

Systemic Sclerosis and Pulmonary Tuberculosis Risk

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Diagnosing pulmonary tuberculosis (TB) in patients with systemic sclerosis (SSc) and interstitial lung disease (ILD) presents a significant clinical challenge due to overlapping symptoms and the impact of immunosuppressive therapy. This diagnostic ambiguity can delay TB detection, necessitating a high index of suspicion and the liberal use of sensitive diagnostic tools.

KEY TAKEAWAYS

- **The Pivot:** Diagnosing pulmonary TB in patients with Systemic Sclerosis (SSc) and interstitial lung disease (ILD) on immunosuppression requires a heightened index of suspicion due to overlapping symptoms and atypical presentations that can mask the infection.
- **The Data:** A recent meta-analysis suggested that TNF inhibitors increase the risk of TB, but the risk with other immunosuppressants used in SSc (e.g., mycophenolate mofetil, cyclophosphamide) is less well-defined.
- **The Action:** Clinicians should employ sensitive diagnostic tools such as sputum cultures, PCR-based assays, and interferon-gamma release assays (IGRAs) liberally when new pulmonary symptoms arise in SSc patients on immunosuppression, especially those from high TB burden regions, even if initial results are negative.

The Diagnostic Challenge

Diagnosing pulmonary TB in patients with SSc-associated ILD presents a formidable challenge.² Symptoms such as cough, shortness of breath, and fatigue are common to both conditions, masking the presence of TB until it reaches an advanced stage. Further complicating matters, the immunosuppressive medications used to manage SSc can blunt the typical inflammatory response to TB, leading to atypical radiographic presentations and delayed diagnosis. Are we, as clinicians, adequately equipped to differentiate between disease progression and opportunistic infection in this context?

The insidious nature of TB in immunosuppressed individuals necessitates a proactive and vigilant approach. Clinicians must maintain a high index of suspicion, particularly in patients from TB-endemic regions or those with a history of TB exposure. Relying solely on clinical symptoms or standard chest radiographs may prove insufficient. More sensitive diagnostic tools, such as sputum cultures, PCR-based assays, and interferon-gamma release assays (IGRAs), should be employed liberally, especially when there is any clinical ambiguity. Repeated testing may be warranted if initial results are negative but suspicion remains high.

Impact on Current Guidelines

Current guidelines from the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) recommend TB screening in high-risk individuals, including those with immunosuppression. However, these guidelines may not adequately address the unique challenges posed by SSc-associated ILD. The overlap in symptoms and the potential for atypical presentations warrant a more tailored approach. This is not to say the ATS or CDC guidance is wrong, simply that it was not designed with this specific patient population in mind. The 2019 EULAR recommendations for the management of systemic sclerosis do mention screening for latent TB before initiating immunosuppressive therapy, but they do not specifically address the nuances of patients already on immunosuppression who develop new pulmonary symptoms. Do we need to add further clarification for high TB burden areas?

Consider the 2021 ACR guidelines for rheumatoid arthritis: these detail recommendations on screening for latent TB before initiating biologic therapies. However, guidance for managing TB risk in SSc patients already on immunosuppressants, who then present with respiratory symptoms, remains less clear. A recent meta-analysis suggested that TNF inhibitors increase the risk of TB, but the risk with other immunosuppressants used in SSc (e.g., mycophenolate mofetil, cyclophosphamide) is less well-defined.¹ More robust data are needed to guide risk stratification and screening intervals in this specific population.

Study Limitations

It is crucial to acknowledge the limitations inherent in case reports. While they can be valuable for highlighting unusual presentations and generating hypotheses, they cannot establish causality or provide definitive evidence to guide clinical practice. This particular case report describes a single patient, limiting the generalizability of the findings.² Furthermore, the diagnosis of TB can be challenging, and there is always the possibility of misdiagnosis or delayed diagnosis, which could influence the interpretation of the case. The study also did not explore latent tuberculosis infection. Latent TB can reactivate with immunosuppression.

Moreover, the report does not delve into the specifics of the patient's immunosuppressive regimen, which could have influenced the risk of TB infection. The type and dosage of immunosuppressants, as well as the duration of treatment, are important factors to consider. Finally, it is important to note that the case report comes from a high TB burden country, which may limit its applicability to regions with lower TB prevalence. We need larger, prospective studies to assess the true incidence of TB in SSc patients and to identify specific risk factors.

Financial and Workflow Considerations

Implementing more aggressive TB screening strategies in SSc patients will inevitably have financial and workflow implications. The cost of IGRAs, sputum cultures, and PCR-based assays can be substantial, particularly if repeated testing is required. Furthermore, the interpretation of these tests can be complex, requiring expertise in both rheumatology and infectious disease. How do we ensure that patients have access to these tests, regardless of their insurance status or socioeconomic background? And how do we integrate these screening protocols into already overburdened clinical workflows?

Consider the workflow bottlenecks. If a patient screens positive for TB, they will require further evaluation and treatment,

potentially involving multiple specialists and prolonged follow-up. This can strain already limited resources and create delays in care. Furthermore, the need for TB treatment may necessitate adjustments to the patient's immunosuppressive regimen, which can have implications for their SSc management. Clear protocols and interdisciplinary collaboration are essential to streamline the diagnostic and treatment process.

CLINICAL IMPLICATIONS

The insidious nature of pulmonary tuberculosis in patients with systemic sclerosis and interstitial lung disease demands a paradigm shift in our diagnostic vigilance. Current guidelines from the American Thoracic Society and the Centers for Disease Control and Prevention, while valuable, do not fully account for the unique diagnostic challenges presented by overlapping symptoms and immunosuppression in SSc. Clinicians must maintain an exceptionally high index of suspicion, moving beyond standard chest radiographs and employing sensitive diagnostic tools like sputum cultures, PCR assays, and IGRAs more liberally, especially in high TB burden regions.

Industry must recognize this unmet need. Pharmaceutical companies developing immunosuppressants for SSc, such as those manufacturing mycophenolate mofetil or cyclophosphamide, should consider sponsoring larger, prospective studies to clarify the true incidence of TB and specific risk factors in this patient population. The existing evidence, particularly for non-TNF inhibitors, is thin and often relies on limited case reports. Robust data are crucial for developing more precise risk stratification and screening protocols.

Patients on immunosuppressive therapy for SSc, particularly those with ILD, face a heightened and often masked risk of TB. European League Against Rheumatism recommendations mention screening for latent TB before initiating immunosuppression, but further clarification is needed for patients already on therapy who develop new respiratory symptoms. This gap in guidance leaves patients vulnerable to delayed diagnosis and potentially severe outcomes. Updated, tailored guidelines are essential to protect this susceptible population.

The current landscape highlights a critical need for collaborative efforts between guideline bodies, clinicians, and pharmaceutical companies. We need to move beyond generic recommendations and develop SSc-specific protocols that address the nuances of TB risk in immunosuppressed patients. This proactive approach will ultimately lead to earlier diagnosis, more effective treatment, and improved outcomes for individuals living with systemic sclerosis.

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