

## Review Article

### Clinical Spectrum of Tuberculosis

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Being the second leading cause of mortality due to infectious diseases, the burden of tuberculosis is huge globally as well as in India. Therefore, timely diagnosis and treatment are essential to improve the clinical outcomes of the disease. It is therefore essential to create awareness and educate all concerned regarding the clinical spectrum of the disease which includes both pulmonary and extrapulmonary manifestations. Apart from typical systemic manifestations, depending on the organ affected infected patients may present with atypical signs and symptoms. The challenge is establishing definitive diagnosis in absence of discrete symptoms. Also, the EPTB generally are insidious in onset and diagnosis usually occurs in advanced stages. Therefore, a high index of suspicion is necessary particularly in absence of fever, weight loss and fatigue to avoid delay in diagnosis and thereby reduce risk of complications. It is worth mentioning that apart from high-risk individuals with HIV, chronic kidney failure, poor glycemic control, patients being treated with immunosuppressants, and both pediatric and geriatric populations who are immunocompromised, TB can be reactivated and EPTB can occur regardless of the individuals' immune status. This review article elucidates different clinical presentations of patients with both pulmonary and extra-pulmonary TB which may facilitate early management even in settings with lack of advanced diagnostic evaluation or additionally offer a right direction to perform appropriate investigations.

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Globally, a total of 1.5 million people die from Tuberculosis (TB) making it the second leading cause of death due to infectious disease<sup>1</sup>. In 2020, India was among the eight countries accounting for approximately 66% of the total TB burden, leading the count, followed by other Asian neighbors and South Africa<sup>1</sup>. In India, 40% of the population has a latent infection that has the potential to flare up<sup>2</sup>.

TB is a droplet infection that occurs due to mycobacterium tuberculosis, with the bacilli settling in the airways after inhalation. In approximately 3-8 weeks the infection spreads locally in the lungs and associated lymph nodes causing Pulmonary TB (PTB). Subsequently, it may encompass other organs leading to Extrapulmonary Tuberculosis (EPTB).<sup>3</sup> In a recent Indian study, EPTB was most frequent followed by PTB and disseminated TB. The clinical manifestations of pulmonary and extrapulmonary TB will be reviewed in this article.

Patients with TB infection can experience a range of clinical manifestations, from no symptoms to critical illness.

#### Primary TB infection :

##### Asymptomatic PTB :

After primary infection, a large portion of hosts remain asymptomatic with the majority of these clearing the infection. Nevertheless, a fraction transforms to the latent

#### Editor's Comment :

- Tuberculosis can manifest in multifarious organ systems.
- Pulmonary tuberculosis is the commonest involvement while TB lymphadenitis is the commonest extrapulmonary TB.
- It is important to recognise early and monitor full treatment.

phase with the probability of possible reactivation in subsequent years, known as latent TB<sup>4</sup>. It is a state in which the bacteria do not multiply with symptoms similar to primary infection on reactivation<sup>4,5</sup>. Reactivation risk is higher in individuals with chronic kidney failure, poor glycemic control, patients being treated with immunosuppressants, and both pediatric and geriatric populations.

##### Symptomatic PTB :

Nearly 10% of the subjects with symptoms develop primary lung infection. Extended hours of fever both low- and high-grade are the most frequent symptom. Other non-respiratory symptoms include pharyngitis, lymphadenopathy, and fatigue<sup>6</sup>. Respiratory symptoms such as chest pain, dyspnoea, and cough are present in only 66% of those with pulmonary involvement<sup>7</sup>. Approximately one-fourth of the patients develop retrosternal pain with half of these revealing pleural effusion on examination. The patient may complain of retrosternal and dull interscapular pain which worsens with swallowing. The physical examination in mild disease is generally normal with non-specific pulmonary findings crackles or tubular breath sounds. These sounds are not noted over consolidation areas. The patient may experience anorexia, weight loss, and loss of muscle mass in advanced stages<sup>8</sup>. Less

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common symptoms may include fatigue, cough, arthralgia, and pharyngitis.

### Postprimary TB and Reactivation TB :

Postprimary TB symptoms appear only late in the course of the disease and hence at risk of delayed diagnosis. Fifty to 66% develop a cough, weight loss, and fatigue, while fever, night sweat or night sweats alone were also present in 50% of patients. Chest pain and dyspnea occur in 33% and hemoptysis in 25% of patients. Due to the high incidence of non-specific symptoms, patients are diagnosed incidentally on consultation for distinct symptoms<sup>9</sup>. Low-grade fever which progresses to high grade with a diurnal pattern associated with night sweats is common in advanced stages.

Cough which is initially mild and non-productive may produce greenish or blood-stained sputum as the disease progresses. In the early stages cough occurs only in the morning or intermittently, however, in advanced stages, it becomes continuous and predominantly nocturnal<sup>10</sup>.

In untreated cases, the disease may worsen to a severe form which manifests as painful ulcers of the upper GI tract. In some patients' anorexia, wasting and malaise could be isolated features of advanced disease.

Older adults present more frequently with dyspnoea and fatigue. Physical findings of PTB are usually lacking in mild-moderate disease. Dullness with diminished fremitus, or posttussive crackles, whispered pectoriloquy may be noted. Extrapulmonary signs include clubbing and findings localized to other regions involved.

### Complications :

The complications of PTB include pneumothorax, broncholithiasis, bronchiectasis, wide-ranging pulmonary destruction, respiratory failure, septic shock, and chronic pulmonary aspergillosis. Manifestations include cough, hemoptysis, wheezing, or evidence of recurrent pneumonia, progressive dyspnea, and weight loss.

### Extrapulmonary TB :

Approximately 15-25% of those with primary lung infection progress to EPTB with numbers snowballing in the last few years. Immunocompromised individuals such as those with human Immune Deficiency Virus (HIV) infection are more susceptible to EPTB. However, EPTB can occur regardless of a patient's immune status<sup>11</sup>.

Usually, EPTB diagnosis is more challenging than pulmonary TB and requires a high index of suspicion since it mimics several other pathological conditions<sup>12,25</sup>. The individuals with EPTB seldom present with typical pulmonary symptoms. Up to 60% of patients with evidence of extrapulmonary TB may not have been diagnosed with PTB.

Depending on the organ affected, the symptoms and clinical manifestations of EPTB vary. They may thus present with a higher frequency of abdominal pain, diarrhoea, infertility, monoarticular joint pain, headache, meningism, or lymphadenopathy depending upon the organ involved.

### Lymphatic Tuberculosis or Lymph node Tuberculosis :

Lymph Node Tuberculosis (LNTB) is one of the most common (40%) extrapulmonary manifestations of tuberculosis which comprises nearly 15-20% of all cases of TB in India<sup>12</sup>. It is particularly common in Asians and Africans and comprises any regional lymph nodes<sup>25</sup>. The clinical manifestation of TB lymphadenitis is mostly based on the anatomical location of the infected nodes and the immune status of the host. However, predominantly affected lymph nodes include those of the neck and supraclavicular regions (scrofula). Cervical lymphadenopathy is the most common representing 63-77% of the cases. Febrile illness has been reported in a greater proportion of individuals with than without HIV infection (60-80% *versus* 20-50%)<sup>13</sup>. Systemic symptoms are not widespread. The most common manifestation in young adults is isolated chronic non-tender lymphadenopathy which may be present for nearly a year before diagnosis<sup>14,15</sup>. Physical examination recognizes a steady, isolated mass of nodes anchored to adjacent structures. The skin spread over the mass may be firm or hardened. Fluctuance, draining sinus, or erythema nodosum is unusual<sup>12</sup>.

Cervical lymphadenopathy may be complicated by ulceration, fistula, or abscess formation. Based on the region in which the lymph nodes are affected the patient may present with dysphagia, vocal cord paralysis, or pulmonary artery occlusion similar to pulmonary embolism<sup>16-18</sup>. If it encompasses the hepatic lymph nodes the clinical presentation may include jaundice and portal hypertension<sup>19,20</sup>.

Persons living with HIV/AIDS (PLWHA) in addition to the above manifestation may also demonstrate systemic symptoms such as sweats, and weight loss<sup>12</sup>.

### Tuberculous pleural effusion or pleurisy :

It is the second most common form of EPTB. These patients are generally febrile with the majority (>90%) presenting with non-productive cough and pleuritic chest pain (>75%) along with constitutional symptoms<sup>21</sup>. Apart from these symptoms PLWHA also manifest hepatosplenomegaly and lymphadenopathy.

### Ocular Tuberculosis :

The prevalence of ocular TB is approximately 10-18%<sup>22</sup>. Ocular tuberculosis may affect any intraocular

or extraocular tissue<sup>22,23</sup>. Posterior uveitis is the most common presentation of intraocular TB. It may not be associated with clinical evidence of pulmonary TB.

Patients with ocular TB usually have normal chest radiographs and no chest complaints. However, these patients may show signs of tubercular lymphadenitis or scrofula. Ocular TB can manifest as any kind of ocular inflammation either acute or chronic inflammation and unilateral or bilateral. Besides these, patient complaints may also include headaches, photopsia, myodesopsias or muscae volitantes, or conjunctivitis. Choroid tubercles in proximity to the macula present with weakened visual acuity and photosensitivity. Small tubercles in the peripheral fundus are likely to be asymptomatic, hence the absence of obvious visual symptoms does not exclude ocular TB<sup>23</sup>.

#### **Musculoskeletal TB :**

Skeletal TB accounts for 10-35% of cases of EPTB and can virtually affect any bone. Children are more predisposed to have skeletal TB than adults<sup>24</sup>. The most usual form of skeletal TB is Pott disease or spondylitis representing ~50% of the cases followed by tuberculous arthritis<sup>25,26</sup>. Tuberculous osteomyelitis is less common than tuberculous arthritis. Primary tuberculous tenosynovitis involving the hand and wrist is very rare. Tuberculous arthritis is typically monoarticular and most often affects the knee or hip. Patients usually have broad clinical symptoms, and imaging findings are similar to those of other inflammatory arthropathies. The clinical symptoms are a result of synovial membrane inflammation and typically cause severe, persistent localized pain and swelling<sup>27</sup>. Nevertheless, in Pott's disease of the spine, the disease progresses insidiously with progressive localized pain occasionally with muscle spasm and rigidity for weeks to months before diagnosis, thus delaying it<sup>25</sup>. The patient is extremely cautious and evades shaking of the spine and walks with head and chest thrown backward and the legs apart<sup>28</sup>. Systemic symptoms occur in less than 40% of cases<sup>29,30</sup>.

Similar to Pott's disease, Tuberculous osteomyelitis is usually insidious but infrequently it may have an acute or subacute presentation. It may present as a 'cold abscess' with swelling, slight erythema or pain, and negligible warmth<sup>27</sup>. Unifocal participation is more common. However, multifocal osteomyelitis is more frequent, particularly in children and affects the femur, tibia, carpals and tarsals spontaneously without any pulmonary manifestations. Depending on the bone affected it may present as a breast mass or facial nerve palsy. Further, it may occur in a previously injured bone resulting in a diagnostic dilemma<sup>27</sup>.

#### **Abdominal Tuberculosis :**

It is the sixth most frequent site of EPTB and

accounts for 5% of all TB cases globally<sup>31</sup>.

#### **Peritoneal TB :**

Clinical manifestations persist for weeks or months before the diagnosis is made which include ascites (>90%), abdominal pain (>70%), and fever (~60%)<sup>32-35</sup>. Nearly 90% of patients at presentation have ascites without cirrhosis<sup>36</sup>. In the remaining cases, the presentation involves dry type with adhesions which is a fibroadhesive form of the disease<sup>37,38</sup>. The absence of signs of chronic hepatic disease should prompt a high clinical suspicion for TB peritonitis<sup>39</sup>. In ESRD patients on peritoneal dialysis, within a year they develop clinical manifestations of tuberculous peritonitis<sup>40</sup>.

#### **Intestinal TB :**

Clinical manifestations indicating intestinal ulceroconstrictive disease which generally occurs in malnourished patients include intestinal colic, abdominal distension, chronic diarrhea, nausea, vomiting, constipation, and bleeding. Involvement of adjoining structures results in ascites, lymph node enlargement and reproductive system-associated symptoms. Systemic manifestations such as fever, fatigue, weight loss, and night sweats do occur.

Almost one-fourth to half of the patients present a palpable abdominal mass in the right lower quadrant<sup>41,42</sup>. Abdominal pain is the most common manifestation. Diarrhoea occurs in 11-37%, bleeding in 5-15% of patients, and constipation in 50% indicating small or large intestine involvement<sup>41</sup>. Bowel obstruction is also a frequent complication. Apart from these symptoms, patients may complain of early satiety and postprandial fullness. Rectal TB classically presents as hematochezia and constipation followed by systemic symptoms. Anal TB may present as pilonidal sinus, persistent perianal growth, anal ulceration with inguinal lymphadenopathy, anal fissure, fistulae, or stricture<sup>43</sup>.

#### **Hepatic TB :**

It includes miliary hepatic disease and isolated hepatic disease which manifest as hepatomegaly (80%), fever, respiratory symptoms, abdominal pain, and weight loss occur in 60-66% of patients. Splenomegaly, ascites, and jaundice have been reported in 20-30% of patients<sup>44</sup>.

Several other forms such as those involving the pancreas, stomach, and duodenum are rare and may manifest as abdominal pain, jaundice, and constitutional symptoms.

#### **Tuberculous meningitis :**

Tuberculous Meningitis (TBM) is a manifestation of extrapulmonary TB, occurring in 1%-5% of the total cases of TB globally. TBM can occur either as a lone manifestation of TB or concomitantly with pulmonary

or other extrapulmonary sites of infection in nearly 50% of cases<sup>45</sup>.

Patients with TBM present subacutely and often without characteristic signs of meningitis in the early stages. Some may develop typical symptoms and signs of meningitis including headache, fever, and stiff neck. Individuals may initially present with nonspecific symptoms and signs including apathy, irritability, headache, malaise, fever, anorexia, nausea, and vomiting, without any change in the level of consciousness (Glasgow Coma Scale GCS 15). Some individuals may present with disturbed consciousness in absence of coma or delirium but with slight focal neurological signs. Symptoms and signs of meningism and meningitis may coexist with focal neurological deficits, isolated CN palsies, and atypical involuntary movements (GCS 15 *with* focal deficits, or GCS 11–14 *without* focal deficits). An advanced stage of the patient manifests as stupor or coma besides dense neurological deficits, seizures, posturing, and/or abnormal movements (GCS $\leq$ 10). Predominantly, TBM individuals from poor-resource settings are in stage 3 at the time of presentation with a GCS of  $\leq$ 10<sup>46-48</sup>. Hemiparesis, paraparesis, seizures, and cranial nerve palsies, are frequently present and should raise suspicion for TBM<sup>49</sup>. The duration of symptoms preceding presentation lies between days to months<sup>47,48</sup>.

### Urogenital TB :

Urogenital tuberculosis (TB) is the third most frequent form of EPTB<sup>50</sup>. It occurs in 2-20% of patients with pulmonary TB<sup>51</sup>. Nearly half of these patients have a history of TB and around 10% may have an active infection<sup>51</sup>. It is usually seen in adults due to a long incubation period<sup>19</sup>.

In the early stages renal and urologic TB are not associated with explicit symptoms. Pyuria or hematuria may be just secondary findings. However, disease progression to the bladder results in dysuria, urgency, and nocturia in 50% of cases with evident hematuria and low back pain in more than 30% of the cases<sup>51</sup>. Systemic symptoms are fairly rare<sup>52</sup>. Indices of advanced disease include end-stage kidney disease and, infrequently, refractory hypertension<sup>53,54</sup>.

PLWHA are more susceptible to tuberculous kidney and prostate abscesses compared to those without HIV infection<sup>55</sup>.

### Genital tract tuberculosis :

It is the third most common form of EPTB. It occurs in 2-20% of patients with PTB.

TB can affect the entire male genital tract, with epididymitis being the most common clinical manifestation in 10-55% of cases<sup>52</sup>. Scrotal nodule and fistula may manifest in 50% of cases with bilateral

involvement in 34% of cases with hydrocele being less frequent.<sup>56</sup> Prostate involvement is usually subclinical and abscess occurs majorly in PLWHA.<sup>57</sup> The most first common symptom is infertility in 10% of males due to poor sperm parameters<sup>57,58</sup>. External manifestations include ulcerated papules mistaken as genital ulcers or deformed penis<sup>59</sup>.

Among women, genital tract TB causes infertility in 0.2 to 21% of infected cases and this is the presenting symptom in the majority of cases. Besides, pelvic or abdominal pain or mass and menstrual disorders may be the manifestations in 25-50% of infected females<sup>51,60,61</sup>.

### Summary (conclusion) :

The most common manifestation of TB is PTB, followed by EPTB, and lastly disseminated TB. The clinical spectrum of affected individuals ranges from being asymptomatic to developing fatal complications depending on the time of diagnosis, degree of immunity, age, and comorbidities. Most of the symptoms of EPTB are non-specific and insidious in development, thus delaying the diagnosis and resulting in an advanced disease stage at presentation. Therefore, most of the manifestations should raise a high degree of suspicion for prompt identification and management.

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