Diagnosis & Management of Tuberculosis

Chapter 1

Tuberculosis: Propagation beyond Lungs

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Abstract

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) still remains a formidable global health challenge particularly considering the fact that one-third of the world's population are infected by TB as currently estimated by World Health Organization. The problem is compounded by the fact that roughly 10% of the infected people are symptomatic. Although TB affects the lungs in 80% of cases, however, in the remaining 20% the disease may affect other organs severely if lately diagnosed or left untreated. Hence, it is pertinent not only to diagnose early and initiate appropriate therapy but understand the pathogenesis of TB and its different types to prevent transmission. This chapter provides a consolidated gist of the different types of TB viz. Meningitis TB, Occular TB, Lymph node TB, Spinal TB, Cutaneous TB, Hepatic TB, Renal TB, Abdominal TB and Genital TB at common platform.

Keywords: *Mycobacterium tuberculosis*; pulmonary tuberculosis; extrapulmonary tuberculosis; diagnosis, pathogenesis

1. Introduction

Tuberculosis (TB) is an infection caused by Mycobacterium tuberculosis (MTB) causing global concern. According to estimates, in 2015, approximately 9.6 million people suffered with TB, of which 1.5 million died [1]. Several genetic, social, environmental and biological determinants of health have been instinctively recognized as risk factors for TB. Among them, human immunodeficiency virus (HIV) infection and diabetes have fuelled the resurgence of

TB worldwide.

TB can affect any organ system in the body despite pulmonary TB being the most common presentation. However, extrapulmonary tuberculosis (EPTB) is also an important clinical problem which has compounded the pathogenesis of TB. Types of EPTB that have been widely reported are Meningitis TB, Occular TB, Lymph node TB, Spinal TB, Cutaneous TB, Hepatic TB, Renal TB, Abdominal TB and Genital TB. In this chapter, we made an attempt to give a brief overview of the most prevailing forms of EPTB (Fig. 1). We have tried to give an account of the various types of EPTB and explain in brief the pathogenesis and current treatment methodologies.

2. Pulmonary Tuberculosis

TB or pulmonary tuberculosis (PTB) is caused by the intracellular bacterium MTB. PTB has been a major health concern since antiquity. TB infects around 8 million people every year leading to approximately 3 million deaths every year. These numbers may increase in the coming years due to increasing HIV patients and the emergence of Multi drug resistance (MDR) [2-4].TB can present as an asymptomatic infection to a life-threatening disease. TB infections can be classified as active TB disease, which is transmissible (active TB) or latent TB infection (LTBI), which is an asymptomatic and non-transmissible state. It is estimated that in 2014, around 9.6 million people developed active TB disease, among 1.5 million died [5].

2.1. Epidemiology and risk factors

Developing active TB infections are quite frequent in exposed infants, but much lower in children 2–10 years of age; risk then rises during adolescence and plateaus around 25 years of age and remaining high throughout adult life. Incidence of active TB infections are approximately two fold higher in men than in women, and approximately 10% of all new cases worldwide occur in children [6,7]. HIV infection is the strongest risk factor for TB; 12% of all new active TB disease cases and 25% of all TB-related deaths occur in HIV-positive individuals. For example, majority (75%) of HIV-associated active TB disease cases and deaths occur in Africa (8). Other risk factors are responsible for the remaining fraction of TB cases in the general population. Other risk factors for TB include type 2 diabetes mellitus, alcoholism and smoking. Therefore, addressing these social and behavioral determinants could help to expand the current biomedical paradigm for TB control [8].

2.2. Pathogenesis and clinical features

Pulmonary alveoli are initial site for the infection, where MTB invade and replicate within alveolar macrophages. Then the inhaled mycobacteria are phagocytized by alveolar macrophages, where macrophages interact with T lymphocytes, resulting in differentiation of

macrophages into epithelioid histiocytes [9]. In the granuloma, CD4 T lymphocytes secrete interferon-γ, which activate macrophages to destroy the bacteria. CD8 T lymphocytes also directly kill the infected cells [10]. It deserves special mention that, bacteria are not always eliminated from the granuloma and they can become dormant resulting in a latent infection. Gon focus in the lungs either enlarges as disease progresses or undergoes healing. At early infection process, MTB commonly spread via lymphatic channels to regional hilar and mediastinal lymph nodes via the bloodstream to more distant sites in the body. The initial infection is generally clinically silent. Approximately 5% of infected individuals show inadequate immunity and clinically active disease develops within 1 year of infection. For most infected individuals, however, TB remains clinically and microbiologically latent for many years for most infected individuals [11]. Endogenous reactivation of latent infection develops many years after the initial infection. This reactivation predominantly involve the apical and posterior segments of the upper lobes and the superior segments of the lower lobes most likely due to a combination of higher oxygen tension and impaired lymphatic drainage in these regions [12]. Progressive extension of inflammation and necrosis, with frequent development of communication with the airways and cavity formation are the main abnormalities during the reactivated PTB.

2.3. Diagnosis

Diagnosis of PTB is challenging due to the difficulty in culturing this slow-growing organism in the laboratory. One way is to culture MTB from a specimen taken from the patient. Tuberculin skin test (TST) is the most common method and has been used for years to diagnose the latent TB in non-immunized person. However, TST has limitations such as false positive test results in Bacille Calmette-Guérin (BCG) vaccinated individual and in individuals with non mycobacterial infections [9,10,13,14]. A new interferon-γ assay has been introduced for the diagnosis of LTB infection, which is found to be reliable method than the TST [11,15]. This test is comparatively cheap and fast TB testing. This new test use polymerase chain reaction (PCR) detection of bacterial DNA and whole-blood interferon-γ assay [12,16]. Chest radiography is a more expensive test but important, especially when clinical suspicion of PTB exists but the sputum is still negative. In HIV patients, the radiological appearances are often less specific as symptoms and signs may not appear to be classical and sputum also may be negative on direct smear. The nucleic acid amplification test detects the MTB nucleic acid sequence using an amplification technique [17,13].

2.4. Management

LTBI treatment regimens recommended by the WHO include 6–9 months of isoniazid, 3 months of rifampicin plus isoniazid, 3–4 months of isoniazid plus rifampicin or 3–4 months of rifampicin alone. All regimens are known to be efficacious, but patient compliance can be poor with the longer regimens [18,19]. Rifampicin-containing regimens are shorter and might

be more suitable in populations with a high prevalence of isoniazid mono-resistant strains. It is always important to ensure adherence and provide patients with adequate counseling regardless of the regimen. The current preferred regimen for active TB disease is a minimum of 6 months of therapy with, first line drugs like isoniazid, rifampicin pyrazinamide and ethambutol during the first 2 months (the intensive phase of treatment), followed by isoniazid and rifampicin for 4 months (the continuation phase) [20,21]. Treatment efficacy and progress are usually monitored with repeat sputum smears, cultures and chest X rays. Although the standard 6 month regimen has a high success rate (approximately 86% under routine, program¬matic field conditions; the regimen itself has higher efficacy), it also has several limitations due to long duration of the treatment. The adverse effects range from gastrointestinal intolerance to severe adverse effects such as hepatitis, immune thrombocytopaenia, agranulocytosis, haemolysis, renal failure, optic neuritis and ototoxicity.

It is always necessary to ensure optimal adherence as lack of treatment completion also contributes to treatment failure, relapse and the emergence of drug resistance. Directly observed therapy (DOT) is the most common adherence monitoring approach. However, various alternative methods are now being tried out to improve adherence, including mobile phone reminders, smart pill boxes, video DOT and the use of call centres to follow-up with patients. Beyond drug therapy, there is a role for surgery in the management of drug-resistant TB. In patients with unilateral disease or apical bilateral disease with adequate lung function, surgical treatment to remove the entire affected area of the lung could be effective. However, in patients with resistant TB, elective partial lung resection (lobectomy or wedge resection) is associated with improved treatment success [22,23].

At present BCG is the only currently licensed vaccine to prevent the development of active TB disease [24]. The BCG vaccine was first used in humans in 1921 and has been evaluated in numerous interventional trials and observational studies looking at less common manifestations of active TB disease. The efficacy of the BCG vaccine against pulmonary TB in adults has been reported to be 0–80% [25]. Despite the variability in its efficacy, BCG vaccine has proven that protective immunity against TB can be induced by a vaccine. Indeed, the main goal of current vaccination research is to help prevent active TB infection from developing in the 10% of infected individuals who cannot contain the infection on their own as LTBI. Since, the BCG vaccine provides only limited protection for neonates and children and no protection against pulmonary TB in adults, it accounts for most of the TB cases worldwide.

Current tools and strategies for diagnosis of TB are inadequate, however, notable advances in TB diagnostic technologies have been made in the past several years, and the potential exists for translating these improvements into meaningful developments in global TB clinical care and control. The current first-line treatment for TB is a multidrug regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol. Clearly, there is an urgent need

to improve treatment by introducing new drugs. Potential new agents should reduce treatment duration, have an acceptable tolerability, active against MDR/XDR TB, can be used in HIV-infected patients with TB and be active against latent TB Different classes of drugs like Nitroimidazopyrans, Diamines, Fluoroquinolones and Diarylquinolines are currently being investigated in clinical trials [26]. Besides developing new anti-tuberculosis drugs, introducing efficacious vaccine is needed for control and prevention. Numerous attempts for obtaining MTB vaccine with enhanced protection over BCG, durability, and safety have been made. Candidate vaccines against MTB have largely focused on targeting immunodominant antigens that are secreted proteins, including Ag85A , Ag85B, ESAT-6, TB10.4, Rv1196 and Rv0125 [27]. Development of new vaccines and diagnostics will be aided by the discovery of additional antigens relevant to both natural and vaccine-induced immune responses to MTB infection. The development of TB vaccines faces numerous challenges. Despite these limitations, present 13 vaccine candidates are currently being tested clinically, which are classified into three platform types: whole-cell or lysates of mycobacteria, adjuvanted recombinant protein vaccines and viral vector vaccines. The MTB specific antigenic make-up ranges from several thousand antigens in mycobacterial vaccines to fewer in the viral vector and recombinant protein vaccines [28].

3. TB Meningitis

TB Meningitis (TBM) is highly devastating infection that affects central nervous system leading to high rates of death and disability. It is a severe form of TB affecting the meninges (system of membrane enveloping the central nervous system) which is present as sheath surrounding the brain and spine. Central nervous system associated TB manifests primarily as TBM and less commonly as other conditions such as tubercular encephalitis, intracranial tuberculoma, or a tuberculous brain abscess. It is reported that approximately 1% of all cases of active TB and 5-10% of EPTB cases have TBM [29]. It is especially common in children and HIV patients [30].

3.1. Pathogenesis and clinical features

In this, mycobacterium invades into host body by liquid droplets containing bacilli leading to deposition in the lung. The primary infection occurs usually in the lungs and disseminated through the blood stream to the meninges or brain parenchyma which is responsible for development of small subpial or subependymal foci of metastatic caseous lesions called as rich foci. Then the size of rich foci increases until it ruptures into subarachnoid space and cause meningitis [31,32]. In adults the symptoms of TBM involves headache, fever and meningismus (stiff neck) along with focal neurological deficits, alteration in consciousness, generally feeling unwell, irritable, tired and not being able to sleep [33]. Children suffering with meningitis TB normally involve stiff neck, fever, seizures, nausea and vomiting [34,35].

3.2. Diagnosis

The diagnosis of TBM depends upon the detection of MTB bacilli in the cerebrospinal fluid (CSF). The current conventional used method such as cultural technique and microscopy are less sensitive. Therefore various alternative methods such as immunoassay and biochemical tests are used nowadays to diagnose TBM. The staining techniques such as Ziehl- Neelsen, auramine-rhodamine or Kinyoun are applied to detect the acid fast bacilli (AFB) in CSF. In addition high sensitive neuroimaging involving radiological methods such as Magnetic resonance imaging (MRI) and CT scan are available for the diagnosis of TBM. Molecular based techniques including PCR is a new promising method for the detection of MTB DNA in CSF because of its sensitivity, rapidity and specificity [36,37].

4. Ocular TB

TB being a multisystem infectious disease may affect other organs including the eye. The ocular infection occurs in the eye, around the eye or on the surface (intraocular and extraocular). It is estimated that 1.4% of persons with PTB develops ocular manifestations but many patients with ocular TB have no evidence of PTB [38-43]. The most common indicator of ocular TB is uveitis which is usually presented as chronic anterior uveitis, panuveitis or choroiditid. It is reported that 12 patients with intraocular TB, 9 of whom are presented with retinal vasculitis, 2 with choroidal tubercles and 1 with chronic anterior uveitis [44]. Although there exists an association between miliary TB and ocular TB but ocular involvement may not be always associated with HIV positivity [45]. Ocular TB (OTB) leads to decreased visual acuity and other ocular symptoms. The general symptoms of OTB include blurred vision and light sensitivity, Headache and redness of the eye and Inflammation on the infected area of eye.

4.1. Pathogenesis and clinical features

The OTB can infect the eye through several different mechanisms. The most common ocular infection is often the result of hematogenous spread. The uveal tract, retina and optic nerve (i.e. the iris, ciliary body, and choroid) are the coats of the eye most commonly involved because of its high vascular content. Primary ocular infection of the eye is the one in which bacilli enters the body through lids or conjunctiva [46] most frequently infecting the children. Other external tissues which are less infected include cornea, sclera lession, eyelid and conjunctival. Secondary ocular infection may occur by direct action from surrounding tissues or by contamination with the patient's own sputum. Additionally, some other forms of eye infection can occur due to the hypersensitivity reaction, such as phlyctenulosis, retinal vasculitis, and interstitial keratitis.

Inappropriate implementation of the Revised National Tuberculosis Control Programme

(RNTCP) causes precipitation of MDR-TB cases in the community. In this situation, India is not well equipped to prevent the propagation and dissemination of MDR-TB cases. So a new reemerging threat is slowly growing within the Indian population that may arise as a big challenge in future. MDR-TB is a man-made phenomenon poor treatment, poor drugs and poor adherence lead to the development of MDR-TB [11].

4.2. Diagnosis

Microbiological and direct histopathological examination can provide evidence of OTB infection. The physical examination includes sputum smear and culture, PPD test, and chest radiography. Sixty percent of patients with EPTB have no evidence of pulmonary disease, and chest X-rays are normal in cases of latent TB [47-49]. The Interferon-gamma release assay (IGRA) is recommended by the US Food and Drug Administration and other countries. IGRAs such as T-SPOT and QFT are more specific and sensitive than TST in detecting active pulmonary TB infections [50]. T-SPOT is more specific for diagnosing TB that involve uveitis, and serves as a better diagnostic tool if used in conjunction with the TST [51]. Molecular techniques are also used for detection of mycobacterial DNA through PCR. Detection of antibodies against purified cord factor, the most abundant cell wall and antigenic component of MTB, can provide strong evidence of the infection [52]. PCR yields results much faster than mycobacterial cultures, which can require several weeks for a positive result.

5. Lymph node Tuberculosis

Lymph node Tuberculosis (LNTB) or scrofula occurs when MTB infects the lymph nodes. LNTB has been called as the “king’s evil” in the ancient times [53]. LNTB remains the most common form of EPTB in India and other developing countries [54].

5.1. Pathogenecity and clinical features

MTB enters the body and undergoes lymphatic dissemination. Usually, tonsils are the most common routes of entry for the pathogen. At the initial stage of infection, the lymph nodes are discrete. Afterwards, the lymph nodes coalesce and break open due to pus development. Wounds so developed may not heal even for years [53]. Patients with LNTB infections may have symptoms like fever, weight loss, night sweats and fatigue. Distressing cough may be a prominent symptom in LNTB [55].

5.2. Diagnosis

TST is positive in majority of patients of LNTB, the probability of false negative test is less than 10% [56].Thus, TST seems to support the diagnosis and a negative test substantially reduces the likelihood of LNTB. Ultrasound assessment of abdomen and CT scan of the chest may be required in a few patients. Engorged lymph nodes may show hypodense areas with

rim enhancement or calcification. Excision biopsy is done to diagnose LNTB but fine needle aspiration cytology (FNAC) seems to have established itself as a safe, cheap and reliable procedure [57]. Typically, tuberculous lymph nodes show multinucleated giant cells, caseation necrosis and epithelioid cell granulomas. Caseating granulomas are seen in nearly all the biopsy specimens and 77% of the FNAC's [58]. New diagnostic methods such as PCR tests of the tissue to identify MTB became promising recently.

6. Spinal Tuberculosis

Spinal TB (STB) is the most frequent form of skeletal TB and accounts for 50% of all cases of skeletal TB [59]. Most cases of STB are seen primarily in immigrants from endemic countries. STB is one of the oldest diseases and has been found in Egyptian mummies dating back to 3400 BC [60]. The exact incidence and prevalence of STB is not known. Approximately 10% of patients with EPTB have possessed skeletal involvement where spine is the primary site of infection, followed by the hip and knee [59].

6.1 Pathogenesis and clinical features

Spinal involvement is usually a result of hematogenous spread of MTB into the dense vasculature of cancellous bone of the vertebral bodies. Either a pulmonary lesion or infections of the genitourinary system are the primary infection sites. The progression of STB is slow and the illness varies from few months to few years, with average disease duration ranging from four to eleven months. Generally, patients seek advice only when there is severe pain, marked deformity, or neurological symptoms. The clinical features of STB include local pain, tenderness, spasm and stiffness of the muscles, gibbus, a cold abscess, and a prominent spinal deformity. Back pain is the most common symptom of SP. The intensity of pain varies from constant mild aching to severe disabling. Pain is normally localized to the site of involvement and is most common in the thoracic region. Pain may be aggravated by spinal motion, weight bearing and coughing because of advanced disk disruption and spinal instability, nerve root compression and or pathological fracture [61]. Spinal distortion is a characteristic feature of STB. Type of spinal deformity depends on the location of the tuberculous vertebral lesion. Kyphosis type of spinal distortion is the most common spinal distortion which occurs with lesions involving thoracic vertebrae [59]. The severity of this distortion depends on the number of vertebrae involved. An increase in kyphotic deformity may be seen even after the treatment.

6.2. Diagnosis

Biopsy is a valuable method to diagnose of STB infection. DNA amplification techniques such as PCR may facilitate rapid and accurate diagnosis of the disease. Culturing the organisms is slow and may be inaccurate. However, it is still a valuable diagnostic method in order to recognize the causative germs. CT provides bony detail, while MRI evaluates the involvement of

soft tissue and abscess formation. Significant bone destruction can be detected on plain radiographs or CT scan. Imaging studies such as Ultra sound (USG), plain radiography, CT scan and MRI are valuable tools for the diagnosis and accurate evaluation of STB. USG is useful to evaluate of soft tissue masses, joint effusions, abscesses, joint effusions, and involvement of tendon sheath. CT scan is helpful for the detection of 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 tuberculous osteomyelitis and arthritis, joint effusion, and cartilage destruction early and more accurately [62].

7. Cutaneous Tuberculosis

Cutaneous tuberculosis (CTB) is uncommon and not a well defined disease, comprising only 1-1.5% of all extra-pulmonary manifestations. CTB is prevalent among children and women mostly young adults. Recently, a rise in the number of CTB cases has been seen due to the prevalence of MDR strains of MTB [63]. Scrofuloderma, lupus vulgaris and TB verrucosa cutis are the two common CTB forms. CTB is more prevalent in HIV positive patients. Two ways of infection have been seen in CTB. In the primary infection, mycobacterium may enter the body through a contaminated injection. In another way, pathogenesis is seen during the incubation period in those people who have contacted primary infection. During the initial stages of the infection, bacteria enter the bloodstream via the lymph nodes and thoracic duct and hence cause infection.

7.1. Pathogenesis and clinical features

The pathogenecity of CTB depends on the root of infection and the level of cell mediated infection (CMI) of the host [64]. As CMI may deteriorate as a result of illness, immunosuppression, ageing, HIV infection and malnutrition, there is a long-term risk of reactivation. This risk is maximum during two to three years after primary infection. CTB can occur following any injury. During this early stage of the infection, a number of mycobacteria reach the bloodstream [65]. This hematogenous TB takes place for a very short time and is unlikely to continue after delayed hypersensitivity develops. Fever is the main clinical manifestation during this period and lasts for few days. The mycobacteria are seeded at various organs may heal completely or become active again during periods of lowered immunity. Microhematoma that occurs at the injection site PTB patients acts as an area of lowered resistance resulting in seedling of mycobacteria that get fixed at these sites and later progress to abscess formation [66]. It is hypothesized that the high lactic acid content and lymphatic tissue with very rich blood supply and absence of reticuloendothelial cells may help in localization of MTB in the muscles [67]. However, such an occurrence in skin is not yet defined. Patra et al. reported that, BCG vaccination scar was found in 59.62% of cases of TB which reflects the incapability of the vaccine to protect TB completely [68]. Thus, CTB infections should be considered in the

differential diagnosis of any chronic infection or local abscess that forms especially if there has been an interval of 2 to3 weeks between injury and the development of abscess.

7.2. Diagnosis

The only absolute criteria in confirming a diagnosis of CTB is a positive culture of MTB from the biopsy material on Lowenstein Jensen's media (LJ media). AFB smear is useful if lesions have a high bacterial load as seen in case of miliary TB, Lichen Scrofulosorum (LS) and TB gumma. PCR technique is found to be efficient in case of multibacillary forms of CTB. This technique is found to be 50-70% accurate in detecting CTB. However, couple of diagnostic tests is generally performed to precisely confirm the diagnosis. Commonly used tests include testing of blood, urine and sputum samples along with CT scan and X ray of chest and bones. Furthermore, the diagnosis relies on histopathology, PCR and culture on LJ medium. Mantoux test is also conducted during the course of diagnosis [68,69].

8. Hepatic Tuberculosis

Hepatic tuberculosis (HTB) is a common manifestation where TB involvement of liver is seen in up to 50-80% cases. With the increasing risk of TB, the rate of hepatic TB has also been increasing particularly in Asian countries such as Philiipines [70]. Hepatic connection was found clinically in 50 80% of all patients dying of pulmonary TB and in up to 91% on autopsy [71]. It is more common in male as compare to female with the ratio of 2:1. There is no specific age but according to one study more patient of HTB fall within the age range of 11-50 year [72]. HTB can be classified into the following: 1) Localized tuberculous involvement of liver in the form of the primary tuberculous complex with caseation of the associated hepatic hilar lymph nodes. These lymph nodes may develop the source of spread causing early systemic generalization. 2) Miliary TB, a part of wide infection, on the liver by clustered miliary tubercles. 3) Tuberculomas, or granulomatous disease, can occur through enlargement of tubercles foci as well as nodular development of tuberculous foci in the tertiary stage [71].

8.1. Pathogenesis and clinical features

HTB infections can occur prenatally, perinatally and postnatally. Perinatally and Prenatally HTB infections are carried through the umbilical vein or the amniotic fluid and presence of maternal placenta tuberculosa is a pre environment for both infections. Postnatally, tubercle bacilli reach the liver by the way hematogenous dissemination or hepatopetal lymph vessels. In case of millary tubercle bacilli reach the hepatobilary tract through the hepatic artery from a primary tuberculous infection of the lungs. If tubercle bacilli reaches the liver by lymphatic spread or due to break of a tuberculous lymph node in the portal tract, this case includes localized hepatic tuberculous. In some case the tuberculous infection reach the liver naturally through the involvement of gastro intestinal tract [71]. Hematogenous dissemination is more

frequent than lymphatic vessels. In miliary TB, through hematogenous spread, it produces a number of small tuberculous of liver foci. Irrespective of the mode of entry, the liver responds by granuloma formation both in case of caseating and non caseating granulomas. The common sign of HTB includes fever, poor appetite, fatigue, pain in the hepatic region and hepatomegaly. It is often hot in the afternoon with chills and night sweat sometimes. Hepatomegaly is the main sign with more than half of patients having haphalgesia. Mild jaundice can develop in upto 15% patients because of the oppression of nodules against the hepatic ducts and bile ducts [73].

8.2. Diagnosis

It may be difficult to be diagnosed clinically because of lack of specific clinical symptoms, and may be unsuspected or confused with primary or metastatic carcinoma of the liver. The suspected cases need diagnostic examination based on the histological and bacteriological studies, as well as PCR analysis. Approximately 75% of patients with HTB were found to have abnormal chest X rays demonstrating PTB [74]. CT and MRI are used to diagnose tuberculoma or tuberculous liver abscess. HTB could also be confirmed by liver biopsy through diagnostic tool laparoscopy, exploratory laparotomy and finally autopsy [73].

9. Renal Tuberculosis

Renal TB (RTB) is subpart of genitourinary tuberculosis (GUTB). GUTB is the second most common form of EPTB after lymph node involvement [75]. The primary infection through different mechanisms that include direct infection of the kidney and lower urinary tract (renal pelvis, ureter, bladder and urethra). In worldwide 15% of patient infected with HIV in which 75% of patients infected with GUTB as well as co infected with HIV [76].

9.1. Pathogenesis and clinical features

RTB cases are mostly affected by milary tuberculous infection, where milliary lesions found in renal tissue as a consequence of hematogenic dissemination, particularly in the cortical region [77]. Furthermore, in the kidneys, the medullary region is the place for colonization by MTB, where granulomatous lesions form which lead to 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. With the progression of disease cause papillary necrosis develop cavities that crash the renal parenchyma and can migrate into other collecting system [78]. In clinical presentation typically granulomata lesions start from the kidney and disseminate to the ureters, bladder, and testicles. Early renal disease may present as the proteinuria, pyuria, and loss of kidney function. Hematuria is another possible symptom of renal TB. It may also involve flank, back pain and constitutional symtoms such as fever, weight loss and fatigue [79-81].

9.2. Diagnosis

Diagnosis usually involves isolation of pathogen in urine sample or by tissue biopsy. To evaluate RTB, partially three different urine samples should be collected for acid-fast staining and mycobacterial cultures. There are some specific features in a urine examination that suggest a diagnosis of RTB, such as acid leukocyturia or hematuria and pH, associated with negative urine culture for the usual bacteria that causes urinary tract infection [78]. Some other molecular biology technique is used to diagnosis such as PCR. CT scan is also helpful in determining the extent of renal and extrarenal spread of disease [82].

10. Abdominal Tuberculosis

Abdominal tuberculosis (ATB) is the sixth most common extrapulomary site of TB after lymphatic, genitourinary, bone and joints, military and TBM [83]. The ATB is mostly seen between the age of 25-45 year. It is estimated that approximately 15%-25% of cases with ATB have associated PTB [84,85]. ATB can involve entire gastrointestinal tract, peritoneum, lymph nodes or solid visceral. In ATB, ileocaecal region is the most common site but rarely occur in ascending colon, jejunum, appendix, duodenum, stomach, oesophagus, sigmoid colon and rectum [86]. Infection in this region leads to the formation of granuloma, caseation, fibrosis, scarring, fibrosis and mucosal ulceration. It is usually difficult to diagnose due to its nonspecific clinical presentation, lack of sensitive tool and variable anatomical location.

10.1. Pathogenesis and clinical features

In the ATB, MTB reaches different site of abdomen such as kidney, lymph nodes and peritoneum usually due to ingestion of infected sputum or from infected source such as milk products, haematogenous or lymphatic dissemination of MTB from the pulmonary site. There are different sites involved in ATB viz. gastrointestinal tract, peritoneum, and visceral [87]. GastroIntestinal tuberculosis is one of the most common forms of TB in the developing world that represents 70-78% cases of abdominal TB. The primary site of TB is the lungs but the tubercle bacteria can affect to other parts such as esophagus, small bowel, ileum, duodenum, jejunum due to ingestion of infected sputum or food infected with Mycobacterium bovis resulting into primary intestinal TB. It mostly affect the iieocecal region bur rarely involve esophagus stomach and duodenum [88]. Peritoneal tuberculosis is another form of TB mostly seen in association with gastrointestinal TB that affect 4-10% patient of EPTB [89]. In this case MTB reach to peritoneum usually due to ingestion of infected sputum or by haematogenous spread from military TB or active pulmonary TB. Moreover it can also spread through ruptured lymph nodes or intra-abdominal organ. It occur in wet ascetic type (commonest, approximately 90%), fibrotic fixed type and dry plastic type [90]. Visceral tuberculosis is less common form of TB that affects 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 but the symptoms of visceral TB are non specific which makes difficulty in diagnosis [91]. The symptom of ATB involves weight loss, fever, diarrhea, constipation, fatigue, malaise, abdominal pain, and abdominal distension. Esophagal TB involves dysphagia, retrosternal pain and odynophagia. Gastric outlet obstruction, epigastric pain and an acute episode of vomiting and dyspepsia are seen in duodenal TB. Ileocecal TB may present 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. Rectal and anal TB may present constipation and multiple fistulae symptoms [87-92].

10.2. Diagnosis

The acid fast staining is the current conventional method for diagnosis of PTB but not applicable for diagnosis of various types of ATB. Therefore some alternative radiology techniques are used to diagnose this disease such as radiographic imaging, chest radiograph, CT, and/or USG of the abdomen. CT of the abdomen is useful to investigate the thickened peritoneum, ascites, mesenteric disease, caseation within lymph nodes, bowel wall thickening, bowel obstruction and omental thickening [93-95]. The diagnosis of gastro intestinal is based on endoscopy and colonoscopy. Endocopy shows the intestinal lesion which shows in the form of ulcers, ulcerohypertrophic or hypertropic. Colonoscopic is helpful to find ulcers, nodules, a deformed ileocecal valve and strictures [96-97]. Barium based studies are advanced sensitive method which is useful to diagnose the area of narrowing and ulceration of intestinal TB whereas USG is helpful to diagnose extraintestinal TB [98].

11. Genital Tuberculosis

Genital TB (GTB) is another common form of EPTB, causing morbidity in developing countries [99]. In case of females, there are involvement of different genital organ such as fallopian tubes (90%-100%), endometrium (50–60%), ovaries (20–30%), cervix (5–15%), and rarely vulva and vagina (1%) [100]. It is the major factor of infertility particularly among women. Similarly in case of males, GTB is associated with TB of the kidney, prostate, epididymis, vas deferens, seminal vesicle and testis as well as scrotum may occasionally be affected. It is more common in males [101].

11.1. Pathogenesis and clinical features

The tuberclli bacilli reaches to the genital tract by three routes such as haematogenous route (90%), abdominal visceral such as the bladder, rectum, appendix and intestines or by lymphatic spread. Fallopian tubes are the main source of infection in genital TB. Tuberclli bacilli reach to fallopian tubes by haematogenous then gradually spread to the endometrium [101,103]. Sometimes it can also be spread during sexual contact with infected person. In

spread to seminal vesicle, deferent duct and epididymis but less common is testicular site [102]. GTB presents various clinical symptoms including oligomenorrhoea, amenorrhoea, menorrhagia, abdominal and pelvic pain, dyspareunia, dysmenorrhoea, infertility and some may be asymptomatic [104]. In case of fallopian TB the fallopian tube is normal in the initial stage of infection but some changes appear like mimicking salpingitis isthmica nodosa, nodular transformation in the latter stages. In endometrium TB, hemorrhage, caseous necrosis and ulceration can been seen whereas adhesion with the fimbria or formation of unilateral or bilateral adnexal mass can be seen in ovary. Male patients with GTB clinically present with lower abdominal pain, epididymitis, prostatitis, testicular swelling, discharging scrotal sinus etc [105].

11.2. Diagnosis

The diagnosis of GTB is difficult as the signs and symptoms are nonspecific [106]. Monteux test is common method to diagnosis of GTB especially in women of childbearing age [107]. AFB is more sensitive method to suspect TB which is based on microscopy. For microscopic examination of AFB at least 10000 organisms per ml should be present in sample but the culturing method is more sensitive only requiring 100 organisms per ml and it can take long time to grow on Lwenstein-Jensen (LJ) media near about 8-6 week. Culturing of menstrual fluid obtained from vagina is the best method in women facing the problem of infertility or abnormal bleeding during the GTB. The AFB in vagina, endometrial, cervix and vulva may be diagnosed directly by biopsy method. Laproscopy is used to determine the lesion in the tubes, ovaries and adnexae. In addition, Heteroscopy is also used for visualization of the uterine cavity in GTB [106]. In case of males, histopathological studies of biopsy specimens possibly to diagnose of genitourinary tract TB. AFB or PCR test is useful to detect AFB in genitourinary tract. TB bacilli detect by microscopically and culturing method in prostatic secretion and ejaculation. Auramine staining and genomic amplification can be performed for scrotal purulent. USG is the traditionally method to diagnose the epididymo-orchitis TB [108].

12. Current anti-TB treatment

Anti-TB drugs still remain the stronghold for the treatment of both PTB and EPTB. Recent guidelines recommend the same regimen for both EPTB and PTB. However, the data for the recommendation for most other forms of EPTB is not based on studies as robust as those for PTB. An important obstacle during the TBM for instance is the ability of the blood-brain barrier to limit intracerebral concentrations of anti-TB drugs. While pyrazinamide, isoniazid, protionamide, and cycloserine penetrate well into CSF, p-aminosalicylic acid and ethambutol have poor or no penetration ability. Steptomycin, Rifampicin and kanamycin penetrate the CSF well only in the presence of meningeal inflammation. Fluoroquinolones such as levo-

floxacin and moxifloxacin have variable CSF penetration, with excellent penetration seen in later generation drugs. In a recent phase 2 clinical trial, high-dose intravenous rifampicin with the addition of moxifloxacin led to three times increase in the plasma and CSF area under the concentration time curve and was connected with a survival benefit in TBM patients [109]. Corticosteroids often have been used as an adjunctive in the treatment of EPTB. The available evidence indicates meaningful clinical benefits only in TBM patients. In TBM patients, recent randomized controlled trials and meta-analysis revealed that corticosteroids significantly decrease the mortality. Thus, adjunctive corticosteroids (either prednisolone or dexamethasone) are recommended to all patients, regardless of disease severity [110]. There are inadequate data to recommend adjunctive corticosteroid therapy in the treatment of GUTB. In these cases, the use of corticosteriods does not significantly reduce the development fibrotic complications like intestinal obstruction or ureteric stenosis.

13. Conclusion

TB is still a major challenge among infectious diseases even in the twenty first century. There is an urgent need to understand the pathogenesis of all the different types of TB and develop novel diagnostic and treatment strategies for the efficient therapeutics against of all forms of TB. Furthermore, stigma associated with TB is another major barrier to health care access and impacts the quality of life for individuals affected by TB hence needs to be addressed to avoid health inequalities. At present, despite the disease being completely curable, it is still facing problems regarding failure and relapse & reoccurrence of the disease. In any of these situations, it must be considered a real possibility that the person has drug resistant TB. Further, finding new targets to combat MDR-TB is another important challenge. Over the past two decades, intensive efforts have been made to develop new vaccines for TB that will boost the immune responses that provide improved protection against MTB infections. Organizations such as WHO and Bill & Melinda Gates foundation aim to advance not only universal access to TB prevention, care and control but also guide the global response to threats and promote innovation in the developing countries.

14. Figure

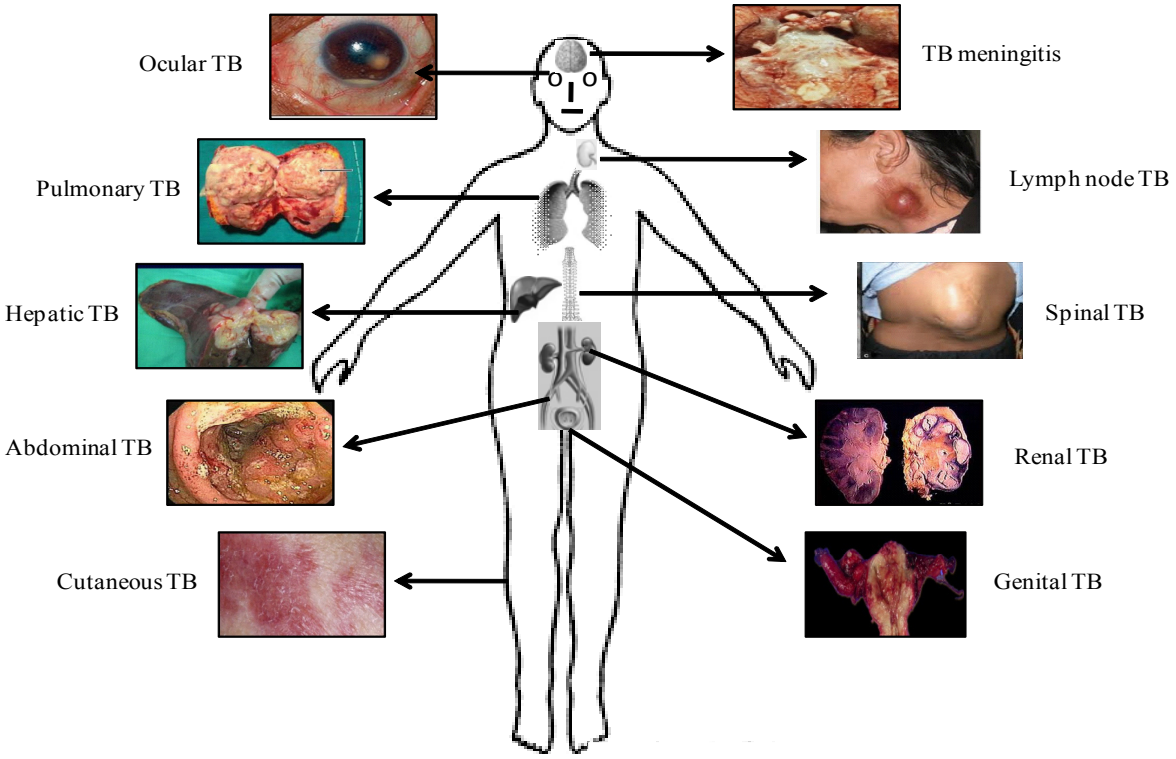

Figure 1. Different types of TB affecting the various anatomical sites of human body (adapted from web resources).

15. References

1. Sharma S, Pal R, Hameed S, Fatima Z. Antimycobacterial mechanism of vanillin involves disruption of cell-surface integrity; virulence attributes, and iron homeostasis. Int J Myco. 2016;5(4): 460-8.

2. Kabra SK, Lotha R, Seth V. Some current concepts on childhood tuberculosis. Indian J Med Res. 2004; 120(4): 387-97.

3. Marais BJ, Pai M. Recent advances in the diagnosis of childhood tuberculosis. Arch Dis Child. 2007; 92 (5): 446-52.

4. Pal R, Fatima Z, Hameed S. Efflux pumps in drug resistance of Mycobacterium tuberculosis, Int J Curr Microbiol App Sci. 2014;3(8):528–46.

5. World Health Organization. Global Tuberculosis Report 2015 (WHO, 2015).

6. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges Clin Infect Dis. 2010; 50:184-94.

7. Dye C. Global epidemiology of tuberculosis. Lancet. 2006; 367(9514):938-40.

8. Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet. 2010; 375(9728):1814-29.

9. Houben EN, Nguyen L, Pieters J. Interaction of pathogenic mycobacteria with the host immune system. Curr Opin Microbiol. 2006; 9 (1):76–85.

10. Kaufmann SH. Protection against tuberculosis: cytokines, T cells, and macrophages. Ann Rheum Dis. 2002; 61(2):54–8.

11. American Thoracic Society. Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis. 1990; 142:725–35.

12. MacGregor RR. Tuberculosis: from history to current management. Semin Roentgenol. 1993; 28 (2):101–8.

13. Mazurek GH, LoBue PA, Daley CL, et al. Comparison of a whole-blood interferon gamma assay with tuberculin skin testing for detecting latent Mycobacterium tuberculosis infection. JAMA. 2001; 286 (14):1740–47.

14. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of bacille Calmette Guerin vaccination on tuberculin skin test measurements. Thorax. 2002; 57 (9): 804–9.

15. Kang YA, Lee HW, Yoon HI, et al. Discrepancy between the tuberculin skin test and the wholeblood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. JAMA. 2005; 293 (22): 2756–61.

16. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. Proc Am Thorac Soc. 2006; 3 (1):103–10.

17. Neqi ss. Diagnostic potential of IS6110, 38kDa, 65kDa and 85B sequence-based polymerase chain reaction in the diagnosis of Mycobacterium tuberculosis in clinical samples. Indian J Med Microbiol. 2007; 25(1):43-9.

18. World Health Organization. Guidelines on the Management of Latent Tuberculosis Infection (WHO, 2014).

19. Landry J, Menzies D. Preventive chemotherapy. Where has it got us? Where to go next? Int J Tuberc Lung Dis. 2008;12(12):1352-64.

20. World Health Organization. Guidelines for Treatment of Tuberculosis 4th edn (WHO, 2010).

21. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016; 63(7):e147-95.

22. Saukkonen JJ, Cohn DL, Jasmer RM et al. An official ATS statement: hepatotoxicity of antituberculosis therapy: Am J Respir Crit Care Med, 2006; 174(8): 935–52.

23. O'Donnell MR, Daftary A, Frick M et al. Re inventing adherence: toward a patient-centered model of care for drug-resistant tuberculosis and HIV: Int J Tuberc Lung Dis.2016; 20(4): 430–34.

24. Mangtani P , Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin. Infect. Dis. 2014; 58(4):470-80.

25. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ. 2014; 349:1-11.

26. van den Boogaard, J., G. S. Kibiki, E. R. Kisanga, M. J. Boeree, and R. E. Aarnoutse. New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob. Agents Chemother, 2009;53(3):849-62.

27. Johnson AJ, Kennedy SC, Arlehamn CSL et al. Identification of mycobacterial RplJ/L10 and RpsA/S1 proteins as novel targets for CD4+ T cells. Infect Immun, 2017; doi:10.1128/IAI.01023-16.

28. Madhukar Pai1,2, Marcel A. Behr1, David Dowdy et al. Tuberculosis. Nat Rev Dis Primers, 2016; 2(1):1-23.

29. Jullien S, Ryan H, Modi M, Bhatia R. Six months therapy for tuberculous meningitis. Cochrane Database Syst Rev. 2016; 1 (9): 1–112.

30. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009; 59(3):167-87.

31. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central Nervous System Tuberculosis: Pathogenesis and Clinical Aspects. Clin Microbiol Rev. 2008; 21(2):243-61.

32. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. J Infect. 2000; 41(1):61-8.

33. Yaramiş A, Gurkan F, Elevli M, Söker M, Haspolat K, Kirbaş G et al. Central nervous system tuberculosis in children: a review of 214 cases. Pediatrics. 1998;102(5):E49.

34. Horne NW. Tuberculous meningitis: problems in pathogenesis and treatment. Edinburgh Med J. 1951;58: 413-29.

35. Török ME. Tuberculous meningitis: advances in diagnosis and treatment. Br Med Bull. 2015; 113(1):117–31.

36. Verdon R, Chevret S, Laissy JP, Wolff M. Tuberculous meningitis in adults: review of 48 cases. Clin Infect Dis. 1996; 22(6):982-8.

37. Takahashi T, Tamura M, Takasu T. The PCR-Based Diagnosis of Central Nervous System Tuberculosis: Up to Date. Tuberc Res Treat. 2012; doi: 10.1155/2012/831292.

38. Chuka-Okosa CM. Tuberculosis and the eye. Nigerian J Clin Pract. 2006; 9:68–70.

39. Gupta A, Gupta V. Tubercular posterior uveitis. Int Ophthalmol Clin. 2005; 45:71–8.

40. Biswas J, Badrinath SS. Ocular morbidity in patients with active systemic tuberculosis. Int Ophthalmol. 1996; 19:293–8.

41. Tabbara KF. Ocular tuberculosis: anterior segment. Int Ophthalmol Clin. 2005;45 :57–69.

42. Morimura Y, Okada AA, Kawahara S, et al. Tuberculin skin testing in uveitis patients and treatment of presumed intraocular tuberculosis in Japan. Ophthalmology. 2002; 109 (5):851–7.

43. Shome D, Honavar S, Vemuganti G et al. Orbital tuberculosis manifesting with endophtalmos and causing a diagnostic dilemma. Ophthal Plast Reconstr Surg. 2006; 22 (3):219–21.

44. Rosen PH, Spalton DJ, Graham EM. 1990. Intraocular tuberculosis. Eye (London) 4:486–92.

45. Bouza E, Merino P, Muñoz P, Sanchez-Carrillo C, Yáñez J, Cortés C. 1997. Ocular tuberculosis. A prospective study in a general hospital. Medicine (Baltimore) 76 (1):53–61.

46. Albert DM, Raven ML. Ocular Tuberculosis. Microbiol Spectr. 2016; 4(6): 1-7

47. Parchand S, Tandan M, Gupta V, Gupta A. Intermediate uveitis in Indian population. J Ophthalmic Inflamm Infect. 2011; 1(2):65–70.

48. Abu El-Asrar AM, Abouammoh M, Al-Mezaine HS. Tuberculous uveitis. Middle East Afr J Ophthalmol. 2009; 16(4):188–201.

49. Cimino L, Herbort CP, Aldigeri R, Salvarani C, Boiardi L. Tubercu¬lous uveitis: a resurgent and underdiagnosed

disease. Int Ophthalmol. 2009; 29(2):67–74.

50. Leung CC, Yam WC, Yew WW, et al. T-Spot.TB outperforms tuberculin skin test in predicting tuberculosis disease. Am J Respir Crit Care Med. 2010; 182(6):834–40.

51. Ang M, Wong W, Ngan CC, Chee SP. Interferon-gamma release assay as a diagnostic test for tuberculosis-associated uveitis. Eye. 2012; 26(5):658–65.

52. Sakai JI, Matsuzawa S, Usui M, Yano I. New diagnostic approach for ocular tuberculosis by ELISA using the cord factor as antigen. Br J Ophthalmol. 2001;85 (2):130–3.

53. Niblock AL. Recurrent neck abscesses due to cervical tuberculosis lymphadenopathy in elderly postmenopausal woman post splenectomy: a rare case report. J Med Case Rep. 2011;5(584): 1-5.

54. Sharma SK, Mohan A, Kadhiravan T. HIV-TB co-infection: epidemiology, diagnosis & management. Indian J Med Res. 2005;121(4):550–67.

55. Gupta AK, Nayar M, Chandra M. Critical appraisal of fine needle aspiration cytology in tuberculous lymphadenitis. Acta Cytol. 1992; 36(3): 391-4.

56. Artenstein AW, Kim JH, Williams WJ, Chung RCY. Isolated peripheral tuberculous lymphadenitis in adults: current clinical and diagnostic issues. Clin Infect Dis. 1995; 20(4): 876-82.

57. Gupta AK, Nayar M, Chandra M. Critical appraisal of fine needle aspiration cytology in tuberculous lymphadenitis. Acta Cytol. 1992; 36(3): 391-4.

58. Lau SK, Wei WI, IIsu C, Engzell UC, et al. Efficacy of fine needle aspiration cytology in the diagnosis of tuberculous cervical lymphadenopathy. J Laryngol Otol. 1990; 104(1): 24-7.

59. Gautam MP, Karki P, Rijal S, Singh R. Pott's spine and Pott's paraplegia. J Nep Med Assoc. 2005; 44(159):106–15.

60. Taylor GM, Murphy E, Hopkins R, Rutland P, Chistov Y. First report of Mycobacterium bovis DNA in human remains from the Iron Age. Microbiology. 2007; 153(4):1243–9.

61. Garg RK, Somvanshi DS. Spinal tuberculosis: a review. J Spinal Cord Med. 2011; 34 (5): 440–54.

62. Rivas-Garcia A, Sarria-Estrada S, Torrents-Odin C, Casas-Gomila L, Franquet E. Imaging findings of Pott's disease. Eur Spine J. 2013; 22(Suppl 4): 567–78.

63. Ramesh V, Sen MK, Sethuraman G, D'Souza P. Cutaneous tuberculosis due to multidrug-resistant tubercle bacilli and difficulties in clinical diagnosis. Indian J Dermatol Venereol Leprol. 2015; 81(4):380.

64. Sehgal VN, Bhattacharya SN, Jain S, Logani K. Cutaneous tuberculosis: the evolving scenario. Int J Dermatol. 1994; 33(2):97-104.

65. Speert DP. Tuberculosis. In: Krugman S, Katz SI, Gershon AA, Wilfort CM, editors. Infectious diseases of children. Missouri Mosby. 1992; 9:551–2.

66. Jones VS, Philip C. Isolated gluteal tuberculosis. Indian Pediatr J. 2005;42: 955.

67. Peter CK. Some thoughts on tuberculosis of fascia and muscle. Lancet. 1937;57:156–9.

68. Patra AC, Gharami RC, Banerjee PK. A profile of cutaneous tuberculosis. Ind J Dermatol. 2006;51(2):105–7.

69. Banashankari GS, Rudresh HK, Harsha AH, Bharathi R, Kamble P. An unusual presentation of cutaneous tuberculosis for surgeons-review of literature Indian. J. Surg. 2012, 74 (4), 314-7.

70. Amarapurkar DN, Patel ND, Amarapurkar AD. Hepatobiliary tuberculosis in western India. Indian J Pathol Microbiol. 2008; 519 (2):175–81.

71. Chaudhary P. Hepatobiliary tuberculosis. Ann Gastroenterol. 2014; 27(3):207-11.

72. Oliva A, Duarte B, Jonasson O, Nadimpalli V. The nodular form of local hepatic tuberculosis. J Clin Gastroenterol. 1990; 12 (2):166-73.

73. Liao JR, Zhang D, Wu XL. Pulmonary tuberculosis combined with hepatic tuberculosis: a case report with literature review. Clin Respir J. 2015; 9(4):501-5.

74. Maharaj B, Leary WP, Pudifin DJ. A prospective study of hepatic tuberculosis in 41 black patients. Quart J Med. 1987;63 (242):517-22.

75. Sharma SK, Mohan A. Extra-pulmonary tuberculosis. Indian J Med Res. 2004;120 (4):316–53.

76. Johnson CW, Lowe FC, Warren JW, Hebel JR. Genitourinary tuberculosis. AUA Update Ser.2003; 22:303–7.

77. Eastwood JB, Corbishley CM, Grange JM. Tuberculosis and the kidney. J Am Soc Nephrol.2001; 12(6): 1307–14.

78. Daher Ede F, da Silva G Jr, Barros E. Renal tuberculosis in the modern era. Am J Trop Med Hyg. 2013; 88 (1): 54–64.

79. Narayana A. Overview of renal tuberculosis. Urology. 1982; 19(3):231-37.

80. Simon HB, Weinstein AJ, Pasternak MS, Swartz MN, Kunz LJ. Genitourinary tuberculosis: clinical features in a general hospital population. Am J Med. 1977; 63(3):410-20.

81. Christensen WI. Genitourinary tuberculosis: review of 102 cases. Medicine (Baltimore). 1974; 53(5):377-90.

82. Wang LJ, Wong YC, Chen CJ, Lim KE. CT features of genitourinary tuberculosis. J Comput Assist Tomogr. 1997; 21(2):254-58.

83. Debi U, Ravisankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: revisted. World J Gastroenterol. 2014; 20(40):14831-40.

84. Akhan O, Pringot J. Imaging of abdominal tuberculosis. Eur Radiol. 2002;12:312–23.

85. Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. Am J Gastroenterol. 1998;93(5):692–6.

86. Rathi P, Gambhire P. Abdominal Tuberculosis. J Assoc Physicians India. 2016;64(2):38 47.

87. Lazarus AA, Thilagar B. Abdominal tuberculosis. Dis Mon. 2007;53(1):32-8.

88. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res. 2004 ;120(4):305-15.

89. Marshall JB. Tuberculosis of gastrointestinal tract and peritoneum. Am J Gastroenterol. 1993;88(7): 989-99.

90. Patel SM, Sweetser S. The wet-ascitic form of tuberculosis peritonitis. Hepatology 2011; 54(1): 364-5.

91. Tirumani SH, Ojili V, Gunabushanam G, Shanbhogue AK, Nagar A, Fasih N et al. Imaging of tuberculosis of the abdominal viscera: beyond the intestines. J Clin Imaging Sci. 2013; 3: 17.

92. Jakubowski A, Elwood RK, Enarson DA. Clinical features of abdominal tuberculosis. J Infect Dis. 1988;158 (4):687-92.

93. Suri S, Gupta S, Suri R. Computed tomography in abdominal tuberculosis. Br J Radiol. 1999;72(853):92-8.

94. Bhargava SK, Pardeep K, Sumeet B. Role of Multi Slice CT in Abdominal Tuberculosis. JIMSA. 2013;26(1): 47-50.

95. Malik A, Saxena NC. Ultrasound in abdominal tuberculosis. Abdom Imaging. 2003;28(4):574-9.

96. Rai S, Thomas WM. Diagnosis of abdominal tuberculosis; the importance of laparoscopy. J Roy Soc Med. 2003;96(12):586-8.

97. Shah S, Thomas V, Mathan M, Chacko A, Chandy G, Ramakrishna BS, Rolston DD. Colonoscopic study of 50 patients with colonic tuberculosis. Gut. 1992; 33(3): 347-51.

98. Kapoor VK, Chattopadhyay TK, Sharma LK. Radiology of abdominal tuberculosis. Austral Radiol. 1988;32:365-7.

99. Sharma JB. Sharma's Python Sign:A new tubal sign in female genital tuberculosis. J Lab Physicians. 2016; 8(2):120-2.

100. Varma, T, Glob. libr. women's med. (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10034.

101. Das A, Batabyal S, Bhattacharjee S, Sengupta A. A rare case of isolated testicular tuberculosis and review of literature. J Family Med Prim Care. 2016;5(2):468-70.

102. Schaefer G. Female genital tuberculosis. Clin ObstetGynecol. 1976; 19(1): 223-39.

103. Gupta N, Sharma JB, Mittal S, et al. Genital tuberculosis in Indian infertility patients. Int J Gynecol Obstet. 2007;97(2):135–38.

104. Kulchavenya E, Kim CS, Bulanova O, Zhukova I. Male genital tuberculosis:epidemiology and diagnostic. World J Urol. 2012; 30(1):15-21.

105. Sharma JB. Current diagnosis and management of female genital tuberculosis. J Obstet Gynaecol India. 2015;65(6):362–71.

106. Raut VS, Mahashur AA, Sheth SS. The Mantoux test in the diagnosis of genital tuberculosis in women. Int J Gynaecol Obstet. 2001;72(2):165-9.

107. Yonguc T, Bozkurt IH. Male Genital Tuberculosis. J Mycobac Dis. 2014; 4(5):169.

108. Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, Borm G, Aarnoutse RE, van Crevel R et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis. 2013;13(1):27–35.

109. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004;351(17):1741–51.

110. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008;(1): p. CD002244.