Clinical Profile of Pulmonary Tuberculosis in Patients with HIV Infection

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Abstracts: **Background**: Tuberculosis is the commonest opportunistic infection and commonest cause of death in HIV/AIDS patients in India. Objective: To study the clinical, radiological and immunological profile of pulmonary tuberculosis in HIV infected patients. Methods: We conducted a retrospective study of 60 patients of pulmonary tuberculosis in patients with Human immunodeficiency virus positive. The diagnosis of tuberculosis was based on clinical evaluation, bacteriological examination including sputum smear and culture, tuberculin skin test and chest radiograph. CD4+ T cell counts were done on all patients. Results: Commonest risk factor for HIV transmission was sexual exposure in 47 cases (78%).35 cases (58.33%) had CD4+ T cell count <200/mm3, 25 cases (41.67%) had CD4+ T cell >200. constitutional symptoms (91.66%)like weight loss, anorexia, fatigue, night sweats are more common than classical symptoms of pulmonary TB like chest pain (66.66%) ,cough with/without expectoration (58.33%), dyspnoea (61.66%), fever (75%) and haemoptysis (8.33%). Most common opportunistic infection was oral/esophageal candidiasis (22%).35% of pstients had typical pattern and 65% had atypical pattern of pulmonary TB on chest radiograph. 80% of patients with CD4+ T cell count <200/mm3 had atypical pattern. In pulmonary tuberculosis sputum smear for AFB was positive in 20% cases & negative in 80% cases. Majority of the patients with positive sputum smear had CD4+T cell count >200/mm3. MDR-TB was documented in 9 (12%) of patients. 4 cases have CD4+ count <200and 5 cases have CD4+count >200. total mortality was 10% among 60 patients. Conclusion: Tuberculosis infection in patients with HIV is more common in second & third decade of life more common in males. Atypical features are more common than typical features in HIV-TB patients. Negative/anergic TST is more common in patients of HIV-TB co infection due to compromised CMI. Disseminated and multifocal lesions were more common in severe degree of immune compromise (CD4+ <200), whereas cavitory lesion and unifocal opacities were relatively more common in patients having CD4+ >200. Sputum AFB negative pulmonary TB is more if CD4 <200 [Suthar R et al NJIRM 2012; 3(3) : 68-74]

Key words: pulmonary tuberculosis, HIV infection, Clinical profile of TB/HIV patients,CD4 count

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Introduction: Tuberculosis is a common and often deadly infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. HIV infection has increased the burden of tuberculosis, especially in populations where HIV has become common, and where the prevalence of tuberculosis infection is high

Tuberculosis is one of the commonest opportunistic infection in cases of HIV infection and may precede the development of AIDS. There is an increased risk of progression of TB infection to disease in presence of HIV infection.[1-4] The higher risk of Tuberculosis in these patients is due to depressed cell mediated immunity and the risk increases by 100 times in endemic areas in patients with old infected foci.[5]

HIV and Tuberculosis have an ominous connection because of the rapidity with which the Mycobacterium Tuberculosis proliferates and disseminates in HIV. Tuberculosis is a major cause of death in HIV infected persons particularly in developing nations, with this most prominent in Sub-Saharan Africa, the Pacific Rim Nations and Indo-Asia.[6] It is estimated that in developing countries, about half of people living with HIV infection will develop active Tuberculosis.[5] One third of increase in TB cases over the last 5 years can be attributed to HIV epidemic.

HIV infected individuals co-infected with TB have an annual risk of 5-15% of developing active TB. Rates of recurrences both due to endogenous reactivation and exogenous reinfection are increased.[7-9] HIV induces immuno-suppression dramatically increases the number of TB cases, changes the clinical course

of the disease, rendering the disease more difficult to diagnose, more complicated to treat and more chances of emergence of multi-drug resistant TB.[10] Thus HIV/AIDS and TB need to be addressed together and harmonization of a package of care between TB-HIV should be established.

The Major Interactions Between Hiv & Tb Are:

- Progressive depletion and dysfunction of CD4+ cells coupled with defect in the macrophage and monocyhte function paves the way for reactivation of latent Tuberculosis.
- Tuberculosis causes accelerated progress towards immunosupression presumably due to augmentation of HIV replication from cytokines (TNF), which are elaborated as part of the granulomatious immune response in Tuberculosis.
- HIV infected persons are more likely to acquire new TB infection from exposure.
- Immuno compromised patients also become more prone to MDR-TB.

Materials And Methods : A study was carried out on 60 patients. Detailed history was elicited in all cases especially emphasizing on age, sex, marital life, occupation and residential area. History of treatment taken for Tuberculosis in the past was taken. Various risk factors associated with HIV infection such as history of blood transfusion, multiple sexual exposure and history of usage of underutilized needles and syringes, IV drug abuse was also elicited. The socio-economic factors contributing to the disease were also taken into consideration. Any past history of anti-retroviral therapy was also asked. Detailed general and physical examination was done in all cases. All routine laboratory investigations, specific investigations for HIV-TB co-infected patients like

- CD4+/CD8+ T cell counts.
- Tuberculin skin test.
- Chest radiograph.
- Sputum smear examination for AFB and sputum culture & sensitivity.
- BAL fluid/Tran bronchial lung biopsy specimen examination for AFB.
- Pleural fluid examination for AFB.

Test for HIV by ELISA and confirmed by standard Western blot analysis were carried out in all the cases.

All chest radiographs were evaluated and the patients selected were assigned into one of the 2 groups: Those with findings of characteristics of post-primary TB (Typical Pattern) or those with findings characteristic of Primary TB (Atypical pattern).

The Atypical pattern included those subjects with lower and middle lobe opacities, anterior segment upper lobe opacities, mediastinal or hilar adenopathy, pleural effusions, diffuse opacities, interstitial nodules or infiltrates, miliary nodules or a normal chest radiograph.

The Typical pattern (post primary pulmonary TB) included upper lobe opacities in the apical or posterior segments with or without cavitation. Special note was made of subjects with reactivation upper lobe disease and a pattern of subsequent less extensive dissemination of Pulmonary TB in middle and lower zone.

Result: 47 cases (78%) were in age group of 20-45 years. The youngest is 21 years and oldest is 74 years. Mean age of presentation was 36.2 +/- 2.3 years.

49 cases (82%) were males and 11 cases (18%) were females, with a Male: Female ratio of 4:1. This suggests that males are commonly affected in HIV with TB than females.

Commonest risk factor for HIV transmission was sexual exposure in 47 cases (78%), mostly by heterosexual route of transmission. Blood transfusion was 12% and intravenous drug abuse in 5% for HIV transmission. In about 5%, the cause of HIV transmission could not be determined.

As far as pulmonary TB is concerned, 35 cases (58.33%) had CD4+ T cell count <200/mm3, 25 cases (41.67%) had CD4+ T cell >200. When immunity in HIV decreases, chances of TB increases.

Clinical features of pulmonary TB included chest pain in 40 cases (66.66%) ,cough with/without expectoration in 35 cases (58.33%), dyspnoea in 27 cases (61.66%), fever in 45 cases (75%) and haemoptysis in 5 cases (8.33%). 55 cases (91.66%) had constitutional symptoms like weight loss, anorexia, fatigue, night sweats etc. Thus atypical features are more common than typical features in HIV-TB patients.

Most common opportunistic infection was oral/esophageal candidiasis (22%) in HIV-TB co infected patents.

Radiologically, pulmonary TB divided in 2 parts, atypical and typical. Atypical pattern of pulmonary TB included those cases with lower & middle lobe opacities, anterior segment upper lobe opacities, mediastinal or hilar adenopathy, pleural effusions, diffuse opacities, interstitial infiltrates or nodules, military nodules.22 Typical pattern of pulmonary TB included those subjects with upper lobe opacities in the apical or posterior segments with or without cavitation.22 21 cases (35%) had typical pattern and 39 cases (65%) had atypical pattern of pulmonary TB on chest radiograph.

30 cases (80%) with CD4+ T cell count <200/mm3 had atypical pattern, whereas rest 5 cases (13.52%) had typical pattern of pulmonary TB on chest radiographs. Most common atypical presentation when CD4+ <200 was multifocal (disseminated) opacities (32%). 16 cases (69.57%) with CD4+T cell count >200/mm3 had typical pattern, whereas rest 7 cases (30.43%) had atypical pattern of pulmonary TB on chest radiographs. Most common chest radiographic appearance seen in patients with CD4+T cell count >200/mm3 is unifocal alveolar opacity most commonly in upper lobe with cavity formation in 11 cases (47.82%).

TST reaction was positive in only 20% cases (12 subjects) & negative / anergic in rest 80% (48 cases). Among 80% cases TST reaction was negative in 38.33% (23 cases) & Anergic in 41.66% (25 cases), that was in most number of cases.

Anergy to TST was seen in all 25 cases (41.66%) with CD4+T cell count <200/mm3. No anergy to TST was seen with patients having CD4+T cell count >200/mm3 but 15 cases (25%) had negative TST reaction.

In pulmonary tuberculosis sputum smear for AFB was positive in 12 cases (20%) & negative in 48 cases (80%). 8 cases (13.33%) with CD4+T cell count >200/mm3 had positive sputum smear for AFB as compared to 4 cases (6.66%) with CD4+ cell count <200/mm3. Majority of the patients with positive sputum smear had CD4+T cell count >200/mm3.

MDR-TB(i.e. TB resistant to at least Isoniazid & Rifampicin with or without resistance to other first line anti-tuberculosis drugs as documented by sputum culture and drug susceptibility testing, which were done in the patients who were to be suspected from clinical history who didn't respond to AKT by the end of 2 months.) was documented in 9 cases (15%) among 60 patients (100%). 5 cases(56% cases of MDR) have CD4+ count <200and 4 cases(44% cases of MDR) have CD4+count >200.While 85% of patients have non-MDR TB. Total mortality was 10% among 60 patients.

Discussion: In present study maximum age group was 20-45 yrs (78%). Present study comparable with S K Agarwal & Aman Makhija et al[11] (20-45 yrs) , Pratima Gupta et al[12] (20 – 45 yrs). This concludes that Pulmonary TB in HIV sero positive patients is more common in the second and third decades of life.

In the present study 82% of the subjects were males and 18% were females, which showed a male dominance with a male: female ratio of 4:1. Study by Gupta-Jayaram et al[13] showed 83% subjects were male & the Anupam Prakash et al[11] study, which included subjects co-infected with TB -HIV showed that 77.52% were males. Thus there is a higher prevalence of TB with HIV in males than female. Commonest profession in males was drivers

In the present study, sexual exposure was the commonest risk factor for HIV transmission in 78.0% cases, mostly by heterosexual route of transmission. This was comparable to Rajsekaran-Mahimaran[14] in which 79% cases had sexual route of transmission in HIV.

Studies showing Distribution of pulmonary TB

in relation to CD4$^+$ count

Study	<200	>200
Anupam Prakash et al [11]	59%	41%
Pratima Gupta et al [12]	53.40%	46.60%
S. Rajsekaran & A. Mahilmaran [13]	62%	38%
Present study	57.5%	42.5%

Our study compare with other studies mentioned above, it was found that our findings were consistent. It is sure that once CD4+ count goes down, chances of pulmonary TB increases.

In study by Anupam Prakash et al[11] patient having pulmonary TB with HIV had constitution symptoms are (84%) compared to typical cough with or without expectoration (50.4%) & hemoptysis (5%). In study by S K Agarwal et al[11] has cough in 57.32% of patients and constitutional symptoms are in 82.3% of patients. This is comparable with our study. Cough & Haemoptysis were seen in lower number of cases than expected possibly because of weak cough reflex due to debilitated conditions of patients with AIDS , absence of cavitation & predominantly interstitial/military lesions which do not communicate with bronchi, so less end bronchial irritation. Thus classical clinical presentation of pulmonary TB was relatively less common in HIV sero positive cases & co-related more with chest radiographic features.

Opportunistic infections in HIV-PULMONARY TB patients are common when CD4+ count decreases. This was comparable with Pratima Gupta et al.[12]

Comparative studies showing Chest radiographic findings of pulmonary TB in HIV sero positive patients in relation of CD4$^+$ T counts

Study	CD4+ count	Unifocal alveolar opacity	Cavitory lesions	Middle & lower zone opacities	Disseminated
S.K.Sharma et al [11]	<200	30%	10%	3%	40%
	>200	58%	40%	30%	18%
B.S.Deswal et al [14]	<200	27%	13%	4.4%	33%
	>200	60.2%	30.4%	18.4%	8%
V S S Attili et al [15]	<200	46%	6%	7%	26%
	>200	70%	10%	2%	8%
S. Swaminathan et al [16]	<200	41%	12%	7%	41%
	>200	48%	42%	36%	18%
Present Study	<200	35%	8%	5%	35%
	>200	47.82%	47.82%	39.13%	30.43%

In our study most common radiological finding at any CD4+ >200 count was unifocal alveolar opacities (47.82-70%) ,which is the most common feature of PTB in non HIV patients but chances were going to be decreased when CD4+ counts decreases. With CD4+ <200, unifocal alveolar opacities was less common (27-46%).Thus in our study unifocal alveolar opacities on chest radiograph was 47.82% when CD4+ is >200 but

when CD4+ <200 it was 35%. Above table shows that disseminated and multifocal lesions were more common in severe degree of immune compromise (CD4+ <200), whereas cavitory lesion and unifocal opacities were relatively more common in patients having CD4+ >200.This was almost similar to other study mentioned in table

Comparative studies showing Categorization of cases based on chest radiographic appearance in relation to CD4$^+$ T cell counts.

Study	CD4+ count	Typical pattern	Atypical Pattern
S.K.Sharma et al [11]	<200	11%	31%
	>200	45.4%	13.6%
B.S.Deswal et al [14]	<200	17.2%	33.2%
	>200	36.21%	14.32%
V S S Attili et al [15]	<200	7%	50%
	>200	27%	16%
S. Swaminathan et al [16]	<200	13%	37%
	>200	32%	18%
Present Study	<200	9.1%	39.4%
	>200	30.3%	21.2%

Present study comparable with other studies mention above. It clearly shows that once CD4+ <200, atypical pattern predominates.

Thus the group into typical and atypical chest radiographic pattern of pulmonary TB is clinically useful. 200 CD4+ T cell count is a logical cut off between these subjects who may respond in a typical versus an atypical manner to infection by Mycobacterium TB and was in this study to reliably indicate those at risk for atypical radiographic manifestations of Pulmonary TB. i.e., those with CD4+ T cell count <200/mm3. Mean CD4+ T cell counts of subjects presenting with radio graphically atypical pulmonary TB and those with typical post-primary pulmonary TB were significantly different 148/mm3 versus 283/mm3 respectively.

In pulmonary TB, TST reaction was positive in 12 cases (20%) and negative / anergic in 48 cases (80%). Only 4 cases (6.66%) with CD4+T cell count <200/mm3 had positive TST as compared to 8 cases (13.33%) with CD4+T cell count >200/mm3. Thus chances of negative/anergic TST is more common in patients of HIV-TB co infection due to compromised CMI.

In present study shows relationship between Tuberculin skin test reactivity in HIV seropositive Patients of pulmonary TB in relation to CD4+ T cell count. It clearly shows that anergy was the most consistent result (29-51%) of TST in HIV patients having CD4<200, reason being immune compromise. Findings of our study were comparable with other studies. TST is basic test for CMI. It is expected that in HIV, CMI is defective making TST to be negative.

Comparative Studies of Tuberculin skin test reactivity in HIV seropositive patients of pulmonary TB in relation to $CD4^+$ T cell count

Study	CD4 count	TST results (% subjects)	
		Positive	Anergy
Rwanda series [17]	<200	4%	33%
	>200	13%	1%
Keiper & Beumounnet[8]	<200	9%	29%
	>200	17%	0%
S. K. Sharma et al [11]	<200	11%	47%
	>200	20%	5%
Janak Maniar et al [18]	<200	7%	43%
	>200	11%	2%
Present Study	<200	6.66%	41.66%
	>200	13.33%	0%

In our study shows that sputum for AFB was positive in 12 cases (20%) & negative in 48 cases (80%). sputum for AFB was positive in only 4 cases where CD4+ <200, and 8 cases where CD4+ >200. This is due to atypical presentation of pulmonary TB in HIV. In HIV patients as cavitation is less common , sputum production is also less , which ultimately results in sputum negative TB. This view was supported by Pratima Gupta et al[12] (82%sputum negative) ,B. S. Deswal et al[14] (78% sputum negative).

Sensitivity of sputum smear microscopy is lowest in patients with significant immune suppression (CD4+ cell count <200/mm3) and with atypical chest radiographic findings of Pulmonary TB. The rate of sputum smear positivity is higher with CD4+T cell count >200/mm3 and typical chest radiographic findings of Pulmonary TB. Moreover AFB identified on sputum smear microscopy may be atypical Mycobactreria or Mycobacteria other than Mycobacterium TB. Thus, the rate of sputum smear positivity co-relates with CD4+ T cell counts. However radiological findings add positivity to sputum examination. Sputum smear positivity is more common in early HIV than late HIV stage.

15% of the subjects who were HIV seropositive with Pulmonary TB, had sputum culture and drug susceptibility results showing MDR-TB. This was comparable with study by Friedman et al[19] (1996) which had MDR-TB documented in 19% of HIV seropositive patients, Pratima Gupta et al[12](17% MDR-TB). Moreover in the present study, majority of the subjects with MDR-TB had CD4+ cell count <200/mm3 (66.6%) implying that MDR-TB was more common with greater degrees of immunosuppression ,however in above mentioned study this separation with CD4+ count not extensively studied but they mentioned that chances of MDR are more common in CD4+<200. However, MDR-TB in most of HIV infected subjects in the present study was not associated with past history of antituberculous therapy or past history of

TB but with exposure to infectious cases and nosocomial transmission as a result of frequent hospital visits.

In present study shows relationship between CD4+ count and mortality among HIV-TB patients. Total deaths were 11 cases (17%), when CD4+ <200 and 5 cases (14.3%) when CD4+ >200. This proved that when immunity decreases in HIV-TB patients, mortality increases.

Conclusion: Tuberculosis is one of the most common diseases in Indian Subcontinent. With the entry of HIV, co infection of HIV-PULMONARY TB has increased the problem further. The present study was an effort to find out the various relationship between HIV-TB, particulary in those patients with CD4 <200+ and CD4 >200+. Chest radiographs suggestive of tuberculosis and clinical symptoms like fever and cough were uncommon findings in HIV tuberculosis coinfected patients. Negative/anergic TST is more common in patients of HIV-TB co infection due to compromised CMI. Disseminated and multifocal lesions were more common in severe degree of immune compromise (CD4+ <200), whereas cavitory lesion and unifocal opacities were relatively more common in patients having CD4+ >200. Sputum AFB negative pulmonary TB is more if CD4 <200.Every patients having HIV-TB needs special attention as they have atypical features, atypical radiological findings, low incidence of sputum AFB positivity, MDR TB and opportunistic infections. HIV-PULMONARY TB co infection may aggravate both condition as both are intracellular organism and TB co infection increase replication of HIV virus. However all patients with co-infection must be treated as per RNTCP guidelines, except when patients has got toxicity of drugs, interaction of drugs or MDR TB.

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