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Clinico-pathological profile of patients with HIV and tuberculosis co-infection

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Abstract

Introduction: Human immunodeficiency virus (HIV) and tuberculosis (TB) are two main leading global causes of mortality and morbidity. TB and HIV increase progressive deterioration of immunological functions by speeding progression of one another.

Material and methods: The present 5-year retrospective study was carried out in the Department of Pathology at a tertiary care hospital in South India. Study included clinico-pathological profile of 80 people living with HIV (PLHIV) and subsequently developed TB co-infection; their CD4+ counts done at the time of admission were examined.

Results: The present study included 80 HIV-TB co-infected cases. The age of the patients ranged from 18 to 65 years. The mean CD4+ T lymphocyte count was 164.7 cells/µl. Pulmonary TB was diagnosed in 59 patients (73.8%), while extra-pulmonary TB was detected in 21 (26.2%) cases. Abdominal TB was the most common site among extra-pulmonary TB cases. Opportunistic infections (OIs) other than TB, included 2 cases with oral candidiasis and 1 case with central nervous system (CNS) toxoplasmosis. Two of the HIV-TB co-infected cases were subsequently diagnosed with primary CNS (n = 1) and retroperitoneal lymphoma (n = 1).

Conclusions: In the present study, HIV-TB co-infection is more common in 25-50 years age group. Antiretroviral therapy has changed the nature of disease from fatal to chronic condition. OIs other than TB and neoplasms reported in our study included oral candidiasis, CNS toxoplasmosis, and lymphoma. PLHIV with low CD4+ count require close monitoring, adequate counselling, and further evaluation for atypical presentation of TB, OIs, and neoplasms to improve their outcomes.

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Introduction

Human immunodeficiency virus (HIV) and tuberculosis (TB) are two of the leading global causes of mortality and morbidity. TB is the most common opportunistic infection (OI) and leading cause of death in people living with HIV (PLHIV). TB and HIV increase progressive deterioration of immunological functions by speeding progression of one another. Immunosuppression in AIDS is attributable to the loss of CD4+ cells, which is the hallmark of the disease, and this in turn increases susceptibility to primary infection or re-infection, reactivation of TB, and other OIs [1]. Increased susceptibility to TB infection is noted in PLHIV even before depletion of CD4+ cell count below 500 cells/µl [2, 3].

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In comparison with general population, the risk of acquiring OI is more in PLHIV. In addition, mortality is highest in those with CD4+ cell count less than 200 cells/µl [4]. In advanced stages of HIV infection, TB often has an atypical presentation and frequently causes extra-pulmonary tuberculosis (EPTB). These factors, combined with negative sputum smears, result in delayed diagnosis [5, 6]. Furthermore, due to frequent association of TB and HIV, it is important to consider TB in case of HIV infection and vice versa. The aim of the present study was to investigate the clinico-pathological characteristics of TB in PLHIV.

Material and methods

The present study is a 5-year retrospective study carried out in the Department of Pathology at a tertiary care hospital in South India. The present study included 80 HIV-TB co-infected cases diagnosed during the study period between January 2013 to December 2018. Cases without a documented HIV test, and those patients who were admitted to hospital for causes other than HIV-TB co-infection were excluded. Institutional Ethics Committee (IECK-MCMLR05-19/245) clearance was obtained prior to the commencement of the study. In each case, relevant data, including demographics, complaints and examination findings, radiological investigations, and laboratory tests (i.e., total count, hemoglobin, lymphocyte count, and CD4+ cell count) were collected from patients case files. CD4+ count of PLHIV was estimated using a flow cytometer with whole blood collected during admission. Final investigation included fine needle aspiration cytology, cerebrospinal fluid analysis, chest X-ray, computed tomography, magnetic resonance imaging, ultrasonography of the abdomen (done to determine EPTB), other OIs, and neoplasms were collected from patients' medical documentation. The collected data were entered into Excel sheet and analyzed with Statistical Package for Social Sciences (SPSS) version 11.5. Results were expressed as proportions and summary measures using appropriate tables and figures. For comparison across the groups, χ^2 test was utilized, and p-value less than 0.05 was considered statistically significant.

Results

The present retrospective study included 80 HIV-TB co-infected cases during the study period. The age of the patients ranged from 18 to 65 years (mean age, 39.7 years), with majority of the patients aged between 25 and 50 years (Table 1). Males (60%) were more commonly affected than females (40%), with M : F ratio being 1.5 : 1 (Table 2). The most common presenting complaint was cough (n = 69, 86.25%), followed by fever (n = 56, 70%), breathlessness (n = 42, 52.5%), loss of appetite (n = 32, 40%), and convulsion (n = 1, 1.25%) (Table 3).

In the present study, laboratory investigations revealed that 66 patients (82.5%) had anemia, with hemoglobin level less than 12 gm/dl, of which 11 cases presented with severe anemia (13.75%) (Table 4).

CD4+ cell count was performed in all the patients. The mean CD4+ cell count was 164.7 cells/µl, and 51 cases (63.8%) had a CD4+ cell count ≤ 200 cells/µl, and 29 (36.2%) had CD4+ cell count > 200 cells/µl (Table 5). PTB was diagnosed in 59 patients (73.8%), and EPTB was detected in 21 (26.2%) cases (Table 6). The majority of the patients with

Table 1. Age distribution of HIV-TB co-infected cases

Age group (years)	Frequency (n)	Percentage (%)
< 25	7	8.8
25-50	62	77.5
> 50	11	13.8
Total	80	100.0

Table 2. Gender distribution of HIV-TB co-infected cases

Gender	Frequency (n)	Percentage (%)
Male	48	60.0
Female	32	40.0
Total	80	100.0

Table 3. Distribution of HIV-TB co-infected cases based on presenting complaints

Symptoms	Frequency (n)	Percentage (%)
Cough	69	86.25
Fever	56	70.00
Breathlessness	42	52.50
Loss of appetite	32	40.00
General weakness	27	33.75
Abdominal pain	10	12.50
Nausea	5	6.25
Diarrhea	5	6.25
Altered sensorium	2	2.50
Convulsion	1	1.25

Table 4. Distribution of HIV-TB co-infected cases based on hemoglobin level

Hemoglobin (g/dl)	Frequency (n)	Percentage (%)
< 7.0	11	13.75
7.0-9.9	35	43.75
10.0-11.9	20	25.00
> 12.0	14	17.50
Total	80	100.00

Table 5. Distribution of HIV-TB co-infected cases based on CD4+ count

CD4+ count	Frequency (*n*)	Percentage (%)
< 200	51	63.8
200-500	28	35.0
> 500	1	1.2
Total	80	100.0

Table 6. Distribution of pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) cases co-infected with HIV

	Frequency (*n*)	Percentage (%)
PTB	59	73.8
EPTB	21	26.2
Total	80	100.0

Table 7. Age distribution of pulmonary tuberculosis (PTB) – extra-pulmonary tuberculosis (EPTB) cases co-infected with HIV

Age (years)	PTB (n)	EPTB (*n*)
< 25	6	1
25-50	45	17
> 50	8	3

PTB or EPTB were aged between 25 and 50 years (Table 7). Out of 59 PTB cases, CD4+ cell count ≤ 200 cells/µl was seen in 39. Out of 21 patients with EPTB, 12 had CD4+ cell count below 200 cells/µl (Table 8). The most common site of EPTB in the present study was abdominal tuberculosis seen in 10 patients. Among these 10 EPTB cases, splenomegaly, hepatomegaly, and abdominal lymphadenopathy were reported in 10, 8, and 10 patients, respectively. In one EPTB case, fungal abscess in the liver was reported, while omental thickness was seen in another case. Peripheral lymphadenopathy was observed in 5 patients, pleural effusion in 4, CNS TB in 3, disseminated TB in 3 patients, and Pott's spine was noted in 1 case (Table 9).

OIs other than TB were reported in 3 patients. Two cases were diagnosed with oral candidiasis, while 1 case was diagnosed with CNS toxoplasmosis. Two of the HIV-TB co-infected cases were subsequently diagnosed with primary CNS lymphoma ($n = 1$) and retroperitoneal lymphoma ($n = 1$).

Discussion

First clinical AIDS case has been reported in the year 1981 in USA, caused by HIV discovered in 1983. HIV weakens immune system; therefore, PLHIV are more susceptible to bacterial, viral, and fungal infections as well as neoplasms,

Table 8. Distribution of extra-pulmonary tuberculosis (EPTB) in HIV-TB co-infected cases based on location

Location	Frequency (*n*)
Abdominal TB	10
Peripheral lymphadenopathy	5
Pleural effusion	4
Central nervous system tuberculosis	2
Tuberculous meningitis	1
Pott's spine	1
Disseminated TB	2

Table 9. Distribution of pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) based on CD4+ count in patients co-infected with HIV

CD4+ count	PTB (*n*)	EPTB (*n*)
< 200	39	12
200-500	19	9
> 500	1	0
Total	59	21

such as lymphomas and Kaposi's sarcomas. OIs must be treated early to prevent transmission and decrease mortality in PLHIV [2, 3]. TB is mainly a respiratory disease caused by *Mycobacterium tuberculosis*, and is one of the leading cause of death in India, with an estimated 60-70% of the population developing TB during their lifetime [5, 6].

HIV-TB potentiates each other by weakening the immune system, and TB infection results in a release of chemical mediators, which cause activation of immune cells infected with HIV and replication of viral DNA integrated in host DNA. Mortality rate is higher in HIV-TB co-infection compared with HIV and TB alone. HIV-TB co-infection is a risk factor for primary infection and reactivation of latent TB. In the years 2008 to 2013, HIV-TB co-infection has increased resurgence of TB from 31% to 63% in India [3, 7]. PLHIV are 18 times more likely to develop TB compared with HIV-negative individuals [8]. It was estimated that in 2020, 37.7 million people have been living with HIV, and 680,000 have died due to HIV and 1.5 million have died due to TB (including 214,000 people with HIV). Among the countries having a high TB burden accounting for an overwhelming majority of new TB cases (86%), India has the highest disease burden, followed by China and Indonesia [9].

The present study included 80 HIV-TB co-infected cases, and the majority belonged to the age group of 25-50 years ($n = 62$, 77.5%). Similar study done in South India by Kamath *et al.* [10] among 684 patients showed that 61.3% of cases were between 31 and 45 years. Whereas study done by Patel *et al.* [8] in North India among 50 HIV-TB co-infected patients reported that 96% ($n = 48$) of patients were between 21 and 50 years.

In the present study, the male to female ratio was 1.5 : 1, similar to a study done in South India by Tiewsoh *et al.* [11] (F : M ratio, 3.46 : 1) among 58 cases co-infected with TB. The most common presenting complaint in the present study was cough (86.25%), followed by fever (70%) and breathlessness (52.5%). Similarly, Patel *et al.* [8] reported cough in majority of patients, followed by fever. In contrast to the above findings, a study by Tiewsoh *et al.* [11] reported fever (67%) as the most common presenting complaint, followed by gastrointestinal symptoms.

Among the laboratory investigation, 66 patients (82.5%) had anemia, of which severe anemia was seen in 11 cases (13.75%). Comparable observations were made by Tiewsoh *et al.* [11], with 6.9% cases reported with severe anemia. Researchers have assumed that anemia in such cases is due to the upregulation of pro-inflammatory cytokines, such as IL-6, during active TB infection, which stimulate hepcidin synthesis by hepatocytes, and drive the processes of anemia of chronic disease [12].

In current study, the mean CD4+ count was found to be 164.7 cells/µl, similar to the findings obtained by Kamath *et al.* [10] (n = 640/684; mean CD4+ count, 174.47 cells/µl), whereas in a study by Tiewsoh *et al.* [11], the mean CD4+ count was slightly higher (n = 58, CD4+ count, 220 cells/µl).

In general, CD4+ cell count is lower among HIV-TB co-infected patients compared with those infected with HIV alone [10]. In our study, 51 cases (63.8%) had CD4+ cell count ≤ 200 cells/µl. Severe immunosuppression and increased mortality is seen patients with CD4+ count ≤ 200 cells/µl [10]. Patient's immune status and the risk of OIs are best assessed by measuring CD4+ cell count.

PTB is seen more frequently than EPTB in patients with intact immune function (CD4+ count > 200 cells/µl) [3]. In the present study, PTB was diagnosed in 59 patients (73.8%), and EPTB was detected in 21 (26.2%). These findings are similar to a study done by Shastri *et al.* [13] involving 6,480 HIV-TB co-infected patients, out of which 4,741 (73.2%) were PTB cases. While Patel *et al.* [8] reported 43 (86%) patients with PTB, and Kamath *et al.* [10] detected 402 PTB cases (58.8%). In a study done by Mohan *et al.* [3], patients with extra-pulmonary TB (61%) were more common compared with pulmonary TB cases (39%). In PLHIV, EPTB accounts for 40-50% of new TB cases, while it is 15-20% in HIV-negative individuals [14].

The commonest form of EPTB in the present study was abdominal tuberculosis observed in 10 patients, peripheral lymphadenopathy reported in 5 cases, and pleural effusion in 4 cases. Patel *et al.* [8] reported that the most common presentation of EPTB was mediastinal lymphadenopathy (n = 17, 34%), followed by pleural effusion (n = 10, 20%), and abdominal TB (n = 6, 12%). The prevalence of pleural TB implies more relation to secondary TB or reactivation of TB. The delay in EPTB treatment is due to difficulty in diagnosis [14, 15].

As seen on USG, lymph nodes > 15 mm were features considered suggestive of abdominal tuberculosis, and were predominantly hypoechoic or necrotic. Visceral involvement may present as organomegaly, multiple small abscesses, or hypoechoic lesions in organs. Other features suggestive of abdominal TB are bowel wall thickening (especially ileo-cecal junction) and mesenteric thickening. The presence of more than one of the above findings is considered as extensive abdominal involvement [16]. Here, abdominal lymphadenopathy was seen in 10 cases. Although HIV infection itself can lead to lymphadenopathy, the size and characteristics of nodes can help differentiate between adenopathy caused by abdominal TB and HIV.

In the present study, central nervous system tuberculosis (CNS-TB) was reported in 3 cases, while Pott's spine was observed in 1 case. In contrast to the current study, Patel *et al.* [8] reported 6% of cases with CNS-TB. In order to reduce the incidence of CNS-TB, ATT should be started as soon as PTB is diagnosed. In PTB, relapse rate of 5% is acceptable, whereas relapse of CNS-TB can result in neuro-disability or can even be fatal [14].

In the current study, disseminated TB was noted in 3 cases. CD4+ count was available in 2 cases, wherein the mean CD4+ count was 73 cells/µl. In contrast, disseminated TB was seen in 25 (50%) patients in a study done by Patel *et al.* [8]. Disseminated disease is suggestive of late phase of immunosuppression, and accounts for higher sputum AFB negativity and increased mortality [8, 14, 17].

CD4+ T cell count evaluation is significant to monitor the progression of HIV after ART initiation. In HIV-TB co-infected cases, as CD4+ count decline, atypical presentations of TB, such as pleural effusion, military TB, and hilar lymph node enlargement, are frequently encountered. Chronic diarrhea is found to be the most common OI in PLHIV, as shown in studies from India [18, 19]. In contrast, in the present study, two patients presented with oral candidiasis, and 1 case was diagnosed with CNS toxoplasmosis. Among the 2 oral candidiasis cases, the mean CD4+ count was 23.5 cells/µl. Mean CD4+ cell count of patients with oral or oropharyngeal candidiasis in a study by Das *et al.* [18] was 117 cells/µl. Oral candidiasis is one of the commonest OI caused by *Candida* sp., due to the depletion of Langerhans cells present in the mucosa [8]. Oral candidiasis can manifest early, and is a strong predictor of AIDS-related illness [18, 20]. Oral candidiasis may be considered as a clinical surrogate for severe CD4+ count depletion [19].

Conclusions

In the present study, HIV-TB co-infection is more common in the 25-50 years age group. Antiretroviral therapy has changed the nature of the disease from fatal to chronic condition. OIs other than TB and neoplasms reported in the current study included oral candidiasis, CNS toxoplasmosis, and lymphoma. PLHIV with low CD4+ count require close monitoring, adequate counselling, and further evaluation for atypical presentation of TB, OIs, and neoplasms to improve their outcomes.

Disclosures

1. Institutional review board statement: The study was approved by the Institutional Ethics Committee of the Kasturba Medical College, Mangalore, with approval number: IECKMCMLR05-19/245.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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