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EXTRA-PULMONARY MANIFESTATIONS OF TUBERCULOSIS AMONG HIV PATIENTS-A CLINICAL STUDY

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ABSTRACT

BACKGROUND

Compared to pneumocystis pneumonia, which is more common in western nations, tuberculosis is the most common opportunistic illness in India. The incidence of tuberculosis is thought to be higher in the HIV population than in the non-HIV population. According to WHO estimations, the incidence of tuberculosis is 16–27 times higher in the HIV population than in the non-HIV population. Despite being contacted by inhaling infected droplets, tuberculosis can cause illness in every organ system apart from the lungs, which are typically the location of the first infection. The number of EPTB (Extra Pulmonary Tuberculosis) cases that have been documented has increased along with awareness of the burden of TB. With a focus on extra pulmonary symptoms, this study sought to describe clinical, demographic, epidemiological, and analytical data related to tuberculosis in HIV patients.

MATERIALD AND METHODS

This was a prospective observational study carried out on 50 patients above the age of 12 years infected with HIV-Tuberculosis presenting to the Department of Tuberculosis and Chest at a tertiary care center over a period of 2 years.

RESULTS

HIV-TB was more common between 21 years and 50 years, with a majority being males (68%). 54% had their CD4 levels in the range of 100-200/mm3. The mean CD4 was 178.6. A majority of (62%) patients had extra pulmonary tuberculosis. Cervical lymphadenopathy was the most common extrapulmonary site of involvement, which was present in 35.29% of patients. Followed by disseminated tuberculosis, which was present in 26.47% of patients.

CONCLUSION

TB has the ability to infect many organs, resulting in extra pulmonary manifestations in a majority of patients with HIV. There is a need for early diagnosis and treatment in this subset of vulnerable patients.

KEY WORDS: HIV, Tuberculosis, Extrapulmonary.

INTRODUCTION

The global co-occurrence of the TB (Tuberculosis) and HIV-1 infection epidemics poses a significant public health problem. The primary known risk factor for tuberculosis development is HIV infection (TB). Control of tuberculosis requires cellular immunity, which is dependent on CD4+ and CD8+ cell activation. Through both fresh infection and the reactivation of a latent infection, the following decrease of CD4+ cells directly leads to the increased risk for tuberculosis. In addition, tuberculosis speeds up the course of acquired immunodeficiency syndrome, which raises the risk of death from other opportunistic diseases.[1]

The two diseases that cause the greatest burden of infectious diseases in nations with limited resources, like ours, are tuberculosis and HIV/AIDS. HIV and M. tuberculosis both intensify one another in the particular host, hastening the decline of immune system capabilities. The most significant risk factor for acquiring active TB in high-burden settings is HIV coinfection, which significantly raises the risk of TB reactivation for patients with latent TB and increases vulnerability to primary infection or reinfection. The immunological response to HIV is negatively impacted by M. tuberculosis infection, hastening the transition from HIV infection to AIDS. The integration of efficient anti-TB treatment, concurrent ART (Antiretroviral Therapy), prevention of HIV-related comorbidities, management of drug cytotoxicity, and prevention/treatment of IRIS (Immune Reconstitution Inflammatory Syndrome) are all part of the clinical management of HIV-associated tuberculosis.

Compared to pneumocystis pneumonia, which is more common in western nations, tuberculosis is the most common opportunistic illness in India.[2] The incidence of tuberculosis is thought to be higher in the HIV population than in the non-HIV population. According to WHO estimations, the incidence of tuberculosis is 16–27 times higher in the HIV population than in the non-HIV population.[3] Despite being contacted by inhaling infected droplets, tuberculosis can cause illness in every organ system apart from the lungs, which are typically the location of the first infection. EPTB has become more common as a result of increased knowledge of the disease's impact. The incidence of EPTB varies from 15 to 50%, depending on the area, ethnic group, and rates of HIV coinfection.[4]

With a focus on extrapulmonary symptoms, this study sought to describe clinical, demographic, epidemiological, and analytical data related to tuberculosis in HIV patients.

MATERIALS AND METHODS

This was a prospective observational study carried out on 50 patients above the age of 12 years infected with HIV-tuberculosis presenting to the Department of Tuberculosis and Chest at a tertiary care center over a period of 2 years. Details pertaining to the study, including demographic data, presence of comorbidities, history of anitubercular treatment received, disease and ART status, CD4 levels, and site of involvement, were recorded. Data collected were presented as mean, median, and percentages.

RESULTS

In the present study, it was observed that HIV-TB was more common between 21 and 50 years of age (88%). It was less common in less than 20 and more than 50 years of age. The mean age in all patients was 36.15 years. In the present study, it was observed that HIV-TB was more common among males (68%). The male:female ratio was 2.12:1 (Table 1).

Age (in years)	No. of Patients	Percentage (%)
13-20	3	6
21-30	11	22
31-40	20	40
41-50	13	26
51-60	3	6
Total	50	100

Table 1: Age Distribution

27 (54%) of patients were residing in rural areas, and 23 (46%) patients were residing in urban areas. 7(14%) patients were having co-morbidities, of which 4(8%) patients had diabetes mellitus and 3 (6%) patients had hypertension. 15 (30%) patients had a past history of anti-tuberculosis treatment. 32 (64%) patients were already diagnosed with HIV. Remaining 18 (36%) patients were newly diagnosed.

32 (64%) patients were already on ART. In the remaining 18 (36%), ART was yet to be started since those patients were recently diagnosed HIV patients.

27 (54%) had their CD4 levels in the range of 100-200/mm3. The mean CD4 was 178.6 and the median CD4 was 144. Mean CD4 among pulmonary TB patients was 176.89 and among extra pulmonary TB patients was 179.64, as shown in Table 2 and Figure 1.

CD4 Levels (/mm3)	No. of Patients	Percentage (%)
10-100	11	22
101-200	27	54
201-300	7	14
301-400	2	4
401-500	1	2
>500	2	4
Total	50	100

Table 2: CD4 Levels

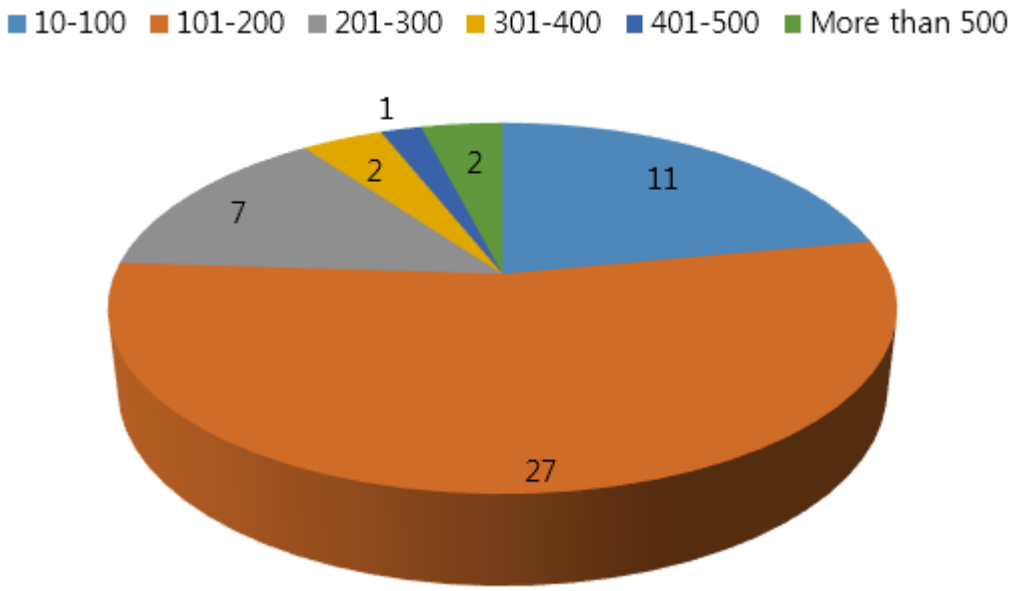

Figure 1. CD4 Levels (/mm3)

19 (38%) of patients had only pulmonary tuberculosis, of which 15 (30%) patients had sputum-positive pulmonary tuberculosis. 1 (2%) patient had sputum negative pulmonary tuberculosis, and 3 (6%) patients had sputum positive pulmonary tuberculosis with extrapulmonary involvement. A majority of 31 (62%) patients had extra-pulmonary tuberculosis.

Cervical lymphadenopathy was the most common extrapulmonary site of involvement, which was present in 35.29% of patients. Followed by disseminated tuberculosis, which was present in 26.47% of patients. Out of nine disseminated tuberculosis patients, three patients had pulmonary tuberculosis along with extrapulmonary involvement. The remaining six patients had only extrapulmonary tuberculosis involving multiple sites. Abdominal tuberculosis and Koch's pleural effusion were present in 14.7% of patients. Axillary lymphadenopathy and tubercular meningitis were present in 2.94% and 5.88% of patients, respectively.

Site	No. of Patients	Percentage (%)
Disseminated Tuberculosis	9	26.47
Abdominal Tuberculosis	5	14.7
KOCH'S Pleural Effusion	5	14.7
Cervical Lymphadenopathy	12	35.29
Axillary Lymphadenopathy	1	2.94
Tubercular Meningitis	2	5.88
Total	34	100

Table 3: Distibution of Extra Pulmonary Tuberculosis

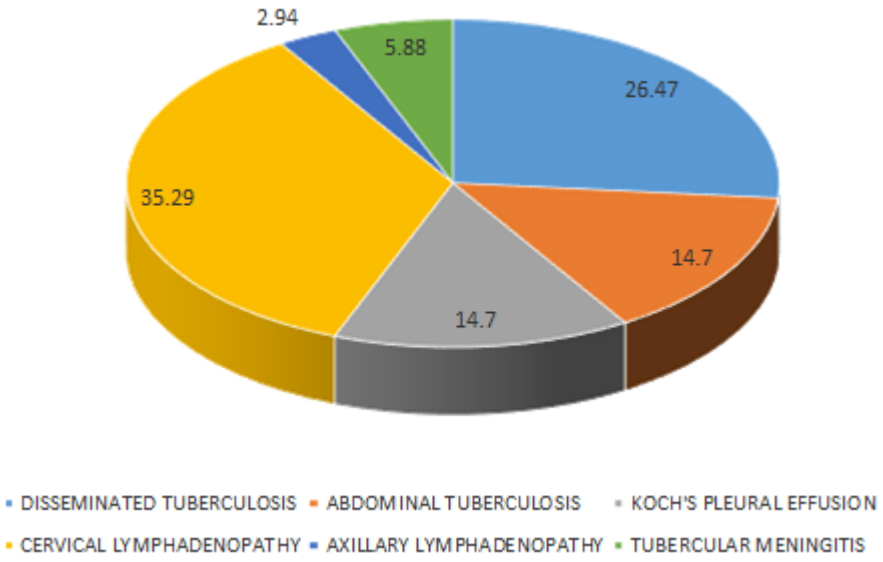

Figure 2: Extra Pulmonary Tuberculosis

DISCUSSION

In the present study, 31 (62%) of patients were of age between 21 and 40 years. Similar findings were observed in a study conducted by Anand K. Patel et al.[5] (76%). The mean age of presentation was 36.15 in the present study. A similar finding was seen in the study conducted by Giselle et al.[6] in which the mean age was 36.4. In the present study, 34 (68%) were male and 16 (32%) were female patients. Similar results were found in a study by Ramachandra Kamath et al.[7] where 24.7% of the participants were women and 75.3% of the participants were men. Fifty confirmed cases of HIV and probable TB infection were included in the Bhanoth et al. study.[8] The bulk of them were men. There were twelve (24%) females and 38 (76%) men. In the present study, more patients were residing in rural areas (54%), which was similar to the observation by Ramachandra Kamath et al.[7] in which 88.2% of patients were residents of rural areas.

19 (38%) of patients in our study had only pulmonary tuberculosis, of which 15 (30%) patients had sputum positive pulmonary tuberculosis. 1 (2%) patient had sputum-negative pulmonary tuberculosis, and 3 (6%) patients had sputum-positive pulmonary tuberculosis with extrapulmonary involvement. A majority of 31 (62%) patients had extra pulmonary tuberculosis. With respect to the confirmation of EPTB, the fact that they have a lower frequency of sputum smear positivity makes the diagnosis more challenging. Similar to past evaluations,[9,10] a recent systematic analysis that examined 25 trials revealed that the estimates of sensitivity (ranging from 0 to 100%) and specificity (ranging from 59 to 100%) for total EPTB offered by commercial serological tests were imprecise and erroneous.[11] The mean sensitivity for pleural EPTB and lymph node was 46% (range 29–63%) and 64% (range 28–92%), respectively. Misdiagnosis of EPTB is widespread worldwide and can consequently lead to increased morbidity and death if the diagnosis is overlooked, particularly in individuals with HIV. Alternatively, it can lead to wasteful therapy if the diagnosis is made incorrectly.[10]

The predominant characteristic of immunosuppression in people with AIDS is the noticeable decrease of CD4+ T lymphocytes in the blood, lymphoid tissues, and mucosa. This undoubtedly plays a significant role in the elevated risk of developing active tuberculosis.[12] Nevertheless, TB susceptibility rises quickly following HIV infection, far before CD4+ T-cell numbers fall to less than 500 cells/μL.[13] demonstrating unequivocally that mechanisms other than the CD4+ T-cell decline account for HIV-infected people's heightened vulnerability to active TB. The mean CD4 count in this study was 178.6. Similar results were observed in the studies of A. Shobana et al.,[14] Kamana NK et al.,[15] and Pradeep et al.[16] where the mean CD4 was, respectively, 212, 152, and 291.6. In this study, the median CD4 was 144. Similar results were seen in the research project carried out by Sten Skogmar et al.[17]

The majority of patients with HIV-TB co-infections in the Bhanoth et al. 8 study had CD4 levels of fewer than 500 cells/μl. Typically, HIV patients with a very low CD 4 count (less than 300 cells/μl) experience toxoplasmosis or cryptococcal meningitis; nevertheless, tuberculosis can occur throughout a wide range of CD 4 levels.

More individuals (38%) in our study had an ESR between 41 and 60 mm/1 hour. Comparable results were observed in the Pradeep et al.[16] 17% trial. In both studies, most of the patients had their ESR levels in the range of 21-80mm/1st hour 32 (64%) patients were already on ART. In the remaining 18 (36%), ART was yet to be started since those patients were recently diagnosed HIV patients. In the study population, Suresh Shastri et al. reported that one-third of the women had co-infections with both HIV and tuberculosis;[18] 78% of patients had their ART started. Compared to patients on ART (80%), treatment success was significantly lower (54%) for co-infected patients who were not on it; the non-ART group also had greater risks of death and default.

Due to the aerobic nature of M. tuberculosis, which grows best in tissues with high oxygen content, the majority of adult TB is preferentially limited to the lungs; however, in HIV-positive patients, TB can be a systemic disease involving multiple organs that lack well-defined granulomas. Therefore, people with HIV have been reported to have all kinds of EPTB, and as immunosuppression worsens, EPTB becomes more prevalent.[19] A 12-year study conducted on 320 EPTB cases in HIV-positive patients in the United States found that low CD4+ T cell counts were independently linked to severe types of EPTB, such as CNS/meningeal.[20]

In the present study Extra pulmonary cases were more (62%), but in the study conducted by Nayak S et al.,[21] and Ziad Ahmed et al.,[22] pulmonary cases were more, 81.82% and 67%, respectively. In the present study, disseminated involvement was seen in 26.47%, and similar findings were seen in the study conducted by Matthew et al. (23.12%). Lymph node involvement was commonly seen in extra-pulmonary cases, i.e., 38.23% in the present study and 27.81% in the study conducted by Matthew.[23] Pleural involvement was seen up to 14% in both the studies. 21.87% of CNS cases were seen in the study conducted by Matthew, but only 5.8% of CNS cases were seen in the present study.

Additionally, extrapulmonary tuberculosis (TB) is more common in HIV-positive individuals than in HIV-negative individuals. This condition may or may not be accompanied by concurrent lung

disease. Compared to 10%–20% of HIV-uninfected individuals, 40%–80% of TB patients with HIV infection develop extrapulmonary illness.[24] A decreased CD4+ T lymphocyte count raises the risk of extrapulmonary tuberculosis.[25] Although pleural and lymphatic diseases are the most prevalent types of extrapulmonary illness, nearly any site can be affected, including the pericardium, soft tissue (such as the psoas muscle, which may be linked to spinal disease), bone and/or joint (especially the thoracic spine), and the central nervous system.

33 of the 50 HIV patients with fatal illnesses, according to Bhanoth et al.[8] had a tuberculosis diagnosis. Of the 33 individuals with confirmed HIV-TB coinfection, 21 patients (42%), had pulmonary tuberculosis, and 12 patients (24%), had extra pulmonary tuberculosis. Clinical presentations of extrapulmonary tuberculosis included TB pleural effusion (5), TB lymphadenitis (2), TB meningitis, TB abdomen, TB pericardial effusion, TB brain granuloma, and TB skin. The percentage of patients with TB pleural effusion (15.1%), TB pericardial effusion (6.06%), TB meningitis (3.03%), TB abdomen, TB pericardial effusion, TB brain granuloma, and TB skin were among the 33 HIV-TB coinfections. The majority of patients with HIV-TB coinfections had CD4 counts <500 cells/μl. According to Namme LH et al.,[26] 33.6% of HIV patients had EPTB. The most common illness locations were the peritoneum (14.3%), lymph nodes (17.8%), pleura (15%), central nervous system and meninges (9%), and bones and joints (29.6%). The strongest significant correlation between HIV infection and neuromeningeal tuberculosis, though less common, was an odd ratio (OR) of 2.3 (95% CI 1.1-5.0, $p < 0.05$). According to Leeds IL et al.,[20] lymphatic (28%), disseminated (23%), and CNS/meningeal (22%) illness were the most prevalent locations of EPTB. Within a year of receiving an EPTB diagnosis, 14.7% of the 184 HIV-positive individuals had also contacted pulmonary tuberculosis, and 48.1% of the individuals were HIV-positive.

According to a meta-analysis by Cho Naing et al.,[27] lymph nodes were most frequently involved in HIV-positive EPTB cases, followed by the pleura. Virtually all organs, especially those that are comparatively inaccessible, can be affected by the unpredictable disease EPTB. There have also been reports of gender disparities concerning the prevalent locations where EPTB occurs. While pleural EPTB is more common in men, lymph node involvement in EPTB is more likely in women.[28] It makes sense that TB pleuritis would be more common in HIV seronegative individuals and in those with high CD4+ cell counts in HIV seropositive individuals, given the significance of the integrity of the delayed-type hypersensitivity response.[29] Individual investigations that have already been published suggested a potential connection between HIV and EPTB; in this research, cases that had both EPTB and PTB concurrently were classified as EPTB. This could be explained by how HIV infection affects a person's immune system. It is noteworthy that PTB may have progressed to EPTB as a result of the immune system's gradual deterioration.[30]

Additionally, childhood infections with the human immune deficiency virus are becoming more frequent. For the previous three decades, the relationship between TB and HIV has been elucidated. With CD4 counts >200 cells/cu.mm, tuberculosis is the most often reported opportunistic infection in India.[31,32]

A reduction in EPTB-associated morbidity and death may follow from improved identification of risk factors for the disease. This could lead to earlier case discovery and treatment. Given the positive correlation found between EPTB and HIV, TB control programs should stand to gain from concentrating on measures meant to lower HIV infection rates, and vice versa. The goal of eliminating tuberculosis depends on a better understanding of the risk factors for EPTB, which would allow doctors to treat HIV-positive patients who are at risk for EPTB with a high index of suspicion. A positive EPTB result should also notify the practitioner if the patient may be HIV positive. It is advised to conduct more research to fully comprehend the mechanisms underlying the two infections' interaction.

CONCLUSION

For HIV patients, tuberculosis is the most prevalent opportunistic illness. Most HIV patients get extrapulmonary symptoms because of TB's capacity to infect several organs. There is a need for early diagnosis and treatment in this subset of vulnerable patients. Also, healthcare workers need to

be aware of the fact that extra-pulmonary manifestations are more common among these patients compared to those not infected by HIV.

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