

# Extra Pulmonary Tuberculosis: An Overview and Review of Literature

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**ABSTRACT-** Tuberculosis (TB) is one of the most virulent diseases, caused by *Mycobacterium tuberculosis* (MTB). It has been estimated that about one-third of world's population to be affected with TB. TB is a chronic infectious granulomatous disease. The causative agent of tuberculosis is *M. tuberculosis*. Extra pulmonary tuberculosis (EPTB) constitutes about 20% of all TB. It is very challenging the diagnosing EPTB because the sample obtained from relatively inaccessible sites. EPTB is the TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). The biochemical markers in TB-affected fluids (adenosine deaminase or gamma interferon) and other techniques such as polymerase chain reaction (PCR) may be useful in the diagnosis of EPTB. Although the disease usually responds to standard anti-TB drug therapy, the duration of treatment has not yet been established because smear microscopy or culture is not available to monitor patients with EPTB, clinical monitoring is the usual way to assess the response to treatment.

**Key-words-** Tuberculosis (TB), *Mycobacterium tuberculosis*, PCR, Pulmonary Tuberculosis, EPTB

## INTRODUCTION

Tuberculosis (TB) is one of the most virulent diseases, caused by MTB<sup>[1]</sup>. It has been estimated that about one-third of world's population to be affected with TB and more than 95% patients died in developing countries<sup>[2]</sup>. Generally TB affects the lungs, but other parts of the body can also be affected<sup>[3]</sup>. The true sign of active TB are a long term cough with blood-containing sputum, night sweats, and weight loss<sup>[4]</sup>.

There are two types of clinical manifestation of TB includes pulmonary TB (PTB) and EPTB. EPTB is the TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). A patient with both pulmonary and EPTB is classified as a case of PTB. For example, miliary TB is classified as PTB because there are lesions in the lungs. On the other hand, tuberculous intrathoracic lymphadenitis (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of EPTB. Tuberculosis is one of the commonest chronic infectious diseases, which is highly endemic in India and approximately five lakh patients die every year due to this disease<sup>[5]</sup>.

It usually affects lungs but cases of extra-pulmonary tuberculosis are not rare. Delay in diagnosis and in initiating treatment results in poor prognosis and squal in up to 25% of cases<sup>[6]</sup>.

Pulmonary Tuberculosis (PTB) can be confirmed by sputum examination and diagnosed easily but diagnosing extra-Pulmonary TB becomes frequently difficult, since the specificity and sensitivity of non-invasive methods is very low<sup>[7]</sup>.

Tuberculosis (TB) continues to be a major health problem in the world. Nearly one third of global tuberculosis burden is contributed by India alone<sup>[8]</sup>. Tuberculosis (TB) is a chronic granulomatous disease caused by *M. tuberculosis*. It is an acid-fast bacillus that is transmitted primarily through the respiratory route through inhalation of infected airborne droplets containing the bacillus, *M. tuberculosis*. TB is nearly always caused by the human type of bacillus, as a result of person to person spread through airborne droplets from a patient with active disease. The main target organ of *M. tuberculosis* is the Bronchopulmonary apparatus, but it also causes EPTB which involves organs other than lungs such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges<sup>[9]</sup>.

**Epidemiology-** About one-third of the world's populations are infected with *M. tuberculosis*. Tuberculosis (TB) is a major cause of morbidity and mortality in developing countries.<sup>[10,11]</sup> EPTB constituted about 20% of all cases of TB. In HIV-positive patients, EPTB accounts for more than 50% of all cases of TB<sup>[12,13]</sup>. In 2016, there were an estimated 10.4 million new TB cases worldwide, 10% of which were people living

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with HIV. Seven countries accounted for 64% of the total burden, with India bearing the brunt, followed by Indonesia, China, Philippines, Pakistan, Nigeria and South Africa. An estimated 1.7 million people died from TB, including nearly 400 000 people who were co-infected with HIV<sup>[14]</sup>.

**Types of Tuberculosis-** The two types of clinical manifestation of TB are PTB and EPTB.

Pulmonary TB is the most common form of disease. EPTB refers to TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). A patient with both pulmonary and EPTB is classified as a case of PTB. For example, miliary TB is classified as PTB because there are lesions in the lungs. On the other hand, tuberculous intrathoracic lymphadenitis (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of EPTB<sup>[15]</sup>.

**Pathogenesis-** The pathogenesis of oral TB usually is self inoculation with infected sputum, resulting from the constant coughing up of bacteria that seed themselves in the oral tissue along their line of discharge through the mouth or it may result from hematogenous dissemination<sup>[16]</sup>.

**Clinical Presentation-** Patients with EPTB may manifest constitutional symptoms such as fever, anorexia, weight loss, malaise and fatigue. Patients with EPTB especially when the disease is located at an obscure site, may present with pyrexia of unknown origin (PUO) and this may be the only diagnostic clue in India. In addition, patients with EPTB manifest symptoms and signs related to the organ system involved sites<sup>[17]</sup>.

**Differential Diagnosis of Tuberculosis-** The differential diagnosis of tuberculous ulcers includes traumatic ulcers, aphthous ulcers, Vincent's angina, actinomycosis and carcinoma. A definitive diagnosis of TB can be made by culturing *M. tuberculosis* organisms from a specimen obtained from the patient. The biopsy report shows epithelioid cell granulomas with Langhan's type of giant cells. In biopsy, the deeper tissue must be included as the granulomas are seen in the deeper dermis. The superficial biopsies only show hyperplasia of stratified squamous epithelium. The demonstration of acid fast bacilli in the biopsy material further confirms the diagnosis.

Alternatively, the tissue may be subjected to molecular diagnostic methods like polymerase chain reaction or even culture. While the former is sensitive and specific, it is also technically demanding and expensive. The culture is still considered to be the gold standard for diagnosis with the additional advantage that precise drug sensitivity of cultured bacilli can be carried out. However it is time consuming and takes weeks<sup>[18]</sup>.

Drug susceptibility testing (DST) should be performed on the first isolate of *M. tuberculosis* from all patients. A

paradoxical reaction during anti-TB therapy occurs more frequently in EPTB patients when compared to those with PTB. Therefore, DST can have important treatment implications to distinguish the paradoxical reaction from the treatment failure due to drug resistance<sup>[19]</sup>.

**Treatment of Tuberculosis-** Six months of standard anti-TB medical therapy is generally considered adequate for most forms of EPTB; longer treatment is suggested for TB meningitis and for bone and joint TB. In case of bone and joint TB, some guidelines recommend 6 months regimens, because these frequently achieve microbiologic and clinical cure. Corticosteroids often have been used as an adjunctive in the treatment of EPTB. Now *M. tuberculosis* can show resistance against antimicrobial drugs. The two most widely used TB drugs such as rifampicin and isoniazid cannot respond their efficacy against Multidrug-resistant tuberculosis (MDR-TB)<sup>[20]</sup>.

**Anti-TB drugs-** Anti-TB treatment is the main stay in the management of EPTB. However, the treatment regimen is one of the controversial aspects of the management of EPTB. Current guidelines recommending the same regimen for EPTB as well as PTB, but the data for the recommendation for most other forms of EPTB is not based on studies as robust as those for PTB. In addition, the ability of the blood-brain barrier to limit intracerebral concentrations of anti-TB drugs is an important consideration in the treatment of TB meningitis. While isoniazid, pyrazinamide, prothionamide, and cycloserine penetrate well into CSF, ethambutol and p-aminosalicylic acid have poor or no penetration. Rifampicin, streptomycin, and kanamycin penetrate the CSF well only in the presence of meningeal inflammation. The fluoroquinolones have variable CSF penetration, with excellent penetration seen in later generation drugs, such as levofloxacin and moxifloxacin<sup>[21]</sup>. In a recent phase 2 clinical trial, treatment incorporating high-dose intravenous rifampicin with the addition of moxifloxacin led to a three-times increase in the plasma and CSF area under the concentration-time curve and was associated with a survival benefit in TB meningitis patients<sup>[22]</sup>.

## CONCLUSIONS

Involvement of Extra pulmonary can occur in isolation or along with a pulmonary focus as in the case of patients with disseminated tuberculosis. The recent HIV and AIDS pandemic has resulted in changing epidemiology and has once again brought EPTB into focus. EPTB constitutes about 15-20% of all cases of tuberculosis in immunocompetent patients and accounts for more than 50% of the cases in HIV-positive individuals. Lymph nodes are the most common site, followed by pleural effusion and virtually every site of the body can be affected. Since the clinical presentation of EPTB is a typical, tissue samples for the confirmation of diagnosis can sometimes be difficult to procure, and the conventional diagnostic methods have a poor yield, the diagnosis is often delayed. Availability of computerised

tomographic scan, magnetic resonance imaging laparoscopy, endoscopy has tremendously helped in anatomical localisation of EPTB. The disease usually responds to standard anti-tuberculosis drug treatment. Biopsy and/or surgery are required to procure tissue samples for diagnosis and managing the complications. Further research is required for evolving the most suitable treatment for EPTB.

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