

Full Length Research Paper

# Various manifestations of extrapulmonary tuberculosis and its relationship with HIV-AIDS

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Tuberculosis is known from ancient times. Recently HIV and Tuberculosis emerged as an important treatable co-epidemic especially in developing countries. Extra-Pulmonary Tubercular involvement is one of the important manifestations of Tuberculosis especially in HIV co-infected patients. But the extra-pulmonary manifestations vary between patients of Tuberculosis with HIV and without HIV co infection. In HIV subgroup lymph node tuberculosis (58.1%) was commonest extra pulmonary presentation with cervical lymph nodes (35.5%) as commonest site. Neurological tuberculosis (32.3%) was second common followed by pleural effusion (29%). Abdominal tuberculosis (19%) was at fourth place with hepatomegaly and omental mass as commonest clinical finding. Ascites was not seen in any of the patient. None of patients with HIV co infection had skeletal and pericardial involvement. EPTB most commonly affects the younger economically productive section of the society. Co-infection with HIV is an important risk factor. The site of organ involvement in EPTB is different in HIV-infected and non-HIV-infected persons. There is higher frequency of disseminated disease among HIV – TB co-infected patients.

**Key words:** Tuberculosis, HIV, extra pulmonary TB (EPTB) manifestations, co- infection, epidemics.

## INTRODUCTION

Tuberculosis is known from ancient times. Recently HIV and Tuberculosis emerged as an important treatable co-epidemic especially in developing countries. Tuberculosis is caused by bacteria belonging to Mycobacterium Tuberculosis Complex and the order Actinomycetales. With the spread of HIV pandemic non tubercular mycobacterium has become an important etiological agent. Tuberculosis can involve any organ system in the body. While pulmonary tuberculosis is the most common presentation, extra-pulmonary tuberculosis (EPTB) is also an important clinical problem. The term EPTB has been used to describe isolated occurrence of tuberculosis at body sites other than the lung.

HIV and TB co-infection (HIV/TB) are commonly referred to as co-epidemics or dual epidemics. The inextricably linked pathogenesis and epidemiology to TB and HIV are well known. HIV fuels progression to active disease in people infected with TB.

In HIV-positive patients, EPTB accounts for more than 50 per cent of all cases of TB. HIV infected persons are at increased risk for primary or reactivation tuberculosis and for second episodes of tuberculosis from exogenous re-infection. HIV infection itself progresses very rapidly in patients with tuberculosis and successful treatment of tuberculosis cause plasma viremia to fall back to previous level. Nearly 40 million people are living with HIV infection worldwide and as many as one-third are co-infected with Tuberculosis (Allen JC and Apicilla MA, 1968; Baydur A, 1977 and Bem C, 1997).

The annual risk of reactivation of latent tubercular infection in HIV positive individual is 7-10% and life time risk is 50-60% as compared to 5-10% lifetime risk in HIV negative individuals. This has been amply demonstrated in countries such as Uganda and Kenya where increasing HIV prevalence was clearly linked to increase in TB incidence. Significantly, the incidence rate for TB, after showing an initial lag phase, continues to rise even as trends for HIV prevalence have reversed in these countries. Similar dynamics have been reported in this region from Thailand ( Beringuer J, Moreno S, Vicenta T,

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**Table 1.** Age distribution of patients.

Age in years	No . of patients	Percentage
18 – 30 yrs	50	25%
31- 40 yrs	76	38%
41 – 50 yrs	34	17%
> 50 yrs	40	20%

1992; Brig SK Sharma, Lt Col RB Deorkar, Col KE Rajan and Lt Col MS Barthioal, 2005).

EPTB should be considered in the differential diagnosis of bone, joint, genitourinary tract and central nervous system (CNS) diseases (Chan CH, Arnold M, Chan CY, Mak TW and Hoheisel GR (1991).

TB is the leading infectious killer of people living with HIV, and accounts for an estimated 13% of AIDS deaths worldwide.

The most common site of EPTB is lymph node affecting mostly the cervical group of lymph nodes. Other forms of EPTB are tuberculosis pleural effusion, tuberculosis pericardial effusion, intestinal, genitourinary, meningeal, bone, skin, and breast tuberculosis.

Very limited data is available about the situation of EPTB in India. The extra pulmonary tuberculosis provides an extraordinary opportunity for research in all its forms as most of the published work related to EPTB is from pre HIV era. Coexistence of HIV infection and tuberculosis is one of the most serious threats to human health and by making a large pool of susceptible population it has further lead to emergence of epidemic of multi drug resistance tuberculosis (MDR-TB).

The present study investigated the various forms of extra pulmonary tuberculosis and its relation to HIV AIDS. This will help us in planning our management of patients in a better way to reduce morbidity and mortality in resource poor areas.

## AIMS AND OBJECTIVES

- ❖ To study the various manifestations of EPTB in the patients admitted in medical wards.
- ❖ To compare the frequency of EPTB in HIV and non HIV patients.

## MATERIALS AND METHODS

Prospective observational study conducted over a period of one year in the Department of Internal Medicine. Written informed consent was obtained from all patients.

### Inclusion criteria

- ❖ All patients with features of EPTB.

- ❖ All the patients willing to participate in study.

### Exclusion criteria

- ❖ Sputum smears positive patients.
- ❖ Patients with radiological evidence of pulmonary tuberculosis.

## STATISTICAL ANALYSIS

Data collected was managed on a Microsoft excel spreadsheet. Categorical & continuous variables of the clinical characteristics of study population was described as percentages & Means's respectively & Chi-Square test was used to compare significance of difference in the distribution of discrete variables. Non-parametric test Mann-Whitney test was used to compare the significance of difference in means of continuous variables. 2 tailed significance at <0.05 was used as statistically significant. All analysis was performed with the Epi-Info version 3.5.1.

## OBSERVATIONS

### Age and Sex Distribution

Mean age of the patients was 40.44 yr. Majority 38% of the patients were in the age group of 31-40 years. 25% patients were in the age group 18-30 years and 17% patients were in the age group of 41-50 years & 20% were above 50 years (Table. 1). Of these 200 patients, 66% were males and 34% were females.

### Profession of Patients

Of the total 132 male patients, 51.51% were farmers by profession. There were 23.48% patients who were drivers, 15.9% were shopkeepers and 7.57% were laborers, 4.57% patients were factory workers and 3.75 % were health professionals. Of the total 68 female patients, 85.29% were housewives and 14.76%% were office workers.

### Educational Status of Patients

Of the total 132 male patients 72% were Literate & 28%

**Table 2.** Shows symptoms of patients on presentation.

Symptom	No. of patients	Percentage
Fever	197	98.5%
Cough	114	57%
Loss of appetite	154	77%
Weight loss	123	61.5%
Diarrhea	39	19.5%
Neurological complaints	61	30.5%

**Table 3.** Summarise the findings on clinical examination in two groups.

CLINICAL FINDINGS	HIV subgroup (n = 31 )	Non HIV subgroup (n= 169 )	p value
Pleural Effusion	9(29%)	89(52.7%)	0.0071
Meningism	10( 32.3%)	39(23.1%)	0.0114
Lymphadenopathy	18 (58.1%)	37(58.1%)	0.000
Ascites	0(0%)	33(19.5%)	0.012
Hepatomegaly	2(6.45%)	3(1.9%)	0.03
Splenomegaly	1(3.22%)	4(2.5%)	0.024
Hepatosplenomegaly	1(3.22%)	13(8.1%)	0.004
Omental mass	2(6.45%)	1(0.6%)	0.27
Bone and joint involvement	0	4(2.3%)	0.0001
Synovial fluid	0	5 (29%)	0.778
Pericardial effusion	0	7(4.3%)	0.30

were illiterate. On the other hand, out of 68 female patients 81% were literate & 19% were illiterate.

### Symptoms of Patients on Presentation

Fever was the commonest symptom on presentation and present in 98.5% patients. Fever was low grade, associated with loss of appetite in 77% & cough in 57% of patients. The mean duration for loss of appetite was six weeks & for cough was four weeks. Cough was dry in 60 % patients. Weight loss was present in 61.5% patients & mean duration was 12 weeks. Diarrhea was present in 19.5% patients with mean duration of 3 weeks. Neurological complaints were present in 30.5% patients with mean duration of 1 week. Of the patients with neurological complaints 90.16% patients had headache as main complaint, 63.93% had vomiting as associated complaint and 26.22% had altered sensorium and 4% had weakness as complaint (Table. 2).

### Findings on Clinical Examination

Out of 200 patients 169 patients were HIV negative patients and 31 patients were HIV positive. In non HIV

subgroup the most common EPTB manifestation was pleural effusion 52.7%. CNS tuberculosis is the second common followed by Lymph node tuberculosis. In CNS tuberculosis patients most commonly presented as meningitis 13%, meningocephalitis 4.7%, encephalitis 1.8% and focal neurological deficit was seen in 1.2% of patients. Lymph node tuberculosis was third common presentation. It was present in 58.1% patients. Cervical lymph nodes was commonly involved in 8.9%, axillary in 8.3%, inguinal lymph nodes was palpable in 3.4%, and 2.7% had generalized lymphadenopathy . Abdominal tuberculosis was the fourth common presentation. Pericardial involvement was seen in 4.3% patients in the form of pericardial effusion. Bone and joint tuberculosis was seen in 2.3% patients in whom hip joint was involved and synovial fluid was positive for TB.

In HIV subgroup lymph node tuberculosis was commonest .18 of 31 patients had lymph node tuberculosis .Cervical lymph nodes 35.5%, Axillary 9.7% & 9.7% had generalized lymphadenopathy. Neurological tuberculosis was second common followed by pleural effusion .On CNS examination 16.1% patients had meningitis followed by meningoencephalitis 12.9% and encephalitis 3.2%. In abdominal tuberculosis hepatomegaly 6.45%, hepatosplenomegaly and splenomegaly 2% was seen.

To conclude most common manifestation in non HIV subgroup was pleural effusion as compared to lymphadenopathy in HIV group. Ascites is common in abdominal tuberculosis in non HIV subgroup. Pericardial and synovial tissue was also common in non HIV group as compared to HIV subgroup (Table. 3).

## CHEST XRAY FINDINGS

Chest X Ray was done in all 200 patients. Pleural effusion was more common in Non HIV group. It was seen in 89 patients in non HIV group and 9 patients in HIV group. Cardiomegaly was seen in 7 patients. These patients were found to have pericardial effusion on further work up that turned out to be tubercular in etiology.

## USG Findings

USG abdomen was done in all 200 patients. It was normal in 112 patients. Ascites was commonest presentation in non HIV group & present in 24.3% cases. Hepatosplenomegaly was present in 9.5% cases. Abdominal lymphadenopathy was found in 5.3% cases. Hepatomegaly was present in 2.4% and splenomegaly was present in 3.6% cases. In HIV group abdominal lymphadenopathy was commonest finding.

## DISCUSSION

Majority of patients were in age group of 31- 40 years (38%). We found on analysis that the incidence of EPTB initially increased as age increased from second decade to third decade and then decreased. As previous published data show, extra-pulmonary sites tend to be more commonly involved in younger than older patients. In Mustafa et al. study ( Fontan Bueso J, Vereza Hernando H, Garcia Beela JP, Dominguez Juncal, Martin Egane MT, Montero Martinez MT, 1988), mean age of patients was 35 ± 14 years. In Ilgazli et al study Fowler NO (1991), mean age of patients was 22.5±17.1 years (range, 1-86 years); 41.4% of cases were <15 years of age and 30.9%, between 20 and 39 years of age. Noertjojo et al study Gonzalez OY, Teeter LD, Thanh BT, Musser JM, Graviss EA (2003), EPTB was more common in women under 30 and over 75 years of age. So the age group commonly affected in our study was in accordance with the published literature.

Pulmonary tuberculosis is more common in males than in females, while the opposite is true for EPTB. In our study, 66% were males and 34% were females. Gonzalez *et al* (Ilgazli A, Boyci H, Basyigit I, Yildiz F, 2004). found that EPTB had been more commonly observed in females (218 female EPTB / 396 female TB cases) as compared to males (320 EPTB cases / 944 male TB cases) in Houston.

Fever was the commonest symptom present in 98.5% of patients. Fever was usually low grade and mean duration of fever was four weeks. Fever was associated with loss of appetite in 77% and cough in 57% of patients. The mean duration for loss of appetite was six weeks & for cough was four weeks. Cough was dry in 60 % patients. Weight loss was present in 61.5% patients and mean duration was 12 weeks. Diarrhea was present in 19.5% patients with mean duration of 3 weeks. It was associated in all patients with weight loss and loss of appetite. In Hussain et al study, fever was present in 71.84% patients.

The site of organ involvement in extra-pulmonary tuberculosis is different in HIV-infected and non-HIV-infected persons. There is higher frequency of disseminated disease among HIV – TB co-infected patients. In non HIV subgroup we found the most common EPTB manifestation was pleural effusion 52.7%. CNS tuberculosis is the second common that was followed by Lymph node tuberculosis.

In Hong Kong study Gonzalez OY, Teeter LD, Thanh BT, Musser JM, Graviss EA (2003), the pleura and lymph nodes were the two most common sites of extra-pulmonary tuberculosis, accounting for 77% of all cases. In Taiwan study, pleural and lymph node diseases accounted for 70.9% of all cases of extra-pulmonary tuberculosis. In our study pleura and lymph nodes accounted for 74.55% of cases. The cause for pleura involvement as commonest extra pulmonary site has been widely investigated. Tuberculosis can affect the pleura at different stages of pulmonary or systemic disease. Rupture of sub pleural caseous focus in the lung into pleural space, direct contiguous spread of disease to pleura or by haematogenous spread or as a complication of thoracic vertebral tuberculosis with par vertebral cold abscess. Tuberculosis osteitis of rib may be associated with pleural effusion. With so many routes involved, it is a commonest extra pulmonary site.

In our study, in NON HIV SUBGROUP (169), 52.7% had tubercular pleural effusion. In these patients pleural fluid was exudative, cytology revealed lymphocytes. It was in accordance with the study of Chan et al<sup>11</sup> where pleural fluid protein level exceeded 5g /dl. Mean value of adenosine deaminase was 85.14. Different studies took different cut off values for adenosine deaminase. But Fontan et al study (Jones BE, Young SMM, Antoniskis D, Davidson PT, Kramer F, Barnes PF and 1993). found that pleural fluid ADA in excess of 70 IU/L is highly suggestive of TB pleuritis, whereas a level below 40 IU/L rules out the diagnosis. In our study none of the pleural fluid samples was positive for AFB. Allen et al study (Kent SJ, Crave SM, Yung A, Lucas CR, Migch AM (1993). proved that it is the intense inflammatory reaction that obstructs the lymphatic pores in parietal pleura, causing proteins to accumulate in pleural space with subsequent retention of fluid. It is delayed hypersensitivity rather than tubercular infection per se,

plays an important role in the development of tubercular pleural effusion.

CNS Tuberculosis was second common extra pulmonary manifestation. In 35 patients with CNS tuberculosis, meningitis 62.8%, meningocephalitis 22.85%, encephalitis 8.5% and focal neurological deficit 5.7%. This is in accordance with Tandon et al (Lee MP, Chan JW, Ng KK, Li PC, 2000). study where TBM accounted for 70- 80% of cases. According to the study of Noertjojo K, Tam CM, Chan SL, Chan Yeung MM (2002) and Thomas et al study Ozvaran Mustafa, Baran Reha, Tor Meltem, Dilek Iknur, Arnic Sibel, Toker Nil (2007), on tuberculosis meningitis cranial nerve palsies can occur in 20 – 30 % of cases. Facial nerve palsy accounted for 17.7% of cases in their study.

In our study, lymph node tuberculosis accounted for 21.89% of cases. The most common site involved was cervical 8.9%, then axillary 8.35% and inguinal 3.4%. The cause for this has been explained as follows: Tonsil is an important portal of entry for tuberculosis. The infection spreads via lymphatics to the nearest cervical lymph nodes.

Abdominal tuberculosis was at fourth place in our study. Ascites (19.5%) was commonest presentation followed by hepatosplenomegaly (8.1%), splenomegaly (2.5%) and hepatomegaly (1.9%).

Pericardial TB may present as acute pericarditis, chronic pericardial effusion, cardiac tamponade or pericardial constriction. In our study pericardial effusion accounted for 4.3% cases.

Skeletal tuberculosis was seen in 2.3% of cases in our study. Potts spine was the common presentation followed by hip joint involvement. This is in accordance to Sharma et al study (Poprawski D, Pitisuttitum P and Tansuphasawadikul S 2000) where it constituted 10% of cases and spine was the commonest site involved.

In HIV SUBGROUP lymph node tuberculosis was commonest. 18 of 31 patients had lymph node tuberculosis. Cervical lymph nodes 35.5%, Axillary 9.7% & 2.7% had generalized lymphadenopathy. Generalized lymphadenopathy was more common in HIV patients as compared to non HIV patients. This is in accordance to Bem et al study (Raviglione MC, Narain JP and Kochi A 1992).

Neurological tuberculosis was second common followed by pleural effusion. Meningitis in 16.1%, meningoencephalitis 12.9%, and encephalitis 3.2%. On imaging, CT head, 2 had basal meningitis and 2 had tuberculomas. On MRI brain 4 had tubercular abscess. This is in accordance with study by Farrar DJ et al (Sharma SK and Mohan A, 2004). where meningitis and tuberculomas are commonest manifestation of CNS tuberculosis. Also CNS tuberculosis is more common in HIV patients as compared to NON – HIV patients & this is in accordance to Berenguer et al study.

In abdominal tuberculosis hepatomegaly 6.45%, hepatosplenomegaly and splenomegaly (3% each) was

seen. USG abdomen revealed small multiple hypo echoic lesions. The finding of small multiple hypo echoic lesions in spleen in HIV-infected patients on sonography is highly suggestive of splenic tuberculosis and this finding is in accordance with study by Brig S K Sharma et al (Thomas MD, Chopra JS, Walia BN and TBM, 1977).

In the study done by Zuber Ahmed et al (Zuber A and Mohd S, 2005). Lymphadenopathy (18%) and pleural effusion (14%) were the commonest forms of extra pulmonary tuberculosis. Brig S K Sharma et al in their study in HIV positive patients found that most common extra pulmonary tuberculosis site is lymph node.

## SUMMARY AND CONCLUSION

The most common affected age group was 31-40 years. Males were affected more than females. Most common affected professional group was of farmers in Non – HIV group and drivers in HIV – group. Fever, weight loss and cough were the commonest symptom on presentation.

In non HIV subgroup the common EPTB manifestation is Pleural effusion in 89% of cases, CNS tuberculosis in 23.1% and Lymph node tuberculosis in 21.89% of cases. The commonest site for lymphadenopathy was cervical 8.9%, axillary 8.3%, inguinal 3.4% & generalized lymphadenopathy in 2.7% cases abdominal tuberculosis was at fourth place. Abdominal tuberculosis was seen in form of ascites (19.5%), hepatosplenomegaly (8.1%) cases, splenomegaly (2.5%) cases, hepatomegaly (1.9%) cases. Tubercular pericardial effusion found in 4.3% of patients. Skeletal involvement was seen in 2.3% percentage of cases. Potts spine was the common presentation.

In HIV subgroup lymph node tuberculosis (58.1%) was commonest extra pulmonary presentation with cervical lymph nodes (35.5%) as commonest site. Neurological tuberculosis (32.3%) was second common followed by pleural effusion (29%). Abdominal tuberculosis (19%) was at fourth place with hepatomegaly and omental mass as commonest clinical finding. Ascites was not seen in any of the patient. None of patients with HIV co infection had skeletal and pericardial involvement.

The conclusions of the study are that extra pulmonary tuberculosis most commonly affects the younger economically productive section of the society. Co-infection with HIV is an important risk factor. Any patient coming with extra pulmonary tuberculosis should be worked up for HIV infection. The site of organ involvement in extra-pulmonary tuberculosis is different in HIV-infected and non-HIV-infected persons. There is higher frequency of disseminated disease among HIV – TB co-infected patients.

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## CONFLICT OF INTEREST

There is no conflict of interest.

## ETHICAL CLEARANCE

No Ethical issues from the Ethical Committee.

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