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# Clinical Manifestations of Tuberculosis

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***Abstract***

*Tuberculosis is an ancient disease which is one of leading infectious killer worldwide. Global TB epidemic continues to cause significant morbidity and mortality especially in developing countries like India. The causative organism M. tuberculosis has infected almost one third of world population. The mode of transmission of tuberculosis occurs by inhalation of droplet nuclei containing tuberculosis bacteria. Infection leads to establishment of granulomas in lungs. There are no clinical symptoms in latent stage of infection. Active disease results when bacteria grow and multiply in the host due to inability of immune system to contain the infection. The primary site of infection is lungs leading to pulmonary tuberculosis. However, M. tuberculosis n infect any part of body resulting in extrapulmonary tuberculosis which has several clinical manifestations.*

***Keywords -*** *Tuberculosis, Mycobacterium tuberculosis, Extra pulmonary tuberculosis, Latent tuberculosis*

## Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* complex. The causative agent of tuberculosis was discovered by Robert Koch in 1882 (Koch, 1932, Koch, 1982). It was commonly known as white plague and was associated with 19th century Romantic-era poets or artists. This romantic disease of the past still haunts the mankind and continues to be the leading infectious killer ranking above HIV. The increase in drug resistance to anti-TB treatment is further aggravating the problem leading to multi-drug resistant (MDR) and extensively drug resistant (XDR) forms of TB. This chronic illness hits majority of people at most economically productive points in their lives and constitutes a global burden. One –third of the world population has been estimated to be infected with *M. tuberculosis* (MTB). There were 10.4 million new tuberculosis cases and 1.4 million deaths according to the 2016 WHO Global Tuberculosis Report (WHO, 2016). India accounts for highest burden of TB and MDR TB incident cases worldwide. One fourth of global incident TB cases occur in India annually. There were 28 lakhs estimated incident cases and 4.8 lakhs deaths in 2016 due to TB. It is of paramount importance to understand the pathophysiology of the disease and myriad of clinical manifestations caused by MTB infection. A comprehensive overview of pathogenesis and types of tuberculosis has been presented in this review.

### *M. tuberculosis*

*M. tuberculosis* is the aetiological agent of tuberculosis. It is a gram positive bacterium with a complex cell wall containing mycolic acids and polysaccharides in addition to peptidoglycan (Kieser and Rubin, 2014). Mycobacteria can be stained by acid-fast dyes, such as Ziehl-Neelsen stain owing to its unusual cell envelope (Hett and Rubin, 2008). It is slow growing bacillus with generation time of 24 hrs contributing to chronic nature of the disease and imposing lengthy treatment regimen (Cole et al., 1998). It is an intracellular pathogen with ablity to survive and grow in macrophages and granulomas formed in various organs of its host.

*M. tuberculosis* belongs to MTBC within the family Mycobacteriaceae. MTBC comprises *M. tuberculosis, M. bovis, M. bovis* BCG, *M. africanum, M. microti, M. canetti, M. caprae* and *Ì. Pinipedii* (Smith et al., 2009). There is genetic homogeneity in the complex. The genome size of of *M tuberculosis* is approximately 4.4 Mbp with high GC content. It codes for more than 4000 protein coding genes (Miyoshi-Akiyama et al., 2012).

## Pathogenesis

Inhalation of aerosol droplets containing bacteria initiates the infection. Innate immune responses involving the recruitment of inflammatory cells to the lung occurs in initial stages of infection. Various phagocytic cells such as neutrophils,

monocyte-derived macrophages, and dendritic cells (DCs) are recruited to the infected lung which express numerous receptors to bind mycobacteria (Schäfer et al., 2009). Subsequently, the bacteria disseminate to lymph node and T cell priming is initiated by presentation of bacterial antigens by dendritic cells. It leads to expansion of antigen specific T cells. For containment of pathogen, granulomas are established in the lungs as result of recruitment of T cells, B cells, activated macrophages and other leukocytes (Nunes-Alves et al., 2014).

This is the latent stage of infection with absence of clinical symptoms. In majority of infected individuals, this stage persists without leading to active disease (Zumla et al., 2011). However, there is eventually progress to development of active disease in small percentage of these individuals. In active disease, MTB is released from granulomas and enters the airways. Infectious droplets are generated by these individuals, which leads to transmission of airborne infection while coughing (McNerney et al., 2012). Secreted proteins and various lipids are determinants of MTB virulence which interact with host to modulate intracellular bacterial trafficking and cell death pathways of host cell (Divangahi et al., 2010). Innate immune responses play a pivotal role in control of infection but it is inadequate to prevent progression to active disease (Philips and Ernst, 2012). It has been well established by various studies that the resolution of infection or development to clinically active disease is determined by effective T-cell responses. There is evidence supporting the role of $CD4^+$ T cells in protection against MTB particularly in HIV infected individuals. Recent studies have demonstrated that effector mechanisms of $CD8^+$T cells contribute to control of MTB infection. In conclusion, the ability of host to contrast the infection depends upon the balance of immune responses (Prezzemolo et al., 2014). The exact mechanism of host-pathogen interactions during latent infection and active disease are yet to be unravelled. Untreated disease leads to formation of cavities with impairment of lung function and may result in death eventually. It is known that immunocompromised conditions such as HIV infection, use of immunosuppressive therapy and co-morbidities such as diabetes, malnutrition and young age, smoking, chronic obstructive pulmonary diseases and impairment of lung function are risk factors for tuberculosis (Narasimhan et al., 2013). However, risk factors in case of immunocompetent healthy individuals are not well-established.

**Clinical Manifestations**

There is a difference in development of tuberculosis among patients due to immune status and various cellular processes (Knechel, 2009). Each stage of tuberculosis has different clinical manifestations.

**A. Latent Tuberculosis**

It is the stage of tuberculosis in

which there are no clinical symptoms, radiological or microbiological evidence of disease in individuals infected with MTB (Lee, 2015). It occurs when the pathogen is contained by the host immune responses without leading to active disease. However, it may progress into disease during the lifetime of individual if immune system becomes compromised.

**B. Primary Disease**

The new tuberculosis infection or active disease in a previously naïve host is described as primary pulmonary TB. This condition occurs subclinically and is often asymptomatic with some self-limiting clinical findings (Knechel, 2009). Pleaural effusion may result due to bacterial infiltration of pleural space and cause symptoms such as chest pain, fever and dyspnea.

**C. Primary Progressive Tuberculosis**

Active disease results when bacteria grow and multiply in the host due to inability of immune system to contain the infection. Early signs and symptoms of disease are often non-specific and are as follows according to CDC guidelines (CDC, 2016):

TB disease in the lungs may cause symptoms such as

- a bad cough that lasts 3 weeks or longer
- pain in the chest
- coughing up blood or sputum (phlegm from deep inside the lungs)

Other symptoms of TB disease are

- weakness or fatigue
- weight loss
- no appetite
- chills
- fever
- sweating at night

Lack of appetite and altered metabolism results in loss of fat and lean tissue leading to wasting and fatigue due to decreased muscle mass (Paton et al., 2004).

**D. Extrapulmonary Tuberculosis**

It is defined as infection of MTB at any site (tissues and organs) of body other than lung parenchyma. The primary site of infection is lungs but 10-25% of infections occur at extrapulmonary sites. The hematogenous and lymphatic spread of the pathogen results in extrapulmonary tuberculosis (Polena et al., 2016). Various risk factors such as age, female gender, HIV infection and co-morbidities such as chronic renal disease, diabetes mellitus or immunocompromised status predispose the patient to development of EPTB (García-Rodríguez et al., 2011). It has been observed that generally older patients present lymphatic, osteoarticular, genitourinary and gastrointestinal forms of the disease as compared to pleural or meningeal manifestations in younger patients (García-Rodríguez et al., 2011)

Various forms of EPTB are as follows:

**1. Lymph Node Tuberculosis**

It is the most common form of EPTB and occurs due to infection of lymph

nodes by MTB (Fontanilla et al., 2011). It mainly affects children and young adults and contributes to 30-40% EPTB cases (Peto et al., 2009). Patients present with enlarged lymph nodes and are usually asymptomatic. Cervical lymph nodes are most common location and other areas are supraclavicular, axillary, thoracic and abdominal nodes.

**2. Pleural Tuberculosis**

It is the second most common form of EPTB. The infection of pleural region by MTB leads to pleural TB also called as tuberculous pleurisy (Vorster et al., 2015). It is the most common cause of pleural effusion in TB endemic areas (Light, 2010, Zhai et al., 2016). Children and HIV patients have higher incidence of this manifestation of EPTB (Light, 2010). The clinical presentation of disease are chest pain, cough, acute illness with fever, and pleural effusion (Zhai et al., 2016).

**3. Genitourinary Tuberculosis**

Infection of MTB in the genital and urinary tracts constitutes Genitourinary TB which affects sites such as kidney, prostrate, testis, epididymis, seminal vesicles in males. Renal involvement is most common. Association has been observed between male genital tuberculosis and renal TB as well as pulmonary TB in less number of cases (Zajaczkowski, 2012). The sites of involvement in female genital TB are fallopian tube, endometrium, ovaries, cervix, myometrium and vulva/vagina (Abbara and Davidson, 2011). Genital TB is an important cause of infertility in developing countries such as India (Ghosh and Chowdhury, 2011). GUTB shows non-specific symptoms causing delayed diagnosis and serious complications like kidney failure (Abbara and Davidson, 2011).

**4. Osteoarticular Tuberculosis**

It is also known as skeletal tuberculosis and can affect any bone and joint. The thoracolumbar region of spine is commonly affected. Complications include compression of spinal cord or swelling and pain of joints (Spiegel et al., 2005). Common symptoms are pain in affected area, low-grade fever, malaise, night sweat and weight loss.

**5. Miliary Tuberculosis**

It is caused by widespread lymphohematogenous dissemination of bacteria to most organs of the body and also known as disseminated TB. The disease has been named according to miliary pattern observed on chest radiograph of patients. It accounts for upto 20% of EPTB cases in immunocompetent individuals while it is more frequently encountered in HIV infected individuals (Sharma et al., 2016). In adults, the symptoms of military TB are obscure and show non-specific clinical manifestations (Sharma and Mohan, 2011).

**6. Central Nervous System (CNS) Tuberculosis**

Infection of CNS with MTB leads to disease with high mortality and morbidity (Thwaites et al., 2006, Torok, 2015). Children

and HIV infected individuals have more predisposition to this devastating clinical manifestation of TB (Marais et al., 2011). Tuberculous meningitis is most prevalent form of CNS TB in high TB burden areas (Jarvis et al., 2010, Török, 2015). Meningeal infection of MTB results in thick exudate in brain and development of hydrocephalus particularly in children due to obstruction of cerebrospinal fluid caused by high protein levels (Christensen et al., 2011).

**7. Gastrointestinal and Peritoneal Tuberculosis**

The ileocecal region of intestine is most common site of gastrointestinal TB though any part of gastrointestinal tract can be affected (Wadhwa et al., 2004, Shi et al., 2016). The symptoms are vague and non-specific such as chronic abdominal pain, change in bowel patterns , fever, weight loss, and night-sweats while it may also lead to serious complications such as intestinal perforation (Awasthi et al., 2015). Hematogenous spread of infection or adjacent gastrointestinal TB can lead to tuberculous peritonitis (Awasthi et al., 2015). Exudation of proteinaceous fluid from tubercles in visceral and parietal peritoneum causes ascites in majority of patients.

**8. Ocular Tuberculosis**

Infection of MTB in the eye, around the eye or on its surface is defined as ocular TB. It is a significant cause of uveitis (Shakarchi, 2015, Dalvin and Smith, 2017). Clinical features of disease depend on the occurrence of ocular manifestations either due to direct infection or hypersensitivity response. The cause plays an important role in management of the disease (Gupta et al., 2015). Choroid is the most commonly affected structure of eye. Various studies have reported association of ocular dissemination with systemic disease (Mehta et al., 2013).

**9. Pericardial Tuberculosis**

Hematogenous spread of MTB from primary site of infection or retrograde spread from lymph nodes causes pericardial manifestation of disease known as tuberculous pericarditis (Maisch et al., 2004). Significant morbidity is associated with the disease due to immune response to MTB. It is more common cause of large pericardial effusion constrictive pericarditis in developing countries as compared to industrialized countries (Syed and Mayosi, 2007). Self-resolving serosanguinous exudative effusion or pericardial constriction are early pathological signs with non specific constitutional symptoms and compromised cardiac function (Syed et al., 2014).

**10. Other types of EPTB**

Any part of the body including skin, blood vessels, bone marrow, breasts, glandular tissue can be infected with MTB leading to varying clinical manifestations (Singal et al., 2013). Cutaneous TB is the caused by infection of the skin by direct inoculation, contiguous spread from underlying structures or hematogenous spread of pathogen (dos Santos et al., 2014,

van Zyl et al., 2015). Tuberculosis of ear, nasopharynx and salivary glands has also been reported (Nalini and Vinayak, 2006).

**Conclusion**

TB is an ancient disease and the pathogen has co evolved with the human race over thousands of years. TB can potentially affect any organ in the human body, except the non-living tissues like nails and hair. The clinical manifestations of TB are dependent on a number of factors: age, immune status, co-infections like HIV, co-morbidities like diabetes, vaccination; virulence of the infecting organism and host-microbe interaction. Extrapulmonary tuberculosis usually presents a more difficult diagnostic problem. It is less common and, therefore, less familiar to most clinicians. It's important to remember that tuberculosis, although commonly a lung disease, can strike anywhere in the body, leaving TB infection in its path. But with treatment, TB can be successfully controlled and cured irrespective of the site of infection.

**Conflict of Interest**: Authors declare no conflict of interest.

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