Review Article

EXTRAPULMONARY TUBERCULOSIS- A REVIEW

Hemant Janugade *, Amit Verma **, Abhishek Bhagat **, Abhinav Kesarwani **
* Professor , Department of Surgery, Krishna Institute of Medical Science, Karad, Dist.-Satara, Maharastra
** Resident, Department of Surgery, Krishna Institute of Medical Science, Karad, Dist.-Satara, Maharastra

ABSTRACT

Extrapulmonary tuberculosis (EPTB) constitutes about 20% of all cases of tuberculosis (TB). Diagnosing EPTB remains challenging because clinical samples obtained from relatively inaccessible sites may be paucibacillary, thus decreasing the sensitivity of diagnostic tests. Whenever practical, every effort should be made to obtain appropriate specimens for both mycobacteriologic and histopathologic examinations. The measurement of biochemical markers in TB-affected serosal fluids (adenosine deaminase or gamma interferon) and molecular biology techniques such as polymerase chain reaction may be useful adjuncts in the diagnosis of EPTB. Although the disease usually responds to standard anti-TB drug therapy, the ideal regimen and duration of treatment have not yet been established. A paradoxical response frequently occurs during anti-TB therapy. It should be distinguished from other causes of clinical deterioration. Surgery is required mainly to obtain valid diagnostic specimens and to manage complications. Because smear microscopy or culture is not available to monitor patients with EPTB, clinical monitoring is the usual way to assess the response to treatment.

KEYWORDS : Extrapulmonary tuberculosis, Mantoux test, lymph node, pulmonary, pleural

INTRODUCTION

The causative agent of tuberculosis is Mycobacterium tuberculosis H37Rv (M. tuberculosis H37Rv) .Resurgence in Tuberculosis cases has been recorded all over the world with about 8 million people estimated of being infected with the disease [1-3]. Tuberculosis remains an endemic and is the seventh leading cause of death globally [4]. It usually attacks the lungs but it can also affect other parts of the body. The two types of clinical manifestation of tuberculosis (TB) are pulmonary TB (PTB) and extrapulmonary TB (EPTB). The former is most common. EPTB refers to TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). A patient with both pulmonary and EPTB is classified as a case of PTB. For example, miliary TB is classified as PTB because there are lesions in the lungs. On the other hand, tuberculous intrathoracic lymphadenitis (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of EPTB[1].

EPIDEMIOLOGY

In the era before the human immunodeficiency virus (HIV) pandemic, and in studies involving immune competent adults, it has been observed that EPTB constituted about 15 to 20 per cent of all cases of TB. In HIV-positive patients, EPTB accounts for more than 50 per cent of all cases of TB . The diagnosis of EPTB, especially involving deeply located inaccessible areas is very difficult. Sparse literature is available regarding the relative contributions of pulmonary and extrapulmonary disease to the total number of tuberculosis cases from India as reliable epidemiological data are lacking [5]. Considering the stigma associated with and the reluctance to perform invasive procedures especially in HIV-positive patients in the Indian setting, even notified estimates of EPTB under the Revised National Tuberculosis Control Programme (RNTCP) are often based on presumptive diagnosis and are an overestimate of the problem23 [6]. Though it is estimated that EPTB constitutes 15 to 20 per cent of tuberculosis

cases in general practice among HIV-negative adults in India [5], a higher proportion of EPTB cases have been documented in tertiary care centres.

LYMPH NODE TUBERCULOSIS

Lymph node Tuberculosis (LNTB) occurs when M. tuberculosis infects the lymph nodes. Lymph node Tuberculosis has been called as the "king's evil" in the ancient times. It was also called as "scrofula" meaning glandular swelling [7]. In India and other developing countries LNTB remains the most common form of EPTB. M. tuberculosis enters the body and undergoes lymphatic dissemination. Generally, tonsils are the most common routes of entry for the pathogen. During the initial stage of infection, the lymph nodes are discrete. Afterwards, the lymph nodes coalesce and break open due to pus formation. The wound so developed may not heal even for years [7].

DIAGNOSIS AND TREATMENT OF LYMPH NODE TUBERCULOSIS

With the wider availability of CT scan, it has been expected that more cases of Lymph Node Tuberculosis can be reported. The symptoms of LNTB include fever, weight loss, fatigue, and night sweats. A culture of M. tuberculosis is also a standard diagnostic method for detection of LNTB [8]. The treatment involves Antituberculous chemotherapy in which initially first line drugs comprising of Rifampicin, Isoniazid, Ethambutol and streptomycin are given to the patient daily before the biopsy samples are taken [9]. The drugs are administered according to the DOTS guidelines. The duration for which the drugs are to be taken by the patient varies from 6 to 12 months depending on the extent to which the patient is infected by the pathogen. Further treatment regimen according to the chemotherapy involves the administration of the second line drugs comprising of cycloserine, thioamides, amikacin and fluoroquinolones.

SKELETAL TUBERCULOSIS

It is also referred to as extra spinal tuberculosis [10] . Skeletal TB constitutes about 10-20% of the extra pulmonary tuberculosis cases and spine is involved in 50% of the skeletal tuberculosis cases [11]. The prevalence of skeletal tuberculosis in children has been noted to be rare [10]. Tuberculosis of the bone can be diagnosed easily and can be managed by physicians and surgeons. The thoracolumbar region is the most affected area in the spine. Skeletal tuberculosis with multiple bone involvement is the rarest in immunocompetent patients [12]. According to the clinical findings, the most commonly encountered symptoms in skeletal tuberculosis include low-grade fever, night sweats, weight loss, anorexia and malaise [13].

DIAGNOSIS AND TREATMENT OF SKELETAL TUBERCULOSIS

Diagnosis of the disease is most important and crucial. Hence, proper diagnostic techniques need to be employed for proper treatment of the disease. Biopsy cannot be performed for each and every case and moreover, in case of biopsy, the diagnostic yield is greatest when the material is submitted for smear. But, this is relevant only in 10-30% cases. Radiography can prove to be an important tool in diagnostics. Chemotherapy consisting of treatment with first line and second line drugs is assumed to be 90% effective in eradicating the infection. Tuberculosis osteomyelitis accounts for about 5% cases of osteoarticular Tuberculosis. Some unusual forms of skeletal tuberculosis include multiple cystic TB, disseminated skeletal TB, and closed multiple diaphysitis and tuberculous dactylitis. Tuberculous arthritis is also a form of skeletal TB, which leads to joint destruction associated with dislocation. About 50% patients with osteoarticular TB will have spinal involvement. Multiple sites of bone and joint involvement commonly occur and they must be considered [7].

OCULAR TUBERCULOSIS

Ocular tuberculosis is the infection in eyes due to the pathogen M. tuberculosis. It usually affects children and young adults [6]. The sites, which are primarily involved in the initial stages of the infection, are conjunctiva, cornea and sclera. On the basis of the part of the eye infected, Ocular TB can be classified as intraocular TB and Extra ocular TB. In case of intraocular TB, iris and the ciliary bodies are infected. Uveitis is a form of intraocular TB, which poses great challenges in diagnosis and involves those structures which not

liable to biopsy or cultures. In case of extra ocular TB, lid abscess is generally involved wherein pus accumulates within tissues as a defensive mechanism in response to the infection caused by the pathogen [8] [9].

DIAGNOSIS AND TREATMENT OF OCULAR TUBERCULOSIS

The most common route through which the tubercle bacilli reach the eyes is through the bloodstream [10]. Although various highly sensitive diagnostic techniques such as PCR are available for detection of M. tuberculosis, but detection of Ocular TB remains a controversial issue. Choroiditis remains the most common form of Ocular TB and Indocyanine green angiography is assumed to be an effective method to diagnose this form of Ocular TB. Retinal periphlebitis is another form of Ocular TB, which is caused by the invasion of retina by the bacilli and is the secondary manifestation to choroiditis. Skin testing is generally performed according to the clinical findings, PPD skin test being the most common one [11] . Further, it has also been suggested through various studies that Ocular TB should be treated in association with anti-tuberculous drugs. Tuberculin treatment has also proven to be an effective technique of treating Ocular TB and it is generally given at the onset of treatment. Along with the tuberculin treatment, the patients are also given hygienic treatment .

PLEURAL TUBERCULOSIS

Pleural Tuberculosis constitutes the tuberculosis infection in the outer covering of lungs i.e. pleura. Pleural Tuberculosis is considered to be a form of primary tuberculosis. It has been found that pleural TB affects people of young age (<45 years) and is pre dominant in males than in females. The effusions developed are moderate in size. Pleural Tuberculosis constitutes for about 3-5% of the tuberculosis cases. Various studies also quote that increased incidence of pleural involvement in AIDS has been diagnosed along with active TB. The symptoms of pleural tuberculosis include illness with cough, pleuritic chest pain and fever [12].

DIAGNOSTIC AND TREATMENT TECHNIQUES FOR PLEURAL TUBERCULOSIS

It is difficult to diagnose Pleural TB, biopsy being the only relevant method. Pleural fluid culture is also used to diagnose tuberculosis in pleural effusion. Furthermore, pleural biopsy can also be used to diagnose the disease; however multiple biopsies need to be carried out in order to detect the disease. CT scan and chest radiography can also be carried out to diagnose pleural Tuberculosis [11]. The patients are treated using DOTS treatment from 6 to 9 months. The most commonly used drug combinations are ethambutol, isoniazid, rifampicin and pyrazinamide, which are given up to 2 months. Apart from these, isoniazid and rifampicin are given up to 4 months as recommended by the DOTS therapy guidelines .

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Tuberculosis in the Central Nervous System (CNS TB) is caused by M. tuberculosis and comprises about 1% of the total cases of TB. It disproportionately affects children and HIV infected individuals. Tuberculosis of the CNS remains a diagnostic challenge. Risk factors include malnutrition and recent measles in children and alcoholism, malignancies and the use of immunosuppressive agents in adults [6]. Infection begins on inhalation of aerosolized droplet nuclei and each droplet consists of tubercle bacilli. The bacillus reaches the alveoli and multiplies in alveolar spaces or macrophages. During the first three weeks, there is no immune response. So, the bacilli are disseminated to extra pulmonary sites, including the CNS. Mycobacteria are filtered from the blood by lungs, liver, spleen and bone marrow. But in the brain, they get trapped because there is no reticulo-endothelial system. Following infection, the bacteria may also be killed due to the cell-mediated immune response within the activated macrophages. The CNS Tuberculosis infection develops in two stages. In the initial stage, tuberculous lesions called “Rich Foci” develop in the CNS, during the primary TB infection [7].

DIAGNOSIS AND TREATMENT OF CENTRAL NERVOUS TUBERCULOSIS

Diagnosis of different forms of cerebral TB is based on numerous neurological signs and symptoms. Further, microbiological and

radiological findings confirm the diagnosis. The currently used conventional methods such as microscopy and cultural techniques are less sensitive. Therefore, alternative diagnostic methods are necessary for specific diagnosis of the infection in the Central Nervous System. Various immunological tests involving immunoassays and biochemical tests involving chromatography are generally carried out in order to detect the disease. Furthermore, accurate results are given by highly sensitive techniques such as PCR assay, neuroimaging involving radiological methods such as CT scan and MRI [13]. Treatment involves the use of various combinations of therapeutic drugs in order to prevent the development of drug resistance. The course of treatment is according to the DOTS therapy. Generally, Anti tuberculous chemotherapy treatment is given to the patient suffering from CNS TB.

USE OF CORTICOSTEROIDS IN THE TREATMENT OF CNS TB

The use of corticosteroids remains a controversial issue. Corticosteroids reduce the effect of inflammation caused by the use of various drugs. In a recent trial, it has been shown that if corticosteroids are administered during the early phases of treatment, it may reduce the complications caused by the drugs [14].

CUTANEOUS TUBERCULOSIS

Cutaneous TB is the rarest case of extra pulmonary TB, comprising about 2% of the total cases of extra pulmonary TB. Mycobacterium tuberculosis, Mycobacterium bovis and Bacilli Calmette Guerin vaccine (BCG) are the causative agents of Cutaneous Tuberculosis [13, 14] . Tuberculosis in children is one of the major devasting threats all over the world. Cutaneous TB infects about 18- 54% of children in India. Recently, a rise in the number of Cutaneous TB cases has been seen due to the prevalence of multidrug resistant strains of M. tuberculosis. Most common sites of Cutaneous TB infection comprises of lower limbs and face. The commonly occurring forms of Cutaneous TB are scrofuloderma, lupus vulgaris and TB verrucosa cutis. Cutaneous TB is more prevalent in HIV positive patients [15] . Cutaneous TB can occur following any sort of injury. Generally, two ways of infection have been seen. In the primary infection, the microorganisms may enter the body through a contaminated injection, this being the rarest case. Secondly, pathogenesis is seen during the incubation period in those who have contacted primary infection. During the initial stages of the disease, a number of bacteria enter the bloodstream via the lymph nodes and thoracic duct and hence cause infection [16] .

DIAGNOSIS AND TREATMENT OF CUTANEOUS TUBERCULOSIS

AFB smear is useful if lesions have a high bacterial load as seen in case of Lichen Scrofulosorum (LS), miliary TB and TB gumma. PCR technique is found to be efficient in case of multibacillary forms of CTB. The PCR technique is found to be 50-70% accurate in detecting CTB. A combination of diagnostic tests needs to be conducted to confirm the diagnosis. The commonly conducted tests include testing of urine, blood and sputum samples along with CT scan and X ray of chest and bones [17]. Furthermore, the diagnosis relies on histopathology, culture on LJ medium and PCR. Mantoux test is also conducted during the course of diagnosis. The DOTS treatment course is generally followed to treat Cutaneous TB. It involves the consumption of first line and second line drugs for varying time duration. The first line drugs administered during the initial course of treatment include Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for 2 months duration followed by Isoniazid and Rifampicin for 4 months in the continuation phase. The side effects of the first line drugs include hepatotoxicity. In the further course of the treatment, the second line drugs, which are recommended, are Amikacin, Kanamycin, Ofloxacin and Levofloxin. Further, treatment with BCG vaccine is assumed to be 0-80% effective depending upon the intensity of infection. Fixed dose combinations are preferably used during the treatment phase. Drugs are consumed daily or three times in a week by the patient [17] .

GENITOURINARY TUBERCULOSIS (GUTB)

Genitourinary tuberculosis involves infection in the genital and urinary tracts by the pathogen M. tuberculosis. GUTB involves infection in the

kidneys, prostrate, testis, epididymis, seminal vesicles and the fallopian tubes [13-15]. GUTB is not very common but is considered to be a severe form of tuberculosis. GUTB affects more men than women in the ratio 2:1. In GUTB, kidneys are the most common sites of infection, which then spreads through the renal and the urinary tract. In case of genital and urethral TB, the infected individual has a superficial tuberculous ulcer on the penis or in case of females; the disease develops due to the contact with mycobacterium during intercourse. Development of disease depends on the interaction between the pathogen and the host immune system. GUTB is very uncommon in children. Prostatic TB is the rarest form of GUTB. Renal TB constitutes about 85% of the cases of GUTB. Testicular TB is less common. Urethral TB is secondary to genital TB [11] .

DIAGNOSIS AND TREATMENT OF GENITOURINARY TUBERCULOSIS

Diagnosis of GUTB is difficult because of non-specific and vague symptoms. The common symptoms include fever, weight loss, anorexia, backache and abdominal pain. 25- 30% of the diagnosis of GUTB is given on the basis of histological patterns or by detection of M. tuberculosis complex by PCR analysis. The presence of pathogen is judged by culture on media and radiological imaging. A positive yellow egg culture, histological analysis of biopsy samples combined with PCR is required for confirming the diagnosis. Results of PCR analysis are found to be 85% accurate [12]. Urine analysis is carried out for the detection of acid-fast bacilli in the urine sample along with determination of leucocytes, erythrocytes and bacteria . It is the primary test for diagnosing GUTB. Five consecutive early morning urine samples are generally examined. Radiological imaging constituting CT scan and intravenous pyelogram is carried out. Usual tests to diagnose GUTB are determination of urine or body fluids and radiological examinations. CT scan and MRI are also carried out for patients with compromised renal functions. According to WHO, GUTB requires a long term anti tuberculous chemotherapy for effective treatment of the disease. The anti tuberculous drug treatment is generally based on an initial two month intensive phase of treatment in which rifampicin, isoniazid, pyrazinamide and ethambutol are given. The initial phase is followed by the continuation phase with two drugs rifampicin and isoniazid for 4 months. In complicated cases of GUTB involving AIDS patients, a 9 to 12 months therapy is recommended [18]. Further, more than 50% of the GUTB patients undergo surgical treatment. Surgery may constitute the removal of TB destroyed kidney or epididymis. In cases of drug resistance, further drugs are prescribed with prolonged treatment. Drug resistant cases and HIV co infection cases pose challenges in treating the disease.

PANCREATIC TUBERCULOSIS

Pancreatic Tuberculosis is very uncommon form of extra pulmonary tuberculosis; however from the past 20 years the reports of pancreatic tuberculosis have been found increasing. Most cases of Pancreatic Tuberculosis are diagnosed after biopsy. Tuberculosis in pancreas occurs as a result of complication of miliary TB and immunodeficiency. Occurrence of Pancreatic TB is rare because of antibacterial pancreatic factors. Different clinical presentations of Pancreatic TB are jaundice, gastro intestinal bleeding, acute or chronic pancreatitis, carcinoma, etc . The symptoms of pancreatic tuberculosis are usually vague and non-specific . Diagnosis and treatment of pancreatic tuberculosis Diagnosing Pancreatic Tuberculosis is extremely challenging. This is because the symptoms are nonspecific in nature [19]. Symptoms of Pancreatic TB include weight loss, abdominal pain, low-grade fever, night sweats, nausea, gastro bleeding and hypertension. Those patients who are HIV positive and the ones who live in endemic areas are more susceptible to Pancreatic Tuberculosis. According to the reviewed literatures by Feng Xia et al. in China, Pancreatic Tuberculosis mostly affects people of young age and is more predominant in females. The diagnostic techniques are of two types viz. Invasive and Non Invasive. The non-invasive techniques generally involve CT scan, ultrasonography that reveals lesions and Ultrasound. In case of Invasive techniques, biopsies are carried out for detecting the disease. Invasive technique is used to obtain tissue for pathologic studies. The invasive technique is considered to be more reliable with respect to the Non Invasive techniques. To confirm the diagnosis, histological confirmation is required.

PCR assay is assumed to be highly specific and accurate. Radiological imaging techniques fail to give satisfactory results . Multidrug anti tuberculosis chemotherapy is recommended for the treatment of Pancreatic TB for 6 to 12 months. The treatment is given according to the DOTS guidelines. In the initial phase of the treatment the first line drugs involving isoniazid and rifampicin are given. In addition to these drugs, pyrazinamide and ethambutol are also given as in continuation phase in severe cases. Further, if the infection persists then the second line drugs involving flouroquinones and cycloserine are also given to the patient [17] .

DIAGNOSIS AND TREATMENT OF PANCREATIC TUBERCULOSIS

Diagnosing Pancreatic Tuberculosis is extremely challenging. This is because the symptoms are nonspecific in nature. Symptoms of Pancreatic TB include weight loss, abdominal pain, low-grade fever, night sweats, nausea, gastro bleeding and hypertension. Those patients who are HIV positive and the ones who live in endemic areas are more susceptible to Pancreatic Tuberculosis. According to the reviewed literatures by Feng Xia et al. in China, Pancreatic Tuberculosis mostly affects people of young age and is more predominant in females. The diagnostic techniques are of two types viz. Invasive and Non Invasive. The non-invasive techniques generally involve CT scan, ultrasonography that reveals lesions and Ultrasound. In case of Invasive techniques, biopsies are carried out for detecting the disease. Invasive technique is used to obtain tissue for pathologic studies. The invasive technique is considered to be more reliable with respect to the Non Invasive techniques [20].

CONCLUSION

In conclusion, high index of clinical suspicion, timely judicious use of invasive diagnostic methods and confirmation of the diagnosis, early institution of specific antituberculosis treatment and close clinical monitoring for adverse drug reactions are the key to the successful management of EPTB.

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