Research Article

Clinico-Epidemiological Profile of Extra-pulmonary Tuberculosis in Central India

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Introduction: Tuberculosis (TB) remains a major global health issue. India being highest TB burden country needs concern. It was found that the percentage of patients with EPTB was more in tertiary care centres of India, ranging from 30% to 53%. The primary objective of this study was to describe the basic demographic, clinical characteristics and risk factors of Extrapulmonary Tuberculosis in patients, registered at DOTS centre of tertiary care teaching hospital. **Materials and Methods:** This is a retrospective, record-based study of patients of EPTB, at the LN Medical College and Hospital, Bhopal, from 1st January 2012 to 30th June 2014. **Results:** Among 491 cases registered for treatment of all forms of tuberculosis, 361(73.53%) had PTB and 130 (26.47%) had EPTB. The ratio of percentage EPTB: PTB is 1:3.6.

Commonest type of EPTB was found in cases of lymph nodes and lymphatic (30.76%), followed by TB in pleural cavity (23.03%). Among different age groups studied, the age group of 20-39 years had the highest proportion of EPTB both in males and females which is the economically productive population of society. **Conclusion:** The frequency of EPTB in this study was higher (26.47%) with the highest proportion in lymph node (30.76%). The burden of EPTB is more among the productive age group, moreover, being male, young adults and having associated diabetes mellitus were significant risk factors for patient being EPTB positive.

Key words: Extrapulmonary Tuberculosis, Lymph node TB, Revised National Tuberculosis Control Programme

Introduction

Tuberculosis (TB) remains a major global public health problem with one-third of the world's population being infected with the MycobacteriumTuberculosis [1].Along with HIV and Diabetes Mellitus, itis causing pandemic worldwide. Recently identified TDR (total drug resistant) tuberculosis is biggest threat for human being. According to WHO,6.1 million TB cases were reported in 2013,out of which 5.7 million were people newly diagnosed and another 0.4 million were already on treatment. [2].The burden of tuberculosis (TB) in India is the highest accounting for one fifth (21%) of the global incidence.[3]. As per Revised National Tuberculosis Control Programme (RNTCP) 2011, in Madhya Pradesh, there were 90,764 cases registered for TB [4].

Tuberculosis infection of any part of body other than lung parenchyma is defined as extrapulmonary tuberculosis [EPTB].Diagnosis of EPTB is done as per RNTCP guidelines which is based on one culture-positive specimen from the extra-pulmonary site; or histological evidence; or strong clinical evidence consistent with active EPTB disease followed by a medical officer's decision to treat with a full course of anti-TB therapy under DOTS[5].The timely detection & accurate diagnosis of any form of EPTB is necessary for the proper treatment of EPTB[6].Atypical presentation, lack of diagnostic resources for procurement of tissue or fluid for diagnosis from inaccessible sites and a poor yield of conventional diagnostic methods leadto considerable delay in making the diagnosis or diagnosis is even missed. Furthermore guidelines regarding diagnosis of EPTB are not covered by RNTCP but all patients are given treatment as per DOTS regimen. Although there is a rising trend in EPTB in recent decade, still EPTB has never been a priority in the campaigns undertaken by Revised National TB Control Programme (RNTCP) for its control [5,7,8]. The percentage of EPTB cases among all TB cases in developed countries ranges from 12% to 28.5%. In developing countries such as India, the percentage of EPTB cases, is between 15% - 20%, which has

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increased to more than 50% among the HIV co-infected patients[4,7] suggesting immunity status of host beinga major risk factor of EPTB[8].

It was found that the percentage of patients with EPTB was more in tertiary care centres of India, ranging from 30% to 53% [5].This implies that, tertiary care centres such as medical colleges, caters a large and varied type of population and provides an excellent place for economical and advanced diagnostic facilities for early diagnosis and treatment of EPTB cases, backed up by research facilities. This is much needed, as HIVTB co-infection, multi-drug-resistant TB, diabetes etc. have made EPTB a major public health threats even in the era of optimally effective DOTS [5].

With this background we conducted the present study from 1st January, 2012 to 30th June, 2014 at the LN Medical College and Hospital, Bhopal, MP, India. The primary objective of this study was to describe the basic demographic, clinical characteristics and risk factors of EPTB patients, registered for TB treatment in DOTS centre attached to a LN Medical College and Hospital, Bhopal (MP).

Material and Methods

Aim- The aim of study is characterising EPTB patients with different anatomical site involvement and study of their clinico-epidemiological profile and their associated risk factors

Study design-This is a retrospective, record-based study of diagnosed patients of EPTB of all age groups.

Study area-The study was conducted in the L N Medical College & Hospital a tertiary care centre, so patients from nearby villages and adjoining districts were referred for diagnosis and treatment.

Study period- Data for this study has been obtained from 1st January 2012 to 30th June 2014.

Study population. The population includes all patients attending various OPD of Hospital who were suspected for extra pulmonary tuberculosis infection during the study period. This study includes total of 491 patients diagnosed for TB clinically, pathologically and radiologically as tuberculosis in L N Medical College &Hospital, out of which 130 were diagnosed as extra-pulmonary tuberculosis.

Source of information - For this study data has been obtained from Patient Record Sheets of Hospital, Lab register, treatment Cards or Referral Registers of RNTCP and utilized for analysis.

Inclusion criteria-

1. All patients suspected of tuberculosis attending OPD of various departments of L N Medical College and Hospital, Bhopal.
2. EPTB - a patient with active tuberculosis of any part of body other than lung parenchyma.

Exclusion criteria-

1. Patients with PTB
2. Patients of EPTB with PTB.

Method

The study was conducted after obtaining institutional ethical clearance from institutional ethical committee. The study includes all patients coming to various OPD of LN Medical College and Hospital during the study period with suspected TB. The diagnosis of Pulmonary and Extra pulmonary Tuberculosis cases were established, following the RNTCP programme guidelines, which required one culture positive specimen from an extra-pulmonary site or histological evidence or strong clinical evidence consistent with active EPTB followed by concerned Medical Officer's decision to treat with a full course of anti-TB therapy. Whenever needed, investigative procedures such as X-Ray, FNAC, Pleural fluid aspiration, ultrasonography, computed tomography, MRI were performed for diagnosis and specimen collection. The specimen was then subjected to a culture or histopathology for evidence of TB. After diagnosis of EPTB, patients were registered at DOTS Centre, whereas patients belonging to other villages or districts were referred to DOTS centres of their respective area. Data analysis has been done using Microsoft Office Excel 2010 and expressed in percentages.

At the first step, all the records pertaining to EPTB cases diagnosed during the study period were collected and analysed. Total 130 cases diagnosed as EPTB were included in the study. Clinical and epidemiologic characteristics of the patients were abstracted from laboratory records, medical files and were categorized as: age in years (0 - 9; 10-19, 20-39; 40-60; >60), gender (male/female), urban or rural, diabetic or non-diabetic and HIV status (positive, negative, not done).In addition, patients with EPTB were grouped into seven categories, based on site of involvement- (1). Pleural cavity, (2) Peripheral Lymphatic and Lymph Nodes, (3) Genitourinary, (4) Bone and Joint, (5) Abdomen, (6) Skin and muscles, (7) Others -miliary, ocular, breast, CNS etc.

Results

Table No 01: Pattern of Distribution of tubercular patients in study population

Type of TB	Number of cases		Total	Percentage
PTB	358	72.91%	361	73.53%
EPTB with PTB	03	00.61%		
EPTB alone	130	26.40%	130	26.47%
Total	491		491	100%

Table no.01 depicts that out of 491cases of tuberculosis, 358 (72.91%) were diagnosed as PTB group, 3 (0.61%) cases had EPTB and TB (so grouped under PTB as per RNTCP). Rest 130 (26.47%) were diagnosed as EPTB. Hence 130 patients of EPTB were included in the study. The ratio of percentage EPTB: PTB was 1:3.6.

Table No 2: Demographic characteristics of EPTB cases

Age Group (In Years)	Sex distribution				Total (%)	
	Male (%)		Female (%)			
0-9 Years	06	04.61%	06	04.61%	12	09.23%
10-19 Years	13	10.00%	07	05.38%	20	15.38%
20-39 Years	25	19.23%	29	22.30%	54	41.53%
40-60 Years	21	16.15%	16	12.30%	37	28.46%
>60 Years	05	03.84%	02	01.53%	07	05.38%
Total	70	53.84%	60	46.15%	130	100%

Table No 03: Frequency distribution of different sites of EPTB

S. NO	Site of Tuberculosis		Type of EPTB	No of cases (%)		Total No of cases (%)	
1	Pleural cavity		Pleural effusion	28	21.53%	30	23.03%
			Hydro-pneumothorax	01	0.76%		
			Empyema	01	0.76%		
2	Lymph nodes & peripheral lymphatics		Cervical LN	35	26.92%	40	30.76%
			Sub-mandibular LN	03	2.30%		
			Supra-Clavicular LN	01	0.76%		
			Parahilar LN	01	0.76%		
3	Genitourinary		Endometrial	02	1.53%	05	03.84%
			Salphingitis	01	0.76%		
			Renal	01	0.76%		
			Spermatic cord	01	0.76%		
4	Bones & Joints		Arthritis of joints(Ankle, hip, knee, wrist)	10	7.69%	15	11.53%
			Pott's spine	04	3.07		
			Dactilitis	01	0.76		
5	Abdomen		Koch's Abdomen	18	13.84%	18	13.84%
6	Skin & Muscles		Cutaneous	06	4.61%	08	06.15%
			Abscess	01	0.76%		
			Psoas abscess	01	0.76%		
7	Others	CNS	TB Meningitis	03	2.30%	14	10.76%
			Tuberculoma	03	2.30%		
		Breast	Fibroadenoma	04	3.07%		
			TB + Carcinoma Breast	01	0.76%		
		Ocular	Ocular TB	02	1.53%		
		Miliary	Miliary	01	0.76%		

Table No-02 shows that women and men each accounted for approximated half of the cases. Out of 130 EPTB patients, 70 (53.84%) were males, 60 (46.15%) were females. Male to female ratio was 1.16:1. Among the 5 age groups studied, the age group of 20-39 years had the highest proportion of EPTB 54 (41.53%) both in males and females which is the economically productive population of society. Next most affected was 40-60 years age group (n-37, 28.46%). Paediatric age group has 9.23% contribution. The lowest proportion (n-7, 5.38%) was observed in the geriatric age group (.>60 years old). In this study out of 130 cases of EPTB, 81 of them reside in urban areas (62.30%) whereas 49 cases (37.69%) came from rural areas.

Table No-03 shows that maximum number of cases belongs to lymph nodes and lymphatic (30.76%), pleural cavity is second most common site with 23.03%. Rest of the cases were found in decreasing order inabdomen 13.84%, bones & joints 11.53%, skin & muscles 6.15% and Central Nervous System 4.61, Genitourinary tuberculosis and breast tuberculosis, eachaccounted for 3.84% of cases. Ocular (1.53%) andmiliary tuberculosis (0.76%) were having minimal incidence. In this study, pleural, bone& joints, skin & muscles, meningeal, miliaryand ocular TB appeared to be more commonly observed among the male patients while lymph nodes, genitourinary and breast TB cases were predominant among females. Abdominal tuberculosis was found in equal proportions in both males and female population.

Table No-04: Clinico-epidemiological trends- Age, Sex and Site specific distribution of EPTB

S No	Site of EPTB		Age Group (In years)																	
			0-9 yrs.			10-19yrs		20-39yrs			40-60 yrs.			>60 yrs.			TOTAL		
			M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
01	Pleural		0	0	0	2	3	5	9	5	14	7	2	9	2	0	2	20	10	30
02	Lymphatics		2	5	7	2	2	4	5	12	16	5	6	11	1	0	1	15	25	40
03	Genito-urinary		0	0	0	0	0	0	1	3	4	0	1	1	0	0	0	01	04	05
04	Bones & Joints		1	0	1	2	0	2	3	3	6	5	1	6	0	0	0	11	04	15
05	Abdomen		1	0	1	2	1	3	4	5	9	2	2	4	0	1	1	09	09	18
06	Skin & Muscles		0	1	1	1	2	3	2	0	2	1	0	1	1	0	1	05	03	08
07	Others	i.Breast ii.CNS iii.Miliary iv.Occular	02 00 02 00	00 00 00 00	02 00 02 00	02 00 00 00	00 00 00 00	02 00 00 00	01 10 10 00	20 00 00 00	21 10 10 00	00 11 11 00	20 00 00 00	30 11 11 00	00 00 01 00	10 00 00 00	10 00 01 00	00 05 02 02	05 00 00 00	05 05 02 02
	Total		6	6	12	11	8	20	26	30	54	22	14	37	5	2	7	70	60	130

Table No. 04 shows that involvement of pleural cavity and lymph nodes were the commonest manifestation among the 20-39 yrs age group (n-14, 10.76% & n-16, 12.30% respectively). In the youngest age group (< 9 years), lymph node TB was the most frequently observed, accounting for more than half of the EPTB cases (n-7/12). In contrast, in the adolescent and in geriatric age group (>60 yrs.) the most common type of EPTB was pleural cavity, lymph nodes, abdomen, skin & muscles. Whereas in the remaining adult population (20-39, 40-60 yrs.), the most common types was pleural cavity (n-23, 17.69%), lymph-nodes (n-27, 20.76%) and abdomen (n-13, 10%).

Table No-5: associated risk factors in EPTB cases

EPTB	**Diabetes**			**Carcinoma**	**COPD**	**HIV**		
Age	M	F	T (%)			Positive	Negative	Not Done
0-9 yrs	0	0	0	0	0	0	0	12
10-19yrs	0	0	0	0	0	0	10	10
20-39yrs	0	0	0	0	0	0	34	20
40-60 yrs	4	3	07(5.38%)		1(0.76%)	0	27	10
>60 yrs	2	1	03(2.30%)	1(0.76%)	2(1.53%)	0	07	0
Total	6	4	10(7.69%)	1(0.76%)	3(2.30%)	0	78(6%)	52(4%)

Table No-05 shows that only 10 cases (7.69%) out of 130 had diabetes mellitus, in which n-6 (4.61%) were males and n-4 (3.07%) were females. All the patients were of age 40 years and above. 3 cases (2.30%) had chronic obstructive lung disease but no cases had associated HIV infection. One patient had coexistent carcinoma.

Discussion

The prevalence of Extra Pulmonary Tuberculosis (EPTB) is increasing over the last several years globally. Risk of EPTB is determined by the degree of exposure to the pathogen and host immune factors like HIV, diabetes, malignancy, malnutrition, chronic renal disease, liver disease, post organ transplant etc [4,7]. Identification of the risk factors that predispose to EPTB would allow for targeted strategies to prevent active tuberculosis infection and hence decrease the prevalence of EPTB.

As per RNTCP, the prevalence of EPTB in non-HIV patients was 15%-20% [4], but in our study it was 26.47%,which is more than the RNTCP statistics. This increase in prevalence is due to availability of advanced diagnostic facilities at low cost in medical college settings and tertiary care referral centre [5]. In this study, the ratio of percentage of EPTB: PTB is 1:3.6 which is similar to other studies and national statistics. [9,10].

In this study 62.30% patients were belong to urban areas and only 37.69% belong to rural areas, whereas in other countries like Ethiopia, majority were rural dwellers (67.4%)[11]. This may emphasize the fact that awareness, diagnosis and reporting of EPTB is still lacking in rural areas of Madhya Pradesh.

Globally, women were found to be more at risk of developing EPTB [12,13,14]. In contrast, in this study, the male: female ratio was found 1.16:1. Prevalence of EPTB was found to be higher in male than female (53.84% Vs 46.15%). Male preponderance has also been found in various other studies from India and other countries like Ethiopia, Nigeria, Turkey etc.[5,11,14,15]. The failure to detect an increased association between female sex and EPTB in our study could be due social stigma associated with TB which hinders female population especially those belonging to rural areas, to seek medical assistance from DOTS centre in developing countries [16,17]. Small sample size may be another possibility.

Although EPTB cases were found in all age groups but majority of cases (41.53%) belonged to the age group of 20-39 years, which constitutes of young adult and working individuals. This is the reproductive and working group in both males and females and is economically productive population. This highlights the socio-economic burden of EPTB on Indian economy also. Similar reports of high prevalence of EPTB among economically and sexually productive age groups, especially in endemic countries, was reported globally by various studies from India, Ethiopia, Pakistan, San Francisco, Saudi Arabia ,USA, Nepal etc.[5,11,13,18,19,20,21]. Our study shows that young adult is itself an independent risk factor for EPTB. The possible explanation of this may be because of reactivation and spread of TB from primary infection from the lungs to extra-pulmonary sites, delayed diagnosis of primary tuberculosis because of lack of time and decreased immunity to due life style changes and improper nutrition.

Globally, lymph node TB continues to be the most common form of EPTB, of which cervical group of lymph nodes is most commonly affected[5,11,20,22].In our study also we found similar pattern, lymph node tuberculosis being the most common site in which majority of cases were of cervical lymph nodes. Similar pattern of distribution was found in studies from Ethiopia, Canada, Turkey, Nepal and other Indian studies [11, 21,23,24,25]. Second most common site of involvement of EPTB was pleural cavity (23.03%). Rest of the EPTB cases distributed in decreasing order of

sites were abdomen, bones & joints, skin & muscles and genitourinary tuberculosis, which is similar to studies from India and world [23,24,25,26]. The national pattern of distribution of EPTB sites, as per RNTCP statistics reports a similar pattern as this studies lymph node 47%, pleural cavity 30%, abdomen 10%, bones and joints 8% TB, CNS 2% and 3% others)[27].

The difference in the occurrence of EPTB by site in different age groups and sexes shows the difference in predilection to involve one site over the other depending on the host factors such as immunity status. In our study most common sites involved in EPTB cases in the age groups 20-39 years was lymph node and pleural cavity (25.38%) as seen in other studies also [5,6]. Tubercular lymphadenitis is more frequent in female whereas tubercular pleural effusion is more common in male. Genitourinary tuberculosis was most common in young females (20-39yrs) and CNS tuberculosis was more common in male adolescents. Such demographic and social factors contributing to the development of EPTB were identified by previous reports as well [5,7,15,21,22,25,26].

A number of environmental and social modifiable risk factors make people more susceptible to tuberculosis infections by decreasing their immunity, the modification of which at the population level could have significant impact on the incidence of TB. The most important risk factor globally is HIV infection where extra-pulmonary involvement can be seen in more than 50% of patients with concurrent HIV and TB infection [4,7]. As per NACO guidelines, HIV testing was carried out only with consent; hence the association between HIV infection and EPTB could not be established due to lack of adequate data. However all the cases tested for HIV was negative. Madhya Pradesh is a low prevalent (0.09%) state for HIV as per NACO statistics 2011[28,29]. Hence, the higher number of EPTB cases in this study is not due to HIV infection but is because of increased availability of advanced diagnostic facilities in medical colleges in recent years.

The cumulative effect of other risk factors such as smoking, malnutrition and alcohol consumption increases the prevalence of both tuberculosis and diabetes [30,31]. Diabetes increases the risk of developing TB approximately three times, as it produces an immuno-compromised state and pleural effusion is the most common site of EPTB involvement [4]. The prevalence of EPTB with diabetes is 7.69% in our study, which is similar to the prevalence in different studies (5.4%-12.8%) [31,32]. So, routine screening of TB patients for DM can be helpful for early diagnosis and hence improve EPTB treatment outcomes.

Elderly, alcoholics, malnourished, HIV-infected, tobacco smoking and those with underlying COPD appears to be significant risk factors especially for relapse in already treated PTB cases [33]. COPD was found in 3 patients (2.30%) EPTB occurs 9 to 22 times more frequently in cancer patients than in the general population due to their immune-compromised state which is the result of the underlying malignancy and its treatment [34]. In our study we had only one case of carcinoma with associated tuberculosis of breast (0.76%).

Our study had several limitations .The main limitation of the study is that the being a retrospective, hospital-based study, the findings cannot be generalized to the community, but it gives valuable information regarding trend of EPTB cases in Bhopal and the associated risk factors. Although associated HIV infection is known risk factors for increasing EPTB infection, HIV status was not known in substantial number of EPTB cases. The small sample size of this study limits the calculation of the true prevalence of EPTB for the state of Madhya Pradesh. Furthermore the study being record based, it did not include information of other possible risk factors such as nutritional status, smoking, alcohol intake, drug addiction, vitamin D3 status etc.

Conclusion

Extra pulmonary tuberculosis remains a significant health problem in developing countries. In conclusion, our study expands the knowledge regarding the epidemiology of EPTB and enhances understanding of the relative contribution of host related factors to its pathogenesis. The frequency of EPTB in this study was higher with the highest proportion in lymph node. Moreover, being male patient was at higher rate of positivity for EPTB than female. Young adults between age 20-39 yrs, and associated diabetes mellitus were significant risk factors for patient being EPTB positive. Based on the above conclusions the following recommendations are forwarded:

(1) Newer diagnostic tests like molecular characterization, PCR etc which are sensitive and specific and easy to use for early detection and confirmation of diagnosis of EPTB, should be made available through government programmes in rural resource-poor settings.

(2) Large scale, community based studies and well-defined programme-specified protocols for education and prevention of EPTB are needed for decreasing its burden as it is a curable disease.
(3) Young adult males of 20-39 yrs. is the target population even in rural areas, who should be examined and investigated thoroughly to rule out EPTB, so that burden of EPTB cases on society decreases and hence improve the nation's economy**.**

List of abbreviations
EPTB: Extra-pulmonary tuberculosis, **PTB:** Pulmonary tuberculosis, **TB:** Tuberculosis, **RNTCP:** Revised National Tuberculosis Control Programme, **DOTS:** Directly Observed Treatment Short course chemotherapy, **HIV:** Human Immunodeficiency Virus

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