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EXTRA PULMONARY TUBERCULOSIS AND ITS CONSEQUENCES IN VARIOUS BODY ORGANS

(A Critical Mini Review)

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Abstract: Pulmonary Tuberculosis (PTB) is primarily brought on by Mycobacterium tuberculosis complex organisms (MTBC), however, these organisms also have the potential to spread disease to Extra Pulmonary (EP) organs, which poses a grave risk to human health globally. About 20–30% of all active TB infections are caused by Extra Pulmonary Tuberculosis (EPTB), which primarily affects both ages of children and adults with enfeebled immunities. EPTB can affect the genitourinary system as well as the brain, eye, mouth, tongue, neck lymph nodes, spine, bones, muscles, skin, pleura, pericardium, gastrointestinal tract, and peritoneum. Additionally, it can spread from a main source i.e., Pulmonary TB. EPTB can be diagnosed by various methods and techniques like clinical, radiographic, microbiological, histological, biochemical/immunological and molecular techniques. To distinguish MTBC from any other Non-Tuberculous Mycobacteria (NTM) species by molecular techniques. However, only culture and molecular methods are regarded as confirmative testing methods. While first-line anti-TB medications (ATD) are effective in treating EPTB caused by MTBC, drug susceptibility profiling is a critical factor in dealing with cases of drug-resistant EPTB (DR-EPTB). In some cases of EPTB, corticosteroid adjuvant therapy has been used in addition to antibiotics to treat the condition. Seldom, surgical interventions are also advised based on the clinical conditions, usually when the patient suffers from organ damage then surgical intervention is advised. Recent epidemiological research reveals a startling rise in DR-EPTB cases, which ranges from 10-15% in different sources. To effectively manage the developing EPTB situation internationally, considerable advancements in speedy and accurate diagnosis as well as better therapeutic strategies are immediately required. We go over the most current developments in the diagnosis clinically in this review.

Index Terms - osteomyelitis, lymph node, anorexia, thoracentesis, tuberculosis complex, meningitis; lymphadenitis, cutaneous; genitourinary; drug resistance.

I. INTRODUCTION

A prominent global mortality disease in Humans is pulmonary TB. Mycobacterium tuberculosis can also infect other organs is called Extra Pulmonary tuberculosis (EPTB) includes brain meningitis, lymphadenitis, eye, mouth, pleuritis, pericarditis, peritonitis, muscle and skeletal, abdominal, genital and urinary, and miliary types of the disease. Most EPTB cases were seen among men than women. So far from the 7.5 million incident cases recorded and reported in 2019 globally 16% of them were EPTB cases (1).

EPTB is a primary or secondary infection that can spread locally from nearby organs or hematogenous or lymphatically from the main organ, reactivating latent TB infection (LTBI) (2). To commence an effective course of treatment requires diagnostic methods like microscopy, histopathology, culture, biochemical/immunological, and molecular testing including testing for drug susceptibility—are performed on the Extra Pulmonary material collected during fine-needle aspiration or biopsy (3).

Different kinds of Extra Pulmonary tuberculosis are categorized according to the organ infected. EPTB types include the following.

1. CENTRAL NERVOUS SYSTEM (CNS) TB

The term "CNS TB" describes the clinical and pathological range of TBM, spinal TB arachnoiditis, and tuberculoma. Regional TB prevalence affects the epidemiology of CNS TB. The epidemiology of CNS TB varies by regional TB prevalence. CNS TB affects children and young adults more frequently in places with a high TB prevalence, whereas TBM predominates and affects adults more frequently as a reactivation illness in low-prevalence settings. (4)

The diseases meningitis (brain), cervical lymphadenitis (neck), ocular (eye), and oral (mouth and tongue) make up the EPTB of the head and neck.

a. Tuberculosis Meningitis

The most frequent CNS-TB finding in children and adolescents is lepto-meningitis, which arises from the haematogenous, spread of M. tuberculosis in particular; contrast-enhanced MRI and CT scans can detect exudates (5).

The severe type of EPTB involves the CNS, which accounts for 10% of all cases, with TB meningitis (TBM) as the most prevalent condition. TB meningitis is commonly found below the age of four years in children and in HIV-positive adults. (6).

If TBM is left untreated it can result in seizures, comas, and stupor and can be fatal. Untreated Stage I corresponds to complete consciousness with no focused deficits, Stage II to awareness with lethargy, disorientation, and moderate cranial nerve palsy or hemi paresis, and Stage III to seizures, coma and palsies, the diagnosis and treatment stages have an impact on the prognosis. (7).

Clinical symptoms identified by computerised tomography scan, and the extra-neural TB are typically used to make the diagnosis of TBM. For CSF samples, a LAMP assay with a specificity of 99% and sensitivity of 76% was described. (8).

Molecular diagnostic techniques like the Xpert Ultra are reported to have 87% to 97% sensitivity, for samples of adult CSF. The WHO recommends using Xpert Ultra as the initial CSF test for adults and kids to identify TBM. (9). Chemotherapy utilizing common anti-TB medicines (ATDs), as indicated for PTB. For children with drug-sensitive TBM cases, the WHO directs an initial treatment phase of 2 months with rifampicin (RIF), pyrazinamide (PZA) ethambutol (ETM), and isoniazid (INH), followed by 12 months of RIF and INH (10,11). Fluoroquinolones, like levofloxacin and moxifloxacin, are effective against MDR strains and have good CSF penetration, hence studies recommend using them also in the conventional treatment for Multi-Drug Resistant-TB Meningitis. (12)

b. Lymphadenitis caused by tuberculosis

The most prevalent type of Extra Pulmonary TB, which accounts for 35–40%, is tuberculous lymphadenitis (TBL), also known as scrofula. (13,14). Because of the materials' nature with paucibacillary, TBL lymphadenitis analysis is very difficult, and verifying the condition necessitates a mix of clinical, radiologic, microbiological, and molecular diagnostic techniques are required to diagnose this disorder. (15, 16).

The typical ATD regimen used for PTB is one of the treatment options for TBL. Surgery is hardly necessary. The existence of remaining lymph nodes following the conventional treatment is not seen as a symptom of recurrence or treatment failure. TBL (17,18)

c. Tuberculosis of the eye

Ocular tuberculosis (OTB) is the general term for MTB infection within and surrounding the eye. The primary disease more frequently affects the retina and optic nerve. It is rare to have an eye's primary progressive tuberculosis. (19). Diagnosis for OTB is quite challenging. An eye exam and a blood test for white blood cell counts and inflammatory markers are the initial signs of Ocular TB analysis. For the diagnosis of OTB, no specific molecular diagnostic test has been advised. The typical ATDs recommended for PTB cases are used for OTB management. (20)

d. TB in the mouth

Another uncommon type of EPTB is oral tuberculosis (OrTB), which can develop as an initial or subsequent infection. Initial infections are rare and typically present with painless ulcers in children and young adults. It is connected to an injury (inflammation or irritability) to the affected area. (21). The secondary infection is typically linked to a PTB. They are characterized by deep, excruciating ulcers, odynophagia, and occasionally, mandibular or maxillary bone TB (22,23). Although PCR has been used in molecular approaches to diagnose Oral TB, its sensitivity and specificity have not been established fully (36,37). However, there hasn't been any information on the use of Xpert MTB/RIF, LAMP, for OrTB analysis. The same course of ATD chemotherapy for PTB is used for the treatment of OrTB. Depending on the clinical presentation, doctors advise administering topical anti-inflammatory medications or mucosal protective agents (24, 25).

2. THORACIC EXTRA PULMONARY TB

Pleuritis (pleura) and pericarditis (pericardium) are both symptoms of EPTB of the thorax.

a. Pleural Tuberculosis

One of the typical kinds of Extra Pulmonary TB related to immunological reaction is said Pleural Tuberculosis (PLTB), Which is uncommon in children ages 2 to 12, although it is frequent in adults and adolescents ages 12 to 16. (26, 27). Fever, chest pain, coughing, and dyspnea are the common clinical signs, and sometimes appetite loss, lethargy, and weight loss are also present. (28). Clinical, radiographic, microbiological, and molecular testing are all used in the diagnostic investigations. ATDs are used in a PTB-like therapy regimen for PLTB. In addition to chemotherapy, thoracentesis could be used to treat dyspnea, lessen pleural thickness, and lessen the functional impairment it causes. (29, 30).

b. Tuberculous Pericarditis

An unusual TB symptom is tuberculous pericarditis (TBP). Constrictive pericarditis, pericardial effusion, and a mixture of tightness and effusion are the three clinical manifestations of TBP. The signs of moderate to high pericardial effusion include increasing temperature, loss of weight, night sweats, coughing, chest pain, and breathing shortness. The next stage is indicated by constrictive pericarditis and thick fibrinous fluid surrounding the heart. (31,32). TBP has increased due to increased haematogenous spread of HIV co-morbidity. (33)

Treatment for TBP seeks to lessen the bacterial burden, relieve heart symptoms including compression, and stop the evolution of constrictive conditions and hemodynamic sequelae. TBP therapy now involves model antibiotics with ATDs, comparable to Pulmonary TB treatment. (34). Although promising, oral or intra pericardial corticosteroids should only be used by immune competent people and are contraindicated in HIV situations. (35,36)

3. EXTRAPULMONARY TB OF THE SKIN, BONE, AND MUSCLE

The common Extra Pulmonary TB that affects the skin, soft tissues, muscles, and skeletal structures (bones and muscles) is discussed here.

a. Acute tuberculosis of the skin (CTB)

CTB accounts for about 1–1.5% of all EPTB. Exogenous, endogenous, or haematogenous spread are possible causes of CTB. When this condition first develops, it looks like a nodule or swelling under the skin that adheres to the skin above it. Later, cutaneous abscesses might discharge watery, caseous physical form. (37). The less frequent form of cutaneous TB is known as artificial TB. The disease results in tender ulcerative disease close orifices, for example, the oral, perineal, and perirectal covering, and it extends from progressive pulmonary, colonic, or GU TB. (38). The sick person's medical record, physical health check-up, laboratory test results, streak, culture, histology, and molecular minute analysis of the cuts must all be taken into account when diagnosing CTB because it is so challenging to do. TSTs are 33-96% sensitive and 62.5% specific for CTB. (39). An appropriate model for CTB analysis by AFB stain and bacilli culture is a skin biopsy.

The PCR molecular test is a quick and simple way to diagnose cutaneous TB employing MBP64 to identify a skin tissue removal that has a susceptibility and accuracy of 25% and 73.7%, respectively. (40)

ATDs are used to treat CTB, just like PTB therapy. (41). For lesions caused by lupus vulgaris, TB verrucose cutis, or scrofuloderma, surgical removal of the sample and testing are also advised (42, 43).

b. Musculoskeletal Tuberculosis

Both Skeletal and muscle components are involved in the typical form of EPTB known as Musculo-Skeletal TB (MSTB). Typically, MSTB is misdiagnosed for protracted periods, and TB is only later diagnosed. The chief causes of musculoskeletal involvement are a renewal of LTBI in men in industrialized nations and hematogenous distribution of the underlying sickness in youngsters, naturally in nations with a prevalent TB (44). With peripheral arthritis, osteomyelitis, tenosynovitis, and bursitis being seen in decreasing frequency order, extra vertebral involvement of TB is uncommon (1-2%) (45).

Clinical and radiologic examinations are used to differentiate between MSTB and other conditions. T-SPOT-TB is 83% specific for TB arthritis and 86% specific for the mononuclear cells in synovial fluid. (46). According to a prior study collectively on joint TB, PCR had a responsiveness of 82.65% and a particularity of 91%. (47). They could replace MRS in the men's joint fluid (SF) model as a preliminary diagnostic test (48).

The treatment recommendations for bones, joints, and the spine call for both surgical intervention and medicinal chemotherapy. MSTB chemotherapy comprises a small period from 6 to 9-month course of regular ATDs or a longer, 18-month course that does not include RIF. (49).

Surgery is necessary for people with neurological abnormalities or those who do not respond well to treatment, spinal instability, cord compression, or varying degrees of kyphosis, especially children (50, 51).

4. TUBERCULOSIS OF THE GENITOURINARY AND ABDOMINAL SYSTEMS

This section also covers the genitourinary system, which includes the kidney and urine system as well as the male and female reproductive organs, as well as the abdominal region, which also includes the pancreas, spleen, liver, gastrointestinal system, and lymph nodes.

a. The term "abdominal tuberculosis" (AbTB)

AbTB is referring to TB of the lymphatic nodes, liver spleen, pancreas adrenals, and peritoneum. Nearly 12% of EPTB cases are due to TB in these organs. (52). The prime signs and symptoms of abdominal TB include stomach pain, fever, anorexia, nausea and diarrhoea. Pathological characteristics can include fistulae, strictures, ulcerations, perforations, obliterations, hypertrophy, ulcero-hypertrophy, and ulceration. (53) Since AbTB resembles other chronic illnesses like cancer, Crohn's disease is very challenging to diagnose. To determine the severity of conditions such as ascites, thickness of the peritoneum, lymphadenopathy, and intestinal strictures, a CT or MRI scan may be used. (54).

Typically, the same ATDs used to treat PTB also work to treat AbTB. (55). Surgery is only recommended when GI tract injury or harm to other internal organs in the abdomen is brought on by fistula formation, strictures, abscesses, and irreversible constrictions. (56).

b. Genitourinary Tuberculosis

Genitourinary Tuberculosis Up to 20% of all EPTB is caused by genitourinary tuberculosis (GUTB). The main organ affected by GUTB is the kidney, and TB of the kidney can potentially cause renal impairment and renal failure. Symptoms can also affect the ovaries, endometrium, and peritoneum. However, they are frequently incorrect for monthly abnormalities, stomach pain, pelvic inflammatory disease, and even infertility. (57,58). Usual ATD chemotherapy, as indicated for Pulmonary TB, is used to treat GUTB. Second-line ATD is implemented wherever drug resistance is seen by the American Thoracic Society (ATS) or WHO standards (59).

II. SUMMARY AND CONCLUSIONS

In 2035, the WHO's "End TB Strategy" seeks to lessen Tuberculosis fatalities by 95% and fresh cases by 90%. To combat TB, better diagnostic procedures, therapeutic methods, and vaccines must be further brought in and need to be developed. To control these diseases globally, it is critical to report the effects of Extra Pulmonary TB and its developing impact of treatment resistance on the economy and global health. Drug susceptibility testing and an early, precise diagnosis are necessary to start the right treatment plan right away.

The majority of EPTB patients can be treated with the same conventional ATDs that are used to treat PTB, however, treatment duration and efficacy largely depend on the organ affected and how the disease manifests itself. The burden of the disease is further increased by the rising trend in DR-EPTB cases. Treatment with corticosteroids as an adjunct to antibiotics can be helpful for TBM, ocular TB, and pericarditis. For individuals with myco bacterial illnesses of the bone, gastrointestinal tract, and Pulmonary TB and DR-Extra pulmonary PTB underscore the critical need for developing new, sophisticated techniques for quick and accurate diagnosis, as well as more effective treatment protocols.

- **NO CONFLICTS OF INTEREST**

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