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ORIGINAL ARTICLE

Spectrum of Tubercular Diseases among HIV Positive Patients and Response to Antitubercular Therapy.

Deepak Jain[1], Nitya Nand[2], Dhiraj Kumar[3]

[1]Professor, [2]Ex. Senior Professor & Head, [3]Resident, Department of Medicine,
Pandit Bhagwat Dayal Sharma University of Health Sciences, Rohtak, Haryana, India

Abstract

Introduction: TB and HIV disease have been inextricably bound together. Infection with M. tuberculosis ranks foremost among opportunistic infections causing comorbidity with HIV infection. This study was planned to look for clinical spectrum of various types of tuberculosis in HIV positive patients, their presentation, relation to CD4 count and response to anti-tubercular therapy.

Material and Method: This prospective study was carried out at the Anti-Retroviral Treatment (ART) centre and indoor patients in Department of General Medicine, Pt. B D Sharma, PGIMS, Rohtak, from March 2016 to August 2016. Individuals diagnosed of any form of tuberculosis was started on Thrice-weekly Rifampicin-based directly observed ATT as per the Indian Revised National TB Control Programme guidelines. Follow up was done for next 6 months.

Results: The study population consisted of 128 patients with a mean age of 35.75 ± 9.83 years. 50% of the population were from 30-45 years age group. There were 94 males and 34 females. 12 patients developed abdominal tuberculosis, 3 had disseminated tuberculosis, 22 had lymph node TB, 23 had sputum negative TB, 41 had sputum positive pulmonary TB, 9 patients developed TB pleural effusion and 18 presented with TB Meningitis. After 6 months of therapy, 75 patients were successfully treated, for 36 patients the treatment had to be extended for durations more than 6 months. 3 patients did not attend the follow up visit and 14 patients expired during the course of study.

Conclusion: Spectrum of tuberculosis in patients with HIV is wide and presentation can be atypical, so all HIV positive patients should be counselled to report any symptoms. It is vital to adequately assess such patients right at the outset, and detect symptoms at an early stage, for holistic and effective management.

Key words: HIV, Tuberculosis, Anti-Tubercular Therapy

Introduction

Acquired immune-deficiency syndrome (AIDS) is a lethal illness caused by a retrovirus known as human immune-deficiency virus (HIV) which breaks down immune system and make person vulnerable to life threatening infections. There were approximately 36.7 million people worldwide living with HIV/AIDS at the end of 2016 [1]. India bears the burden of 2.5 million people infected with HIV. Of these, 40% suffer coinfection with TB [2].

Tuberculosis primarily affects lungs and causes pulmonary tuberculosis. It can also affect intestine, meninges, bones and joints, lymph nodes, skin and other tissue of the body.

Address for Correspondence
Dr. Deepak Jain, Professor, Department of Medicine, Pandit Bhagwat Dayal Sharma University of Health Sciences, Rohtak - 124001, Haryana, India E-Mail: jaindeepakdr@gmail.com

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In 2016, 10.4 million people fell ill with TB, and 1.7 million died which includes 0.4 million among people with HIV [3]. There is wide variation in HIV seropositivity among TB patients in India, ranging from 9.4% to 30% [4]. Person infected with TB have 10% chance of developing tuberculosis in lifetime, while 10% of HIV and TB co-infected person develop disease annually [5]. The significant increase in tuberculosis has occurred in locations with highest HIV prevalence, which indicates that HIV epidemic is responsible for resurgence of TB [6]. While HIV and TB can individually be the major causes for public health threats, the combination of the two has proven to have a far greater impact on the epidemiologic progression and consequently on the global health scene. The dual infection has been termed *"The Cursed Duet"* [7].

Clinical presentation of TB in early stages of HIV infection resembles to that observed in immuno-competent individuals but in later stage, the clinical presentation of TB is atypical. Co-infection with HIV poses challenges in

both diagnosis and treatment of tuberculosis. Diagnosis of tuberculosis in HIV infected patients may be delayed because of atypical presentation, involvement of inaccessible sites and low sputum smear positivity [8]. Also, there has been an increase in rates of drug resistant tuberculosis, like multi-drug (MDR-TB) and extensively drug resistant TB (XDR-TB) in HIV patients, which are difficult to treat and contribute to increased morbidity and mortality.

Many studies has been done in past from various parts of the Globe to assess the burden of co-infection. Most of the Indian work has been done to look for pulmonary manifestation of tuberculosis in HIV. There are very limited data on spectrum of tubercular diseases in HIV from northern India. The study aimed to drawing out the demographic and clinical profile of the dual infection, frequency of different types of newly diagnosed tuberculosis amongst HIV positive patients, their relation to CD4 count and treatment outcome at 6 month of standard DOTS therapy according to RNTCP guidelines.

Material and Methods

This prospective study was carried out at the Anti-Retroviral Treatment (ART) centre and indoor patients in department of General Medicine, Pt. B D Sharma, PGIMS, Rohtak, from March 2016 to August 2016.

A pre-informed consent was obtained from every patient before inclusion in the study. A specific proforma was made for initial clinical assessment of the patients, which included demographic details, presenting complaints, detailed history, general physical examinations, routine investigations and special investigations wherever required.

Study Design

HIV positive Patients of age between 15-60 years and without any previous history of tuberculosis were screened for symptoms suggestive of tuberculosis. Patients with previous history of tuberculosis, ATT intake, or any concomitant disease like DM, hypertension, malignancy or any opportunistic infections and having pre-treatment liver dysfunction were excluded from the study. Standard diagnostic guidelines according to RNTCP were followed to diagnose tuberculosis.

Pulmonary Tuberculosis was diagnosed by:

1. Two sputum sample, either of them positive for AFB was taken as sputum positive tuberculosis.
2. If sputum is negative for AFB and chest x-ray suggestive of tuberculosis but no response to 14 days antibiotic was taken as sputum negative tuberculosis.

Extrapulmonary Tuberculosis:

1. Demonstration of AFB/caseating granuloma in FNAC/excision biopsy of involved organ.
2. Demonstration of AFB in body fluids either by staining or culture.
3. RT-PCR for M. Tuberculosis in appropriate sample.

TB was diagnosed using investigations as indicated and possible. These included Ziehl Neelson smear microscopy followed by Lowenstein Jensen culture of sputum and any body fluids, secretions, tissue or pus. *Mycobacterium tuberculosis* polymerase chain reaction (PCR), histopathological and cytological examination of tissue or fluid, and various imaging modalities. ESR and Tuberculin skin test was performed in all suspected cases.

All patients diagnosed as HIV-TB co-infection during the period of March 2016 to August 2016 were included in the study and they were started on Thrice-weekly Rifampicin-based directly observed ATT as per the Indian Revised National TB Control Programme guidelines [9]. Follow up was done for next 6 months. Blood samples were collected periodically, and was processed for liver function tests, renal functions tests and other investigations as required. Every month follow up was done to see response of treatment, failure and for any toxicity. DOTS treatment was supervised from record every month to see for the compliance.

Extension of ATT was considered in patients who showed clinical and/or radiological signs of disease progression or partial response, or persisting sputum smear positivity at the end of the intensive phase. Rifampicin sensitivity was done in these patients in appropriate samples.

Those who are sensitive to Rifampicin the treatment extensions were of one, two or three months, of either the intensive (1 month) or continuation phase (maximum 3 months). In rifampicin resistant cases therapy was modified.

Statistical Analysis

Data was obtained carefully and master chart was prepared using Microsoft excel 2013. For all descriptive and statistical analysis, statistical package of social sciences (SPSS) version 23 was used. The value of all continuous variables was expressed in mean and standard deviation for each group separately. All categorical variables were expressed in numbers out of total and their respective percentages. A statistical analysis using one way analysis of variance (ANOVA) was run to compare the mean differences in between the groups, and the mean difference of CD4 count. A statistical analysis using independent student T-test was done for CD4 count correlation sputum

AFB positivity. For all tests, p value of less than 0.05 was considered as significant and confidence interval was kept at 95%.

Results

418 HIV positives patients having symptoms suggestive of Tuberculosis were screened and investigated for Tuberculosis. Out of which 128 patients were found to have some form of active Tuberculosis and they were included in the study. The mean age of presentation was 35.75 ± 9.83 years. 50% of the population were from 30-45 years age group. There were 94 males and 34 females. The mean duration for presentation of symptoms was 2.46 ± 1.23 weeks, with a maximum duration of 8 weeks and minimum of 1 week. Table 1 shows categories of tuberculosis in these patients. Fever (99.2%), anorexia (96.9%) and fatigue (95.3%) were the common symptoms and present in majority of the patients regardless of the organ involved, while symptoms like cough (54.7%), haemoptysis (25.8%) and altered sensorium (14.8%) were more specific for organ involved. Clinical presentations are summarised in Table-2. It was also observed that atypical radiological findings like consolidation (17.1%) and infiltration (15.6%) were common on chest skiagram compared to typical cavitation (10.2%). Tuberculin skin test was positive only in 27.3% of the patients. We were able to detect AFB positivity in 52.3% of the patients. Radiological and microbiological characteristics of the patients are summarised in Table-3.

After 6 months of therapy, 75 patients were successfully treated, for 36 patients the treatment had to be extended for durations more than 6 months, 3 patients lost follow up visits and 14 patients expired during the 6 month study duration. In 36 patient's treatment were prolonged because of various reasons. 25 patients showed poor response to therapy. Out of these 25, 19 were drug sensitive so and 6 were diagnosed rifampicin resistant. In 7 patients there was compliance issue and in 4 there was hepatotoxicity. Various outcomes are shown in Table-4 and Table - 5. It was observed that at higher mean CD4 count the common types of tuberculosis like lymph node TB and sputum positive pulmonary TB were more common and at relatively low CD4 count the chances of developing severe disease like disseminated TB and tubercular meningitis were high (P=0.002). The occurrence of different types of tuberculosis with relation to mean CD4 count are shown in Figure 1. On comparing sputum positivity with mean CD4 count it was found that the chances of having sputum negative tuberculosis increases at relatively low CD4 count. The mean CD4 count for occurrence of sputum positive PTB was 324.37 ± 239.11 and sputum negative PTB was 200.65 ± 197.10 and this value was statistically significant with P=0.038. This is depicted in figure-2.

Discussion

India is among the few high burden country for tuberculosis since many decades. But now there is a decline in morbidity as well as mortality related to tuberculosis. The biggest hurdle in Tuberculosis control programme is its co-infection with HIV. Mycobacterium tuberculosis in coordination with HIV enhances the descent of immunological functions and pathogenicity of one another leading to death if left untreated.

In this study, 50% of the patients were married male in age group of 30-45 years. Atypical chest X-Ray findings such as infiltration and consolidation were more common. Pulmonary TB was identified as the most common form followed by lymphadenitis, meningitis, abdominal and pleural effusion. Overall sputum positive pulmonary tuberculosis was found to be the commonest form.

Low grade fever was most common presenting symptoms followed by anorexia, fatigue and weight loss. These were present in almost all types of tuberculosis. Similar results were observed by Gagiya A. etal. where fever (75.71%), weight loss (68.57%) and decrease appetite (65.57%) were predominant symptoms [10]. Fever was

Table-1: Categorywise Distribution of Tuberculosis (n=128)

TB Type	Number of Cases	% of Total
Sputum Positive Pulmonary TB	41	32
Sputum Negative Pulmonary TB	23	18
Lymph Node TB	22	17.3
TB Meningitis	18	14
Abdominal TB	12	9.4
1. Tubercular ascites	8	6.25
2. Intestinal	4	3.13
TB Pleural Effusion	9	7
Disseminated TB	3	2.3

Table -2: Clinical Presentation (n=128)

Presenting Symptoms	Number of cases	% of total
Fever	127	99.2
Cough	70	54.7
Hemoptysis	33	25.8
Anorexia	124	96.9
Weight Loss	92	71.9
Fatigue	122	95.3
Altered Sensorium	19	14.8
Headache	18	14.1
Vomiting	30	23.4
Pain Abdomen	16	12.5
Abdominal Distension	8	6.3

Table-3: Radiological and Microbiological Characteristics of the Patients (n=128)

	Number of Cases	% of Total
Chest X-Ray		
● Normal	52	40.6
● Consolidation	22	17.1
● Infiltration	20	15.6
● Miliary	9	7.0
● Pleural Effusion	9	7.0
● Cavitation (bilateral/unilateral)	13 (5/8)	10.2(3.9/6.25)
● Fibrosis	3	2.3
Mediastinal lymphadenopathy		
● Present	34	26.5
● Absent	94	73.5
Tuberculin Skin Test	35	27.3
AFB positive	67	52.3
Caseating Granulomas of lymph nodes	24	18.8
TB-PCR	13	10.2

Table-4: Overall Outcomes (n=128)

Outcome	Number of cases	% of total
Treated	75	58.6
Lost to follow up	3	2.3
Extended treatment	36	28.1
Expired	14	10.9

Table - 5: Outcomes in different types of tuberculosis

	Treated	Extended	Lost Follow up	Expired
Abdominal TB	7	5	0	0
Disseminated TB	0	2	0	1
Lymph Node TB	13	9	0	0
Sputum Positive Pulmonary TB	23	12	1	5
Sputum Negative Pulmonary TB	19	3	1	0
TB Pleural Effusion	7	1	1	0
TB Meningitis	6	4	0	8

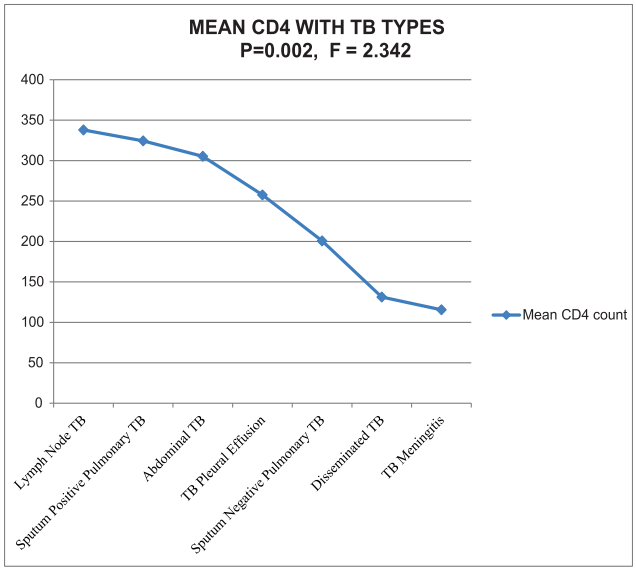

Figure 1: Relation of TB Types with Mean CD4 Counts

present in100 % of the cases in a study from south India [11]. Sputum positive tuberculosis was the commonest form of pulmonary tuberculosis and Lymph node tuberculosis was the commonest form of extrapulmonary tuberculosis. Chandra N. et. al observed Pulmonary TB in 67.66 % and extra pulmonary TB in 32.33% of the cases [12]. In Ethiopia it was found that out of 1153 co-infected patients, the proportions of smear positive pulmonary TB, smear negative pulmonary TB, isolated extrapulmonary TB and disseminated TB cases were found to be 29.6%, 22.2%, 43.9% and 2.9%, respectively. TB lymphadenitis accounted for about 61% of the extrapulmonary cases [13]. Various other studies also reported the similar results [14,15].

CD4 count had positive correlation with sputum AFB positivity (P=0.038). The cavity formation and sputum smear positivity decreases with increasing level of immunosuppression which is characterised by decrease in CD4 count. Acid-fast smear positivity to negativity was almost 1:1 in CD4 count between 0-200 whereas it was 3:1 in cases of CD4 count above 200 [16]. Grades of sputum smear also decreases as the CD4 counts decreases but the relation was found to be nonlinear [17]. It was also observed that the more severe and disseminated forms of TB occurred at relatively low CD4 count and this value was also statistically significant. It is evident that as the CD4 counts decreases, the incidence of sputum negative PTB increases. Therefore, it can be inferred that clinical manifestation of TB in HIV-infected patients is variable and shows different patterns with high or low CD4 count values. In patient with relatively high CD4 count, the typical form of pulmonary reactivation occurs, while in patients with lower CD4 count atypical types like sputum negative tuberculosis, tubercular meningitis and disseminated disease are more common. Giri PA et. al. Observed that Low CD4 count (< 50/µl) had statistically significant association with HIV/TB co-

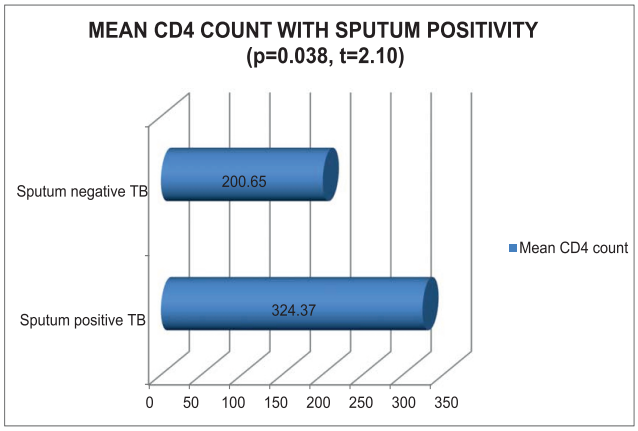

Figure 2: Relation of Mean CD4 Count with Sputum Positivity

infection as compared to HIV infection only (p < 0.0001) [18]. Davoudi S. et. al. reported that patients with more severe and lethal forms of tuberculosis had lowest number of CD4 count [19].

In this study, 58.6% of the patients were cured at the end of 6 month while 10.9% have died. In two similar studies treatment success rates of 60.3% & 61% and death rate of 15.5% & 19.5% was observed respectively [20,21]. Most deaths have occurred in TB meningitis patients and patients who were having severe disease at time of presentation. Deaths had occurred mostly in severe forms, which was also associated with low CD4 count and higher degree of immunosuppression. These patients had poor general condition at time of presentation. Exact cause of death cannot be ascertained in these patients as there could be other opportunistic infection at presentation or may have acquired later during the follow up.

Out of 36 patients who required extended treatment, 19 patients showed poor response but were sensitive to drugs so therapy period was extended according to study protocol by increasing the duration of both intensive and maintenance phase. Mean CD4 count was low, level of immunosuppression was high and compliance to ART was poor in the patients who required extended treatment, compared to those who were successfully treated. Compliance to ART is associated with better TB treatment outcome because it increases the CD4 count and boosts the immune system. Patients compliant to ATT but non-compliant to ART may have poorer TB treatment outcome compared to those who are compliant to both. Poor compliance, Poor response to ATT and associated other complication related to HIV may be attributed to the extension of treatment.

Limitations of the study

As old tuberculosis was not taken in the study so exact prevalence of co-infection and chances of developing tuberculosis in already treated patients cannot be

determined. Also, the comparison with HIV negative groups were not done, so the difference between spectrum of disease and outcomes cannot be compared with general population. We were not able to follow up the drug resistant cases and there treatment outcomes because the study period was short.

Conclusion

From this study we infer that the most commonly sexually active age group are affected in their productive years of life. Spectrum of tuberculosis in patients with HIV is wide and presentation can be atypical, so all HIV positive patients should be counselled to report any symptoms. Also, symptoms varies with the stage of disease and has serious outcomes. Hence, it is vital to adequately assess such patients right at the outset, and detect symptoms at an early stage, for holistic and effective management.

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