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Ethambutol-Induced Severe Cutaneous Hypersensitivity: A Case of Recurrent Smear-Negative Pulmonary Tuberculosis in a Poorly Controlled Diabetic Patient

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CASE REPORT

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ABSTRACT

Diabetes mellitus (DM) is a well-established risk factor for tuberculosis (TB), significantly influencing disease severity, clinical presentation, recurrence rates, and overall treatment outcomes. We report a case of recurrent smear-negative pulmonary TB in a 63-year-old patient with poorly controlled type 2 diabetes mellitus (T2DM) who had completed anti-tubercular therapy (ATT) five years earlier. Upon re-initiation of standard first-line therapy, the patient developed a severe generalized cutaneous hypersensitivity reaction during the intensive phase. Sequential drug re-challenge identified ethambutol as the causative agent. Withdrawal of ethambutol led to complete resolution of dermatological manifestations, and the treatment regimen was modified accordingly. This case highlights the bidirectional relationship between T2DM and TB, diagnostic challenges of smear-negative disease, and the importance of systematic drug evaluation in ATT-related adverse reactions.

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Introduction

Tuberculosis (TB) remains a major global health problem, particularly in low- and middle-income countries [1]. According to the World Health Organization, millions of new TB cases occur annually, with a substantial proportion occurring in individuals with comorbidities such as diabetes mellitus. The association between diabetes and TB is bidirectional; diabetes increases susceptibility to TB, while TB infection can worsen glycemic control [2].

Smear-negative pulmonary TB presents diagnostic challenges. Patients often exhibit nonspecific respiratory symptoms with negative sputum smear microscopy for acid-fast bacilli, requiring radiological and molecular diagnostic support [3]. Diabetic patients are more likely to present with atypical radiographic findings, lower bacillary loads, and delayed sputum conversion.

Recurrent TB, defined as disease occurring after successful completion of therapy, may result from relapse or reinfection. Poor glycemic control has been identified as a risk factor for recurrence due to impaired cell-mediated immunity. Adverse drug reactions (ADRs) to first-line anti-tubercular therapy (ATT) are common and may complicate management [4]. Ethambutol, a bacteriostatic agent targeting mycobacterial cell wall synthesis, is generally well tolerated, though optic neuritis and cutaneous reactions have been reported. Severe hypersensitivity reactions, while uncommon, require prompt recognition and modification of therapy. Aim of this case report is to describe recurrent smear-negative pulmonary TB in a poorly controlled diabetic

patient and the identification and management of ethambutol-induced hypersensitivity during treatment.

Case Presentation

A 63-year-old male, known case of type 2 diabetes mellitus for 12 years, presented with low-grade fever, persistent dry cough, night sweats, weight loss, and generalized weakness for two months. He had a documented history of smear-negative pulmonary TB at the age of 58 years, for which he completed a six-month course of first-line ATT with clinical and radiological resolution.

His diabetes had been poorly controlled, with irregular medication compliance. On presentation, his fasting blood glucose was 238 mg/dL, postprandial glucose 356 mg/dL, and HbA1c 10.4%, indicating chronic poor glycemic control.

Clinical Examination: The patient appeared cachectic with a BMI of 18.5 kg/m². Vital signs were stable except for low-grade fever (99.8°F). Chest auscultation revealed bilateral scattered crepitations in the upper lung zones.

Investigations: Sputum smear microscopy for acid-fast bacilli was performed on three consecutive samples and all were negative. Chest radiography revealed bilateral upper zone patchy infiltrates with minimal fibrotic changes. Molecular testing using GeneXpert MTB/RIF detected *Mycobacterium tuberculosis*, and rifampicin resistance was not identified. Hematological evaluation showed mild anemia with a hemoglobin level of 10.8 g/dL. Liver and renal function tests were within normal limits. Based on the clinical presentation, radiological findings, and positive molecular confirmation despite negative smear results, a diagnosis of recurrent smear-negative pulmonary TB was established.

Management and Clinical Course: The patient was initiated on the standard first-line ATT intensive phase regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol. In addition, insulin therapy was optimized to improve glycemic control given his poorly controlled diabetes mellitus.

Development of Adverse Reaction: Approximately ten days after initiation of ATT, the patient developed a generalized erythematous maculopapular rash associated with intense pruritus, facial edema, and mild fever. There was no mucosal involvement and no clinical features suggestive of Stevens–Johnson syndrome. Repeat liver function tests remained within normal limits, effectively ruling out drug-induced hepatotoxicity. In view of suspected drug hypersensitivity, all anti-tubercular medications were immediately withheld. The patient was managed with antihistamines and systemic corticosteroids, resulting in gradual resolution of the rash over the course of one week.

Drug Re-Challenge: After complete resolution of symptoms, anti-tubercular drugs were reintroduced sequentially under close medical supervision to identify the offending agent. Isoniazid was restarted first and was well tolerated, followed by rifampicin and pyrazinamide, both of which were also tolerated without recurrence of symptoms. However, upon reintroduction of ethambutol, the patient developed a recurrence of generalized rash within 48 hours. Ethambutol was therefore identified as the causative agent and was permanently discontinued.

The treatment regimen was subsequently modified by substituting ethambutol with levofloxacin for the remainder of the intensive phase. The patient tolerated the revised regimen well, with no further adverse events observed during follow-up.

Outcome and Follow-Up: Glycemic control improved with insulin titration (HbA1c reduced to 7.8% at 3 months). Symptoms gradually resolved, and repeat imaging after the intensive phase showed radiological improvement. The patient completed the full course of therapy with no recurrence of hypersensitivity reactions.

Discussion

Diabetes mellitus is a significant risk factor for the development, adverse outcomes, and recurrence of TB. A growing body of epidemiological evidence demonstrates that patients with diabetes have a higher risk of acquiring TB, worse outcomes during treatment, and increased risk of relapse after successful therapy completion. Recent cohort studies indicate that diabetes approximately doubles the risk of recurrent pulmonary TB even several years post-treatment, independent of age and sex, and that poor glycemic control potentiates this risk [5].

The immunopathological basis for this association is multifactorial. Chronic hyperglycemia impairs innate and adaptive immune mechanisms, including macrophage phagocytosis, cytokine production, and T-cell function, which are crucial for control of *Mycobacterium tuberculosis* infection. Hyperglycemia may also alter the granulomatous response, predisposing to reactivation of latent foci. These defects contribute not

only to higher incidence of active disease but also to increased severity, delayed sputum conversion, and higher treatment failure rates in TB-diabetes comorbidity [6].

Clinical studies corroborate these mechanistic insights. A retrospective cohort in Eastern China observed a significantly higher hazard of TB recurrence among diabetic patients compared with non-diabetic individuals over median 5.5 years after treatment completion (HR ≈ 2.40) [7]. Another multi-center case-control study from Bangladesh found uncontrolled HbA1c and diabetes to be independently associated with retreatment episodes.[7] Earlier case–control evidence from Taiwan similarly reported nearly doubled odds of TB relapse in patients with concomitant diabetes, emphasizing the need for integrated glycemic management during and after TB therapy [8].

The presented case reflects these broader observations. The patient's poor glycemic control likely contributed to immune dysfunction, facilitating a second episode of smear-negative pulmonary TB five years after initial cure. While recurrence can represent reinfection or relapse, the extended interval and negative sputum smears highlight the diagnostic challenges of smear-negative disease particularly prevalent in diabetic populations with atypical radiological patterns and lower bacillary loads. Molecular diagnostics such as nucleic acid amplification tests offer higher sensitivity in this context and were instrumental in confirming diagnosis here.

ATT-associated adverse drug reactions (ADRs) complicate management further. Although ethambutol is generally considered among the least hepatotoxic first-line agents, cutaneous hypersensitivity reactions ranging from mild maculopapular rash to severe dermatitis have been documented. As with other ATT agents, hypersensitivity is mediated by immunologic mechanisms and may occur unpredictably. Sequential drug re-challenge remains the gold standard for identifying the offending drug once serious hypersensitivity is suspected, allowing regimen modification while maintaining treatment efficacy.

This case underscores several clinical imperatives: rigorous glycemic optimization in TB-diabetes comorbidity, high vigilance for atypical and recurrent TB presentations, utilization of sensitive diagnostics in smear-negative disease, and methodical evaluation of ATT adverse reactions. Integrated management strategies between endocrinology and infectious disease services can improve outcomes and reduce recurrence risk in vulnerable populations.

Conclusion

Poorly controlled diabetes significantly increases the risk of recurrent tuberculosis and complicates treatment outcomes. Smear-negative recurrence requires a high index of suspicion and molecular confirmation. Severe cutaneous hypersensitivity during ATT necessitates prompt recognition and systematic drug re-challenge. Ethambutol, although generally safe, can cause significant allergic reactions requiring regimen modification. Optimizing glycemic control remains essential for successful TB management and prevention of recurrence.

Authors' contributions

ICMJE criteria	Details	Author(s)
1. Substantial contributions	Conception, OR	1
	Design of the work, OR	2
	Data acquisition, analysis, or interpretation	3
2. Drafting or reviewing	Draft the work, OR	2,3
	Review critically for important intellectual content	1
3. Final approval	Approve the version to be published	1,2,3
4. Accountable	Agree to be accountable for all aspects of the work	1,2,3

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Ethics Review Committee of King Edward Medical University/ Mayo Hospital Lahore approved the study. Informed consent was taken from the volunteer participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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