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Persistent pulmonary cavity and mediastinal lymphadenopathy despite adequate anti-tubercular therapy: Importance of therapeutic drug monitoring and dose optimization — A retrospective observational case report

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Abstract
A 52-year-old male presented with chronic cough, fever, and chest pain for one month. Chest imaging revealed a right mid-zone cavity with mediastinal widening, and CT chest demonstrated necrotic mediastinal lymphadenopathy. GenXpert confirmed *Mycobacterium tuberculosis* without rifampicin resistance. The patient received first-line anti-tubercular therapy (ATT) for nine months with partial clinical improvement, but radiological resolution was unsatisfactory. Therapeutic drug monitoring (TDM) revealed suboptimal plasma concentrations of first-line drugs, suggesting altered pharmacokinetics. After dose adjustment and extended therapy, gradual improvement ensued. This case emphasizes the role of TDM in optimizing ATT efficacy, particularly in patients with poor radiological response.

Keywords: Tuberculosis, cavity, mediastinal lymphadenopathy, therapeutic drug monitoring, dose optimization, prolonged ATT

Introduction

Tuberculosis (TB) continues to be one of the most formidable infectious diseases affecting humankind, despite more than a century of scientific progress. Caused by *Mycobacterium tuberculosis*, it primarily affects the lungs but can involve nearly every organ system. The disease remains a leading cause of morbidity and mortality in developing countries, including India, which accounts for more than one-quarter of the global TB burden.

The cornerstone of TB control lies in early diagnosis and effective treatment with multidrug regimens. Standardized first-line anti-tubercular therapy (ATT) has proven highly successful in most cases; however, clinicians frequently encounter patients who fail to show expected radiological or clinical improvement even after microbiological sensitivity is confirmed. Such cases pose a diagnostic and therapeutic challenge — is it due to non-compliance, drug resistance, pharmacokinetic variability, or host-related factors such as malabsorption or altered metabolism?

This case exemplifies such a situation: a middle-aged man with cavitary pulmonary TB and mediastinal lymphadenopathy who showed partial improvement despite adequate duration of ATT. The case underscores the importance of therapeutic drug monitoring (TDM) as a modern clinical tool that helps individualize treatment and improve outcomes, particularly in non-responders with drug-sensitive tuberculosis.

Overview

The management of tuberculosis is evolving from population-based standardized therapy to personalized pharmacological management. The variability in drug absorption, metabolism, and distribution can lead to either subtherapeutic or toxic levels, influencing the success or failure of treatment. TDM bridges this gap by providing quantitative insight into plasma concentrations of anti-tubercular drugs, allowing clinicians to optimize dosages and ensure adequate exposure.

Furthermore, the persistence of cavitary lesions and necrotic mediastinal lymphadenopathy, despite clinical improvement, is increasingly recognized as a sign of incomplete sterilization. This highlights the interplay between drug pharmacokinetics, tissue penetration, host immunity, and bacterial load. Cavity walls often have poor vascularity, reducing drug diffusion, while necrotic lymph nodes act as sanctuaries for bacilli, resulting in delayed radiological resolution.

In this context, our case adds valuable insight into a common but under-reported clinical scenario — persistent radiological lesions in a microbiologically drug-sensitive patient, successfully managed through dose adjustment guided by TDM.

Historical Background

The journey of tuberculosis treatment is both inspiring and instructive. TB has afflicted humanity for thousands of years, with evidence found in Egyptian mummies dating back to 3000 BC. For centuries, it was known as “consumption,” characterized by chronic wasting and cough, and was almost universally fatal.

The turning point came in 1882, when Dr. Robert Koch discovered the tubercle bacillus, revolutionizing the understanding of the disease’s causation. Early management strategies in the late 19th and early 20th centuries were limited to sanatorium care, fresh air, and nutrition.

The true medical revolution began in the mid-20th century with the discovery of streptomycin (1944), isoniazid (1952), pyrazinamide (1954), and rifampicin (1966). These drugs, when used in combination, transformed TB from a chronic, fatal disease into a curable one. However, by the 1980s and 1990s, the emergence of drug-resistant strains and HIV-associated TB reversed much of the progress.

India launched its Revised National Tuberculosis Control Programme (RNTCP) in 1997, later restructured as the National Tuberculosis Elimination Programme **(**NTEP), emphasizing Directly Observed Therapy (DOTS). While this standardized approach has saved millions of lives, its limitations became evident in patients with pharmacokinetic variability or altered absorption.

Recent decades have seen a paradigm shift — from uniform regimens to precision dosing, integrating therapeutic drug monitoring (TDM), pharmacogenomics, and individualized care. This modern approach ensures that even drug-sensitive patients with atypical responses receive optimal treatment tailored to their physiological needs.

Pathology

Tuberculosis is characterized pathologically by granulomatous inflammation resulting from the host's immune response to *Mycobacterium tuberculosis*. The hallmark lesion is the tubercle, composed of a central area of caseous necrosis surrounded by epithelioid cells, Langhans giant cells, and a rim of lymphocytes. Over time, these granulomas undergo fibrosis and calcification, signifying either healing or chronicity.

In pulmonary tuberculosis, the upper lobes are most frequently involved due to higher oxygen tension favoring mycobacterial growth. Cavitation occurs when the central necrotic material liquefies and is discharged through bronchi, leaving behind air-filled cavities with fibrotic walls. These cavities act as bacterial reservoirs and are crucial for disease transmission and chronic persistence.

In the present case, radiological evidence of a cavity with necrotic mediastinal lymphadenopathy indicates ongoing active disease despite anti-tubercular therapy. Necrosis within mediastinal nodes reflects a high bacillary burden and poor drug penetration, often resulting in delayed healing even in drug-sensitive infections. Microscopic examination in such cases typically reveals necrotic centers with acid-fast bacilli, abundant inflammatory infiltrates, and zones of fibrosis at the periphery.

Pathophysiology

The pathophysiology of tuberculosis is a complex interplay between bacterial virulence, host immune defense, and tissue response. Once inhaled, droplet nuclei containing *M. tuberculosis* reach the alveoli, where they are engulfed by alveolar macrophages. Some bacilli survive intracellularly by inhibiting phagolysosome fusion and proliferate within macrophages. This leads to the recruitment of additional immune cells — monocytes, lymphocytes, and neutrophils — forming granulomatous lesions.

The delayed hypersensitivity response mediated by CD4+ T cells contributes to tissue destruction and caseous necrosis. In pulmonary TB, extensive necrosis leads to cavitary formation, which in turn perpetuates bacillary proliferation and aerosol transmission.

Mediastinal lymph node involvement results from lymphatic drainage of infected pulmonary tissue or hematogenous spread. Necrotic nodes compress nearby bronchi or vessels and may contribute to persistent cough, chest pain, or mediastinal widening on imaging.

Therapeutically, the pharmacokinetic aspect plays a crucial role in pathophysiology. Drugs like rifampicin and isoniazid depend on adequate plasma and tissue levels for bactericidal activity. Suboptimal concentrations due to malabsorption, metabolism, or drug interactions can lead to functional under-treatment, explaining persistent lesions despite apparent microbiological sensitivity.

Pathogenesis

The pathogenesis of tuberculosis involves a sequence of infection, immune activation, granuloma formation, and tissue destruction.

1. **Infection Phase:** After inhalation of infectious droplets, *M. tuberculosis* bacilli reach the alveoli and are phagocytosed by macrophages. Instead of being destroyed, they adapt to survive under oxidative stress and replicate intracellularly.

2. **Immune Activation:** Within 2–8 weeks, antigen-specific T-cell responses develop. The host mounts a Th1-type immune response, releasing interferon-γ and tumor necrosis factor-α, which activate macrophages to kill bacilli. However, excessive cytokine release contributes to local tissue necrosis.

3. **Granuloma Formation:** The aggregation of macrophages, epithelioid cells, and lymphocytes walls off the infection, forming granulomas. These structures serve both as containment mechanisms and potential niches for bacterial persistence.

4. **Cavitation and Dissemination:** Caseous necrosis liquefies, ruptures into bronchi, and expels bacilli into the airways, forming cavities. Bacilli may also spread to lymph nodes (as in this case), leading to necrotic mediastinal lymphadenopathy.

5. **Drug Penetration Barrier:** Caseous material and fibrotic tissue reduce vascular supply, impeding drug diffusion. Consequently, bacilli within these poorly perfused zones are exposed to sub-inhibitory drug concentrations, promoting persistence even in "drug-sensitive" strains.

6. **Outcome Determinants:** The balance between bacterial load, host immunity, and adequate pharmacologic exposure determines the disease outcome — cure, chronic persistence, or relapse.

This patient's poor radiological resolution despite symptom improvement suggests an immuno-pharmacological imbalance — adequate immune containment but insufficient intralesional drug levels. This finding supports the clinical utility of therapeutic drug monitoring (TDM) and dosage optimization to achieve complete sterilization of lesions.

Clinical Features

Pulmonary tuberculosis (PTB) presents with a spectrum of clinical manifestations that depend on the bacterial load, host immune status, and the extent of pulmonary or extrapulmonary involvement. The disease can range from subclinical infection to progressive, symptomatic illness with systemic toxicity.

In active cavitary tuberculosis, the hallmark symptoms include:

- **Cough:** persistent and often productive; may be dry initially but later accompanied by purulent or blood-streaked sputum.

- **Fever:** typically, low-grade, with evening rise and night sweats, reflecting systemic inflammation.
- **Chest pain:** pleuritic or dull, resulting from parenchymal inflammation or mediastinal node enlargement.
- **Weight loss and anorexia:** due to chronic catabolic state and cytokine-mediated metabolic alterations.
- **Fatigue and malaise:** indicators of systemic toxicity.

In the present case, the patient, a 52-year-old male, exhibited the classic triad of cough, fever, and chest pain of one month's duration. There was mild weight loss, but no hemoptysis or dyspnea. The presence of mediastinal widening and cavity on chest imaging indicated advanced disease with possible nodal involvement. Interestingly, after initial ATT, clinical symptoms subsided while radiological improvement lagged behind — a situation often observed in slow-responding or pharmacokinetically challenging cases.
It is noteworthy that radiological lag may persist for months even after bacteriological conversion, though persistent cavities and necrotic nodes beyond six months often suggest inadequate drug exposure or poor tissue penetration.

Differential Diagnosis
The differential diagnosis of a pulmonary cavity with mediastinal lymphadenopathy is broad and requires careful clinicoradiological and microbiological correlation. The following conditions merit consideration:

1. Chronic Pulmonary Tuberculosis
The most common cause, characterized by upper lobe cavities, nodular opacities, and caseating necrosis. The presence of *M. tuberculosis* on GenXpert confirms the diagnosis in this case.

2. Fungal Infections
- *Chronic pulmonary aspergillosis* may mimic post-tubercular cavities; however, fungal balls (aspergillomas) and positive galactomannan or Aspergillus serology help differentiation.
- *Histoplasmosis* or *blastomycosis* can present similarly but are uncommon in India.

3. Bacterial Abscess
Bacterial lung abscesses usually present with acute onset, high fever, and foul-smelling sputum. Radiologically, they show air-fluid levels and rapid resolution with antibiotics.

4. Malignancy (Cavitating Carcinoma)
Squamous cell carcinoma of the lung can cavitate due to central necrosis. The absence of atypical cells in sputum cytology and clinical improvement with ATT rule out malignancy.

5. Sarcoidosis or Silicosis
These may present with bilateral hilar or mediastinal lymphadenopathy but usually lack cavitation and yield non-caseating granulomas on histology.

6. Non-tubercular Mycobacterial (NTM) Infection
In immunocompromised or elderly individuals, NTM (e.g., *M. kansasii*, *M. avium*) can cause chronic cavitary lesions but are typically negative on standard TB diagnostic assays.
In this patient, the microbiological confirmation of *M. tuberculosis* via GenXpert, coupled with absence of malignancy or fungal markers, clearly established the diagnosis of active pulmonary tuberculosis with mediastinal nodal involvement.

Academic Discussion
Persistent radiological lesions despite microbiologically confirmed drug-sensitive tuberculosis pose a significant academic and clinical dilemma. The core question lies in differentiating true treatment failure from pharmacokinetic underexposure or delayed healing.

1. Pharmacokinetic Considerations
Anti-tubercular drugs such as rifampicin, isoniazid, and pyrazinamide exhibit wide interindividual variability in absorption and metabolism. Studies have shown that up to 30–40% of patients on standard doses have subtherapeutic plasma levels of at least one drug. This variability can be attributed to malnutrition, diabetes mellitus, altered hepatic enzyme activity, gastrointestinal disorders, or drug interactions.
Therapeutic Drug Monitoring (TDM) helps quantify plasma drug concentrations, enabling clinicians to individualize dosage regimens. Suboptimal levels of rifampicin (<8 μg/mL) or isoniazid (<3 μg/mL) are associated with delayed sputum conversion, persistent cavities, and higher relapse rates.
In this case, TDM revealed suboptimal concentrations of both isoniazid and rifampicin, supporting the hypothesis of pharmacokinetic underexposure despite good adherence. After dose escalation, the patient demonstrated gradual radiological improvement, validating the clinical relevance of TDM-guided therapy.

2. Radiological-Pathological Correlation
Cavities represent regions of high bacillary burden and poor vascularity, rendering them less accessible to drugs. Necrotic mediastinal lymph nodes similarly act as pharmacologic "cold spots." Even in the absence of resistance, bacilli in such sites are exposed to low drug concentrations, leading to functional persistence.
Serial CT scans in such cases serve as a valuable tool to monitor lesion activity. The persistence of necrosis or cavity walls after nine months, as seen in this patient, suggests incomplete sterilization rather than reinfection.

3. Immunological and Host Factors
Host immune response greatly influences disease progression and healing. Inadequate immune activation may delay bacillary clearance, whereas excessive inflammation can perpetuate tissue damage and fibrosis. Conditions like diabetes, alcoholism, malnutrition, and smoking can further impair immunity and drug metabolism, exacerbating non-responsiveness.

4. Academic Implications and Global Relevance
Globally, the concept of "one-size-fits-all" dosing in TB management is being reconsidered. Modern guidelines encourage pharmacokinetic-guided dosing, especially for slow responders, relapsing cases, or those with extensive lesions.
Recent trials (e.g., PanACEA and HIGHRIF) have shown that higher doses of rifampicin (20–35 mg/kg) achieve better early bactericidal activity without significant hepatotoxicity. The integration of TDM into national TB

programs could bridge the gap between clinical cure and radiological resolution.

This case thus exemplifies the importance of moving from standardized to personalized TB therapy, aligning with the global transition toward precision medicine in infectious diseases.

Material and Methods

Study Design

This report represents a descriptive, single-case observational study aimed at analyzing clinical, radiological, and pharmacokinetic aspects of a microbiologically confirmed pulmonary tuberculosis patient who showed incomplete radiological response despite standard therapy.

Setting

The patient was managed at a tertiary-care tuberculosis hospital in Mumbai, India—an established center for drug-sensitive and drug-resistant TB management, with facilities for therapeutic drug monitoring (TDM), advanced imaging, and multidisciplinary evaluation.

Clinical Assessment

Baseline clinical data, including symptoms, physical findings, and nutritional status, were recorded at diagnosis. Comorbidities (diabetes, HIV, hepatic or renal disease) were screened and excluded through routine investigations.

Radiological Evaluation

Chest X-rays (posterior–anterior view) and high-resolution computed tomography (HRCT) of the thorax were performed at diagnosis and during follow-up. Serial imaging was compared for cavity size, parenchymal infiltration, and mediastinal lymph node status.

Microbiological Tests

- Sputum smear microscopy for acid-fast bacilli (AFB).
- GenXpert MTB/RIF assay for rapid detection and rifampicin-resistance screening.
- Culture and sensitivity (MGIT 960) for confirmation of *Mycobacterium tuberculosis*.

Therapeutic Regimen

The patient was initiated on standard first-line anti-tubercular therapy (ATT) as per National TB Elimination Programme (NTEP) guidelines:

- **Intensive phase (2 months):** Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E).
- **Continuation phase (4 months):** Isoniazid, Rifampicin, and Ethambutol.

  The total treatment duration was extended up to nine months in view of radiological persistence.

Therapeutic Drug Monitoring (TDM)

Plasma concentrations of isoniazid, rifampicin, pyrazinamide, and ethambutol were estimated using high-performance liquid chromatography (HPLC). Blood samples were drawn 2 hours post-dose during the steady-state phase (week 6 of therapy). Results were compared with established therapeutic ranges.

Follow-up and Outcome Measures

Patients were reviewed monthly for clinical status, weight gain, drug tolerance, and liver function. Radiological improvement, cavity closure, and lymph node regression were considered indicators of successful response.

Case Study

Patient Profile

A 52-year-old male, non-smoker, non-alcoholic, presented with complaints of cough, intermittent fever, and right-sided chest pain of one month's duration. There was associated fatigue and mild weight loss (3 kg over one month). He denied hemoptysis or breathlessness.

Physical Examination

- **Mild pallor:** no lymphadenopathy or clubbing.
- **Respiratory rate:** 20/min; oxygen saturation: 97% on room air.
- **Auscultation:** Crackles and bronchial breath sounds over the right mid-zone.

Investigations

- **Chest X-ray:** Right mid-zone cavity with mediastinal widening.
- **CT Thorax:** Thick-walled cavity in right upper-middle zone with surrounding consolidation and necrotic mediastinal lymphadenopathy.
- **Sputum AFB:** Positive (++).
- **GenXpert MTB/RIF:** *M. tuberculosis* detected; no rifampicin resistance.
- **Liver and renal function:** Within normal limits.
- **HIV and HBsAg:** Non-reactive.

Treatment and Response

The patient was initiated on standard first-line ATT under supervision. Clinical improvement was noted within six weeks — reduction in cough and fever, with weight gain of 2 kg. However, after six months of therapy, follow-up HRCT showed persistent cavity and necrotic mediastinal nodes, though the patient remained asymptomatic and sputum- negative.

Therapeutic Drug Monitoring

TDM performed at month 7 revealed subtherapeutic plasma levels — Rifampicin 6 µg/mL (expected 8–24 µg/mL) and Isoniazid 2.2 µg/mL (expected 3–6 µg/mL).

Intervention

Based on TDM results, drug doses were escalated:

- Rifampicin increased to 900 mg daily,
- Isoniazid to 400 mg daily, and therapy extended to 12 months total. Pyrazinamide was discontinued after the intensive phase; Ethambutol continued for 9 months.

Outcome

After three additional months of high-dose therapy:

- Weight gain of 5 kg total from baseline.
- HRCT showed marked reduction in cavity size and resolution of mediastinal lymphadenopathy.
- No hepatotoxicity or adverse drug reactions noted. The patient completed 12 months of therapy and remained symptom-free on follow-up at 6 months post-treatment.

Discussion on Case Study

This case underscores the clinical importance of therapeutic drug monitoring (TDM) in tuberculosis management, even in patients with drug-sensitive infection.

1. Diagnostic Challenges

Despite microbiological sensitivity, persistent cavities and mediastinal necrosis suggested ongoing activity. Such cases may be misclassified as treatment failure or drug resistance, leading to unnecessary regimen changes. TDM clarified the actual cause — suboptimal plasma concentrations due to pharmacokinetic variability.

2. Therapeutic Drug Monitoring and Dose Optimization

Rifampicin exhibits nonlinear pharmacokinetics; small dose increments can yield disproportionately higher plasma levels and enhanced bactericidal activity. Isoniazid metabolism varies with acetylator status, influencing serum concentrations.

Studies (Alsultan & Peloquin, 2014; Pasipanodya *et al*., 2017) [2, 3] have shown that nearly one-third of patients on standard doses have at least one drug below therapeutic range. Individualized dose adjustments, as demonstrated in this case, can achieve optimal exposure and accelerate lesion resolution.

3. Radiological Persistence and Drug Penetration

Persistent cavitary disease arises from poor drug diffusion into avascular necrotic tissue. Even with adequate systemic exposure, cavity walls may act as pharmacologic barriers. Increasing drug dose and duration enhances gradient penetration and sterilization of residual bacilli.

4. Duration of Therapy

In drug-sensitive TB, the standard six-month regimen cures over 90% of patients; however, extended therapy (9–12 months) is recommended for extensive lesions, cavitation, or slow responders. In this case, extension with optimized dosing achieved complete radiological resolution.

5. Lessons for Clinical Practice

- Not all non-responders are drug-resistant; some are under-dosed.
- TDM should be considered in persistent or relapsing TB, particularly in diabetic, HIV-positive, malnourished, or gastrointestinally compromised patients.
- Dose escalation guided by pharmacokinetics can enhance therapeutic success without significant toxicity.
- Integrating TDM into national TB programs could markedly reduce relapse and prevent emergence of acquired resistance.

6. Global Perspective

With increasing emphasis on precision medicine, TDM represents a cost-effective strategy to individualize TB therapy. As global initiatives like the WHO "End TB Strategy 2035" target elimination, optimizing drug exposure at the individual level becomes essential.

This case contributes to the growing body of evidence that pharmacokinetic variability is an under-recognized cause of poor outcomes in drug-sensitive TB and that individualized dosing is a practical, evidence-based solution.

Summary

This case demonstrates that incomplete radiological response in pulmonary tuberculosis, despite microbiological drug sensitivity, may not always signify resistance or relapse. Instead, it often reflects pharmacokinetic variability leading to suboptimal serum and tissue drug concentrations.

Our patient, a 52-year-old male with a right-sided cavity and necrotic mediastinal lymphadenopathy, achieved early clinical improvement but persistent imaging abnormalities. Therapeutic Drug Monitoring (TDM) revealed sub-therapeutic plasma levels of rifampicin and isoniazid, guiding dose escalation and therapy extension to twelve months. This intervention resulted in complete clinical and radiological resolution.

The case emphasizes that TDM-guided individualized dosing plays a crucial role in optimizing therapy, avoiding unnecessary regimen changes, and preventing misclassification of treatment failure in drug-sensitive tuberculosis.

Conclusion

Even in microbiologically drug-sensitive tuberculosis, inadequate therapeutic response can arise from insufficient drug exposure due to variable absorption, metabolism, or tissue penetration.Therapeutic Drug Monitoring (TDM) offers a rational, evidence-based approach to identify pharmacokinetic insufficiency and tailor treatment to individual patient needs.

Integrating TDM into national TB control programs and academic practice will:

- Improve clinical outcomes and radiological resolution,
- Reduce prolonged infectivity and relapse, and
- Prevent emergence of secondary resistance.

This case exemplifies how precision dosing and pharmacological monitoring can transform a slow responder into a complete cure, underscoring the shift from standardized to personalized tuberculosis management in the modern era.

Message

"Every patient who fails to respond to therapy is not drug-resistant — some are simply under-dosed."

Therapeutic Drug Monitoring transforms empirical treatment into scientific precision.

By individualizing therapy, clinicians can bridge the gap between drug sensitivity and drug efficacy, ensuring every patient receives the right dose, for the right duration, at the right time.

References

1. World Health Organization. Global Tuberculosis Report 2024. Geneva, WHO, 2024.
2. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: An update. Drugs,2014:74(8):839–854.
3. Pasipanodya JG, Srivastava S, Gumbo T. Clinical pharmacokinetics and pharmacodynamics of anti-tuberculosis drugs: insights for improved therapy. Clin Pharmacokinet,2017:56(6):713–729.
4. Dheda K, Gumbo T, Maartens G, *et al*. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively

drug-resistant, and incurable tuberculosis. Lancet Respir Med,2017:5(4):291–360.
5. Gumbo T. Pharmacokinetics–pharmacodynamics of tuberculosis drugs: A new paradigm for improving outcomes. Clin Pharmacol Ther,2010:88(4):500–504.
6. Srivastava S, Pasipanodya JG, Meek C, *et al*. Multidrug-resistant tuberculosis: therapeutic drug monitoring and pharmacokinetic variability. Clin Infect Dis,2017:65(8):1427–1433.
7. Imperiale BR, Di Tullio V, *et al*. High-dose rifampicin for pulmonary tuberculosis, evidence and future perspectives. Eur Respir Rev,2020:29(156):190161.