Diagnosis and Management of Tuberculosis

Chapter 1

Association of Tuberculosis with HIV & Non Communicable Diseases

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1. Introduction

Tuberculosis is a contagious disease caused by the organism Mycobacterium Tuberculosis through adroplet mode of spread and a variable period of latency of infection. The organism had been identified in many specimens of almost 6000 years old as well as in various civilizations and amongst several prominent personalities too.

2. Diabetes mellitus [DM]

DM is an established risk factor for tuberculosis. Its prevalence is 2.1% to 16.4% in tuberculosis patients. Tuberculosis due to Diabetes Mellitus occurs because of impaired cell-mediated immunity, microangiopathy, kidney failure and micronutrient deficiency [2]. Diagnosis of tuberculosis is established by Oral Glucose Tolerance Test [2], Fasting Blood Sugar Level, and Glycosylated Hemoglobin. Regular screening of TB patients for DM in TB endemic regions is highly recommended as DM causes delayed sputum/culture conversion, increased case fatality, and treatment failure.

Clinical recovery in patients with DM-TB comorbidity shows slower improvement leading to a higher mortality during anti-tubercular treatment, BMI and hematocrit compared to those with TB alone at 2 and 5-months of follow-up.

Treatment of Diabetes Mellitus in Tuberculosis is parenteral Insulin, Oral Hypoglycemic Agents as the corner stones with the optimal goals of therapy being an HbA1c of <7%, RBS <180 mg/dL and FBS<120 mg/dl [2].

3. Disorders of Calcium and Vitamin D Metabolism

Hypercalcemia is commonly associated with Tuberculosis. The prevalence of the disease is affected by the incidence of preexisting hypocalcaemia due to highly prevalent hypovitaminosis D. Nearly 12% of the patients show symptomatic hypocalcaemia, wanting treatment[2]. Higher skin pigmentation, immuno suppression like HIV, malabsorption, lower sunshine exposure, renal and liver dysfunction are common risk factors for hypovitaminosis D. A strong association between Vitamin D Deficiency and TB may be evidenced by increased production of cytokines by the immune cells. [An antimicrobial peptide], Calcitriol reducing the viability of Mycobacterium TB bacilli. There is an enhanced process of fusion of the phagosome and lysosome in infected macrophages showing an increase in intra cellular oxidative stress [2].

3.1. Adrenal Diseases

Patients with pulmonary tuberculosis present with refractory hypotension & hyponatremia have often been implicated to have adrenal involvement resulting in an ADDISONIAN CRISIS or disease in 40% cases.

The common clinical manifestations are refractory hypotension, fatigue, salt craving, myalgia, recurrent nausea vomiting, abdominal pain, hypotension & hyperpigmentation. on Lab Investigations these patients present with hyponatremia, hyperkalemia, hypoglycemia, and eosinophilia. Diagnosis of adrenal insufficiency is established by ACTH stimulation test [a 30-minutes cortisol level ≤414 nmol/L after a 1 µg ACTH stimulation test] and Early morning cortisol level. The adrenal gland is involved by tuberculosis directly or by cytotoxic inflammatory mediators.

Management of the Addison's disease requires daily low dose oral glucocorticoid, mineral corticoid replacement therapy with anti-TB therapy as per RNTCP guidelines and monitoring of Rifampicin doses [2].

3.2. Thyroid Dysfunction

It's commonly noted in patients with Tuberculosis with Sick euthyroid syndrome. Tuberculosis causes disruption of the hypothalamic-pituitary-thyroid axis, resulting in reduced stimulation of the thyrotropes and impairment of thyroid hormones release. Case reports of TB of the thyroid gland with subsequent destructive thyroiditis and thyroid dysfunction have also been documented [2].

Diagnosis of hypothyroidismis established by the decreased levels of free triiodothyronine (T3) concentration in the absence of clinical or biochemical features of primary or secondary hypothyroidism with a reduced thyroid stimulating hormone level. Thyroid diseases

coexisting with tuberculosis is associated with adverse clinical outcomes. Early and regular-Screening, and treatment of thyroid dysfunction among suspected TB patients is therefore very much advisable. On being diagnosed a hypothyroid the patient may be treated with appropriate thyroid replacement [2].

4. Tuberculosis and the Kidney

There is a commonly observed association in between kidney and genitourinary diseases, with 14% to 41% prevalence [3]. The usual causative agents are the Mycobacterium tuberculosis complex and its symptomsare of conventional bacterial cystitis with poor response to the usual antibacterial agents. Biochemistry reveals sterilepyuria associated back, flank, suprapubic pain, hematuria, increased nocturnal frequency of urination which may or may not be associated with renal colic and also occasionally constitutional symptoms are seen.The diagnosis of urinary tract tuberculosis is based on the finding of pyuria in the absence of infection as judged by culture on routine media [3].

In early disease, it is often possible on intravenous urography to detect changes in a single calyx with evidence of parenchymal necrosis, and typically there is calcification on the plain film. In more advanced disease, urography will show calyceal distortion, ureteric strictures and bladder fibrosis [3].

Ultrasound examination of the urinary tract may reveal renal calyceal dilation and more overt evidence of obstruction which on histology reveals chronic tubulointerstitial nephritis with granuloma formation.

Usual complications of GU TB include multisystem spread of the tuberculosis, gradual fall in GFR, pyuria, amyloidosis, miliary tuberculosis and end-stage renal disease.

Contamination of the dialysis machine by environmental mycobacteria may occur causing a typical mycobacteriosis. In transplant patients, tuberculosis is a serious complicating factor in renal and other forms of transplantation, with an incidence, depending on geographic region, of 0.35% to 15.0%., the treatment for which is Isoniazid prophylaxis for 1 year.

5. Genital Tuberculosis

The epididymis is the most common site of tubercular infection in the genitourinary tract, commonly involved secondary to heamtogenous spread from a distant primary. The route of spread is usually heamtogenous.

Other parts of the GU system like the prostate, face testicular involvement by direct invasion from epididymis and prostatitis due to antegrade infection.

Diagnosis is supported byevident radiologic abnormalities in the urinary tract, Hyper-

calcemia, elevated levels of Calcitriol (1, 25- (OH) 2D3) [3].

Microbiologic diagnosis is done by isolation of the bacilli using inoculation or molecular methods. Acid-fast bacilli may be seen on microscopy of centrifuged urine or by Nucleic-acid amplification techniques, such as PCR. The morphology of the lesions depends on the site of infection,the virulence of the organism and the immune status of the patient [3].

Mode of spread of the tubercle bacilli is heamtogenous or by direct renal involvement, which occurs as a result of reactivation or relapse.

Renal tuberculosis are usually present bilaterally as compared to unilaterally presence. The renal medulla is the site of preference while the other pathological presentations are tuberculous pyelonephritis and "Cement" or "Putty" kidney. Scarring develops within the renal pelvis with calcification in 24% of cases, identifiable as renal or ureteric stones in up to 19% of cases. Infection frequently spreads down to the ureters into the bladder, producing cystitis associated with scarring [3].

The clinical consequences of an extensive renal lesion include auto nephrectomy. Destructive renal lesions may spread outside the renal capsule and produce a mass lesion, which can mimic a neoplasm. Ureteric involvement also may produce irregular ureteric strictures.

6. Tuberculosis in Hepatic diseases

A higher prevalence of tuberculosis is seen in cirrhotic as compared to the general population. Prevalence rate of tuberculosis is found to be 15 times higher than in the general population. Higher prevalence of tuberculosis was also noted in alcoholic liver disease [4].

In cirrhosis patients, extra pulmonary tuberculosis is more common. Ascites due to peritoneal tuberculosis may be difficult to diagnose in the setting of liver cirrhosis where portal hypertensive ascites is common. Patients with liver cirrhosis generally have impaired cellular immunity. A higher likelihood of false negative tuberculin test is seen. AFB smears are generally negative in such patients. Moreover, a high index of suspicion is required to exclude tubercular ascites and an ascitic fluid examination need to be done in all such cases [4].

Tubercular ascites in the setting of cirrhosis reveals anelevated SAAG [serum albumin ascites gradient] and high protein ascites with a lymphocytic predominant high cell count fluid. The ADA levels are usually more than PCR asMTB may be positive. The need for critical review of treatment of tuberculosis in cirrhotic arises because 3 of the 5 first line anti-tubercular drugs are potentially hepatotoxic. The administration of these drugs can lead to worsening LFT with decompensation of stable cirrhotic and sometimes cause fulminant hepatic failure with a high mortality. Current guidelines take a broad perspective regarding treatment of tuberculosis in liver cirrhosis. There is a recommendation that the more advanced the liver disease, the

lesser the amount of hepatotoxic drug that is used. It must be remembered that pyrazinamide has the highest hepatoxicity followed by Rifampicin and Isoniazid.Safer anti tubercular drugs are Ethambutol, Quinolones, Aminoglycosides and Cycloserine.

Cirrhotic patients with essentially normal baseline liver function tests may be treated with standard 4 drug regime for two months followed by two drugs for remaining four months (total 6-months treatment). Since Pyrazinamide is potentially the most hepatotoxic drug, it may be completely avoided and a nine month, three drug regime may be used. Regular monitoring of LFT is recommended [4].

Patients with varying degrees of cirrhosis can be treated with two hepatotoxic drugs - nine months of Isoniazid, Rifampin and Ethambutol (until or unless isoniazid susceptibility is documented) - two months of Isoniazid, Rifampin, Ethambutol and Streptomycin followed by six months of Isoniazid and Rifampin. Category A patients may be treated with one hepatotoxic drug for two months of Isoniazid, Ethambutol and Streptomycin followed by 10 months of Isoniazid and Ethambutol.

In severe liver dysfunction, no hepatotoxic drugs but 18-24 months of Streptomycin, Ethambutol and Quinolones can be administered.

Regular LFT monitoring should be done in all cirrhotic patients receiving anti-tubercular treatment and drug therapy may be stopped /altered as per the LFT reports.

Hepatotoxicity due to antitubercular treatment is more commonly observed in patients with hepatic cirrhosis [4]. In the general population, the criteria for stopping anti tubercular treatment is AST / ALT >three times upper limit of normal and symptomaticor AST/ALT >t five times upper limit of normal even if asymptomatic.

As a general principle a rising trend of liver abnormalities on two consecutive testing may be an indication for stopping treatment. The absolute level of transaminases cannot be used as the sole criteria in cirrhotic. Any rise in S Bilirubin should be treated with great caution and hepatotoxic drug treatment stopped immediately [4].

Treatment should be stopped and re-started after serum bilirubin and transaminase return to near normal. Drugs are re-started in a sequential fashion starting with rifampin first followed by isoniazid and lastly pyrazinamide which may be avoided altogether.

The prognosis of patients with hepatic cirrhosis depends on the stage of disease and associated complications. The 1-year mortality is 34% whereas patients with complications admitted in ICU have 1-year mortality rate of 69% [4]. The mortality rate in patients with tuberculosis who have not received treatment (or delayed treatment) is >50%. The prognosis in patients of liver cirrhosis who develop tuberculosis is poorer compared to either disease alone.

The 30-day case fatality rate was found to be 27.3% and one year case fatality rate was found to be 47.7% [4].

7. Tuberculosis in Patients with Hematological Malignancies

Tuberculosis (TB) is an infectious disease that causes more than 1 million deaths worldwide every year. In addition, it is estimated that one-third of the world population is infected with M. tuberculosis in a latent state, which involves an eventual risk of progressing to active TB disease. Patients with immunodeficiency, such as those suffering from hematological malignancies, have a greater risk of progressing to TB disease once infected. It is estimated that the Relative Risk of TB disease in patients with hematologic malignancies is 2 to 40 times that of the general population. The diagnosis of TB in these patients is often challenging as they often present clinical characteristics that are distinct to those of patients without any other underlying disease. Mortality due to TB is higher. Therefore, it is recommended to diagnose latent TB infection and consider preventive therapy that could avoid the progression from a latent state to active TB disease. There are currently two methods for diagnosing latent TB infection: The Tuberculin Skin Test (TST) and the Interferon-Gamma Release Assays (IGRA). Due to the lack of sensitivity in patients with immunodeficient conditions, a combined TST-IGRA testing is probably the best way for latent TB diagnosis in order to gain sensitivity. Treatment of latent TB infection and TB disease is based on same principles as treatment of routine tuberculosis cases.

Patients with Hematological Malignancies have immunodeficient status which facilitates the emergence of infections [6]. Alteration in the Th1 cell response of the HM itself or that caused by antineoplastic chemotherapy or hematopoietic stem cell transplantation (frequently associated to the administration of high doses of corticosteroids) lead to an impaired immune response that particularly promotes the progression from LTBI to active TB.

The risk of developing TB can vary depending on the type of Blood Dyscrasia. Acute Myeloid Leukemia, Chronic Lymphocytic Leukemia and Chemotherapy were also associated to a higher risk of developing the disease [6]. Patients with HM have a higher risk of TB reactivation than the general population [7].

8. Tuberculosis & Cardiovascular Diseases

Tuberculosis and non-communicable diseases have an established association [7]. Several Infections have been identified which may have a causative role in causing CVS disorders like Chlamydiapneumoniae, *Helicobacter pylori* , Influenza virus and Human immuno deficiency virus (HIV). Infections due to hepatitis B virus, hepatitis C, Epstein Barr virus, cytomegalovirus (CMV) and periodontal bacteria have also been associated with atherosclerosis and CVD through chronic systemic inflammation and other mechanisms. Latent tuberculosis

infection (LTBI) is associated with chronic inflammation.

The possible effects of tubercular infection on cardiovascular disease are an increase in inflammation leading to coronary artery plaque formation and/or plaque rupture, autoimmune disease. The most common cross reaction of antibodies from infection, autoantibodies in atherosclerosis centers on the heat shock protein (HSP) system. M. tuberculosis may not only affect the coronary vessels, but also the myocardium.The potential effects of tuberculosis disease do not appear to be limited to coronary heart disease (CHD) but extend to other atherosclerosis-mediated vascular diseases such as stroke. The possible mechanism of action ismyocarditis, arteritis, and excessive cytokine release [7].

A potential link between tuberculosis and Takayasu's arteritis is seen, but causative role of either diseases in this interaction is yet to be established conclusively [7].

9. Relation between tuberculosis & Cerebrovascular accidents

Tuberculosis in age and gender-matched subjects has shown to have a high likelihood of ischemic stroke, nearly 1.52-times greater among tuberculosis patients in the initial follow up period [5]. Almost 6.0% of the tuberculosis patients had an ischemic stroke, which is higher than that of the general population [5]. The actual mechanisms behind this association is not very clear. Infection causes the activation of a persistent inflammatory response that starts a shower of cytokines and chemokines and acts as a link between infection and atherosclerosis. Recent respiratory tract infections increase the risk for cardio embolic and large-vessel athero-thromboembolic strokes. Association between tuberculosis and stroke may be partially explained by the synergistic effect of tuberculosis and smoking on vessel pathology [5].

10. Tuberculosis & COPD

Tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) carry a significant burden in terms of morbidity and mortality worldwide [8].

Susceptibility of an individual to the development of active tuberculosis and COPD is poorly understood [8].

A study from Turkey, which reviewed 5480 cases of active pleuropulmonary TB found that COPD was the second most common co-morbid condition [8]. No changes were noted between the two groups in symptoms of dyspnea and cough but a higher frequency of hemoptysis was noted.

11. Tuberculosis & HIV

TB & HIV CO INFECTION is a major challenge to medical resources of countries in the African & Asian sub continents where by an estimated 33.3 million people are co infected

[9]. TB is the most common opportunistic infection among HIV-infected individuals and co infected individuals are at high risk of death.

The spectrum of radiographic manifestation of pulmonary TB is dependent on the relative level of HIV-related immunodeficiency [9]. During the early phase of HIV, when individuals are not immunosuppressed, the radiographic pattern is similar to HIV uninfected individuals with more typical lesions - upper lobe infiltrates with or without cavities. With the advancing of immunosuppression, extra pulmonary involvement, intra-thoracic/mediastinal lymphadenopathy, lower lobe infiltrate and miliary TB become more common [9].

The most commonly used method of TB detection involves microscopic examination of sputum for acid-fast bacilli (AFB). Microscopy has the advantage of being inexpensive, relatively rapid to perform, and specific in most settings. However, to be considered smear positive a specimen needs to contain approximately 105 mycobacteria per milliliter.

Culture of Mycobacterium tuberculosis is much more sensitive than smear microscopy and has been recommended to assist in the diagnosis of TB in HIV-infected individuals. Culture also allows subsequent strain characterization and drug susceptibility tests. The traditional method of inoculating solid medium such as the Lowenstein-Jenson (L-J) medium or Middlebrook medium is sensitive but slow, as growth may not be visible until after 6-8 weeks of incubation. The WHO endorsed the use of Gene pert-Rif for the rapid diagnosis of TB as well as rifampicin resistance among HIV-infected individuals with clinical suspicion of TB [9].

GeneXpert is a TB-specific automated, cartridge-based nucleic acid amplification assay, having fully integrated and automated sample preparation, amplification and detection using real-time PCR, providing results within 100 minutes. Xpert MTB/RIF detected rifampicin resistance with 99.1% sensitivity and excluded resistance with 100% specificity.

New diagnostic techniques are developed to detect M. tuberculosis MPB-64 (TAUNS) antigens in peripheral blood, early secreted antigenic target 6 in the cerebrospinal fluid, lipoarabinomannan (LAM) in the urine, etc. by ELISA–based commercial assays. Urine LAM assays tend to perform better in HIV-infected compared to HIV uninfected TB patients. The combination of urine lipoarabinomannan testing and sputum smear microscopy needs further evaluation for use in settings with a high HIV burden.

Performance of various immune based tests to detect antibodies to M. tuberculosis antigens has been reviewed extensively. Conventional tests like tuberculin skin test are still in common practice,though their role in diagnosis of tuberculosis is very limited. The WHO recently made a negative recommendation against the use of serological tests{Interferon-γ release assay (IGRA)} for TB, based on data suggesting that these tests could neither replace sputum microscopy nor be used as an add-on test to rule out TB. Latest diagnostic tools like

Sensing volatile organic compounds and electronic nose devices are under research and yet to be included in mass screening programs.

About detecting HIV among individuals with active TB, provider initiated HIV testing is recommended for all TB patients, as standard of care. The rapid expansion of HIV testing for TB patients has been particularly encouraging in Africa, where only 4% of TB patients were tested for HIV in 2004, but by 2008 that number had increased to 45% t4. In a pilot study of implementation of provider initiated HIV testing and counselling in India, HIV status was successfully ascertained for 70% of TB patients and this was found to be feasible and acceptable. The policy has been rapidly scaled up with over 60% of TB patients being aware of their HIV status in 2011.

The WHO currently recommends that all HIV-infected persons be screened for TB, and HIV-infected persons without active TB disease be evaluated for treatment of latent TB infection 69. The National AIDS Control Organization (NACO) intends to test the effectiveness and feasibility of the WHO IPT guidelines in ART clinics as a precursor for adopting this recommendation [9].

The basic principles of treatment for HIV-associated TB are the same as for HIV uninfected individuals. Certain areas of uncertainty remain, including the regimen duration, dosage and frequency of administration of anti-TB drugs, optimal timing of initiation of ART and optimal anti-TB drug combination for patients on second line treatment [9].

Currently, standard therapy consists of four drugs in the intensive phase for two months namely isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) followed by H and R in the continuation phase of four months. In India, under RNTCP, a fully intermittent thrice-weekly regimen Category I ($2EHRZ_3/4HR_3$) is recommended for newly diagnosed TB. This regimen is reinforced with streptomycin (Sm) in the intensive phase and the total duration increased to eight months for retreatment cases - Category II [9] ($2EHRZS_3/1EHRZ_3/5EHR_3$)78. Rifampicin plays a key role in the treatment of HIV-associated TB because of its ability to destroy both intracellular and intermittently and slowly growing TB bacilli. Non-rifampicin containing regimens are associated with inferior cure rates and prolong the period of treatment 79. A meta-analysis on the duration of rifampicin showed that recurrences were 2-3 times higher if rifampicin use was restricted to 2 months [9].

The WHO guidelines for management of HIV-infected TB patients in resource- limited settings recommend a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) along with one non-nucleoside reverse transcriptase inhibitor (NNRTI) for first line therapy 89. In India, the NACO recommends a regimen containing zidovudine or stavudine along with lamivudine and efavirenz 90. Rifamycin's induce the cytochrome CYP-450 enzyme system in the liver and intestinal wall, there by increasing the metabolism of protease inhibitors (PIs) and

NNRTIs 91. The effect is weaker with rifabutin than with rifampin [9].

Evidence from randomized controlled trials shows that early initiation of ART during TB treatment is associated with reduced mortality rates, especially in patients with profound immunosuppression (CD4<50 cells/microlitre) [9].

Transient worsening of symptoms and signs of tuberculosis or radiological deterioration after the initiation of ART, despite a reduction in HIV load (>1 log10 copies/μl) and immunological recovery, is known as IRIS. Drug resistance and other opportunistic infections need to be ruled out before a diagnosis of IRIS is made. Hypercalcemia is a unique feature of tuberculosis IRIS. There are two types of IRIS presentation: unmasking of undiagnosed tuberculosis and a paradoxical deterioration of existing tuberculosis lesions or appearance of new lesions after initial improvement.

In a study conducted among HIV/TB patients in Tamil Nadu, the prevalence of drug resistance among patients with no history of previous treatment was 13.2% to INH, 2.4% to EMB, 7.8% to SM and 4.2% to RMP, either alone or in combination with other anti-tuberculosis drugs [9].

At least four effective drugs - including a fluoroquinolone, an injectable agent (capreomycin, kanamycin, or amikacin) and at least two agents from the remaining second-line anti-tuberculosis drug classes (cycloserine, thioamides like ethionamide or prothionamide, and p-aminosalicyclic acid)- along with pyrazinamide and EMB, if still sensitive, should be used. Therapy may be individualized on the basis of drug susceptibility test results; however, many countries use standardized regimens that are based on surveillance of antituberculosis drug resistance in the community. DOTS plus regimen is currently followed in India comprising of kanamycin, levofloxacin, ethionamide, cycloserine, ethambutol, and pyrazinamide given for a period of 6-9 months daily in the intensive phase followed by all drugs except kanamycin and pyrazinamide during the continuation phase of 18 months, with dosages prescribed for 3 weight bands [9].

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