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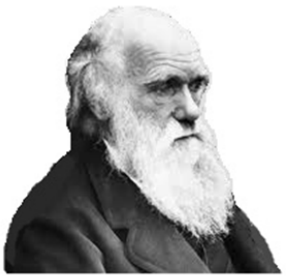

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Extrapulmonary tuberculosis: An overview on infection beyond Lungs

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ABSTRACT

Extrapulmonary tuberculosis (EPTB) involves 10-15% of all tuberculosis (TB) cases. Recent statistical report showed that EPTB accounts for more than 50% of all cases of TB in HIV-positive patients. In spite of existing anti-tubercular drugs based treatment of EPTB, the ideal regimen and duration of treatment have not yet been established. In general, EPTB is a kind of TB infecting diversified tissues and organs of body other than lungs. In fact, people suffering from TB and co-infected with HIV are prone to develop EPTB much more frequently. The present chapter discusses on the general overviews of EPTB infecting distinct body sites other than lungs. Currently, the treatment of EPTB completely relies on existing anti-tubercular drugs. In addition, significant efforts, particularly close clinical monitoring would be an imperative step towards its therapeutic strategy.

***Keywords*:** Clinical monitoring, Extrapulmonary tuberculosis, Organs, Tissues, Tuberculosis

1. INTRODUCTION

Tuberculosis (TB) is an asymptomatic airborne tropical infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). At present, TB is one of the deadliest chronic tropical infections of 21st century, infecting almost one third of the world's populace with high morbidity rate and causing over a million mortalities per year [1-4]. According to the recent statistical data of World Health Organization (WHO), there were an estimated 10.4 million new TB cases worldwide, 10% of which were co-infected with human immunodeficiency virus (HIV) [5].

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Approximately 1.7 million people died of TB, including about 400000 people co-infected with HIV [6]. The disease remains a devastating health issue in developing countries. Tuberculosis can infect any parts of the body but generally affects the lungs. The development of TB outside the lungs is termed as extrapulmonary TB (EPTB) and occurs mainly in young adults and immune suppressed persons [7, 8].

While pulmonary TB is the most common presentation, 10-15% of TB cases have EPTB involvement. People suffering from TB and co-infected with HIV are prone to develop EPTB much more frequently. Generally, lungs are the usual route of TB. When someone with TB infection coughs, sneezes, or talks, tiny droplets of saliva or mucus are expelled into the air, which could be inhaled by another person. Once infectious particles reach the alveoli, small sacs in lungs, another cell called the macrophage engulfs *M. tuberculosis*.

Then the bacteria can be transmitted to lymph system and bloodstream and spread to other organs, thereby causing EPTB. In HIV-positive patients, EPTB accounts for more than 50% of all cases of TB [9-12]. Though it is estimated that EPTB constitutes 15-20% of TB cases in general practice among HIV-negative adults in India, a higher proportion of EPTB cases have been documented in tertiary care centres [13]. Patients infected with EPTB may manifest constitutional symptoms viz. fever, anorexia, weight loss, malaise, and fatigue. Like pulmonary TB, EPTB requires notification of local public health authorities and proper infection control measures.

2. TYPES OF EPTB

Till date, diversified types of EPTB have been reported such as Osteoarticular TB (OAT), Ocular TB (OTB), Ear and nasal TB, Larynx and oral cavity TB, Neurological TB, Lymph node TB (LNTB), Abdominal TB, Cutaneous TB, Hepatic and renal TB, and Genitourinary TB (GUTB).

2. 1. Osteoarticular TB

Osteoarticular TB is the TB of bone and joints that represents 2-5% of all TB and 11-15% of EPTB. In fact, it is an ancient disease whose evidence was detected in Egyptian mummies [14], Iron Age remains from Asia [15], and skeletons of Europeans living in the Middle Ages [16] using diversified molecular techniques. The signs and symptoms of OAT are easily misdiagnosed as brucellosis, tumormetastasis, and juvenile rheumatoid arthritis, thereby making this disease difficult to diagnose. The delay in diagnosis may prolong for several months that may cause damaging of joints as well as compression of spinal cord, resulting in paralysis. In Africa, up to one-third of adults infected with OAT are HIV positive [15]. Bone and joint TB show a bimodal age distribution: in natives of developed countries, the disease commonly affects people older than 55 years, whereas in immigrants, it is more common in younger individuals (20-35 years old) [17].

Spinal TB or TB spine is the most common form of skeletal tuberculosis, and majority of patients are under 30 years of age at the time of diagnosis. Weakness, loss of appetite and weight, evening rise of temperature, and night sweats generally occur before the symptoms related to the spine manifest. Back pain is the most common symptom of spinal TB. Spinal TB affects mainly the lower thoracic and lumbar vertebrae, followed by middle thoracic and cervical vertebrae.

Sometimes, the disease affects multiple vertebrae. The infection primarily affects the cancellous area of vertebral body. The infection spreads and destroys the epiphyseal cortex, the intervertebral disc, and the adjacent vertebrae. It may also spread beneath the anterior longitudinal ligament to reach neighbouring vertebrae. The vertebral body becomes soft and gets easily compressed to produce either wedging or total collapse. Anterior wedging is commonly seen in the thoracic spine where the normal kyphotic curve accentuates the pressure on the anterior part of vertebrae. The exudate penetrates the ligaments and follows the path of least resistance along fascial planes, blood vessels, and nerves, to distant sites from the original bony lesion as cold abscess. In the cervical region, the exudate collects behind prevertebral fascia and may protrude forward as a retropharyngeal abscess. The abscess may track down to the mediastinum to enter into the trachea, oesophagus or the pleural cavity. It may spread laterally into the sternomastoid muscle and form an abscess in the neck [18].

In the thoracic spine, the exudate may remain confined locally for a long time and may appear in the radiographs as a fusiform or bulbous paravertebral abscess and may compress the spinal cord. Rarely, a thoracic cold abscess may follow the intercostal nerve to appear anywhere along the course of nerve. It can also penetrate the anterior longitudinal ligament to form a mediastinal abscess or pass downwards through medial arcuate ligament to form a lumbar abscess. The exudate formed at lumbar vertebrae most commonly enters the psoas sheath to manifest radiologically as a psoas abscess or clinically as a palpable abscess in the iliac fossa. Abscess can gravitate beneath the inguinal ligament to appear on the medial aspect of thigh. It can spread laterally beneath the iliac fascia to emerge at the iliac crest near anterior superior iliac spine. Sometimes an abscess forms above the iliac crest posteriorly. Collection can follow the vessels to form an abscess in Scarpa's triangle or gluteal region if it follows femoral or gluteal vessels respectively [18]. Paraplegia or Pott's paraplegia is the most serious complication of spinal TB and its occurrence is reported to be as high as 30% in patients with spinal TB [18]. Early onset paraplegia develops during the active phase of infection. Paraplegia of late onset can appear many years after the disease has become quiescent even without any evidence of reactivation.

Ultrasound, plain radiography, Computed tomography scan (CT scan), and Magnetic resonance imaging (MRI) are valuable tools for the diagnosis of spinal TB. Ultrasound is useful to examine joint effusions, abscesses, and involvement of tendon sheath. CT scan is used to detect joint involvement, presence or absence of periosteal reaction, and soft tissue calcifications, sclerosis, and soft tissue abscesses. MRI is the ideal technique to reveal bone marrow changes in OAT.

2. 2. Ocular TB

Ocular TB is defined as an infection due to *M. tuberculosis* in the eye, around the eye, or on its surface. Ocular TB is usually not associated with clinical evidence of pulmonary TB, as up to 60% of EPTB patients may not have pulmonary TB. Ocular TB is either primary in which the eye is the primary port of entry of the mycobacterium into the body, or secondary as a result of seeding by hematogenous spread from a distant site. Primary disease is rare, and includes eyelid, conjunctival, corneal, and scleral lesions, while the uveal tract, retina, and optic nerve are involved in secondary disease. Inflammation of the uveal tract is the most common eye manifestation of the disease, due to its high blood supply [19]. The general symptoms of ocular TB include blurred vision, light sensitivity, headache, redness of the eye, and inflammation on

the infected area of eye. Microbiological and direct histopathological examination can provide evidence of OTB infection.

2. 3. Ear and nasal TB

Mycobacterium infection in the ear is uncommon. In fact, ear TB as primary site is rare. However, lupus vulgaris of the external ear has been reported [20]. The disease is known to affect children more often. Tuberculosis of the ear develops when the bacteria invade the eustachian tube while the infant is being fed, or, by haematogenous spread to the mastoid process. The focus in the middle ear cleft may present as painless otorrhoea. Pale granulation tissue may be present in the middle ear with dilatation of vessels in the anterior part of the tympanic membrane. Multiple perforations of tympanic membrane may occur as a result of caseation necrosis. Peripheral facial paralysis, retroauricular fistulae, labyrinthitis, meningitis, tuberculous osteomyelitis of the petrous pyramid, subperiosteal, cerebral or cerebellar abscesses, acute mastoiditis, and cellulites are the major complications due to late diagnosis [21].

Likewise, TB of nose, paranasal sinuses, and nasopharynx is uncommon. However, occasionally maxillary sinus may be involved [22]. Other sites which can be involved include inferior turbinate, septal mucosa, and the vestibular skin. Nasal discharge, mild pain, and partial nasal obstruction are important presenting features. Tuberculosis of the nose can cause complications like septal perforation, atrophic rhinitis, and scarring of nasal vestibule.

2. 4. Larynx and oral cavity TB

Laryngeal TB is rare which represents <1% of all TB cases. The laryngoscopic features mimic malignancy in several cases. The prevalence of TB in larynx has reduced due to the development of efficacious anti-TB chemotherapy. Tuberculosis of larynx has often been diagnosed by clinicians attempting to rule out carcinoma. In a study of 500 patients with pulmonary TB from India, laryngeal involvement was observed in 4% of them [23].

In like manner, TB of pharynx is uncommon. The oral cavity is an uncommon site of involvement by TB. Infection in the oral cavity is usually acquired through infected sputum coughed out by a patient with open pulmonary TB or by haematogenous spread. Tongue is the most common site of involvement and accounts for nearly half the cases. The lesions are usually found over the tip, borders, dorsum, and base of the tongue. The lesions may or may not be painful. Other sites of involvement include floor of mouth, soft palate, anterior pillars, and uvula [24]. Primary infection of the salivary glands is also known, but, it is rare. Parotid gland is most commonly involved.

2. 5. Neurological TB

Tuberculosis meningitis (TBM) and tuberculoma are the major diseases categorized under neurological TB. Tuberculosis meningitis constitutes about 70-80% of all neurological TB cases, mainly caused by *M. tuberculosis*. The disease affects central nervous system, particularly meninges, thereby causing high rate of mortalities. Approximately 1% of all cases of active TB and 5-10% of EPTB cases have TBM. It is more common in children and HIV infected patients.

M. tuberculosis invades into host body by liquid droplets containing bacilli and deposits in the lung. Lungs are the primary infected sites. The bacterium disseminates through the blood

stream to the meninges and develops small subpial or subependymal foci of metastatic caseous lesions called as rich foci. Later, the size of rich foci increases until it ruptures into subarachnoid space and cause meningitis [25]. In adults, the symptoms of TBM involve headache, fever, meningismus (stiff neck), focal neurological deficits, and alteration in consciousness. On the other hand, children suffering with meningitis TB normally show symptoms like stiff neck, fever, seizures, nausea, and vomiting [26].

Tuberculoma is a mass of granulation tissue made up of a conglomeration of microscopic small tubercles. The size of cerebral tuberculomas varies from a few millimetres to centimetres [27]. Despite reduction in last few decades, tuberculomas still constitute about 5-10% of intracranial space occupying lesions in the developing world. The neurological TB is five times more common in HIV-positive compared to HIV-negative patients [28]. HIV infected patients account for over 50% of the cases of TBM seen in the industrialised nations [28]. According to the report of Bishburg et al [29], intravenous drug abusers with acquired immunodeficiency syndrome (AIDS) exhibited increased risk of developing neurological TB.

2. 6. Lymph node TB

In ancient times, LNTB was known as “King’s evil”. It is also called as “scrofula”. In developing countries, LNTB continues to be the most common form of EPTB and lymphadenitis due to non-tuberculous mycobacteria (NTM) is seldom seen [30]. On the other hand, NTM are the most common cause of lymphadenopathy in the developed countries [31]. *M. tuberculosis* enters into the body via the respiratory tract and undergoes haematogenous as well as lymphatic dissemination. Sometimes, tonsil is an important portal of entry process. The disease then spreads via the lymphatics to the draining cervical lymph nodes. Initially, the nodes are discrete. Periadenitis results in matting and fixation of the lymph nodes. The lymph nodes coalesce and break down due to formation of caseous pus. This may perforate the deep fascia and present as a collar-stud abscess. Overlying skin becomes indurated and breaks down, resulting in sinus formation which may remain unhealed for years. Healing may occur from each of the stages with calcification and scarring. On the other hand, NTM enters into the lymph nodes directly via oropharyngeal mucosa, salivary glands, tonsils, gingival, or conjunctiva [32].

The disease affects more often children and young adults. Female predilection has been reported in some studies. According to Bem et al [33], among HIV-negative as well as HIV-positive patients, cervical lymph nodes were most commonly affected followed by axillary and inguinal lymph nodes. Multifocal involvement, intrathoracic and intraabdominal lymphadenopathy, and associated pulmonary disease are more common in HIV-positive patients [33]. Fever, weight loss, fatigue, and occasionally night sweats are the symptoms of LNTB infection.

2. 7. Abdominal TB

Abdominal TB is a kind of mycobacterial infection in the gastrointestinal tract, peritoneum, omentum, mesentery and its nodes, and other solid intra-abdominal organs. It represents sixth most common extrapulomary site of TB. The abdominal TB can infect entire gastrointestinal tract, peritoneum, lymph nodes or solid visceral. The ileocaecal region is the most common infected site but it affects rarely the ascending colon, jejunum, appendix, duodenum, stomach, oesophagus, sigmoid colon, and rectum [34]. Pancreatic TB may present as acute or chronic pancreatitis or may mimic malignancy [35]. Gastrointestinal TB is one of

the most common forms of TB in the developing countries, representing 70-78% cases of abdominal TB. Lungs are the primary site of TB. Bacteria can infect oesophagus, small bowel, ileum, duodenum, and jejunum because of the ingestion of infected sputum, causing primary intestinal TB. Peritoneal TB represents 4-10% of EPTB and is mostly seen in association with gastrointestinal TB [36]. In this kind of EPTB, *M. tuberculosis* reaches to peritoneum because of ingestion of infected sputum too. Moreover, it can also spread through ruptured lymph nodes or intra-abdominal organ. Visceral TB is less common form of TB. It affects approximately 15-20% of all abdominal TB patients. It is disseminated through blood from pulmonary site which mainly affects genitourinary organs followed by liver, spleen, and pancreas. It is difficult to diagnose visceral TB due to its non-specific symptoms [37].

Weight loss, fever, diarrhea, constipation, fatigue, malaise, abdominal pain, and abdominal distension are the most common symptoms of abdominal TB. Dysphagia, retrosternal pain, and odynophagia are the most common symptoms of oesophageal TB. Duodenal TB is identified due to symptoms such as gastric outlet obstruction, epigastric pain, and an acute episode of vomiting and dyspepsia. Ileocecal TB represents symptoms such as abdominal pain, malabsorption, nausea, and vomiting. In the colonic TB, the symptoms may be focal or multifocal with pain, fever, anorexia, weight loss, and change in bowel habits. On the other hand, rectal and anal TB may present symptoms like constipation and multiple fistulae [37-39].

2. 8. Cutaneous TB

Cutaneous TB is rare and represents about 1-2% of all EPTB. However, a significant increment in the cutaneous TB was observed in the last few years due to the emergence of drug resistant *M. tuberculosis*. Scrofuloderma, lupus vulgaris, and TB verrucosa cutis are common forms of cutaneous TB. This infection can occur following any injury. During this early stage of the infection, a number of mycobacteria reach the bloodstream [40]. The disease is more prevalent in HIV positive patients. In HIV positive patients, the lesions are usually present as papules, nodules, vesicles or induration. Ulceration and discharge from the surface of the lesions may occur.

2. 9. Hepatic and renal TB

The incidence of Hepatic TB is increasing worldwide, particularly in Asian countries such as Philippines. The disease was reported clinically in 50-80% of all patients infected with pulmonary TB and in up to 91% on autopsy [41]. It is more common in male as compare to female with the ratio of 2:1, and generally affects the age group of 11-50 years [42]. Hepatic TB is classified as - Localized TB (involvement of liver in the form of the primary TB complex with caseation of the associated hepatic hilar lymph nodes), Miliary TB (a part of wide infection, on the liver by clustered miliary tubercles, and Tuberculomas, or granulomatous disease (through enlargement of tubercles foci as well as nodular development of tuberculous foci in the tertiary stage) [41]. Hepatic TB infections can occur prenatally (through the umbilical vein or the amniotic fluid), perinatally (through the umbilical vein or the amniotic fluid), and postnatally (by hematogenous dissemination or hepatopetal lymph vessels). Fever, poor appetite, fatigue, pain in the hepatic region, and hepatomegaly are the common symptoms of hepatic TB. Hepatomegaly is the major sign with more than half of patients having haphalgesia. The oppression of nodules against the hepatic ducts and bile ducts causes mild jaundice [43].

Renal TB is second most common form of EPTB and considered as sub-part of GUTB. In the kidney, the medullary region is the place for bacterial colonization, causing the formation of granulomatous lesions followed by tissue destruction. The renal lesion starts at the cortex which tends to migrate to the cortico-medullary junction and develop cortical granulomas. These granulomas invade the renal medulla and causes papillitis [44]. Proteinuria, pyuria, loss of kidney function, back pain, fever, weight loss, fatigue, and hematuria are the common symptoms of this disease [45].

2. 10. Genitourinary TB

Genitourinary TB occurs due to the haematogenous dissemination from an active site of infection. Active GUTB usually develops 5-25 years after the primary pulmonary infection. Patients present symptoms such as dysuria, haematuria, non-healing wounds, sinuses or fistulae, and haemospermia. Acute presentation mimicking pyelonephritis has also been reported. The GUTB is more common in males. In case of females, various genital organs such as fallopian tubes, endometrium, ovaries, cervix, vulva, and vagina are involved in causing this disease. It is one of the major factors of infertility among women. On the other hand, in case of males, GUTB is associated with TB of the kidney, prostate, epididymis, vas deferens, seminal vesicle, testis, and scrotum. The bacteria reach to the genital tract by three routes such as haematogenous route, abdominal visceral, and lymphatic spread. Fallopian tubes are the main source of infection in genital TB. The bacteria reach to fallopian tubes by haematogenous then gradually spread to the endometrium [46, 47]. Sometimes it spreads during sexual contact with infected person. Lower abdominal pain, epididymitis, prostatitis, testicular swelling, discharging scrotal sinus etc. are the major symptoms of GUTB in males.

3. CONCLUSIONS AND FUTURE PERSPECTIVES

The EPTB is known to infect a huge percentage of population. Despite the complications of existing TB therapy, the anti-tubercular drugs based treatments are the mainstay for controlling the epidemiology of EPTB. Early diagnosis and specific anti-tubercular drugs treatment are essential for successful management of EPTB. Most importantly, clinical monitoring would be an imperative approach towards its treatment.

LIST OF ABBREVIATIONS

AIDS - Acquired immunodeficiency syndrome
CT scan - Computed tomography scan
EPTB - Extrapulmonary tuberculosis
GUTB - Genitourinary TB
HIV – Human immunodeficiency Virus
LNTB - Lymph node TB
M. tuberculosis - *Mycobacterium tuberculosis*
MRI - Magnetic resonance imaging
NTM - Non-tuberculous mycobacteria
OAT - Osteoarticular TB
OTB - Ocular TB
TB - Tuberculosis

TBM - Tuberculosis meningitis
WHO - World Health Organization

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