2. CLINICAL PRESENTATION AND TREATMENT OF HIV − TB

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The HIV epidemic has increased the burden of tuberculosis (TB) among young adults, especially in populations where the prevalence of TB infection is high. Infection with HIV is the most potent risk factor for progression to active tuberculosis. Individuals who are infected with *Mycobacterium tuberculosis* only have an approximately 10% lifetime risk of developing active tuberculosis, compared with 60% or more in persons infected with HIV and TB. This is particularly important in India where more than half the adult population harbours *M. tuberculosis.* It is estimated that there are about 14 million cases of tuberculosis in India, about 2 million new cases occur annually, and we are home to 1/4th the world's TB prevalence. The situation is likely to get worse as the prevalence of HIV in the community increases. Therefore, it is important to understand the effect of TB and HIV on each other and take adequate measures to control this dual epidemic. Tuberculosis is the commonest opportunistic infection in HIV/AIDS patients with an attack rate of 7 per 100 person-years[1]. The sero-prevalence of HIV among TB patients in India varies widely[2,3] and many studies have reported increasing rates[4,5], reflecting the spread of HIV in the general population. Most cases of tuberculosis in HIV infected patients are due to reactivation of previous lesions. However, HIV infection also greatly increases the risk of developing TB following fresh infection, and the actual proportion of each type in India needs further study. Tuberculosis may occur at any time after HIV infection, but becomes more common as the immune system weakens.

The clinical presentation of TB among the HIV infected is dependent on the degree of immune suppression. Patients with relatively preserved immune function, with CD4+ T cell counts above 200/cu.mm are more likely to have typical symptoms, upper lobe disease and sputum smears positive for AFB. Patients who are severely immunosuppressed are more likely to have atypical clinical and radiographic features: extra-pulmonary disease including meningitis and miliary TB is also more common in the later stages of the disease. The absence of cavitation and combined pulmonary and extra-pulmonary disease are seen more often in patients with lower CD4 counts[6]. The symptoms of TB are similar to those of many other opportunistic infections and a thorough work-up may be required to establish the diagnosis.

DIAGNOSIS

An HIV positive patient with any of the following symptoms should be suspected of having TB and investigated further :

Cough of more than 2 weeks' duration.
Fever lasting more than 2-3 weeks
Weight loss
Fatigue, listlessness
Unexplained dyspnoea or chest pain
Hemoptysis
Lymph node enlargement (especially localised enlargement)
Headache, vomiting, alteration of sensorium or convulsions.

Physical examination should include search for pallor, enlarged lymph nodes, localized respiratory signs, hepatosplenomegaly, ascites and neurological signs. Oral thrush and emaciation are common accompanying signs.

Sputum smear positivity among HIV positive patients is less than in HIV negative TB patients[7,8]. However, we have found similar sputum smear positivity among the culture confirmed HIV seropositive and seronegative tuberculosis patients (unpublished observation). Severe immuno

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suppression among HIV infected patients with pulmonary tuberculosis is associated with a high bacillary load; such patients are less likely to have a granulomatous response in the lung tissues to *M. tuberculosis.* less cavitation and excretion of fewer bacilli from the lungs. Among HIV-infected persons, there is not only need for an early and accurate diagnosis of smear positive TB, to prevent further spread of infection in the community. but there is a need to accurately diagnose and treat smear negative cases as wel1 to prevent progression to infectiousness. 'Globally, and under RNTCP. a diagnostic algorithm based on response to antibiotics is used to improve the specificity of diagnosis of smear-negative tuberculosis[9].

INVESTIGATIONS

The initial investigations should include:

Chest X-ray - Radiographic abnormalities met with are parenchymal infiltrates, hilar or mediastinal lymph node enlargement, miliary mottling and pleural effusion. The lesions may be bilateral and extensive or minimal. Cavitation and upper lobe disease are relatively uncommon. A normal chest Xray does not exclude the diagnosis of tuberculosis.

Sputum smear examination for AFB i.e. three specimens, including two over-night collections of sputum, should be obtained for AFB smear and culture tests. Smear examination by ZN or auramine-rhodamine (fluorescent) staining is the simplest test to perform. In our experience, over 70% of patients with HIV and culture confirmed pulmonary TB had positive smears. In the case of a negative result, 3 more specimens should be collected and examined. Mycobacterial culture increases the chance of isolating *M tuberculosis* from specimens but takes a long time (6-8 weeks), requires special microbiological facilities and is not widely available. The BACTEC radiometric method significantly reduces the time required for culture (10 to 14 days) but is expensive.

Tuberculin skin test (Mantoux test) - This test does not play a major role in diagnosis of tuberculosis as 60% of adults in India are tuberculin positive. We have found that about 50% of the asymptomatic HIV+ persons are tuberculin positive' i.e. have more than 5 mm reaction with 1 TU of PPD RT 23. A positive Mantoux test only indicates infection with *M. tuberculosis* and not necessarily active disease; besides, tuberculous disease may occur in the absence of a positive reaction. In the late stages of HIV, the tuberculin test may be negative because of anergy but anergy testing with a panel of antigens (tetanus. mumps, Candida) is not recommended as the results are not reproducible.

Depending on the clinical manifestations, the following additional investigations may be required:

Examination ofclinical specimens from non-pulmonary sites e.g. blood, urine, CSF, stool and bone marrow for AFB, if extra-pulmonary TB is suspected.

Fine needle aspiration cytology of enlarged lymph nodes (FNAC)

CT scan of chest for presence of enlarged lymph nodes or parenchymal lesions that are not visible on plain X–ray.

Induced sputum/gastric lavage: inhalation of nebulised hypertonic saline or Salbutamol 2 mg given three times daily for a week are used in order to induce sputum production. Gastric lavage can be performed in patients unable to expectorate. These specimens are tested for AFB by smear and culture.

Flexible fibreoptic bronchoscopy with lavage (BAL) and transbronchial biopsy: Though BAL in itself is not better than sputum test for AFB, it may help to rule out other infections like *Pneumocystis carinii.*

Total lymphocyte and CD4 counts: The percentage and absolute number of CD4 cells in blood provide a good index of the stage of HIV disease and have a prognostic value, especially when considered with the extent of viral load. Tuberculosis also produces a decline in CD4+ T cells, thereby worsening the immunologic status. Further, at very low CD4+ cell counts, the manifestations of tuberculosis may be atypical and a high index of suspicion is required for making a diagnosis. Hence,

the CD4 count, if available, is useful in assessing the prognosis as well as for recommending anti-retroviral treatment. The absolute lymphocyte count has been found to correlate broadly with the CD4 count and has been recommended as a cheaper alternative to CD4 testing. A total lymphocyte count of < 1500 cells/cu.mm may indicate a CD4 count of < 200 cells/ cu.mm.

The following newer diagnostic techniques are also available:

BACTEC: This is a radiometric culture system using an enriched liquid medium which shortens the time required for culture and sensitivity testing to 2 weeks, However, it is expensive as the culture medium has to be imported and the facility is only available in major cities. The sensitivity of BACTEC has been found to be similarto conventional culture. The BACTEC technique may be useful for the diagnosis of mycobacteremia as a cause of unexplained fever (PUO) in HIV+ persons.

PCR (Polymerase chain reaction): This is a rapid and sensitive technique to detect the nucleic acid of tubercle bacilli in clinical specimens. However, this technique is still under evaluation and its role in the clinical management of HIV-TB has not yet been finally determined. Further, the commonly used DNA probe IS6110 has a lower sensitivity for south Indian strains because of the lower copy number of insertion sequence. However, a combination of primers may improve the sensitivity of this assay.

Serologic assays for antimycobacterial antibodies are not presently promising. both in HIV infected and non infected patients.

TREATMENT

If the results from investigations are not conclusive and TB is just a diagnostic possibility, a trial of broad spectrum antibiotics (e.g. Co-trimoxazole) may be given for 2 weeks and the patient may be re-assessed. If the X-ray lesion is persistent or has deteriorated, then TB is a strong possibility. In addition, sputum smears may become positive for AFB after a few weeks.

Response of patients to Short Course Chemotherapy

In the past decade, several studies have examined the effectiveness of SCC for HIV infected patients. Although optimal treatment of tuberculosis among HIV infected patients is crucial, current knowledge and recommendations for duration of treatment are inconclusive. In a randomized trial in Zaire, the relapse rate of patients treated for 6 months was 9% as compared with 1.9% among those treated for 12 months[10]. In a prospective study, a shorter duration of treatment and low CD4 cell counts were found associated with a higher risk of relapse''. Relapses were seen in 3.4% of patients treated for 9 months or more (1.7/100 patient-years) and in 24% of patients who were treated for less than 9 months (10.9/100 patient-years). A randomized trial of 6 vs. 9 months of therapy. however, showed acceptable relapse rates, approximately 2%. in both groups'?. Several other studies have shown that treatment for 6 months leads to high cure rates[13-15]. The American Thoracic Society/Centres for Disease Control recommend a 6-month duration of treatment unless the patient is slow to respond to anti-TB treatment[16], replacing the earlier recommendation (treatment for at least 9 months). The IUATLD also recoinmends standard SCC regimens for the treatment of HIV associated tuberculosis''.

Recently, the effect of Trimethoprim-Sulfamethoxazole (Co-trimoxazole) in significantly decreasing mortality and hospital admission rates in HIV infected patients with tuberculosis has been demonstrated[18]. Another study has suggested that post-treatment maintenance therapy with a Combination of Isoniazid and Sulfadoxine-Pyrimethamine significantly reduces recurrence rates and decreases mortality following short-course chemotherapy[19].

The Revised National TB Control Programme (RNTCP) of India advocates treating new sputum positive TB patients with a 6 month supervised intermittent short course regimen ($2EHRZ_3/4RH_3$). Patients who have relapsed or failed or have taken more than 1 month of previous chemotherapy are to be treated with an 8 month intermittent regimen ($2SHRZE_3/1EHRZ_3/5SEHR_3$). These regimens should be given under observation,

at least in the initial intensive phase of DOTS (Directly observed treatment, short course). DOTS providers can be either health workers or volunteers from the community. Under RNTCP, the HIV/TB patients are currently being treated with the standard regimens, but the effectiveness of these regimens in this group in the Indian context has not been ascertained. The efficacy of these regimens in patients with HIV and TB is currently being evaluated in a controlled clinical trial at the Tuberculosis Research Centre, Chennai. In Haiti. however. the cure rate was 81% among HIV positives as against 87% among HIV negative TB patients[20,21].

Treatment of patients with drug resistance

Drug resistance to single and multiple drugs is increasing in the community, mainly due to wrong prescriptions by doctors and poor compliance by patients. Drug resistant tuberculosis in HIV infected patients is no greater than in the general population, in developing countries. If the patient has INH resistant *Mycobacterium tuberculosis*, the response to standard short course regimens is usually good but presence of INH & Rifampicin resistance (MDR-TB) is associated with treatment failure rates upto 70% and a high mortality. Hence, for MDR-TB, at least 3 effective drugs should be used (preferably 4 or 5) based on drug susceptibilities or past treatment history. The duration of therapy is 18-24 months or at least 6 months after sputum conversion. The drug regimen and duration of therapy in cases of MDR-TB should be determined by experienced physicians.

Evaluation of Response to Treatment

The most effective means of assessing therapeutic response is through monthly sputum tests smears and cultures for AFB. More than 85% of patients will convert from positive to negative status after 2 months of therapy which includes INH and Rifampicin. Persistently positive smears after 4 months of therapy suggest the possibility of disease due to drug resistant organisms or non-compliance with therapy. Patients who convert should have at least one additional smear and culture done before completion of therapy. A follow up chest radiograph can also be obtained at completion of treatment.

In patients who were treated presumptively, with negative sputum smears and cultures, the response to therapy should be evaluated clinically and with a follow-up chest X–ray at 3 months. Failure of radiographic improvement after three months of therapy should lead to re-examination of the diagnosis. Evaluation of response to treatment of extra-pulmonary TB will have to be individualized according to the site and extent of disease.

Drug toxicity and Monitoring of treatment

Adverse events with anti-tuberculosis drugs are more frequent in HIV infected patients. This is partly due to multiple medications these patients may be taking. Only serious or life threatening side effects warrant the discontinuation of therapy and most cases can be managed symptomatically. Thioacetazone should not be given to HIV positive patients as there is a high incidence of severe reactions including Stevens-Johnson syndrome. which may be fatal. Drug interactions between anti-TB drugs and other medications can also occur e.g. concomitant use of protease inhibitors results in high serum levels of Rifampicin and lower levels of protease inhibitors. Similarly, serum levels of anti-fungal agents like fluconazole and ketoconazole are lower when given along with Rifampicin.

Preventive therapy

Preventive therapy (PT) of TB with one or more anti-tuberculosis drugs is advocated to prevent progression to active disease of latent focii. HIV is the major cause of such progression. Several studies have now demonstrated that PT is effective in preventing TB breakdown in individuals dually infected with HIV and *M tuberculosis* [22-27]. Studies conducted in USA, Africa and Haiti indicate that preventive therapy is efficacious in HIV positive persons with tuberculin reaction > 5mm, and that the duration of preventive Isoniazid therapy should be longer than six months. Recently, a two-month regimen of daily Rifampicin and Pyrazinamide was found to provide protection equivalent to daily Isoniazid for one year[25]. Intermittent 2 to 3-month regimen of Rifampicin and Pyrazinamide has also been recommended [26,27]. The advantage of shorter duration regimens is better patient compliance and

possibly earlier sterilization of lesions; however, the risk of drug toxicity may be higher. The efficacy of preventive therapy in tuberculin negative HIV positive persons has not been clearly established; most studies show it to be of limited value.

Several issues regarding preventive therapy for tuberculosis in HIV positive persons need to be addressed in the Indian setting. Due to the high risk of exposure to *M tuberculosis*. it is likely that HIV positive persons are at increased risk due to both reactivation and re-infection. Hence, HIV infected persons who are tuberculin negative could also be at a high risk of developing tuberculosis following primary infection. Therefore. there is a need to evaluate the efficacy of prophylaxis for tuberculosis in both tuberculin positive and negative individuals. The duration of preventive therapy in an endemic setting is another area requiring further investigation. If risk of re-infection remains high, then short-term preventive treatment may be of limited benefit. Currently, preventive therapy is not a part of the RNTCP. However, the growing problem of HIV in India could make prevention of tuberculosis in this high-risk group a priority area in the years to come.

Impact of Tuberculosis on HIV Infection

Clinical studies have shown the detrimental effect of tuberculosis on the course of HIV infection [28]. The risk of death in HIV infected persons with TB is reported to be twice as high as that in HIV infected patients without tuberculosis. The higher mortality rate is due to progressive AIDS rather than tuberculosis. *M. tuberculosis* probably increases viral replication by inducing macrophages to produce tumour necrosis factors, IL-1 and IL-6. The degree of immunosupression is the most important predictor of survival in HIV infected patients with tuberculosis. The widespread use of anti-retroviral therapy in the United States has reduced the number of cases of tuberculosis among HIV-infected persons[29]. Thus, an improved access to anti-retroviral drugs could lead to significant public health benefit, especially in high HIV and TB prevalence areas.

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