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Reactivation of Pulmonary Tuberculosis Vs. Connective Tissue Disease Related Interstitial Lung Disease – A Diagnostic Conundrum

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Abstract:

- ***Background***

Distinguishing between reactivation of pulmonary tuberculosis (TB) and interstitial lung disease (ILD) associated with connective tissue diseases poses a diagnostic challenge due to overlapping clinical and radiological features. This case highlights the complexities in differentiating these conditions and the need for a multidisciplinary approach.

- ***Case Presentation***

An 18-year-old male, a farmer and a part time driver by occupation, presented with cough with expectoration, fever with chills and exertional breathlessness for 15 days. He had a history of incomplete antitubercular treatment therapy (ATT) initiated six months prior based on radiological suspicion of pulmonary TB. Examination revealed digital clubbing, calcinosis cutis and skin thickening of the upper extremities

- ***Investigations:***

Chest Xray (CXR) and high resolution computed tomography (HRCT) of the thorax demonstrated fibrobronchiectatic and fibrocavitatory changes with diffuse lung involvement suggestive of active Koch's infection. However, sputum CBNAAT was negative and further autoimmune workup revealed a positive rheumatoid factor and strongly positive anti-SCL-70 antibodies indicative of an underlying connective tissue disease. Pulmonary function tests showed a restrictive pattern and echocardiography suggested mild pulmonary hypertension.

- ***Management and Outcome***

The patient was initiated on antibiotics for infection control, antifibrotic therapy for ILD management and closely monitored for disease progression. The case underscores the necessity of comprehensive immunological and microbiological workup in patients with suspected TB, especially in endemic areas to avoid misdiagnosis and delayed intervention.

- ***Conclusion:***

The overlap in clinical and radiological features between TB and connective tissue disease associated ILD necessitates a high index of suspicion and thorough diagnostic evaluation. Early differentiation is crucial to guide appropriate treatment and improve patient outcomes. A multidisciplinary approach, including pulmonologists, rheumatologists and infectious disease specialists, is essential in managing such diagnostic dilemmas.

Keywords*: Pulmonary Tuberculosis, Interstitial Lung Disease, Connective Tissue Disease, Diagnostic Challenge, High Resolution CT, Autoimmune Screening.*

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I. INTRODUCTION: CASE REPORT

Distinguishing pulmonary tuberculosis (TB) from connective tissue disease- associated interstitial lung disease (CTD-ILD) poses a significant diagnostic challenge due to overlapping clinical and radiological features. Both conditions can present with chronic cough, progressive dyspnea, weight loss and even low grade fever, leading clinicians in TB endemic regions to often misattribute ILD symptoms to TB[1]. Tuberculosis can closely mimic the clinical and radiological features of many ILDs, resulting in diagnostic errors and delays[1]. Conversely, ILD may initially be misdiagnosed as smear negative or atypical; TB especially when chest imaging reveals infiltrates or fibrosis. A study from a high TB prevalence country, found that 38% of patients with ILD had been previously treated as TB before the correct diagnosis was established[2]. Such confusion is exacerbated by similar chest Xray or CT findings (e.g., reticulonodular opacities or cavities) and nonspecific symptoms. Misdiagnosis has serious implications: patients can be subjected to months of unnecessary anti-tubercular therapy (ATT) with no benefit[1], while the underlying ILD progresses unchecked. This report highlights a case exemplifying these challenges and underscores the need for careful evaluation including consideration of autoimmune aetiologies to avoid pitfalls in differentiating pulmonary TB from CTD related ILD.

II. CASE PRESENTATION

A. Patient Demographics and History:

An 18-year-old male farmer (and part-time driver) with no prior comorbidities presented with a 2-week history of productive cough with scanty sputum, intermittent fever with chills and progressive breathlessness on exertion. Six months prior, he had been empirically started on anti-tubercular therapy in view of constitutional symptoms and chest radiograph findings suspicious for pulmonary TB. He took ATT (first line, four drug regimen) for approximately 3 months but self-discontinued the medications when his symptoms initially improved. There was no documented microbiological confirmation of TB at the time.

He denied any smoking or exposure to occupational lung irritants. Notably, he reported occasional joint pains in the past year and progressive tightening of the skin over his finger and forearms, which had been overlooked during the earlier TB treatment.

There was no history of rash, photosensitivity, oral ulcers, or Raynaud's phenomenon elicited at initial presentation, although careful re-questioning revealed episodes of cold-induced finger pallor (suggesting Raynaud's) that he had not considered significant. Family history was negative for tuberculosis or connective tissue disorders.

B. Clinical Examination:

On presentation, the patient was afebrile with stable vitals (BP:110/70mmHg, HR 82/min, RR19/min, SpO_2 97% on room air). He appeared thin but not cachectic. There was evident digital clubbing. Dermatologic examination revealed calcinosis cutis (calcium deposits) over the extensor elbows and skin thickening of the fingers and forearms with a taut, shiny appearance consistent with sclerodermatous changes. No telangiectasias were noted on the face or hands. He had a restricted oral aperture (mild trismus), possibly from perioral skin tightening. Musculoskeletal exam revealed mild tenderness of the small hand joints without deformities. There was no peripheral lymphadenopathy. Chest examination found symmetric expansion and bilateral coarse crepitations (Velcro-like rales) over both lung bases and mid zones. Heart sounds were normal aside from a loud P2 (suggestive of pulmonary hypertension). The rest of the systemic examination was unremarkable.

C. Investigations:

Initial laboratory tests showed a leucocytosis (total count 15,000/µL) with neutrophil predominance and elevated C-reactive protein, suggesting an acute inflammatory process. Erythrocyte sedimentation rate (ESR) was 50mm/h. Renal and liver function parameters were within normal limits. Microbiological studies for tuberculosis were performed. Sputum smear for acid-fast bacilli was negative on three samples. A cartridge based Nucleic Acid Amplification Test (CBNAAT/GeneXpertTB) on sputum was negative for *Mycobacterium tuberculosis* as well. Subsequently, a mycobacterial culture (MGIT) was done, which later showed no growth. Given the prior history of TB treatment, these findings raised doubt about active TB. HIV test done was negative.

- Imaging: A chest X-ray showed bilateral reticulonodular opacities with fibrosis; changes were more pronounced in the right upper zone with some cystic lucencies suggesting cavities. A high-resolution CT (HRCT) of the thorax was obtained to further characterize the lung findings. HRCT revealed diffuse fibrotic changes with traction bronchiectasis throughout both lungs along with areas of fibrocavitatory changes in the upper lobes. There were patchy consolidations and small airspace nodules in both the lungs and branching centrilobular nodular opacities ("tree-in-bud' pattern) diffusely, especially in the right upper lobe. These radiologic features were initially interpreted as consistent with post primary (reactivation) pulmonary TB. Notably, however, the fibrosis was not confined to apices; there was also basal subpleural reticulation. No mediastinal lymphadenopathy or pleural effusion was present.

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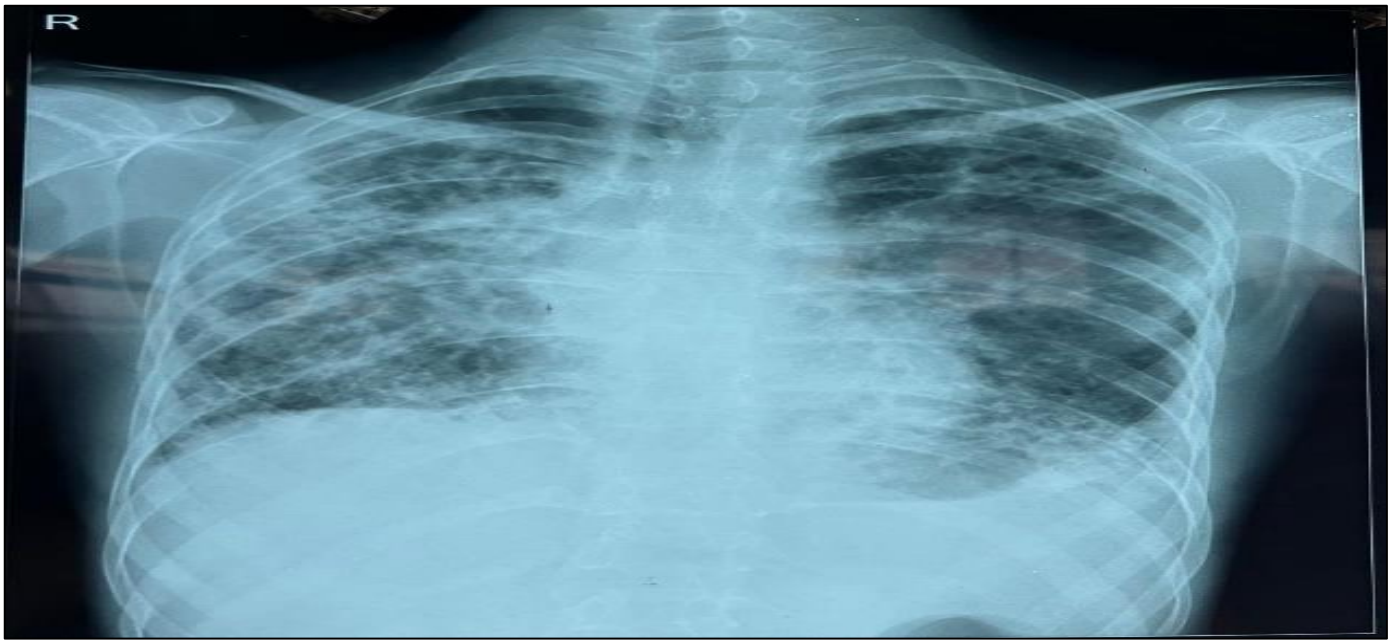

Fig 1: C Xray Shows Bilateral Reticulonodular Opacities

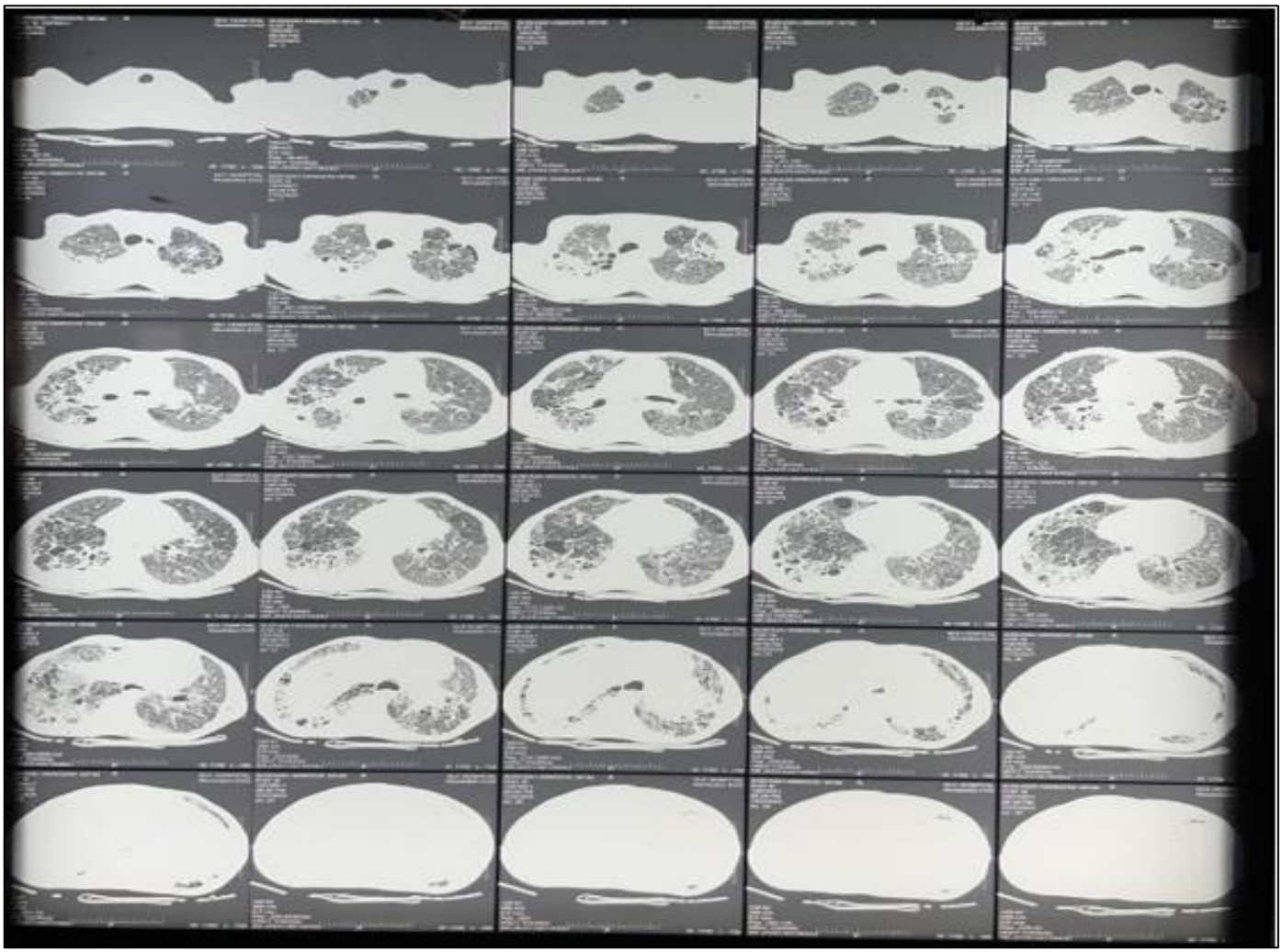

Fig 2: HRCT revealed diffuse fibrotic changes with traction bronchiectasis throughout both lungs along with areas of fibrocavitatory changes in the upper lobes. There were patchy consolidations and small airspace nodules in both the lungs and branching centrilobular nodular opacities (“tree-in-bud’ pattern) diffusely especially in the right upper lobe.

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- **Autoimmune Workup:** In light of the unexplained skin findings and the possibility of a connective tissue disorder, an autoimmune serological panel was conducted. Rheumatoid factor (RF) was positive (titres 120IU/ml).An anti-nuclear antibody (ANA) test by immunofluorescence was positive at 1:320 titres with speckled pattern. Extractable nuclear antigen (ENA) panel revealed a strongly positive anti Scl 70 (anti topoisomerase I) antibody and a borderline positive anti SSB (La) antibody. Anti ds DNA and anti Sm were negative. The Scl 70 positivity in the context of skin thickening and calcinosis pointed towards systemic sclerosis as an underlying connective tissue disorder.
- **Pulmonary function tests:** Spirometry and lung volumes showed a restrictive pattern- forced vital capacity (FVC) was 58% of the predicted, indicating significant gas exchange impairment. There was no obstruction. These results were consistent with interstitial lung disease. Arterial blood gas analysis on room air revealed mild resting hypoxemia (PaO_2 68 mmHg) with normal $PaCO_2$
- **Additional Tests:** A transthoracic 2D echocardiogram showed normal left ventricular function (LVEF 60%) but revealed mild pulmonary artery hypertension (estimated pulmonary artery pressure~ 45 mmHg) and mild atrial enlargement. This finding correlated with his ILD and scleroderma (pulmonary hypertension is a known complication).Ultrasound of the abdomen was done; it showed mild hepatosplenomegaly but no focal lesions. Ophtalmologic examination- fundoscopy was normal.
- **Diagnostic Dilemma and Differential Diagnosis:** The patient's presentation posed a diagnostic conundrum. On one hand, his radiological findings (upper lobe fibrosis, cavities, tree-in-bud nodules) and prior partial treatment raised concern for **reactivation pulmonary tuberculosis**. On the other hand, the negative microbiological tests for TB and the new evidence of a **connective tissue disease (systemic sclerosis)** with ILD suggested an alternate cause for his lung pathology. The differential diagnoses considered were:
- **Post-primary (reactivation) Tuberculosis:** Possibly explaining cavities, nodules, fever and weight loss. However, this was undermined by negative GeneXpert/culture and presence of systemic sclerosis features.
- **Connective Tissue Disease-Associated ILD:** Systemic sclerosis with ILD (most likely NSIP pattern) could produce diffuse fibrosis and ground-glass opacities; yet, classic scleroderma-ILD usually shows basilar predominance rather than apical cavitation. An overlap syndrome (scleroderma with rheumatoid arthritis features) was considered given positive RF, which could account for unusual lung nodules or cavities (e.g., rheumatoid necrobiotic nodules).
- **Combined TB and CTD-ILD:** The possibility that the patient had **both** conditions was also considered – e.g., an underlying CTD-ILD with a superimposed mycobacterial infection. This is plausible since immunosuppression or lung damage can predispose to TB, and **TB infection in ILD patients has been documented** (though imaging can be atypical in that context)[3,4]

Given the ambiguity, further invasive diagnostics were contemplated. A **bronchoscopy with bronchoalveolar lavage (BAL)** for TB PCR/culture and even a **surgical lung biopsy** for histopathology were discussed as potential next steps. However, weighing the risks, a consensus was reached to first utilize the available non-invasive data to guide management, as described below.

III. MANAGEMENT AND OUTCOME

- **Treatment Approach:** After multidisciplinary deliberation, we elected to **withhold empirical ATT** in the absence of any microbiological confirmation of active TB. This decision was justified by the high likelihood of an alternate diagnosis and the risk of unnecessary drug toxicity. Instead, the management was tailored towards CTD-ILD. The patient was initiated on an **anti-fibrotic therapy** with *Nintedanib* (150 mg twice daily). Nintedanib was chosen in light of evidence that it can slow the progression of pulmonary fibrosis in ILDs, including those associated with connective tissue diseases [5]. This therapy was started under close monitoring, given his relatively young age, to address the fibrotic component of his lung disease.
- At the same time, a short course of broad-spectrum **antibiotics** (intravenous piperacillin-tazobactam) was administered empirically to treat a possible acute superimposed pneumonia (given his fever, elevated WBC count, and patchy consolidations on HRCT). Over the next week, the fever subsided and inflammatory markers trended down, suggesting any acute infection was controlled. No organisms grew on blood or sputum cultures, and antibiotics were de-escalated accordingly.
- **Rationale for Withholding ATT:** Initiating ATT without evidence was avoided for several reasons. First, prior partial TB treatment could complicate interpretation of any response. Second, misdiagnosis of ILD as TB is common and can lead to **"maltreatment with anti-tuberculous drugs when they are not needed," which should be avoided** [1]. Treating this patient for months with hepatotoxic TB drugs, when his condition was actually due to progressive fibrosis, would delay proper therapy and risk drug-induced harm. Moreover, starting high-dose corticosteroids or immunosuppressants for ILD without ruling out TB could be dangerous, as **undiagnosed TB can worsen under immunosuppression**. Therefore, the plan was to observe closely for any evidence of TB while managing ILD, rather than rushing into either TB therapy or immunosuppression.
- **Rationale for Anti-fibrotic Therapy:** The introduction of antifibrotic medication was based on the recognition that the patient's ILD had a fibrosing phenotype (with traction bronchiectasis and volume loss on HRCT) and evidence of progression (symptoms worsening within months). **Nintedanib** has been shown in clinical trials to **reduce the rate of FVC decline in progressive fibrosing ILDs, including CTD-ILD**[5].This offered a chance to preserve lung function in a disease (scleroderma-ILD) that otherwise can be relentlessly progressive. Additionally, because nintedanib is not an immunosuppressant, it was a safer initial choice in a scenario where latent or active TB

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was still a concern. (Pirfenidone, another antifibrotic, was considered but has less evidence in CTD-ILD and was thus not used[5].)

- **Immunosuppressive Therapy:** After discussion with Rheumatology, we planned to start disease-specific treatment for systemic sclerosis once active TB was definitively excluded. High-dose corticosteroids were **avoided** initially (steroids can trigger scleroderma renal crisis in systemic sclerosis, and also would suppress signs of TB). Instead, a moderate dose of oral prednisolone (20 mg daily) was given as a compromise to address possible organizing pneumonia components, with careful watch for any TB flare. We also initiated oral **mycophenolate mofetil** 500 mg twice daily after two weeks, aiming to slowly uptitrate (target 1.5 g BID) as a steroid-sparing agent for scleroderma-ILD, consistent with standard care. This cautious immunosuppressive approach was instituted only after repeat sputum studies remained negative, and with plans for rigorous monitoring.
- **Outcome and Follow-Up:** The patient was observed in the hospital for two weeks. During this time, his cough and breathlessness improved modestly. He did not develop any night sweats or hemoptysis. Sputum AFB smears and cultures repeated after antibiotics continued to be negative. With clinical stability, he was discharged on home oxygen (2 L/min at night) and the above medications.

On outpatient follow-up at 3 months, he reported improvement in exercise tolerance (from being breathless after 100 meters to able to walk 500 meters slowly). His weight was stable. There were no fevers or new symptoms. Crackles on chest exam persisted but were slightly less extensive. Laboratory monitoring showed normal liver enzymes (on nintedanib) and stable blood counts. Immunologically, his complement levels and inflammatory markers had decreased.

IV. DISCUSSION

This case illustrates the intricate overlap between pulmonary tuberculosis and connective tissue disease-related ILD, and highlights important considerations for differentiation. In regions with high TB prevalence, clinicians often face a diagnostic dilemma when patients present with chronic respiratory symptoms and abnormal chest imaging. **Tuberculosis and ILD can resemble each other in clinical presentation** – both may cause chronic cough, weight loss, and malaise – and in radiological patterns – both can produce reticular-nodular opacities or fibrosis on chest X-rays[1]. As a result, misdiagnosis is frequent. Studies have documented that ILDs are frequently unrecognized and mistaken for TB by primary physicians in endemic areas.

As a result, misdiagnosis is frequent. Studies have documented that ILDs are frequently unrecognized and mistaken for TB by primary physicians in endemic areas [2].Such diagnostic errors lead to inappropriate therapy: patients receive prolonged ATT with no improvement, while the actual ILD progresses. Indeed, treating an ILD as TB can be harmful – aside from drug side effects, the **delay in correct diagnosis allows fibrotic lung disease to advance, leading to worse outcomes**[1].Misdiagnosis of TB also has societal implications, including unnecessary contact tracing and stigma for the patient.

- **Autoimmune Screening in Atypical TB Presentations:** This case underscores the importance of evaluating for underlying autoimmune disease when a patient suspected of TB has atypical features or fails to confirm on microbiology. A high index of suspicion for CTD-ILD is warranted if there are extrapulmonary clues (e.g. skin changes, arthritis, Raynaud's phenomenon) or if the pattern of lung involvement is unusual for TB. In our patient, the presence of sclerodermatous skin changes and positive autoantibodies (Scl-70, RF) were red flags that pointed away from infection and toward an autoimmune etiology. **Up to 10–30% of patients may present with ILD as the first manifestation of a connective tissue disease**, preceding any overt rheumatologic symptoms by years[6]. Hence, performing an autoimmune panel (ANA and specific antibodies) can be crucial in "TB suspects" who have negative bacteriology or clinical hints of autoimmunity. In this case, the serological tests were diagnostic, revealing systemic sclerosis. It should be noted, however, that **TB infection itself can cause transient autoantibody positivity** – for example, one study in a TB-endemic area showed **32% of active TB patients had elevated autoantibodies (such as anti–Scl-70 and anticardiolipin)**[7].

Thus, positive ANA or other antibodies must be interpreted in the clinical context; not every positive antibody means a definitive CTD. The converse is also true: a negative autoimmune screen does not rule out CTD-ILD, as some patients (especially early or limited disease) may seroconvert later or have antibody-negative disease. Overall, this case advocates that **routine autoimmune screening should be part of the workup for presumed pulmonary TB cases that are atypical or unresponsive**, to unmask an underlying CTD-ILD. Early identification of a CTD has therapeutic implications, allowing timely initiation of appropriate immunomodulatory or antifibrotic therapy.

- **Radiological and Histopathological Differentiation:** High-Resolution CT scanning is an invaluable tool in distinguishing TB from ILD, although overlap can occur. Certain HRCT features are more suggestive of one diagnosis over the other. **Pulmonary TB** classically presents with upper lobe predominant lesions, including *centrilobular nodules with tree-in-bud appearance*, cavitary lesions, and calcified granulomas in a reactivation setting[3].Miliary TB yields innumerable uniform micronodules. In contrast, **CTD-associated ILD** often shows patterns like nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP), typically with a *basilar and subpleural predominance of ground-glass opacities, reticular markings, and traction bronchiectasis*[8]. For instance, systemic sclerosis-ILD usually manifests an NSIP pattern: peripheral ground-glass changes and fibrosis mainly in the lower lobes. Honeycombing (cystic changes) can occur in advanced

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ILD (UIP pattern) but is less common in CTD-ILD than in idiopathic pulmonary fibrosis. In our patient, the HRCT showed a mix of features – diffuse fibrosis with traction bronchiectasis (pointing to ILD) *and* nodules/cavities (pointing to TB) – hence the radiologist's initial impression of TB reactivation. Such mixed patterns can occur in overlap scenarios or when previous TB has caused structural lung damage that coexists with ILD. In ambiguous cases, imaging of extrapulmonary sites (e.g., hand X-rays for erosive arthritis, or CT sinuses for granulomatosis) and serial radiographs (to see if lesions migrate or respond to therapy) can provide clues.

When imaging is indeterminate, **histopathology remains the gold standard** to definitively differentiate infections from ILD. A lung biopsy (surgical or transbronchial) with histology can identify the characteristic **caseating granulomas of TB (with acid-fast bacilli on Ziehl-Neelsen staining) versus the interstitial fibrosis and inflammation of ILD (e.g., NSIP showing uniform thickening of alveolar walls with lymphoplasmacytic infiltrates, and UIP showing patchy fibrosis with honeycombing). In this patient, a biopsy was deferred due to clinical improvement and the invasiveness of the procedure, but in general, bronchoscopy with bronchoalveolar lavage and biopsy is recommended when the diagnosis is uncertain. Cultures or PCR from BAL can increase TB detection in smear-negative cases, and biopsy can also rule out other granulomatous diseases like sarcoidosis or hypersensitivity pneumonitis that may mimic both TB and CTD-ILD. It is worth noting that obtaining tissue in suspected CTD-ILD can also reveal a pattern (e.g., organizing pneumonia, lymphocytic interstitial pneumonia) that might change management. However, in practice the decision to biopsy balances the potential diagnostic yield against patient risk; a multidisciplinary discussion is critical in making this decision. In our case, the convergence of clinical, serological, and radiologic evidence in favor of CTD-ILD obviated the need for an invasive biopsy.**

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- **Clinical Implications and Recommendations:** For pulmonologists and clinicians, this case highlights a few key recommendations. **First, always seek microbiological confirmation of TB** whenever possible, via sputum GeneXpert, culture, or histology. Empiric therapy should be a last resort in atypical cases. If a patient presumed to have TB is not improving or tests negative, reconsider the diagnosis early. **Second, conduct a broad workup for alternative diagnoses**. This includes an autoimmune serology panel, as well as considering other differentials like sarcoidosis, malignancy, or endemic fungal infections, depending on the context. In our patient, a simple ANA test was life-changing in directing the correct diagnosis. **Third, use a multidisciplinary approach.** Complex cases at the intersection of pulmonary and rheumatologic disease benefit from input by specialists from both fields. Regular **multidisciplinary team (MDT) discussions** – involving pulmonologists, rheumatologists, radiologists, and pathologists – can significantly improve diagnostic accuracy and confidence [1,6].In fact, guidelines for ILD management emphasize that an MDT diagnosis is the diagnostic gold standard for ILDs, ensuring that clinical, radiologic, and pathologic data are interpreted together. Such collaboration was crucial in our case to decide on withholding ATT and starting antifibrotic therapy.

Finally, once a diagnosis of CTD-ILD is established, appropriate therapy should be instituted promptly. **Immunosuppressive therapy** (e.g., corticosteroids, mycophenolate, cyclophosphamide) remains the cornerstone for many CTD-ILDs to address inflammation. In systemic sclerosis-ILD, for example, cyclophosphamide has shown short-term improvements in lung function (though not sustained long-term) and mycophenolate is now frequently used as first-line treatment[8].

Antifibrotic therapy is an emerging adjunct for progressive fibrosing CTD-ILD, supported by trials like SENSCIS (for scleroderma-ILD) that demonstrated slower FVC decline with nintedanib. Our decision to start nintedanib reflects this evolving paradigm; indeed, **nintedanib is now conditionally approved for progressive fibrosing ILDs** and has shown efficacy in CTD-ILD by **retarding lung function decline.**

Importantly, management should be individualized: in TB-endemic areas, some clinicians prefer treating latent TB infection (LTBI) before starting immunosuppressants in autoimmune ILD, even if active TB is not proven, especially if the patient has risk factors or indeterminate TB tests. In our case, we were prepared to implement LTBI therapy if any suggestion of TB arose. **Close follow-up** is mandatory in such cases to monitor for any emergence of TB (e.g., rechecking sputums, chest imaging) and to track ILD progression.

In summary, the case and literature both reinforce that differentiating TB from CTD-ILD requires vigilance and a comprehensive approach. **Thorough history (including extrapulmonary symptoms), appropriate lab investigations (microbiological and serological), and**

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integration of imaging findings are all needed to resolve the diagnostic dilemma. When in doubt, involving a multidisciplinary team and considering invasive diagnostics can prevent misdiagnosis. The goal is to ensure the patient receives the correct therapy – antibiotics for infection, or immunosuppression/antifibrotics for ILD – in a timely manner, which in turn improves outcomes.

V. CONCLUSION

This case highlights several key takeaways for clinical practice. **Firstly, not all that fibroses is TB** – in patients with chronic lung infiltrates, especially when **TB tests are negative or atypical features are present, clinicians must consider alternative diagnoses like CTD-associated ILD**. Overlapping clinical and radiologic features can mislead even experienced physicians, so maintaining a broad differential is crucial. **Secondly, clues to an underlying connective tissue disease should be actively sought** in difficult TB cases; features such as skin changes, joint symptoms, or serological autoantibodies can unveil a rheumatologic diagnosis that explains the lung findings. This underscores the need for a multidisciplinary evaluation – pulmonologists, rheumatologists, radiologists, and pathologists should collaborate to dissect such diagnostic puzzles. In our case, an MDT approach helped avoid a potential misdiagnosis. **Lastly, an accurate diagnosis directly informs proper management**: the decision to forgo empiric TB therapy and initiate antifibrotic treatment in this patient was validated by his subsequent improvement and lack of TB evidence. It exemplifies how tailoring therapy to the correct diagnosis (and not reflexively treating for TB in every suspected case) benefits the patient.

In conclusion, distinguishing TB from CTD-ILD requires diligence and an open mind. This case demonstrates the value of combining microbiological tests with autoimmune screening and high-resolution imaging to reach the right diagnosis. For pulmonologists in TB-endemic areas, the message is clear – **always confirm the diagnosis**. When faced with a **diagnostic dilemma between infection and ILD, engage a multidisciplinary team and consider all possibilities**. Such an approach will ensure timely, appropriate treatment, whether it is anti-tubercular therapy, immunosuppression, or anti-fibrotic therapy, thereby improving patient outcomes in these challenging scenarios[1,6].

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