Original Research Article

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Prevalence of tuberculosis in newly diagnosed HIV patients and its relationship with CD4 count in a tertiary care hospital

Archana B.1, Vivek K. U.2*

¹Department of Pulmonary Medicine, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India ²Department of Pulmonary Medicine, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

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*Correspondence:

Dr. Vivek K. U.,

E-mail: vivek.kotyal@gmail.com

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ABSTRACT

Background: Tuberculosis (TB) is the commonest opportunistic infection among Human Immunodeficiency Virus (HIV) positive patients in India and HIV/TB co-infection poses a major public health challenge in developing countries. It is estimated that 60-70% of HIV positive patients will develop tuberculosis in their lifetime. The aim of the present study is to record the clinical, radiological profile of pulmonary and Extrapulmonary Tuberculosis (EPTB) in HIV positive patients.

Methods: This was a prospective study conducted in the department of Pulmonary medicine, Kempegowda institute of medical sciences. All newly diagnosed HIV patients during the study period were included and screened for tuberculosis irrespective of whether they had signs and symptoms.

Results: Among 44(15.94%) patients among 276 HIV positive patients were diagnosed to have tuberculosis. Males (72.72%) were affected more than females (27.27%). Most common affected age group was 31-40 years with a mean age of 38.08 years. Unprotected heterosexual contact was the most common mode of HIV transmission. Fever, weight loss and cough were the commonest symptoms at presentation. Pulmonary TB was diagnosed in 10(22.7%) patients, EPTB in 30(68.3%) and disseminated TB in 4(9%) patients. All the pulmonary TB patients had CD4 count below 250, EPTB below 150 and disseminated TB patients below 50.6(13.63%) patients had pleural effusion, 5(11.36%) had abdominal TB, 5(11.36%) had tubercular meningitis, 4(9%) had intra thoracic lymphadenopathy and one (2.27%) patient had pericardial effusion. Low CD4 count (<150) had statically significant association with HIV/TB coinfection.

Conclusions: The prevalence of HIV-TB co-infection was high. Moreover, HIV positive patients need early diagnosis and treatment of active TB. The study has shown clear correlation between clinical data and the laboratory parameter of immunodeficiency (CD4 count) and the temporal development of TB.

Keywords: CD4 count, Extrapulmonary tuberculosis, Pulmonary tuberculosis, Human immunodeficiency virus - tuberculosis, People living with the human immunodeficiency virus

INTRODUCTION

Global increase in pandemic Human Immunodeficiency Virus (HIV) has led to increase in prevalence of Tuberculosis (TB). Among People Living with the Human Immunodeficiency Virus (PLHIV) tuberculosis is the leading cause of death worldwide. 1.2 Due to the high

burden of TB-HIV co-infection, the World Health Organization (WHO) recommends intensified case finding for active TB among PLHIV in high-burden areas, including screening for TB at every health care encounter. In the pre-HIV era, annual incidence of TB worldwide was 4 million and in the post-HIV era it is 10 million.^{3,4} TB is the commonest opportunistic infection

among HIV positive patients in India and HIV/TB coinfection poses a major public health challenge in developing countries.⁵ It is estimated that 60-70% of HIV positive patients will develop TB in their life time.⁶ By suppressing the immune response, HIV infection favors the progression the from latent infection to active TB. The prevalence of HIV/TB co-infection ranges from 50%-80% in sub-Saharan Africa. In India it varies from 1%-13% and may be as high as 40% in high prevalent states and districts. The CD4+ lymphocyte is a principal target of HIV infection and over the time CD4 count decreases as the disease progresses. The CD4+ lymphocyte count is an important prognostic marker in staging and progression of HIV infection.⁸⁻¹¹ Hence the level CD4 T Lymphocytes suggest the immune state of HIV patients, therefore could determine the trend and pattern of chest manifestations of opportunistic infection. 12-14 TB and HIV infections have a synergistic influence on the host immunoregulation. TB can develop at any stage of immunosuppression regardless of the level of the circulating CD4+ T-lymphocytes.

The patients with early course of the disease present with similar pattern as immunocompetent individuals, whereas those individuals with advanced diseases presents atypically. In India to combat and control the HIV/TB coinfection, a strategy of intensified case finding is adopted. It includes the routine screening of TB patients for HIV at Integrated Counseling and Testing Centers (ICTCs) and Anti-Retroviral centers (ART). The aim of the present study is to record the clinical, radiological profile of pulmonary and Extra Pulmonary Tuberculosis (EPTB) in HIV positive patients and their correlation with the CD4 count. To win the battle against AIDS author have to fight against TB. Unlike HIV/AIDS, TB is completely curable in the vast majority of cases.

METHODS

This prospective study was conducted in the department of pulmonary medicine, Kempegowda Institute of Medical Sciences, Bangalore, India from April 2014 to September 2015. All newly diagnosed HIV patients during the study period were included and screened for TB. HIV infection was confirmed by enzyme linked immunosorbent assay using two different antigens and a rapid test as recommended by NACO and also processed for CD4 count. CD4 T-lymphocyte count was determined by flow cytometry. They were used to assess the magnitude of injury to the host immune system and to monitor the effectiveness of antiretroviral treatment. Informed consent was taken from the study subjects. Ethical committee approval was taken. All the patients, irrespective of whether they had signs and symptoms, were screened for TB by microscopic examination of sputum for acid fast bacilli, radiological features suggestive of tuberculosis and positive skin tuberculin testing, histopathological demonstration of caseous granuloma, pleural/ ascetic/ pericardial/ cerebro spinal fluid analysis when present. Sputum samples were sent for microscopic examination using Ziehl- Neelsen's method and cultured with Lowenstein-Jensen or Ogawa medium.

Radiographs were evaluated for the presence of atypical or typical patterns of pulmonary TB. A pretreatment Posteroanterior (PA) chest radiographs were evaluated by a consultant radiologist, who was blind to the HIV status and CD4 T-lymphocyte count. All radiographs had been obtained within 48 hours of the sputum cytology/cultures. Evaluation for the presence and location of pulmonary parenchymal opacities. mediastinal and lymphadenopathy, pleural effusions, cavitation and interstitial nodules were performed. A post primary M. tuberculosis (typical) pattern was defined as airspace consolidation in the apical or upper zone, or superior segment of lower lobe, with or without cavitation and without lymphadenopathy or pleural effusion. The primary (atypical) pattern included middle and/or lower zones opacities, mediastinal or hilar lymphadenopathy, pleural effusion, miliary TB, or a normal chest radiograph. Although author realized that the superior segment of the lower lobe could not be accurately located by frontal chest radiograph alone, presence of infiltrates above and below the horizontal fissure may strongly suggest lesions in this region. Regardless of age, induration of 5 mm or more on tuberculin test is considered as positive in HIV-infected patients.¹⁵ Fine needle aspiration cytology and excisional biopsy that showed the presence of tuberculoid granulomas with epithelioid cells and giant cells facilitated diagnosis of lymph node TB.

Exclusion criteria

 Subjects with concomitant opportunistic infection or currently receiving antibiotic therapy for TB were excluded from the study.

Statistical analysis

All data was analyzed using SPSS Statistics version 17.0 (Chicago, USA). Microsoft Excel was used for graph and table presentations. Continuous variables are presented as mean±SD. Independent sample t-test and one-way ANOVA were used to compare the means of variables between various patient subsets. The chi-square test was used to evaluate the association between subjects with CD4 T-lymphocyte count of above and below 200 cells/ul and their radiographic features, p-values less than 0.05 were considered to indicate statistical significance.

RESULTS

Among 276 newly diagnosed HIV positive patients, 44(15.94%) patients were diagnosed to have TB. 32(72.72%) were males and 12(27.27%) were females. Most common affected age group was 31- 40 years with a mean age of 38.08 years.

Table 1: Chest x-ray findings.

Chest x ray findings	No of patients
Pulmonary infiltrates	14
Pleural effusion	6
Intra thoracic lymph nodes	4
Cavity	3
Pericardial effusion	1

Table 2: Relationship between different forms of tuberculosis and CD4 count.

Type of TB	No of patients (%)	Mean CD4 count
Pulmonary tb	10(22.7)	236
Extra thoracic lymphadenopathy	9(20.45)	105
Pleural effusion	6(13.63)	205
Abdominal tb	5(11.36)	148
Tubercular meningitis	5(11.36)	98
Intrathoracic lymphadenopathy	4(9)	69
Pericardial effusion	1(2.27)	71
Disseminated tb	4(9)	32

Unprotected heterosexual contact was the most common mode of HIV transmission. The average CD T lymphocyte count in patients with HIV-TB was 120.5. Fever, weight loss and cough were the commonest symptoms at presentation. Chest x-ray findings of HIV/TB patients are shown in (Table 1, 4 and 5).

Pulmonary infiltrates was the most common chest x-ray findings overall. Atypical chest x-ray findings like middle/lower zone opacities, mediastinal lymphadenopathy, pleural effusion, miliary tuberculosis common in patients with CD4 count less than 200 as shown in (Table 5). Pulmonary TB was diagnosed in 10(22.7%) patients, EPTB in 30(68.3%) and disseminated TB in 4(9%) patients. Among the EPTB patients, 9(20.45%) patients had extra thoracic lymphadenopathy.

Table 3: CD4 count and its correlation with HIV and TB.

CD4 count	HIV-TB	HIV alone	Total
< 50	9(20.45%)	21(9.05%)	30(10.86%)
50-150	19(43.18%)	57(24.5%)	76(27.5%)
150-250	12(27.27%)	46(19.82%)	58(21.01%)
>250	4(9%)	108(46.55%)	112(40.57%)
Total	44	232	276

Table 4: Relationship by frequency and percentage between CD4 count lymphocyte count and chest radiographic pattern in HIV-TB coinfection patients.

CD4	Chest radiographic pattern		Total
count	Typical	Atypical	Total
>200	11(25%)	5(11.36%)	16(36.36%)
< 200	5(11.36%)	23(52.27%)	28 (63.63%)
Total	16 (36.36%)	28(63.63%)	44 (100%)

Table 5: Radiographic findings according to the CD4 T-lymphocyte count.

CD4 T-lymphocytes count*	Radiographic appearances(number)	Number of patients
Above 200 cells/ul	 A. Atypical presentation (5) Middle/lower zone opacities (0) Mediastinal lymphadenopathy (1) Pleural effusion (2) Miliary tuberculosis (0) Normal chest radiograph (3) B. Typical presentation (11) Upper zone opacities, with or without cavitation 	16
Below 200 cells/ul	 A. Atypical presentation (23) Middle/lower zones opacities (3) Mediastinal lymphadenopathy (3) Pleural effusion (4) Miliary tuberculosis (1) Normal chest radiograph (12) B. Typical presentation (5) Upper zone opacities, with or without cavitation 	28
Total		44

Cervical lymph node was the commonest lymph node involved, 6 (13.63%) patients had pleural effusion, 5 (11.36%) had abdominal TB, 5 (11.36%) had tubercular

meningitis, 4 (9%) had intra thoracic lymphadenopathy and 1 (2.27%) patient had pericardial effusion (Table 2).

Relationship of CD4 count with different types of tuberculosis in HIV patients (Table 2).

All the pulmonary TB patients had CD4 count below 250, EPTB below 150 and disseminated TB patients below 50. Extra thoracic lymphadenopathy, pleural effusion, abdominal TB, tubercular meningitis, intrathoracic lymphadenopathy, pericardial effusion common in patients with mean CD4 count 105, 205, 148, 98, 69,71 respectively (Table 2). Out of 44 HIV-TB cases, 19 cases (43.18 %) have CD4 count in the range of 50-150 (Table 3). Low CD4 count (<150) had statically significant association with HIV/TB co-infection.

DISCUSSION

The clinical course of both diseases altered in Mycobacterium tuberculosis and HIV co-infection. 16,17 Immune derangement found in co-infected patients is different from that of patients infected with either of these pathogens alone. HIV-1 replication and progression to AIDS is increased in the presence of mycobacterial infection.¹⁸⁻²¹ HIV-patients with tuberculosis presents with diffuse pulmonary involvement, and frequent extrapulmonary dissemination.²² Co-infected patients shows decreased proliferative response to M. tuberculosis antigens, and reduced production of IL-2 and IFN γ , compared to patients with tuberculosis and no HIV.²¹ T lymphocytes play a pivotal role in host responses to M. tuberculosis and HIV-1 infections. Immunophenotyping of peripheral T lymphocytes in HIV infected patients showed an imbalance of naive and memory/ effector cells on CD4+ cells and enhanced expression of activation surface markers, such as CD38, on the CD8+ cells. 23,24 However, there is little data available in patients coinfected with M. tuberculosis and HIV-1.

In the present study, author showed the relationship of HIV and TB and it was found to be mutually beneficial. HIV positive patients are susceptibility to Mycobacterium tuberculosis infection. They are more likely to develop active rather than latent infection and are also susceptible to reactivation of latent tuberculosis infection with an annual risk of 5-10%.25 They are usually susceptible to rapid progression to active disease. 18 Tuberculin-positive co infected persons have a risk of TB development of 8 to 10% per-year compared to <0.1% annually in those without HIV infection.²⁶ Thus, once infection is established, progression to clinical disease is faster and more severe in HIV-positive patients. In the present study pulmonary TB developed in subjects with mean CD4 count greater than 200, EPTB developed with mean CD4 count less than 200 and disseminated TB developed in patients with mean CD4 count of <50. Hence in the present study author noted more the immunosuppression (lower CD4 count) there is increased incidence of EPTB and disseminated TB.

Lymph node involvement is the most common form of EPTB in the present study as evidenced by previous

studies. The chest radiographic appearances of patients presenting with pulmonary symptoms are frequently nonspecific. Several studies have described the unusual manifestations of pulmonary TB in patients with advanced stages of HIV infection, and conversely, the usual pattern of reactivation tuberculosis in those patients early in the course of HIV infection. In HIV-infected persons with higher CD4 counts (i.e., >200 cells/µl), the radiographic pattern tends to be one of reactivation disease with upper-lobe infiltrates with or without cavities.²⁷ In HIV-infected persons who have a greater degree of immunosuppression (i.e., CD4 count <200 cells/µL), a pattern of primary disease with intrathoracic lymphadenopathy and lower-lobe infiltrates is seen. Atypical radiographic findings included unifocal and multifocal alveolar opacities, interstitial opacities, cavitary opacities, mediastinal or hilar adenopathy, miliary nodules, pleural effusion, normal chest radiography. Cavitation and atelectasis are less common in the HIV-seropositive group than in the seronegative group. This is not surprising, as one would expect that cavity formation require an intact delayed-type hypersensitivity response and vigorous lymphocyte reactivity to M. tuberculosis antigen as chest radiographs may appear normal in up to 21% of those with culturepositive TB and CD4 counts of <50 cells/µl, a high index of suspicion must be maintained in evaluating an HIVinfected patient with symptoms suggestive of TB.28-30 Similarly in the present study, chest X-ray with upper lobe infiltrates and cavitation predominate in those with CD4 count greater than 200 and lower lobe and bilateral infiltrates and intrathoracic lymphadenopathy predominate in subjects with CD4 count less than 200.

Tuberculin Skin Test (TST) is the only tool to diagnose latent tuberculosis but lacks sensitivity in HIV positive individuals. The main advantage of TST is its low cost, but with some limitations like, patients may not return to read the result and interpreting results need expertise. Interferon (IFN) γ Release Assays (IGRAs), are T-cell-based assays allowing measurement of IFN-g, which is released from T cells following stimulation by 2 unique antigens of *Mycobacterium* TB (MTB) like early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).³¹ In the present study author have not done IGRAs, so there is high chance of missing the latent tuberculosis infection.

This study hopes to provide an objective framework for the evaluation of pulmonary TB in the AIDS population and provide a method for early recognition, treatment, and isolation of a pathogen that is potentially hazardous to the general population. In addition, clinical trials have shown that anti-TB regimens can prevent or decrease the likelihood of TB infection progressing to active TB disease in an HIV-infected individual, making it an important intervention for increasing the length and quality of life for co-infected patients and their families and communities.

The strength of this study is, study is a prospective study with enrolment of all the HIV positive patients regardless of the symptoms. Hence it guides finding the HIV-TB cases in early stage and prevent spread. The limitations of the present study are small sample size, virologic markers and search for primary drug resistant TB were not assessed due to financial constraints. The high rates of AFB smear-negative disease in HIV patients, culture can be essential to confirm the diagnosis of HIV. In this study sputum culture was not done. Despite these limitations, this study shed light on the prevalence and determinants of HIV-TB co-infection in a tertiary care hospital in Bangalore.

CONCLUSION

The prevalence of HIV-TB co-infection was high. Moreover, HIV positive patients need early diagnosis and treatment of active TB. The study has shown clear correlation between clinical data and the laboratory parameter of immunodeficiency (CD4 count) and the temporal development of TB. However large sample size prospective studies are needed to correlate the clinical and CD4 count with the occurrence of different types of tuberculosis.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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