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Challenges and diagnostic insights in extrapulmonary tuberculosis: A commentary on experiences from a high-burden region in Iran

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Editorial

Background and public health importance

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains one of the oldest and deadliest infectious diseases worldwide. Despite substantial advances in medical science, TB continues to pose a major global public health challenge, particularly due to the emergence of drug-resistant strains and the persistent diagnostic and therapeutic difficulties associated with extrapulmonary tuberculosis (EPTB) (1). Current estimates indicate that approximately one-third of the world's population is infected with TB, with 95% of TB cases and 98% of TB-related deaths occurring in developing countries (2). Although Iran generally has a low TB incidence (<14 per 100,000 population), Golestan Province represents a notable exception, ranking second nationwide in TB incidence after Sistan and Baluchestan Province. The region reports an incidence of 19 per 100,000 population, with EPTB accounting for 29% of all TB cases (3,4).

Extrapulmonary tuberculosis: A diagnostic challenge

EPTB, which affects organs outside the pulmonary system-including the lymph nodes, pleura, bones, central nervous system (CNS), and genitourinary tract-is notoriously difficult to diagnose. This challenge arises from its insidious onset, nonspecific clinical manifestations, and the paucibacillary nature of the affected specimens (5). In Golestan Province, diagnostic delays are common, averaging 2-4 months, and contribute to increased morbidity, irreversible complications (e.g., spinal deformity, infertility, and meningitis), higher healthcare costs, and preventable mortality.

Key diagnostic challenges include:

- Nonspecific clinical manifestations, such as weight loss, night sweats, and malaise, which are frequently overlooked by both patients and healthcare providers.
- The low sensitivity of acid-fast bacilli (AFB) smear microscopy in extrapulmonary specimens (e.g., cerebrospinal fluid, synovial fluid, and urine).
- Limited access to mycobacterial culture and molecular diagnostic testing in certain regional healthcare facilities.
- Heavy reliance on histopathological findings (demonstration of caseating granulomas) and imaging modalities (CT, MRI, and CXR) rather than bacteriological confirmation.
- Interference from Bacillus Calmette-Guérin (BCG) vaccination, which is routinely administered at birth in Iran, with tuberculin skin testing (TST), thereby reducing the reliability of TST for the diagnosis of EPTB in this population.

Laboratory diagnosis: Current approaches and recommendations

A comprehensive laboratory approach is essential for optimizing the diagnosis of EPTB. The following diagnostic strategies are recommended:

Microscopy

AFB staining has low sensitivity in extrapulmonary specimens (e.g., synovial fluid, cerebrospinal fluid, and urine). Nevertheless, the presence of sterile pyuria should raise suspicion for renal TB and prompt further diagnostic evaluation.

Mycobacterial culture

Mycobacterial culture remains the gold standard for TB diagnosis; however, it is time-consuming, often requiring several weeks for bacterial growth. It is indispensable for drug susceptibility testing (DST), particularly in view of the increasing risk of multidrug-resistant (MDR)-TB among retreatment cases.

Molecular testing (NAATs)

The World Health Organization (WHO) recommends rapid nucleic acid amplification tests (NAATs), including Xpert MTB/RIF and the more sensitive Xpert MTB/RIF Ultra, for the simultaneous detection of the *Mycobacterium tuberculosis* complex and rifampicin resistance (6). Although these assays were originally developed for pulmonary specimens, they are increasingly being used for extrapulmonary samples, including cerebrospinal fluid, pleural fluid, lymph node aspirates, and urine. Their sensitivity for EPTB ranges from 55% to 90%, while their specificity approaches 99%. Notably, the Xpert MTB/RIF assay is currently available at the Gorgan Health Center; however, its use has largely been limited to pulmonary TB cases. Expanding its application to extrapulmonary specimens represents a valuable opportunity to reduce diagnostic delays in the region.

Histopathology

The identification of caseating granulomas in biopsy specimens (e.g., lymph node, pleura, and bone) remains a cornerstone of EPTB diagnosis, particularly in resource-limited settings where molecular diagnostic testing may not be readily available.

Interferon-Gamma Release Assay (IGRA)

The interferon-gamma release assay (IGRA) is useful for detecting latent TB infection; however, it cannot differentiate latent TB infection from active EPTB. Its principal advantage over the tuberculin skin test (TST) is that its results are not affected by prior Bacillus Calmette-Guérin (BCG) vaccination.

The role of Xpert MTB/RIF and ultra in the local context

Despite WHO recommending Xpert MTB/RIF and Xpert MTB/RIF Ultra as frontline diagnostic tools, their integration into EPTB diagnostic algorithms in Golestan Province remains suboptimal. Although the Xpert MTB/RIF assay is available at the Gorgan Health Center, it is used predominantly for sputum specimens obtained from patients with suspected pulmonary TB. This underutilization for extrapulmonary specimens represents a missed opportunity, as these molecular platforms can provide results within two hours while simultaneously detecting rifampicin resistance, information that is critical for guiding timely and appropriate treatment.

Strengthening laboratory capacity to process a broader range of extrapulmonary specimens and increasing clinicians' awareness of the availability and clinical utility of Xpert testing for EPTB should be considered urgent priorities.

Conclusion

The experience in Golestan Province underscores that EPTB represents a hidden epidemic in high-risk regions of Iran and is frequently diagnosed at advanced stages because of low clinical suspicion and limited laboratory resources. To address this challenge, medical laboratories should:

- Actively communicate with clinicians regarding the possibility of EPTB and the most appropriate specimens for diagnostic testing.

- Prioritize molecular diagnostic methods (GeneXpert, PCR) for extrapulmonary specimens (CSF, pleural fluid, lymph node aspirates, and urine) whenever feasible by leveraging the existing Xpert capacity at the Gorgan Health Center.

- Ensure that culture and DST are performed for retreatment cases or whenever drug resistance is suspected.

- Report ancillary findings, such as sterile pyuria, lymphocytic predominance in CSF, and characteristic imaging features, to facilitate clinical diagnosis.

Without strengthening laboratory infrastructure, expanding access to molecular diagnostic technologies, and improving clinical awareness, EPTB will continue to result in preventable disabilities, prolonged suffering, and avoidable deaths in this high-burden region.

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