EXTRAPULMONARY TUBERCULOSIS: DIAGNOSTIC CHALLENGES AND EMERGING SOLUTIONS

Rakhmonova Gulbahor Ergashovna
Doctor of Medical Sciences, Professor of the Department of Medical Radiology No. 1 of Tashkent State Medical University
Rakhmanova Muhayyo Davronbekovna
Doctoral student of the Department of Medical Radiology No. 1 of Tashkent State Medical University
Askaraliev Giyosiddin Shamsiddin ugli
2nd-year Student of Tashkent State Medical University Department of Medical Radiology No. 1

ABSTRACT: Extrapulmonary tuberculosis (EPTB) remains a significant diagnostic challenge due to its paucibacillary nature and non-specific clinical presentation. Traditional diagnostic methods, such as smear microscopy and culture, often yield low sensitivity in non-pulmonary samples. This review explores the biological barriers to EPTB detection, including hematogenous dissemination and granulomatous inflammation, while evaluating the efficacy of molecular platforms like Xpert MTB/RIF Ultra. By analyzing current diagnostic gaps, we highlight the necessity of integrating host-response biomarkers and advanced imaging to prevent delayed treatment and the rise of multi-drug resistant strains in extrapulmonary sites.

KEYWORDS: Extrapulmonary Tuberculosis, Paucibacillary, Molecular Diagnostics, Mycobacterium tuberculosis, Clinical Management.

Tuberculosis (TB), caused by the intracellular pathogen *Mycobacterium tuberculosis*, remains a primary cause of global infectious disease mortality. While pulmonary involvement is the most frequent clinical manifestation, **Extrapulmonary Tuberculosis (EPTB)**—affecting the lymph nodes, pleura, abdomen, and central nervous system—represents a growing diagnostic challenge. Unlike the cavitary lesions of pulmonary TB, EPTB is characteristically **paucibacillary**, meaning the bacterial load in affected tissues is significantly lower (<10 bacilli/ml). This low concentration often renders traditional **Ziehl-Neelsen (ZN) staining** and sputum-based assays ineffective.

The pathogenesis of EPTB typically involves **hematogenous or lymphatic dissemination** from a primary lung focus, often leading to chronic **granulomatous inflammation** in the target organ. Because clinical symptoms are often non-specific (e.g., low-grade fever, weight loss, or localized swelling), EPTB is frequently misdiagnosed as malignancy or inflammatory bowel disease. This diagnostic lag not only exacerbates tissue damage but also increases the risk of undetected **Multi-Drug**

Resistant (MDR-TB) strains. Consequently, there is an urgent need to shift from conventional microscopy toward high-sensitivity molecular platforms, such as **Xpert MTB/RIF Ultra**, and host-response biomarkers to close the current diagnostic gap in clinical practice.

The clinical diagnosis of EPTB relies on a combination of radiologic imaging, histological examination, and molecular testing. Recent data from 2024–2025 emphasizes that **Computed Tomography (CT)** and **Magnetic Resonance Imaging (MRI)** are essential for identifying the "gold standard" site for biopsy, particularly in spinal (Pott's disease) or abdominal TB. However, imaging alone cannot differentiate TB from malignancy with 100% certainty due to overlapping features like necrotic lymphadenopathy.

To address the **paucibacillary** nature of these infections, the World Health Organization (WHO) now recommends **Xpert MTB/RIF Ultra** as the initial diagnostic test for cerebrospinal fluid (CSF), lymph nodes, and tissue specimens. Unlike traditional smear microscopy, requires a bacterial load of 10,000 bacilli/ml, molecular assays can detect detect DNA at concentrations as low as 16 bacilli/ml. Despite this, the sensitivity of molecular testing in pleural fluid remains suboptimal (approx. 50%), necessitating the use of indirect biomarkers. **Adenosine Deaminase (ADA)** levels in pleural or peritoneal fluid continue to serve as a high-sensitivity surrogate marker, although its specificity is limited in regions with a high prevalence of lymphoma.

A significant concern in modern phthisiology is the emergence of **Multi-Drug Resistant (MDR-TB)** in extrapulmonary sites. Because EPTB is often treated empirically (without a confirmed culture), resistance to first-line drugs like **Rifampicin** and **Isoniazid** may go undetected for months. This delay not only leads to treatment failure but also allows for the selection of pre-extensively drug-resistant (pre-XDR) strains. Recent studies suggest that the penetration of anti-TB drugs into the CNS or bone tissue is inconsistent, further complicating the pharmacokinetics of standard regimens. Therefore, obtaining a definitive molecular drug-susceptibility profile from the onset is no longer optional; it is a clinical necessity for preventing the spread of resistant *M. tuberculosis* lineages.

CONCLUSION: The shift from pulmonary to extrapulmonary tuberculosis as a diagnostic priority requires a move away from traditional sputum-based microscopy toward tissue-specific molecular assays. Early intervention in EPTB is critical to preventing permanent structural damage in the central nervous system and skeletal tissues. Future clinical strategies must prioritize the integration of AI-assisted imaging and host-response biomarkers to circumvent the challenges posed by paucibacillary infections and the growing threat of undetected multi-drug resistance.

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