

Study of Clinical, Laboratory and Radiological Spectrum of Tuberculosis in HIV-Infected Individuals and Its Correlation with CD4 Count

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ABSTRACT

BACKGROUND

Tuberculosis is often more difficult to diagnose and more complicated to treat among people who are human immunodeficiency virus (HIV) positive. This study was conducted to assess the clinical, microbiological, laboratory and radiological spectrum of tuberculosis (TB) in HIV seropositive patients, and explore its possible correlation with their CD4 count.

METHODS

A total of 104 patients who were western blot positive for HIV and co-infected with tuberculosis were studied in Salem district of Tamil Nadu. A detailed history was obtained and patients were examined clinically. CD4 count, sputum smear for acid fast bacilli (AFB), chest x-ray, and tuberculin test, were done along with other relevant investigations. The relationship between CD4 count, and the type of tuberculosis, sputum smear, chest x-ray, and tuberculin test, were analysed statistically, and $P < 0.05$ was considered significant.

RESULTS

Most of the patients were between 30 to 39 years. Males (84.6 %) outnumbered females (15.4 %). Pulmonary tuberculosis alone was seen in 47 patients, while extra pulmonary tuberculosis in 36 cases, and both pulmonary and extra pulmonary occurred in 21 cases. They had a mean CD4 count of 237.7 cells / μL , 135.2 cells / μL and 120.9 cells / μL respectively. Extrapulmonary tuberculosis and combined forms were associated with lower CD4 counts (P -value 0.005). The mean CD4 count of sputum positive, sputum negative, and multiple drug resistant (MDR) tuberculosis were 294.2, 168.3 and 90.2 cells / μL respectively. Lower CD4 count was associated with sputum - ve TB ($P < 0.041$). Lower CD4 counts were associated with atypical chest X-ray findings ($P < 0.006$) and negative tuberculin test ($P < 0.001$).

CONCLUSIONS

Sputum smear positivity for AFB decreases as CD4 count reduces. Involvement of lungs tend to be atypical in immunocompromised patients. The diagnosis of TB in HIV positive individuals is complex and a high index of suspicion is needed.

KEYWORDS

HIV, Tuberculosis, CD4 Cell Count, Sputum Smear for AFB, Chest X-Ray

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BACKGROUND

HIV / AIDS (acquired immunodeficiency syndrome) and tuberculosis are so closely connected that the term "co-epidemic" or "dual epidemic" is often used to describe their relationship. HIV and TB forms a lethal combination, each speeding the other's progress.

TB is one of the most common disease among HIV-infected patients worldwide and is responsible for an estimated 20 - 25 % of all HIV related mortality (around 390,000 deaths per year).¹ It is the leading cause of death among people with HIV. Globally people living with HIV were 19 times more likely to fall ill with TB than those without HIV.² In India, tuberculosis is the most common opportunistic infection among HIV seropositive patients as well as the leading cause of death.^{3,4}

Tuberculosis is often more difficult to diagnose and more complicated to treat among people who are HIV-positive. Chest x-ray findings tend to be atypical in late stages, with primary tuberculosis like pattern, diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy.¹ Sputum smears may be positive less frequently among tuberculosis patients with advanced HIV infection than among those without.¹ Thus, the diagnosis of tuberculosis may be unusually difficult in HIV tuberculosis co-infection.

This study was conducted to assess the clinical, microbiological, laboratory and radiological spectrum of TB in HIV seropositive patients and explore its possible correlation with their CD4 count.

METHODS

This cross-sectional study was carried out in Vinayaka Mission's Kirupananda Variyar Medical College Hospital, and Government Mohan Kumaramangalam Medical College Hospital, in Salem district of Tamil Nadu, from June 2019 to March 2020.

Patients who were western blot positive for HIV and co-infected with tuberculosis were studied. Patients of age more than 12 years with TB confirmed by sputum smear for AFB or histopathological findings, patients who were presumptively diagnosed with chest x-ray showing features suggestive of pulmonary involvement and with ultrasonogram of the abdomen showing enlarged matted lymph nodes or matted peripheral lymphadenopathy were included. But patients with diagnosis of active symptomatic bacterial infection (other than TB) or fungal or protozoal infection were excluded.

A total number of one hundred and four (104) patients were included in the study based on the study criteria for selection. Detailed history was taken by preformed questionnaires and patients were thoroughly clinically examined.

Blood samples collected from each patient were tested for HIV antibodies by enzyme-linked immunosorbent assay (ELISA). Western blot test was used to confirm reactive samples. CD4 count was done by flow cytometry. Severely immunocompromised patients were defined as those having

CD4 count < 200 cells / μ L. Early morning sputum sample was collected from patients who had productive cough on 3 consecutive days. Examination of the sputum for AFB was done by the Ziehl-Neelsen method. Chest x-ray was done in all the cases to look for manifestations of tuberculosis. Tuberculin skin test was performed by the Mantoux method. The interpretations were made as follows: anergy or no response (0 mm), negativity (0 - 4 mm), positivity (\geq 5 mm).

Other investigations like abdominal ultrasound, fine needle aspiration cytology (FNAC) / biopsy for peripheral lymphadenopathy, CT guided bone biopsy for skeletal TB and study of pleural and cerebrospinal fluid were done wherever indicated.

Statistical Analysis

Data was analysed using descriptive and inferential statistics. P-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

In this study the common age group of presentation was between 30 to 39 years (58.7 %), and the mean age being 36.56 years. Males (84.6 %) outnumbered the females (15.4 %). 89 (85.6 %) were married. Majority of the study population were drivers (23.1 %), followed by farmers and labourers (21.2 % each). Most of the females were house wives. In our study the most common clinical presentation noticed was weight loss > 10 % of body weight in 91 (87.5 %), followed by prolonged fever in 87 (83.7 %), cough for > 3 weeks in 79 (76 %) and night sweats in 76 (73.1 %). Dyspnoea was present in 18 (17.3 %). Lymphadenopathy was present in 21 (20.2 %). Other symptoms were pleuritic chest pain in 9 (8.7 %), diarrhoea in 7 (6.7 %), abdominal pain in 7 (6.7 %), headache in 7 (6.7 %), vomiting in 7 (6.7 %), haemoptysis in 6 (5.8 %), altered sensorium in 5 (4.8 %), low back ache in 2 (1.9 %), non-healing ulcer in 2 (1.9 %) seizures in 2 (1.9 %) and diplopia in 1 (0.96 %).

Associated clinical findings like oral candidiasis was found in 12 (11.54 %) individuals. 8 (7.7 %) of them had systemic hypertension and 9 (8.65 %) were diabetic. Herpes zoster was seen in 2 (1.9 %) individuals and 1 (0.96 %) of them had oesophageal candidiasis.

In this study most of the subjects N = 96 (92.3 %) had CD4 count below 300 cells / μ L. 26.9 % had CD4 count below 100 cells / μ L, 35.6 % had CD4 count between 101 - 200 cells / μ L and 29.8 % had CD4 count between 201 - 300 cells / μ L (Figure 1).

Out of 104 patients, pulmonary tuberculosis alone was diagnosed in 47 cases (45.2 %) and 36 cases (34.6 %) had extra pulmonary tuberculosis. Pulmonary and extra pulmonary tuberculosis occurred together in 21 cases (20.2 %) which included 6 cases (5.8 %) of miliary tuberculosis.

Among the 47 patients with pulmonary tuberculosis, the most common presentation was sputum positive PT 29 (61.7 %). Sputum negative PT and MDR TB accounted for 13 (27.7 %) and 5 (10.6 %) respectively. Mean CD4 count for pulmonary TB was 237.7 cells / μ L. Mean CD4 count for

sputum positive PT, sputum negative PT, MDR TB were 294.2 cells / μ L, 168.3 cells / μ L and 90.8 cells / μ L respectively.

Among the 36 subjects who had extra pulmonary TB, lymphadenopathy in 10 individuals (27.8 %) was the commonest presentation, closely followed by TB meningitis in 8 (22.2 %). The other presentations were pleural effusion and TB abdomen in 7 (19.4 %) each, skeletal tuberculosis in 2 (5.6 %), tuberculoma in 1 (2.8 %) and salpingitis in 1 (2.8 %). Mean CD4 count for extra pulmonary TB was 135.2 cells / μ L, of which lymphadenopathy had mean CD4 count 193.4 cells / μ L, followed by genitourinary TB (158 cells / μ L), pleural effusion (151.4 cells / μ L), skeletal TB (128.5 cells / μ L), TB abdomen (103.1 cells / μ L), TB meningitis (86.5 cells / μ L) and tuberculoma (44 cells / μ L).

Among the 21 patients who presented with both pulmonary and extrapulmonary tuberculosis, 8 (38.1 %) of them had pulmonary tuberculosis with lymphadenopathy with a mean CD4 count of 150.9. Pulmonary tuberculosis was seen with pleural involvement in 4 (19 %) and TB meningitis in 3 (14.3 %) with a mean CD4 count of 104.5 and 108 respectively. Miliary tuberculosis was seen in 6 (28.6 %) with a mean CD4 count of 98.2 cells / μ L.

In this study, among patients with extrapulmonary TB and combined pulmonary and extra pulmonary TB none of them had a CD4 count above 300 cells / μ L. Of those with pulmonary TB 82.9 %, had CD4 count below 300 cells / μ L and 46.8 % had CD4 count between 201 - 300 cells / μ L. 83.3 % of subjects with extra pulmonary TB had CD4 count below 200 cells / μ L. Among those patients with both pulmonary and extra pulmonary TB 85.7 % had CD4 count below 200 cells / μ L. The relationship between CD4 count and types of tuberculosis were evaluated by using Pearson chi-square test and the chi-square value 25.3974 was statistically highly significant (P-value < 0.00001). (Table 1)

In our study group (N = 104) sputum smear examination for acid fast bacilli was done in 98 patients (94.2 %), in those patient's sputum, smear for AFB was negative in 59.6 % and positive in 34.6 %. Among those patients who were sputum positive for AFB, 58.3 % had CD4 count > 200 cells / μ L, 41.7 % had CD4 count \leq 200 cells / μ L. In those who were sputum negative for AFB, 71 % had CD4 count \leq 200 cells / μ L and 29 % had CD4 count > 200 cells / μ L. On analysing the relationship between CD4 count and sputum for AFB by using Pearson chi-square test, the chi-square value 8.1615 (P value 0.004) was significant. Thus, there was a significant association between sputum smear negativity and CD4 count \leq 200 cells / μ L. (Table 1)

In our study population, 26 (25 %) had normal chest x-ray, 55 (52.9 %) had atypical presentation and 21 (20.2 %) had typical presentation. Among the 21 patients with typical chest x-ray presentation apical lobe opacity was the commonest (66.6 %), followed by apical lobe cavity (23.8 %) and apical lobe fibro cavity (9.6 %). Among those with atypical chest x-ray presentation lower zone opacity accounted 43.7 %, followed by pleural effusion (16.3 %), multifocal opacity (14.5 %) and hilar adenopathy (10.9 %). Miliary nodules and midzone opacity accounted 5.5 % each. In subjects with typical chest x-ray presentation, 71.4 % had CD4 count > 200 cells / μ L and among those with atypical

chest x-ray presentation, 63.6 % had CD4 count \leq 200 cells / μ L. (Table 1). On statistical analysis the Pearson chi-square value 7.521 (P-value 0.006) was highly significant. This indicates that there was a significant association between atypical chest x-ray presentation and severe immunodeficiency.

In this study, 73.1 % had negative tuberculin skin test and 26.9 % had positive tuberculin skin test. Out of 104 patients, 73.1 % had negative tuberculin skin test and 26.9 % had positive tuberculin skin test. Of those patients (N = 65) with CD4 count \leq 200 cells / μ L, 90.8 % had negative tuberculin skin test and among the patients (N = 39) with CD4 count > 200 cells / μ L, 56.4 % had positive tuberculin skin test (Table 1). The association between CD4 count and tuberculin skin test was evaluated by using Pearson chi-square test and the value 27.577 was statistically highly significant (P-value < 0.00001) showing that severe immunodeficiency was associated with negative tuberculin test.

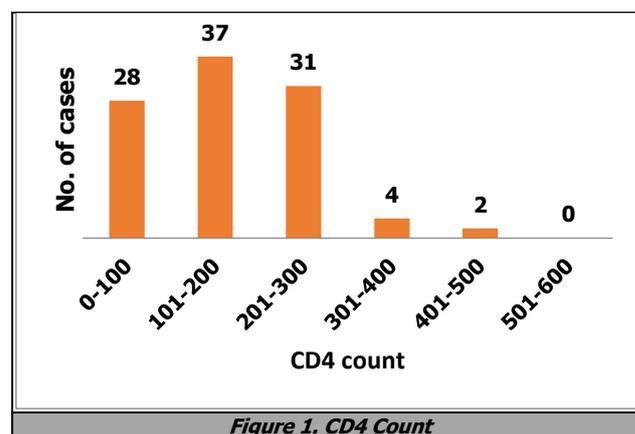


Figure 1. CD4 Count

Variables	CD4 Count (cells / μ L)		χ^2 -Value (P-Value)	
	\leq 200 N (%)	> 200 N (%)		
Diagnosis	Pulmonary TB	17 (16.35 %)	30 (28.85%)	25.3974 (P < 0.00001)*
	Extra-pulmonary TB	30 (28.85 %)	6 (5.7 %)	
Sputum smear	Pulmonary + extra-pulmonary TB	18 (2.9 %)	3 (17.3 %)	8.1615 (P = 0.004)*
	Positive	15 (15.3 %)	21 (21.4 %)	
CXR presentation	Negative	44 (44.9 %)	18 (18.37 %)	7.5212 (P = 0.006)*
	Typical	6 (7.9 %)	15 (19.7 %)	
Tuberculin skin test	Atypical	35 (46.05 %)	20 (26.3 %)	27.577 (P < 0.00001)*
	< 5 mm (negative)	59 (56.7 %)	17 (16.35 %)	
	\geq 5 mm (positive)	6 (5.7 %)	22 (21.15 %)	

Table 1. Association between CD4 Count and Type of Tuberculosis, Sputum Smear, Chest X-Ray and Tuberculin Skin Test

*indicates statistically significant association

DISCUSSION

The demographic profile of our study was similar to previous studies done in India.^{5,6} The most common clinical presentation in our study was weight loss followed by fever and cough, which was similar to the observations in previous studies.^{7,8}

Out of 104 patients, pulmonary tuberculosis was diagnosed in 47 cases (45.2 %) and 36 cases (34.6 %) had

extra pulmonary tuberculosis. Among subjects with extra pulmonary TB, lymphadenopathy (27.8 %) was the commonest presentation, closely followed by TB meningitis 22.2 %. Rajasekaran S⁹ et al. and Janak K. Maniar¹⁰ et al. observed a similar pattern with TB lymphadenopathy being the commonest presentation of extrapulmonary TB.

We found that patients with pulmonary TB had mean CD4 count 237.7 cells / μ L and patients with extra pulmonary TB had mean CD4 count about 135.2 cells / μ L. We found a strong correlation between occurrence of extra pulmonary TB and profound immunosuppression (CD4 count < 200 cells / μ L). This was in accordance with previous studies done by various authors.^{11,12} Thus, patients with relatively intact immune function (CD4 count > 200 cells / μ L), pulmonary TB is more frequently seen than extra pulmonary TB and as immunosuppression progresses, extra pulmonary TB becomes increasingly common.

On analysing the mean CD4 count in pulmonary TB we found subjects with sputum positive PT (294.2 cells / μ L) had higher count than those with sputum negative PT (168.3 cells / μ L) and MDR-TB (90.8 cells / μ L). On statistically analysing, we found an association between sputum smear negativity and CD4 count \leq 200 cells / μ L (P-value 0.041). S.K Verma¹³ et al. quoted that the sputum negativity tends to increase as the HIV disease and immuno-suppression progresses. Mugusi et al.¹⁴ quoted that AFB density falls with falling CD4 count and sputum AFB smear is less sensitive in severe immunosuppression. Similar findings have been observed in other previous studies.^{15,16,17}

In this study among patients with typical chest x-ray presentation, 71.4 % had CD4 count > 200 cells / μ L and among those with atypical chest x-ray presentation, 63.6 % had CD4 count \leq 200 cells / μ L. On statistically analysing our data the P-value 0.006 was highly significant. Thus, there is a significant association between atypical presentation and severe immunodeficiency. Rajendra Prasad, et al.¹⁸ observed a wide spectrum of radiographic shadows with varying CD4 count. Padyana et al.¹⁹ concluded that noncavitary infiltration and consolidation predominated when CD4 count was below 200. A high index of suspicion is necessary for accurate and timely diagnosis of tuberculosis in HIV positive patients.

A large population study in 8078 TB and HIV co-infected patients by Janak K. Maniar¹⁰ et al. found that 60.9 % had negative tuberculin skin test and 39.1 % were positive for tuberculin skin test. Belete Tegbaru²⁰ et al. found in his study that tuberculin skin reactivity was higher (62.8 %) in those with absolute CD4 counts of \geq 200 cells / μ L whereas negativity was higher (72.4 %) in those with CD4 count < 200 cells / μ L. In this study also we found a strong association between CD4 count \leq 200 cells / μ L and negative tuberculin skin test (P-value 0.001).

CONCLUSIONS

In HIV and TB co-infected individuals, extra pulmonary and combined form (pulmonary + extra pulmonary) of tuberculosis are common, especially at lower CD4 counts.

Tuberculin skin test is more likely to be positive when the CD4 count is more than 200 cells / μ L.

Sputum smear for AFB depends on the degree of immunodeficiency, is positive when CD4 count is higher. Atypical chest x-ray presentations are common among HIV and TB co-infected patients at lower CD counts.

The diagnosis of tuberculosis in HIV co-infected patients is complex, and therefore a thorough knowledge of the spectrum of disease manifestations and a high index of suspicion is needed.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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