioning, as these can help in establishing a definitive diagnosis and prevent delays in treatment.

Categories: Pulmonology, Internal Medicine, Infectious Disease
Keywords: acid-fast bacilli, anti tubercular therapy (att), ebus-tbna, haematogenous infection, miliary tuberculosis

Introduction

Tuberculosis remains one of the most serious infectious diseases worldwide. According to the Global TB Report published in 2024 by WHO, more than 10 million people were affected by TB in the year 2023 [1]. It is caused by the bacterium *Mycobacterium tuberculosis* and is the leading cause of death from a single infectious agent [2].

The most common form is pulmonary TB, which is spread by airborne droplets and affects the lungs, causing symptoms like chronic cough with or without hemoptysis, chest pain, night sweats and weight loss. Miliary tuberculosis is a more severe form of TB that occurs when the pathogen enters the bloodstream, affecting multiple organs. The lesions on the affected organs have a characteristic ‘millet seed’-like appearance, hence the name miliary [3]. It can present with a diverse spectrum of clinical manifestations such as fever, night sweats, generalised weakness, weight loss, fatigue, and a persistent dry cough. These symptoms can be slow to start and are similar to those of other systemic diseases, which can lead to delayed or missed diagnoses. It is important to consider miliary TB in the differential diagnosis of patients with compatible clinical features, especially in those with risk factors, such as recent travel to endemic regions, and when conventional respiratory samples are negative [4].

Case Presentation

A 34-year-old woman, living in the UK for the past 4 years, presented to her general practitioner with a 1-month history of fever and persistent cough with white sputum. She did not report weight loss or any other constitutional symptom that could suggest TB. An otherwise fit and healthy adult with no significant medical history, she was treated for a presumed respiratory infection.

With her symptoms persistent even after the general practitioner’s treatment, she presented to the hospital in April 2026. Initial investigations (Table *1*), which also included a blood and midstream urine culture, were requested but no abnormal findings were reported except mildly low haemoglobin.

Tests	Results	Reference Range
Haemoglobin	109 g/L	120-150 g/L
White Cells Count	4.8* 10^9/L	4.0- 11.0* 10^9/L
Neutrophils	3.38* 10^9/L	2.0-7.0* 10^9/L
Lymphocytes	0.94*10^9/L	1.0-4.0* 10^9/L
Platelets	289*10^9/L	150-400* 10^9/L
CRP	2 mg/L	<5 mg/L.
Bilirubin	9 µmol/L	0-21 µmol/L
Sodium	143 mmol/L	133-145 mmol/L
Potassium	3.9 mmol/L	3.5-5.3 mmol/L
Urea	2.9 mmol/L	2.5-7.8 mmol/L
Creatinine	46µmol/L	45-84 µmol/L
Urine MSU	No Growth	-
Blood Cultures	No Growth	-
Malarial Parasite	Negative	-
ESR	27 mm/h	3-15 mm/h

TABLE 1: List of initial Investigations requested for the patient

CRP: C-reactive protein; MSU: mid-stream urine specimen; ESR: erythrocyte sedimentation rate

A chest radiograph was performed and reported as normal, although a subtle hilar prominence was subsequently noted (Figure *1*). She was treated with doxycycline and discharged.

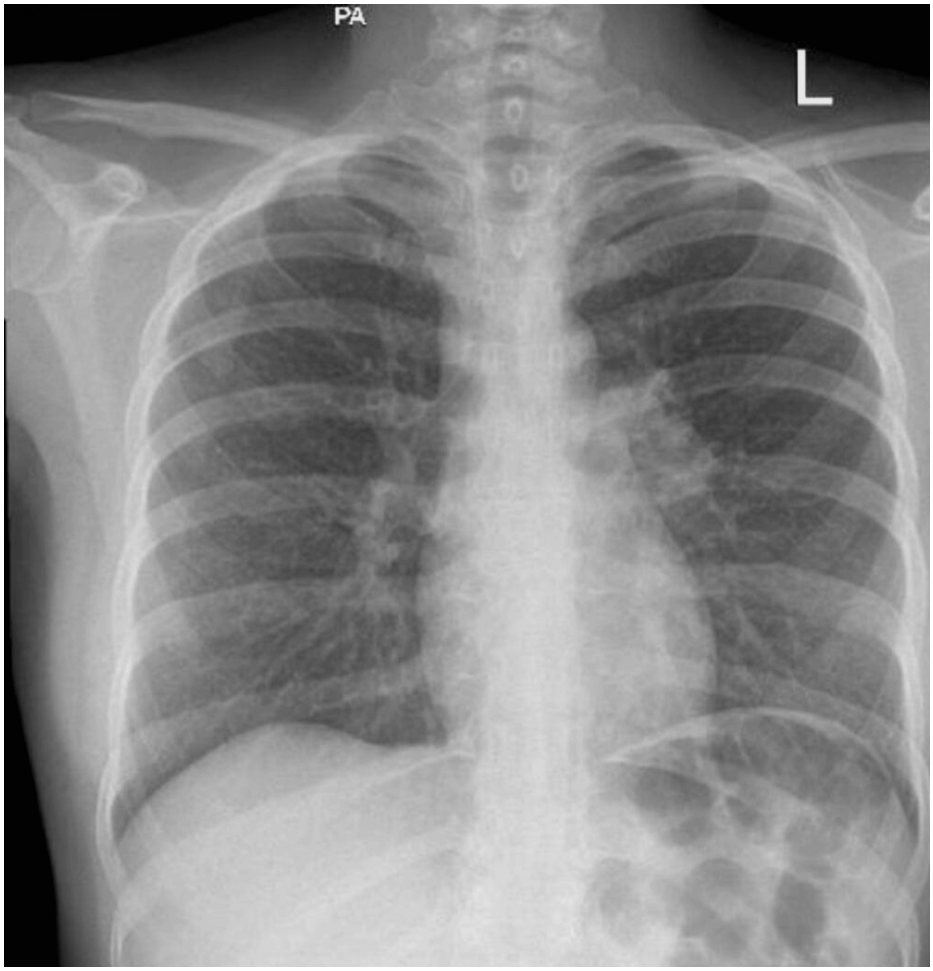


FIGURE 1: Chest radiograph

Hilar prominences visible on the left side of the X-ray.

Further history revealed that she had travelled to India in October 2025. During this visit, she had developed a non-specific cough-like illness. Attributing her symptoms to being caused by air pollution, she was treated with antibiotics and an emergency inhaler. She could not recall receiving Bacillus Calmette-Guérin (BCG) vaccination or having a BCG scar. She re-presented to the hospital after two weeks, with worsening symptoms. Her cough had become continuous and was associated with fever, palpitations, and a rash over the left lower abdomen. She also reported reduced appetite and weight loss. Considering the possibilities of TB, sarcoidosis and haematological malignancy, further investigations were done (Table *2*), including respiratory viral PCR, angiotensin-converting enzyme (ACE) level, and hepatitis serology, but were reported negative. Her sputum culture showed mixed upper respiratory tract flora. An IGRA test for TB was also negative.

Tests	Results	Reference Range
ACE	100 U/L	12-71 U/L
ANCA	Negative	-
ANA	Negative	-
Serum C3 levels	1.7 g/L	0.75-1.85g/L
Serum C4 levels	0.5 g/L	0.10-0.60 g/L
Beta D-Glucan	Negative	-
Sputum Culture	Mixed respiratory flora noted	-
Respiratory PCR (GeneXpert)	Negative	-
Hepatitis A	Negative	-
Hepatitis B	Negative	-
Hepatitis C	Negative	-
HIV	Negative	-
IGRA for TB	Negative	-

TABLE 2: Further investigations, including tests for tuberculosis requested to rule out causes for pyrexia of unknown origin

ACE: angiotensin-converting enzyme, used in the diagnosis of sarcoidosis. ANCA: antineutrophil cytoplasmic antibodies, used to help diagnose autoimmune and connective tissue disorders. ANA: antinuclear antibody, used to help diagnose autoimmune and connective tissue disorders. Serum C3 and C4 levels: blood tests that measure the levels of two major proteins part of the complement system; low levels are commonly seen in autoimmune conditions like systemic lupus erythematosus. Beta D-glucan: used in the diagnosis of fungal infections. GeneXpert: a rapid, automated molecular diagnostic test used primarily to detect tuberculosis and test for rifampicin resistance from a sputum or fluid sample. HIV: human immunodeficiency virus. IGRA: interferon-gamma release assay (IGRA), a blood test used to detect *Mycobacterium tuberculosis* infection.

In view of her persistent symptoms and with no abnormality in the investigations, she was labelled as having pyrexia of unknown origin and started on amoxicillin for a possible secondary bacterial pneumonia. Despite the negative microbiological and immunological investigations, tuberculosis remained within the differential diagnoses because of the patient's epidemiological background and evolving clinical picture.

Subsequently, a CT of the thorax, abdomen and pelvis was requested and demonstrated extensive bilateral pulmonary micronodules (Figure *2*) with rim-enhancing necrotic hilar and mediastinal lymphadenopathy (Figure *3*). An endobronchial ultrasound (EBUS) was planned to obtain tissue and microbiological samples; however, her clinical condition deteriorated and precluded the procedure.

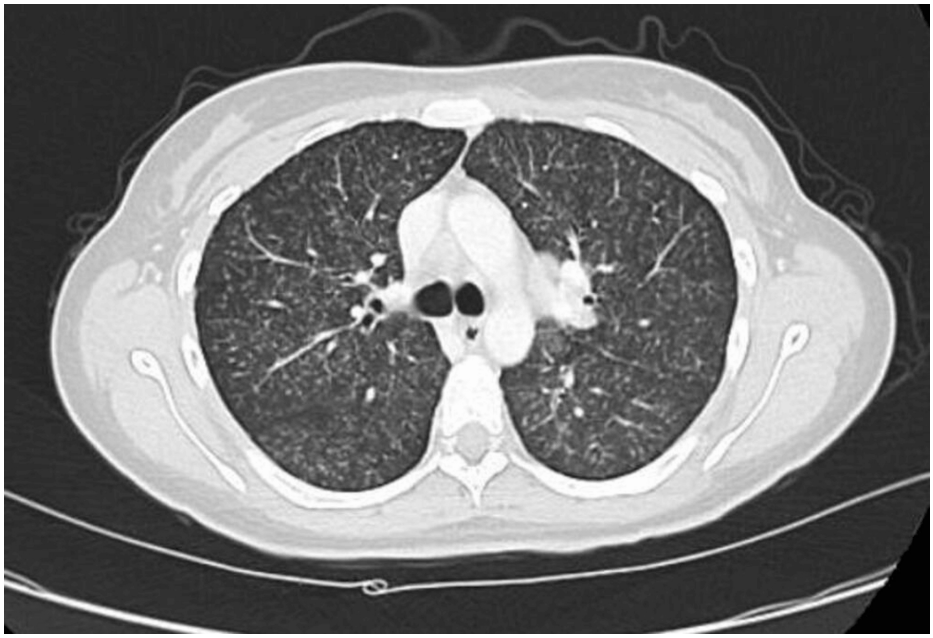


FIGURE 2: CT chest

Extensive bilateral pulmonary nodules noticed

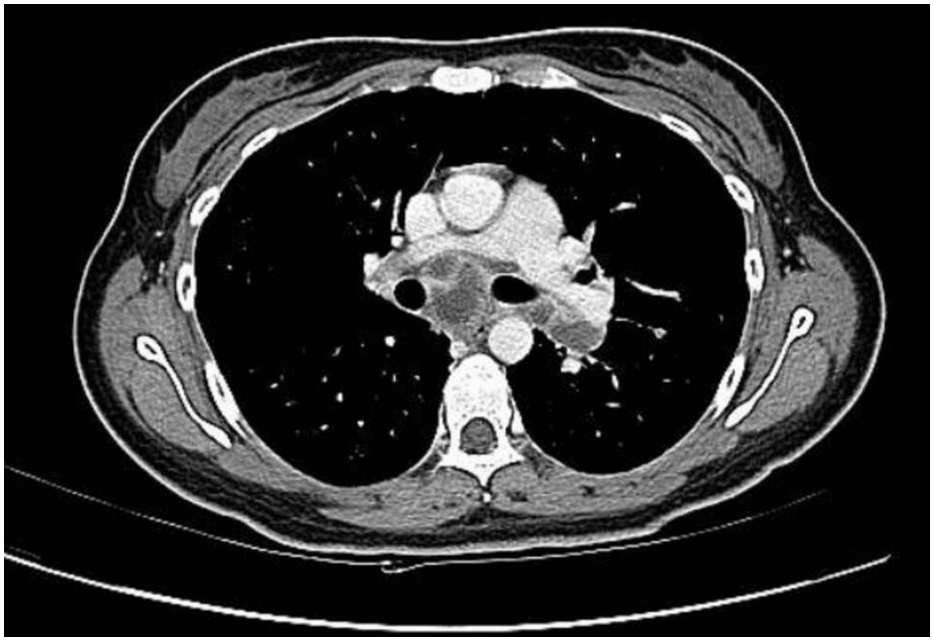


FIGURE 3: CT chest

Mediastinal and hilar lymphadenopathy visible

She developed respiratory failure and was admitted to the intensive care unit requiring high-flow nasal oxygen. A CT pulmonary angiography (CTPA) was performed to exclude pulmonary embolism and showed no evidence of embolism, effusion, or cavitation. However, there was an interval increase in the extensive miliary nodules with superadded diffuse ground-glass consolidation in all lobes (Figure *4*).



FIGURE 4: CT pulmonary angiography

Extensive miliary nodules and diffuse ground-glass consolidation seen in all lobes

In view of the progressive clinical deterioration and the high clinical and radiological suspicion of TB despite negative initial investigations, empirical anti-tubercular therapy (ATT) was commenced. The patient demonstrated marked clinical improvement within three days of starting ATT. Once clinically stable, bronchoscopy with EBUS-guided sampling was performed, with the histopathological examination demonstrating abundant granular necrotic material and degenerated cells. No malignant cells were identified. The histopathological findings were considered consistent with an infective process and, in the clinical context, supportive of TB. Subsequent mycobacterial culture from the sampled material was also positive for *Mycobacterium tuberculosis*, confirming the diagnosis.

Discussion

This case demonstrates the diagnostic difficulty that can arise in miliary TB when initial microbiological and immunological investigations are negative. The patient initially presented with relatively non-specific respiratory symptoms and had a low CRP despite significant underlying disease. Her initial chest radiograph was also reported as normal. These findings contributed to the initial diagnostic uncertainty.

The subsequent CT findings were considerably more concerning, demonstrating extensive pulmonary micronodularity together with necrotic hilar and mediastinal lymphadenopathy. A miliary pattern on chest imaging has a broad differential diagnosis, including TB, disseminated fungal infection, metastatic malignancy, and granulomatous disease such as sarcoidosis. The clinical differential diagnoses in this case appropriately included TB, sarcoidosis and haematological malignancy [5,6].

The patient's previous travel to India represented an important epidemiological clue. However, she had initially attributed her previous respiratory symptoms to air pollution, and could not recall a history of BCG vaccination or a BCG scar. The previous episode of cough could potentially have represented an earlier manifestation of TB, although this cannot be established retrospectively.

One of the most important features of this case was the initial negative TB investigations. The patient's IGRA was negative, sputum microscopy did not demonstrate AFB and TB PCR/GeneXpert was negative. A negative IGRA, however, does not exclude active TB in a patient with clinical features suggestive of disease. Similarly, negative sputum smear microscopy cannot rule out TB [7,8]. The subsequent radiological progression was particularly significant. The initial CT demonstrated extensive bilateral pulmonary micronodules and necrotic hilar and mediastinal lymphadenopathy. When the patient deteriorated, repeat CTPA demonstrated progression of the miliary nodularity with new ground-glass changes and consolidation. The combination of progressive radiological disease and clinical deterioration increased the likelihood of an active infective process despite the negative initial investigations.

The patient subsequently required ICU admission and high-flow nasal oxygen (HFNO). At this point, waiting for definitive microbiological confirmation would have risked further clinical deterioration. Empirical ATT was therefore initiated based on the overall clinical and radiological picture. The rapid improvement within three days of treatment further supported the working diagnosis, although clinical response alone should

not be considered diagnostic.

The EBUS findings provided additional diagnostic evidence. Samples from a mediastinal lymph node demonstrated abundant necrotic material and epithelioid and multinucleated histiocytes, supporting necrotising granulomatous inflammation. No malignant cells were identified. Necrotising granulomatous inflammation has a broad differential, but in the context of the characteristic radiological findings and clinical presentation, TB was strongly supported.

Definitive microbiological confirmation was subsequently obtained when mycobacterial culture grew *Mycobacterium tuberculosis*. Culture remains an important reference method for confirmation of TB and enables subsequent susceptibility testing [7,9].

The treatment administered was consistent with the standard six-month regimen for active TB without central nervous system involvement: rifampicin, isoniazid, pyrazinamide and ethambutol for the first two months, followed by rifampicin and isoniazid for a further four months. Pyridoxine was given alongside isoniazid. National Institute for Health and Care Excellence (NICE) recommends this regimen for active TB without CNS involvement, with modification according to drug susceptibility results [10]. WHO guidance similarly recognises two months of rifampicin, isoniazid, pyrazinamide and ethambutol followed by four months of rifampicin and isoniazid as the standard six-month regimen for drug-susceptible pulmonary TB [11].

The principal learning point from this case is that negative initial TB investigations should not be interpreted in isolation when the clinical and radiological suspicion remains high. In this patient, the combination of epidemiological history, progressive systemic and respiratory symptoms, characteristic CT findings and subsequent clinical deterioration justified escalation to invasive investigation and empirical treatment despite negative initial tests.

The case also demonstrates the value of obtaining tissue from mediastinal or hilar lymph nodes when sputum-based investigations are non-diagnostic. EBUS provided material that demonstrated necrotising granulomatous inflammation and ultimately allowed microbiological confirmation.

Conclusions

Miliary TB can present with non-specific respiratory and constitutional symptoms and may initially be difficult to distinguish from malignancy, sarcoidosis and other infective or inflammatory conditions.

This case highlights that negative IGRA, sputum AFB microscopy and TB PCR/GeneXpert do not exclude active TB when clinical and radiological suspicion remains high. Progressive miliary pulmonary nodularity with necrotic hilar and mediastinal lymphadenopathy, particularly when accompanied by clinical deterioration, should prompt urgent specialist assessment and consideration of invasive sampling. In this patient, empirical ATT was commenced because of progressive clinical and radiological disease despite negative initial investigations, resulting in rapid clinical improvement. EBUS- guided sampling demonstrated necrotising granulomatous inflammation, while subsequent culture confirmed *Mycobacterium tuberculosis*. Early recognition and treatment of miliary TB are important because clinical deterioration can be rapid, and waiting for definitive microbiological confirmation may not always be appropriate in a clinically unstable patient.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Muhammad Zeeshan Khan, Asad Anwar

Acquisition, analysis, or interpretation of data: Muhammad Zeeshan Khan, Asad Anwar

Drafting of the manuscript: Muhammad Zeeshan Khan

Critical review of the manuscript for important intellectual content: Muhammad Zeeshan Khan, Asad Anwar

Supervision: Asad Anwar

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all

participants in this study. **AI use statement:** The authors used ChatGPT as follows: language polishing, structure or formatting in the Introduction section. I have used ChatGPT (OpenAI, San Francisco, CA, US) for polishing the language, structure, and formatting of the article. The authors confirm that they have reviewed and verified all AI-assisted content and take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. WHO Global Tuberculosis Report 2024. (2024). Accessed: November 19, 2026: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024.
2. Sun MR, Xing JY, Li XT, Fang R, Zhang Y, Li ZL, Song NN: Recent advances in research on Mycobacterium tuberculosis virulence factors and their role in pathogenesis. J Microbiol Immunol Infect. 2025, 58:497-507. 10.1016/j.jmii.2025.03.017
3. Centers for Disease Control and Prevention. Clinical overview of tuberculosis disease . (2025). https://www.cdc.gov/tb/hcp/clinical-overview/tuberculosis-disease.html.
4. M S, Yelne S, Chaudhary M, Agrawal A: Unveiling the silent invader: a case report on miliary tuberculosis . Cureus. 2023, 15:e41817. 10.7759/cureus.41817
5. Nishino M, Itoh H, Hatabu H: A practical approach to high-resolution CT of diffuse lung disease . Eur J Radiol. 2014, 83:6-19. 10.1016/j.ejrad.2012.12.028
6. Ferrazza AM, Baldassarri P: Presentation and diagnosis of interstitial lung diseases . Thoracic Radiology. Carbone I, Anzidei M (ed): Springer, Cham; 2020. 10.1007/978-3-030-35765-8_9
7. Centers for Disease Control and Prevention. Clinical and laboratory diagnosis for tuberculosis . (2025). https://www.cdc.gov/tb/hcp/testing-diagnosis/clinical-and-laboratory-diagnosis.html.
8. Centers for Disease Control and Prevention. TB blood tests (interferon-gamma release assays [IGRA]) (2/2) . (2025). https://www.cdc.gov/tb/webcourses/tb101/page202.html.
9. Centers for Disease Control and Prevention. Bacteriological examination - culture. TB 101 . (n.d.). https://www.cdc.gov/tb/webcourses/TB101/page17045.html.
10. National Institute for Health and Care Excellence. Tuberculosis (NG33): recommendations . (2024). https://www.nice.org.uk/guidance/ng33/chapter/Recommendations.
11. WHO consolidated guidelines on tuberculosis: module 3: diagnosis . (2025). https://www.who.int/publications/i/item/9789240107984.