HIV-Tuberculosis Co-Infection

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Abstract

Tuberculosis has become a major public health problem with Asia and Sub Saharan Africa having the major burden. Increasing spread of Human Immunodeficiency Virus (HIV) causing Acquired Immunodeficiency Syndrome (AIDS) has become a major contributor in increasing the incidence of tuberculosis. Both the problems should be simultaneously taken care of to stop the future pandemic.

INTRODUCTION

Tuberculosis, an ancient disease, continues to remain even today a major public health problem in much of the developing world. It is the most prevalent infectious cause of human suffering and death world wide[1]. The problem is now further complicated by relentless spread of HIV which causes AIDS pandemic and the emergence of multidrug-resistant strains. HIV fuels progression to active disease in people infected with tuberculosis; HIV infected individuals co-infected with tuberculosis have an annual risk of 5-15% of developing active tuberculosis[2]. The South East Asia region of the World Health Organization (WHO) accounts for nearly 40% of all tuberculosis cases globally and 18% of the world's HIV infected also live in this region[3]. In India, tuberculosis is the most common opportunistic infection among HIV seropositive patients[4]. Moreover, HIV and tuberculosis are intricately linked to factors such as malnutrition, poverty, homelessness and overcrowding.

EPIDEMIOLOGY

About a third of the HIV-positive population worldwide is co-infected with Mycobacterium tuberculosis. This accounts to about 14 million people worldwide. Globally, 9% of all tuberculosis cases in adults are attributable to HIV[5]. Studies from Sub-Saharan Africa have recorded HIV seroprevalence rates of 50 to 70% in patients with tuberculosis. In Asia, where the HIV epidemic is still at early stage, the rate of HIV infection in tuberculosis patients has been lower. A HIV-positive person infected with Mycobacterium tuberculosis has a 50 - 60% lifetime risk of developing TB disease as compared to an HIV-negative person who has only a 10% risk. This is especially important in India where it is estimated that 40% of the adult population harbors Mycobacterium tuberculosis. Hospital based HIV seroprevalence studies amongst tuberculosis patients from different regions of India have shown a great variation – the prevalence rates varying from 0.4% - 28.1% have been reported. The prevalence of HIV infection among patients of tuberculosis is rising at an alarming pace in the western parts of the country like Mumbai (2.56-10.15%), Pune (10-25.75%) and south India (0.59-8.89%) but at a much slower pace in north India. A rising trend of HIV infection in patients of pulmonary tuberculosis has also been seen in Lucknow (1.25% in 1996 to 4.28% in 2001)[6]. In India, there were an estimated 5.1 million people living with HIV at the end of the year 2002. Assuming that about 40% of these persons are co-infected with TB, the estimated TB-HIV co-infection figures will be around 2 million[7].

PATHOGENESIS

Mycobacterium Tuberculosis (MTB), the causative organism of tuberculosis spreads almost exclusively by the respiratory route. A person with active pulmonary tuberculosis releases infectious droplets while coughing or sneezing. When a susceptible individual inhales droplets < 10 microns in size, they will reach the alveoli (tiny air sacs) in the lungs, and seed a tuberculosis infection. Given a robust immune system, he does not progress to tuberculosis disease. Persons with latent tuberculosis infection are asymptomatic and do not spread tuberculosis to others. The only evidence of them having had tuberculosis infection will be a positive tuberculin skin test. Because of the progressive depression of the cell mediated immunity in patients with HIV disease, the immune system cannot hold the organism in check. Rapid

multiplication occurs in multiple organ sites simultaneously. Patients with HIV disease may be unable to limit the multiplication of Mycobacterium tuberculosis after initial dissemination and thus HIV infected persons may have involvement of multiple sites. More commonly, HIV infected patients with dormant tuberculosis infection will have reactivation of the latent infection because of diminished cell mediated immunity.

IMPACT OF HIV ON TUBERCULOSIS

The HIV epidemic has the potential to worsen the tuberculosis epidemic as has happened in certain African countries. This is mainly because HIV increases the risk of disease reactivation in people with latent tuberculosis and because HIV-infected persons are more susceptible to new tuberculosis infection[8]. These patients would add to the incidence of tuberculosis thereby leading to increase in new infections and re-infection. HIV is the most powerful risk factor for progression of tuberculosis infection to tuberculosis disease. Also, HIV-infected persons who become newly infected with Mycobacterium tuberculosis rapidly progress to active tuberculosis disease.

Tuberculosis is the most common opportunistic infection and a major cause of mortality among HIV-positive persons. It is the first manifestation of AIDS in more than 50% of cases in developing countries. HIV by itself does not cause multi-drug resistant tuberculosis, but fuels the spread of this dangerous condition by increasing susceptibility to tuberculosis infection and also accelerating the progress from infection to disease. In persons with AIDS, factors such as (i) increased vulnerability to tuberculosis;(ii) increased opportunity to acquire tuberculosis due to overcrowding, exposure to patients with multidrug resistant tuberculosis, increased hospital visits; and (iii) malabsorption of antituberculosis drugs resulting in sub-optimal therapeutic blood levels inspite of strict adherence to treatment regimen have all been postulated as the possible causes for increased risk of acquired MDR tuberculosis[8].

CLINICAL PRESENTATION

The clinical presentation of tuberculosis in HIV infected patients varies depending on the severity of immunosupression. Clinical presentation of tuberculosis in persons with early HIV infection has been found to be similar to that observed in immuno-competent and HIV-negative patients. In immuno-competent patients, pulmonary tuberculosis is the most common form of tuberculosis encountered and accounts for about 80% of the cases. While extra pulmonary tuberculosis accounts for only 20% of the cases of tuberculosis in HIV-negative patients, it accounts for 53-62% of cases in HIV-positive patients[9]. The most common extra pulmonary site is the lymph node. However, neurological, pleural, pericardial, abdominal and virtually every body site can be involved in HIV-positive patients. In studies reported from India, extra pulmonary tuberculosis constituted 45 to 56% of all the cases of tuberculosis in persons with AIDS[10]. Further, extra pulmonary tuberculosis by itself was not associated with decreased CD4 but patients with a combination of pulmonary and extra pulmonary tuberculosis had significantly lower CD4 counts.

DIAGNOSIS

The diagnosis of tuberculosis in HIV positive persons requires a high index of suspicion and a combination of clinical, radiographic and bacteriologic investigations. The presence of following symptoms should alert the clinician to the possibility of associated HIV infection in a patient with tuberculosis: weight loss more than 10Kg or more than 20% of the original body weight, pain on swallowing (oral candidiasis) and burning sensation of the feet (peripheral sensory neuropathy).

Diagnosis of tuberculosis in HIV infected patients is difficult because of absence of fever and constitutional symptoms, negative sputum smears, atypical chest radiography, higher prevalence of extra pulmonary tuberculosis especially at inaccessible sites, resemblance to other opportunistic pulmonary infections, among others. However, the conventional methods of smear and culture must be applied to sputum, body fluids and secretions. Attempts must also be made to procure material for histopathological, cytopathological and microbiological testing employing radiologically guided procedures or minimally invasive diagnostic methods such as Video-assisted Thoracoscopy, laparoscopy and colonoscopy where relevant[8].

A negative tuberculin skin test may reflect the immunodeficiency status and does not rule out the presence of active tuberculosis. PPD positivity is much less in HIV seropositive tubercular patients as compared to HIV seronegatives (20% vs 75.27%) by a study done in Lucknow[6].

In HIV-infected individuals, the radiographic manifestations of pulmonary tuberculosis can be atypical or different. A study compared the radiographic findings at baseline and at the end of anti-tuberculosis therapy in HIV-positive and HIV-negative patients with tuberculosis[11]. The commonest

radiographic presentations among HIV patients were diffuse soft parenchymal opacities followed by cavities, pleural effusion, military tuberculosis and hilar lymphadenopathy. Cavities were more frequent among tuberculosis patients without HIV infection. On the completion of anti-tubercular therapy, patients with HIV have less radiographic sequelae in the form of fibrosis[11].

Sputum microscopy is the cornerstone of diagnosis of tuberculosis even in high HIV-prevalence areas. Patients suspected of having tuberculosis should have three sputum specimens examined for acid fast bacilli. HIV-infected, smear positive patients tend to excrete significantly fewer organisms per ml of sputum than HIV- negative patients, which can lead to AFB being missed if the appropriate number of sputum samples as well as high power fields is not examined by microscopy. In early HIV, smear positive pulmonary tuberculosis is as common as the non-HIV patients. The sputum negativity tends to increase as the HIV disease and immuno-suppression progress. In Indian studies AFB smear negativity has been reported as high as 82%.

TREATMENT

It is essential to start standard anti-tuberculosis treatment promptly following the DOTS strategy in HIV patients diagnosed to have tuberculosis as majority of these patients respond well to the standard anti-tuberculosis treatment. In a known HIV positive individual with active TB, Category-I is to be used. Treatment-regimens recommended under RNTCP are the same irrespective of patient's HIV-status. The duration of therapy will be as per treatment regimen and category.

Treatment in Special Situations

1. Extra pulmonary Tuberculosis: The basic principles that support the treatment of extra pulmonary tuberculosis in HIV uninfected individuals also apply to HIV infected patients. The drug regimens and treatment durations that are recommended for treatment of extra-pulmonary tuberculosis in HIV negative persons are also recommended for treating HIV positive patients. But if the clinical or bacteriologic response is slow, treatment may be prolonged as mentioned previously.

2. Pregnancy: HIV-infected pregnant women who have tuberculosis or are

suspected of having tuberculosis should be treated without delay. Streptomycin should not be given during pregnancy because of potential adverse effects on the foetus. Other drugs used in the RNTCP are safe during pregnancy. In patients on concomitant anti-retroviral therapy, efavirenz should be avoided in view of its teratogenicity.

Figure 1

ART Recommendations for individuals with Tuberculosis Disease and HIV Co-infection (WHO- 2006)

CD4 Cell Count	Recommended Regimen Comments
CD4<200 cu mm	Start TB treatment. Start ART as soon as TB treatment is Tolerated. (between 2 weeks and 2 months). EFV containing regimen. EFV is contraindicated in pregnant women or women of child bearing potential without effective contraception.
CD4 between 200-350/ cu mm	Start TB treatment. Start one of the below regimens after intensive phase (if severely compromised start earlier) EFV containing regimen or NVP containing regimen in case of Rifampicin-containing continuation Phase TB treatment regimen.
CD4>350 cu mm	Start TB treatment, Defer ART
CD4 not available	Start TB treatment, Consider ART

PARADOXICAL REACTIONS

Paradoxical reactions, also called immune restoration syndromes have been reported in 32 to 36% of patients with HIV-related tuberculosis within days to weeks after the antiretroviral treatment has been initiated. It most commonly occurs within 3 months of starting anti retroviral therapy but can also occur as early as within 5 days. Manifestations range from isolated instances of fever to increased or initial appearance of adenopathy, new or worsening pulmonary infiltrates, serositis, cutaneous lesions and new or expanding central nervous system mass lesions. These pose a problem and have to be distinguished from tuberculosis treatment failure, drug hypersensitivity and other infections common among immuno-compromised patients[13]. It is more common if anti retroviral therapy is started early in the course of tuberculosis treatment and in patients with low CD4 count.

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