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CASE REPORT

Latent Tuberculosis Infection and Cryptococcus and Rhinovirus Co-Infection in an Immunosuppressed Patient

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SUMMARY

Background: **Mycobacterium tuberculosis may persist latently within the host, often presenting with atypical clinical features. In the context of immunosuppression, latent infection can reactivate, and the increased susceptibility to opportunistic infections further complicates the diagnosis and management of tuberculosis.**
Methods: **We report the case of a patient with connective tissue disease and a history of pulmonary nodule resection, who developed respiratory symptoms following two months of methylprednisolone therapy. The initial diagnosis was community-acquired pneumonia. Targeted next-generation sequencing of sputum identified pathogens.**
Results: **tNGS identified multiple pathogens, including Mycobacterium tuberculosis, Cryptococcus, and rhinovirus. Retrospective analysis suggested that tuberculosis likely resulted from the reactivation of latent Mycobacterium tuberculosis bacilli at the site of a previously resected pulmonary lesion.**
Conclusions: **In immunosuppressed patients, latent tuberculosis reactivation and rare infections should be considered. When symptoms are atypical, tNGS provides an effective tool for rapid and accurate pathogen detection to guide treatment.**
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KEYWORDS

Mycobacterium tuberculosis, cryptococcus, co-infections, connective tissue diseases, next-generation sequencing

CASE REPORT

A 75-year-old woman was admitted on 2025-02-01 with a 10-day history of cough and dyspnea after catching a cold. She had an 8-year history of bronchiectasis and compromised airway function. A chest CT performed on 2022-10-20 revealed multiple scattered pulmonary nodules, which were not further evaluated. A follow-up chest CT on 2023-05-19 showed enlargement of a right upper lobe nodule with a central solid component and mixed density, raising suspicion for malignancy (Figure 1). A wedge resection of the right upper lobe was performed, and a solid pulmonary nodule measuring 0.5 cm in diameter was excised. Histopathological examination revealed chronic granulomatous inflammation with caseous necrosis. Immunohistochemistry showed

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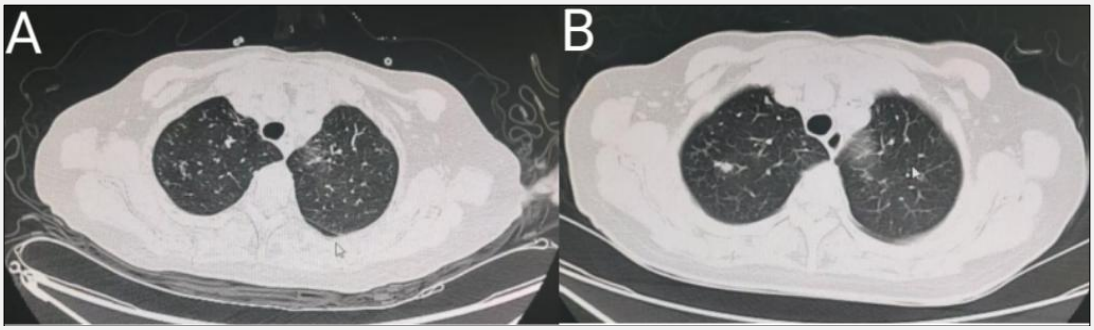

Figure 1. Chest CT Changes: 2022-10-20 Chest CT (A) shows multiple scattered pulmonary nodules of varying sizes. 2023-05-19 Chest CT (B) shows a significant enlargement of the right upper lobe nodular shadow, with a central solid component and heterogeneous density, compared to (A).

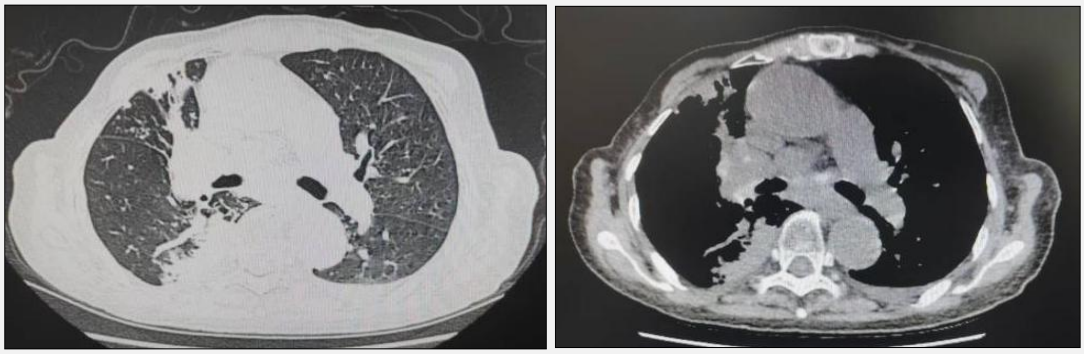

Figure 2. 2025-02-06 Chest CT shows patchy infiltrative shadows in the right lower lobe of the patient's lungs, along with thickened lung markings throughout the lung fields.

CD68 (+), CD163 (+), PAS (−), and methenamine silver stain (−). As detection of antibodies against Mycobacterium tuberculosis was negative preoperatively, no acid-fast bacilli were observed in tissue sections, and there were no clinical signs of active tuberculosis (low-grade fever, night sweats), anti-tuberculosis therapy was not administered postoperatively. In November 2024, the patient presented with knee joint pain, xerostomia, and Raynaud's phenomenon affecting both hands. Autoimmune serology revealed positive antinuclear antibody IgG, anti-Ro-52 (LIA) positivity, and strongly positive anti-CENP-B (+++). Erythrocyte sedimentation rate (ESR) was elevated at 78 mm/hour. Based on clinical features and laboratory findings, a diagnosis of connective tissue disease was established, and the patient was discharged on oral methylprednisolone 20 mg/day. Upon admission for the current episode, auscultation revealed coarse breath sounds with occasional moist rales in both lungs. Laboratory tests showed a white blood cell count of 5.1 x 10^9/L, a neutrophil percentage of 84.7%, and a C-reactive protein (CRP) level of 46.70 mg/L. On 2025-02-06, the chest CT results showed patchy infiltrates in both lungs as well as denser pulmonary markings, all pointing toward inflammatory alterations (Figure 2). A presumptive diagnosis of community-acquired pneumonia was made. The patient was started on piperacillin for anti-infective therapy, and inhaled budesonide was administered to relieve dyspnea; however, no significant clinical improvement was observed after several days. Due to elevated myocardial

enzymes and fluctuating oxygen saturation (95%), bronchoalveolar lavage via bronchoscopy was not performed after risk assessment. Sputum samples were submitted for targeted next-generation sequencing (tNGS), which revealed the following pathogens: Cryptococcus neoformans (25,491), human rhinovirus C (18,765), and Mycobacterium tuberculosis complex (665). Based on the diagnosis of triple infection with Cryptococcus, Mycobacterium tuberculosis, and human rhinovirus C, the patient was transferred to a specialized infectious disease hospital for further management.

DISCUSSION

Pulmonary tuberculosis lesions can present with a wide range of pathological changes, including consolidation, cavitation, exudation, fibrosis, and caseous necrosis [1]. Pulmonary granulomas, formed by immune cells encapsulating pathogens that are difficult to eliminate, are considered a hallmark of tuberculosis [2,3]. Globally, approximately one-quarter of the population is estimated to have latent tuberculosis infection (LTBI) as reported [4]. In immunocompromised individuals, LTBI may be reactivated and progress to active tuberculosis. LTBI is typically asymptomatic, and currently, there is no direct method for detecting latent M. tuberculosis. Patients with connective tissue diseases are particularly vulnerable to latent tuberculosis infection (LTBI) due to long-term immunosuppressive therapy. When prednisone is administered at a dose > 15 mg/day, it can impair cellular immune responses, which not only increases the risk of LTBI reactivation but also leads to false-negative PPD results [5,6].

In immunocompromised individuals with community-acquired pneumonia, rhinovirus co-infection with M. tuberculosis is not uncommon [7]. Rhinovirus can disrupt the epithelial barrier of the respiratory tract, creating a favorable environment for secondary bacterial or fungal infections and increasing the risk of coinfection. Cryptococcosis is an opportunistic fungal infection, mainly of type Cryptococcus neoformans and Cryptococcus gattii. Cryptococcus neoformans, an encapsulated basidiomycetous yeast found in bird droppings, has a long latency period and a mortality rate ranging from 20% to 70% [8,9]. It usually starts in the lungs, where symptoms include shortness of breath, coughing, chest pain, and hemoptysis, and in most cases spreads to the central nervous system. A positive serum CrAg-LFA test is considered diagnostic for cryptococcosis [10]. Immunosuppression is the primary risk factor for cryptococcal disease, which commonly occurs in AIDS patients, with early symptoms resembling bacterial community-acquired pneumonia [11]. Cryptococcal infections are increasingly recognized among non-HIV immunosuppressed patients, particularly in those receiving corticosteroid therapy. Cryptococcus may suppress host immunity by inhibiting tumor necrosis factor-alpha production and lymphocyte proliferation, further increasing susceptibility to or reactivation of M. tuberculosis [12]. Studies show that patients with cryptococcosis are at significantly higher risk of developing active tuberculosis. Of note, a history of pulmonary tuberculosis is a known risk factor for asymptomatic cryptococcal antigenemia in immunocompromised individuals [13]. In such contexts, infection with either pathogen may enhance sensitivity to the other, increasing the risk of co-infection.

Upon reviewing the clinical course and medical history of our patient, we speculated that latent Mycobacterium tuberculosis persisted at the site of the previously resected nodule. Histopathology revealed chronic granulomatous inflammation with caseous necrosis. Although acid-fast staining did not detect M. tuberculosis, this does not entirely rule out infection. Under normal immune surveillance, the host may suppress bacterial proliferation to levels undetectable by pathology. After the patient was diagnosed with a connective tissue disease and began long-term corticosteroid therapy, pulmonary infection developed. This suggests that immunosuppression may have allowed the transition from latent to active tuberculosis.

The patient's tNGS results showed higher sequence abundance for Cryptococcus than M. tuberculosis, suggesting that cryptococcal proliferation may have further impaired host immunity and facilitated tuberculosis reactivation [12]. Due to overlapping imaging features and nonspecific clinical manifestations of cryptococcosis and tuberculosis [11], identifying causative organisms in mixed pulmonary infections can be challenging. In this case, we employed tNGS - a high-throughput sequencing technique capable of detecting hundreds to thousands of targets - to achieve rapid and sensitive pathogen identification [14], enabling accurate diagnosis and guiding individualized treatment strategies.

CONCLUSION

Mycobacterium tuberculosis possesses a latent capability that is often clinically overlooked. In immunosuppressed patients, atypical imaging findings and opportunistic co-infections complicate diagnosis. Even without clear immunodeficiency or epidemiological risk, clinicians should remain vigilant. Next-generation sequencing (NGS) offers a valuable adjunct for pathogen detection and diagnosis. The optimization of infection diagnostics and the risk-benefit balance between immunosuppressive and anti-infective therapies represent key challenges in the management of immunosuppressed patients and warrant continued clinical attention.

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Ethical Approval:
This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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