



Retrospective analysis of extrapulmonary tuberculosis: a cross sectional study from a medical college, Chitwan, Nepal.

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Abstract

Background

Extrapulmonary tuberculosis (EPTB) is an important clinical problem which can cause various complications and lifelong disabilities. Various sites of the body can be affected by EPTB. The aim of this study was to find out the common sites of EPTB, in different organ systems and to assess the pattern of disease correlating age and gender among the patients of Chitwan, Nepal.

Methods

This study was carried out on 89 cases of EPTB, diagnosed in Pathology Department of Chitwan Medical College Teaching in biopsy specimens from April 2009 to March 2011. All the cases of EPTB were divided into two major groups, depending on the involvement of lymph node.

Results

Lymph nodes were common sites (42%) of EPTB, and 43% cases cervical lymph nodes involved. Females were more prone for lymph node tuberculosis. Among males, cervical, inguinal lymph node infections were more. Axillary and supraclavicular regions were affected more in females. Majority of the lymph node infections were observed in the age group below 20 years. Axillary lymph node involvement was only observed in 20-40 years of age group; same as supraclavicular lymph node infection in >40 age group.

Conclusion

EPTB can occur in various parts of the body and lymph nodes are most common sites. Cervical lymph node infections were commonly observed. Most of the cases are seen in 2nd to 4th decades. Clinical presentation changes, depending to site of infection in extrapulmonary tuberculosis, so biopsy with histopathological examination may play significant role in diagnosis.

Key words

Biopsy, extrapulmonary tuberculosis, histopathology, lymphadenitis, Nepal.



Background

Tuberculosis (TB) is considered as a major global public health problem. According to a survey, one-third of the world's population is infected with mycobacterium tuberculosis [1]. After primary infection with the bacillus, there is a chance of reactivation and other organ involvement. Recent scientific reports have suggested that sites of infection of extra-pulmonary tuberculosis (EPTB) in the human body vary with geographic location [2-5]. Immunocompetence is a cause of EPTB infection about 15 to 20% of all cases of tuberculosis and a major risk factor 50% among the HIV-positive individuals. The most common site of infection in EPTB is Lymph node which is followed by pleural effusion and any other human body organs [6, 7]. Cervical adenopathy, inguinal, axillary, mesenteric, mediastinal, and intramammary infections in EPTB is well documented [8-12]. In most of the cases, lymphadenitis occurs at the age of 20 to 40 years, and in the patients without HIV infection shows chronic, nontender lymphadenopathy [10-12]. Lymph node biopsy including histological characteristics, AFB stain, and mycobacterial culture is the most useful choice of diagnosis for this disease [11-12]. In EPTB, there is involvement of other organs like skin, abscess wall, joints, intestine, perianal fistula, sinus tract, pleura, breast, testes, larynx, other# [13-22]. Organ involvement severity also varies in different conditions. Although less, pleural tuberculosis in United States responsible for 5% of total cases [20]. In contrast, bone and joint TB relatively more, 35% of cases, which sometimes involves spine, followed by tuberculous arthritis, a clinical condition which affects weight-bearing joints and extraspinal tuberculous osteomyelitis [15-17]. Abdominal tuberculosis affects gastrointestinal tract, peritoneum, mesenteric lymph nodes. Military tuberculosis is responsible for EPTB in other organs like liver, spleen, adrenal glands [23].

In developing countries, TB is considered as the major infectious disease, accountable for maximum death. According to the Global Tuberculosis Report 2014, WHO, Tuberculosis was considered as one of the world's deadliest communicable diseases. Most striking finding by the WHO, in the year 2013, 9.0 million people developed TB and mortality was 1.5 million, 360 000 of whom were diagnosed with HIV infections. There is a progressive slowness in the growth rate each year. 37 million lives were saved worldwide, between a period of 2000 and 2013 through effective diagnosis and treatment. Globally, there is also a decline in the TB mortality rate around 45% between 1990 and 2013 and the TB prevalence rate fell by 41% during the same period [24]. Estimates of the burden of diseases caused by TB in the SAARC Region 2012 shows highest rate of TB in Pakistan followed by Bangladesh, Bhutan, Afghanistan, India, Nepal, Sri Lanka and Maldives. For the

detection of cases, Nepal is in 3rd position. According to the report, prevalence of TB (all cases / 100 000 population) is 243 and mortality (deaths/100 000 population) is 51 in Nepal [25]. Neighboring country India, responsible for one-fifth of the global TB incidence, around 1.98million cases each year. Diagnosis of EPTB is a clinical challenge for physicians because of frequently atypical clinical presentation mimicking other inflammatory and neoplastic conditions. So, a high index of suspicion helps in the early detection, and more than one procedure is required for the diagnosis. This is a difficult challenge for underdeveloped countries due to poor diagnostic infrastructure potential [26].

There are few retrospective studies and case report available mainly from the valley of Kathmandu, not from any other places in Nepal. Therefore, we carried out this study to find out the most common sites of infections in EPTB prevailing in the central region of Nepal, correlating demographic factors [27-29].

Material and Methods

Study Period

This retrospective study was carried out in Pathology Department of Chitwan Medical College Teaching Hospital (CMCTH) from April 2009 to March 2011.

Study design and collection of data

A total of 89 cases of EPTB were diagnosed in histopathology department of CMCTH in these three years period in biopsy specimens. Age, gender, site and histopathological findings were retrieved from the biopsy records of pathology department. Cases with epithelioid cell granuloma with Langhans giant cells and, with or without caseation necrosis were diagnosed as tuberculosis. The cases of EPTB were divided into two groups, depending on the association of lymph nodes, which was further classified according to the involved group of lymph nodes.

Inclusion criteria

All the cases diagnosed as EPTB in biopsy specimens were included in the study.

Exclusion criteria

Level of serum creatinine more than 2 mg/dL, under medication of corticosteroids or other immunosuppressive agents during diagnosis, malignancy and diabetes mellitus were set up as exclusion criteria.

Outcome variable

Site of extra-pulmonary tuberculosis, involvement of lymph Node was considered as outcome variable



Table – 2 Gender variation, groups of lymph nodes and involvement of other organs in EPTB

Lymph Node involved n(%)	Other organs involved																	
	Lymph node (cervical)	Inguinal	Axillary	Submandibular	Supraclavicular	Submental	Postauricular	Skin	Abscess wall	Joints	Intestine	Perianal fistula	Sinus tract	Pleura	Breast	Testes	Larynx	Other#
Male	10(21.3)	4(8.5)	1(2.1)	2(4.3)	1(2.1)	0(0)	0(0)	4(8.5)	4(8.5)	3(6.4)	2(4.3)	4(8.5)	3(6.4)	2(4.3)	0(0)	2(4.3)	3(6.4)	2(4.3)
Female	6(14.3)	2(4.8)	3(7.1)	2(4.8)	2(4.8)	2(4.8)	2(4.8)	7(16.7)	2(4.8)	1(2.4)	2(4.8)	0(0)	1(2.4)	1(2.4)	2(4.8)	0(0)	0(0)	7(16.7)
Total	16(18.0)	6(6.7)	4(4.5)	4(4.5)	3(3.4)	2(2.2)	2(2.2)	11(12.4)	6(6.7)	4(4.5)	4(4.5)	4(4.5)	4(4.5)	3(3.4)	2(2.2)	2(2.2)	3(3.4)	9(10.1)
P value	0.109																	

Table – 4 Relation between age groups, involvement of lymph nodes and other organs in EPTB

Lymph Node involved	Other organs involved																	
	Age	Lymph node (cervical)	Inguinal	Axillary	Submandi bular	Supraclavicular	Submental	Postauricular	Skin	Abscess wall	Joints	Intestine	Perianal fistula	Sinus tract	Pleura	Breast	Testes	Larynx
<20	7(31.8)	2(9.1)	0(0)	1(4.5)	0(0)	1(4.5)	1(4.5)	2(9.1)	2(9.1)	1(4.5)	0(0)	1(4.5)	1(4.5)	0(0)	0(0)	0(0)	0(0)	3(13.6)
20-40	5(13.2)	1(2.6)	4(10.5)	3(7.9)	0(0)	0(0)	1(2.6)	6(15.8)	3(7.9)	1(2.6)	3(7.9)	3(7.9)	0(0)	2(5.3)	0(0)	2(5.3)	0(0)	4(10.5)
>40	4(13.8)	3(10.3)	0(0)	0(0)	3(10.3)	1(3.4)	0(0)	3(10.3)	1(3.4)	2(6.9)	1(3.4)	0(0)	3(10.3)	1(3.4)	2(6.9)	0(0)	3(10.3)	2(6.9)
Total	16(18.0)	6(6.7)	4(4.5)	4(4.5)	3(3.4)	2(2.2)	2(2.2)	11(12.4)	6(6.7)	4(4.5)	4(4.5)	4(4.5)	4(4.5)	3(3.4)	2(2.2)	2(2.2)	3(3.4)	9(10.1)
P value	0.076																	

Explanatory variables

Demographic factors like age group, gender were set up as explanatory variable

Ethical committee approval

The samples used in this study were from routine clinical specimens. Acquiring the samples did not involve direct patient contact and did not interrupt routine clinical care, consent was not required. Permission to conduct the study was obtained from the Head of the Pathology Department.

Data management and statistical analysis

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS) for Windows Version 20.0 (SPSS Inc; Chicago, IL, USA). The associations between different variables (age group, gender, site of infection etc.) were tested using the Chi-square test. A p value less than 0.05 was considered statistically significant.

Results

A total of 89 cases (47 male, 42 female) of EPTB were diagnosed in pathology department during the two years period. Among 89 cases, 37 cases (42%) were associated with lymph nodes and remaining 52 cases (58%) were in extra nodal sites. On histopathological examination, caseation necrosis was absent in 10 cases (11%) and Ziehl-Neelsen stain (Z-N stain) was positive in only 7 cases (8%).

Table-1: Gender wise distribution of site of infection in EPTB.

Gender	Site of extra-pulmonary tuberculosis n(%)			P value
	lymphnode	other organs	Other#	
Male	18 (38.3)	27(57.4)	2 (4.3)	0.069 ^x
Female	19 (45.2)	16(38.1)	7(16.7)	
Total	37(41.6)	43(48.3)	9(10.1)	

^xP>0.05, statistically not significant

Females were more prone for lymph node tuberculosis than males. Among males infections were more in other organs (Table -).

Table 2 explains gender variation, groups of lymph nodes and involvement of other organs in EPTB. Among males, cervical, inguinal lymph node infections were more. Axillary and supraclavicular regions were affected more in females. Considering other organs, males were infected more in EPTB with abscess wall, joints, perianal fistula sinus tract, pleura; whereas skin, intestine and other# were more frequent site of infection in females, apart from respective reproductive organs.



Table – 3: Age distribution and site of extra-pulmonary EPTB

Age	lymphnode	other organs	Other#	P value
<20	12(54.5)	7(31.8)	3(13.6)	0.489*
20-40	14(36.8)	20(52.6)	4(10.5)	
>40	11(37.9)	16(55.2)	2(6.9)	
Total	37(41.6)	43(48.3)	9(10.1)	

*P>0.05, statistically not significant

Majority of the lymph node infections were observed in the age group below 20 years. On contrast, other organ involvement were relatively more in the age group 20-40 years and >40 years (Table 3).

Table 4 represents relation between age groups, involvement of lymph nodes and other organs in EPTB. Maximum infection in cervical lymph node was observed in the age group below 20 years. Axillary lymph node involvement was only observed in 20-40 years of age group; same as supraclavicular lymph node infection in >40 age group. Submandibular lymph node affected more in 20-40 years of age. 20-40 years age was most vulnerable for EPTB in skin, abscess wall, intestine, perianal fistula, pleura and others#. On contrary, among the >40 years of age group, ECT infection was evident in joints, sinus tract and larynx.

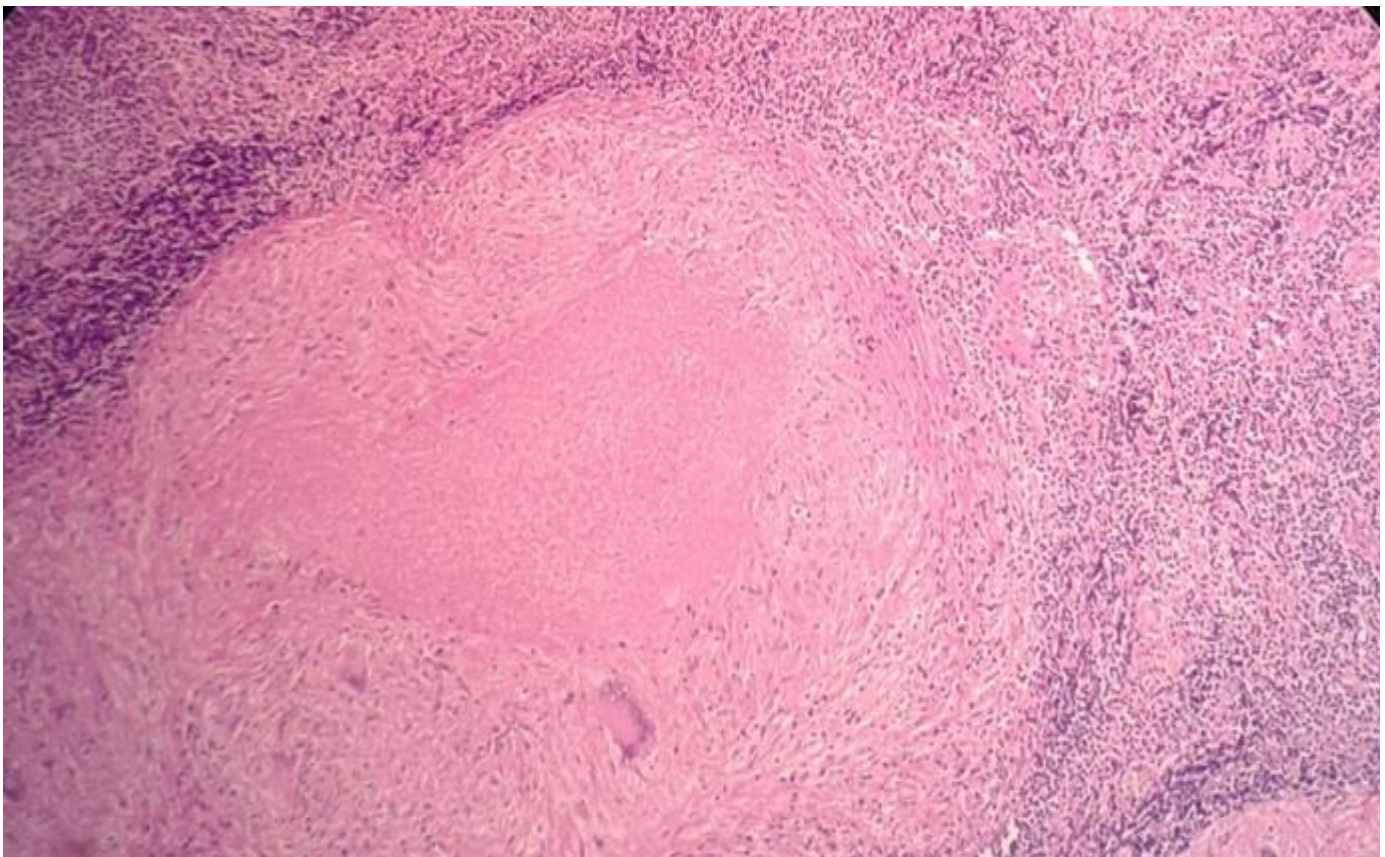
DISCUSSION

Out of the investigated samples from the various extrapulmonary sites, most of the isolates were obtained from urinary, pelvic and cold abscess. Some researchers found caseating granuloma in 62-72% of cases and Z-N stain is positive for acid fast bacilli (AFB) in 8% of cases, in our study we observed caseation necrosis was absent in 11% cases and Z-N stain is positive for 8% [30]. Another obtained a wide range of AFB positivity, upto 75% [31].

Influence of gender and site of infection in EPTB.

EPTB can involve different organs of the body at any age and gender. Cases of EPTB are increased with human immunodeficiency virus infection. Our study shows higher number of EPTB in male than in female with male to female ratio 1.17:1. This finding is in accordance with several other studies [2, 4, 32] but contradictory to other researchers, where, female preponderance was observed, which explain sociocultural factors leading to malnutrition in females as main cause [33-37].

Figure - 1 Microscopic features of epithelioid cell granuloma of lymph node with central caseation necrosis and Langhans giant cell. (H&Estain;10X)





Gender variation, groups of lymph nodes and involvement of other organs in EPTB

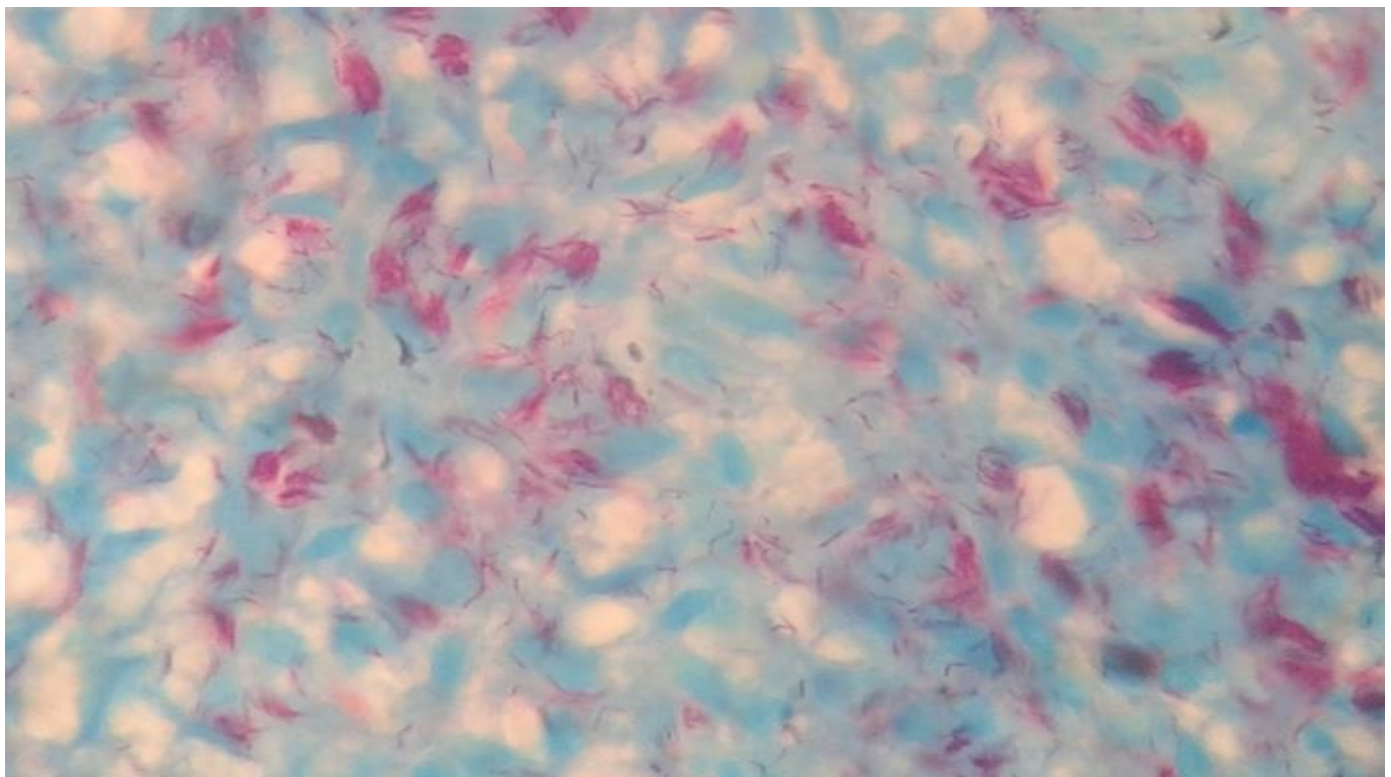
Earlier researches show that cervical lymph node is the commonest area for infection and Lymph nodes were the most common site of EPTB, involved in 66.4% of the cases [34]. Our findings resemble this result, where maximum numbers of cases were in the cervical Lymph nodes. This is also in accordance with some other findings, where pleura, or bone and joints as the commonest site of EPTB [2, 38]. Researchers from Nepal, and the Netherlands have also reported high number of cases with lymph node involvement [33, 35].

In the earlier studies, it was observed that females were more prone for Lymph node TB, central nervous system (CNS) tuberculosis and tuberculosis of bones, joints and males with pleural TB and abdominal TB. In our research, we observed that males were infected more in EPTB with abscess wall, joints, perianal fistula sinus tract, pleura; whereas skin, intestine and other[#] were more frequent site of infection in females [39].

Age distribution and site of EPTB

In the present study maximum number of lymphnode infection was observed in the age group of 20-40 years.

Figure-2: Microscopic PICTURE OF Mycobacterium tuberculosis in lymph node. (AFB stain;100X)



This findings resembles to other studies [10] but contradictory to the findings of Prakasha SR *et al.*, where lymph node manifestatio occurred mostly, less than 14 years' age group [40]. This may be related to duration of exposure of bacilli.

[[#] - there were two cases amongst male- tuberculosis of phalynx and peritoneal tuberculosis. In females, there were 7 cases – tuberculosis of right kidney, omentum, tonsil, fallopian tube, nasopharynx, corn on left sole and ureter].

Conclusion

EPTB can occur in various parts of the body and lymph nodes. Among them, cervical lymph node is the most commonest one. It is frequent in 2nd to 4th decades and less common in children and old age. Biopsy with histopathological examination is important for its diagnosis as clinical presentation may vary according to the site of infection. This present study gives a relatively clear scenario in the Bharatpur, which facilitate the govt. policy makers to plan health care programme in this area.

Limitations & future scope of the study

This was a retrospective study with small number of cases with limited available data. Further study can be done on the basis of socioeconomic details, caste, area of residence rural or urban, to find out the correlation with the risk factors of



EPTB. Detailed study, comparing various parameters of pulmonary tuberculosis with EPTB will also help to understand the clinical scenario.

Abbreviations

Acid fast bacilli (AFB), Chitwan medical college teaching hospital (CMCTH), Extrapulmonary tuberculosis (EPTB), Human immunodeficiency virus (HIV), Tuberculosis (TB), World health organization (WHO), Ziehl-Neelsen Stain (Z-N stain)

Competing interests

Authors do not have any competing interests.

Authors' contribution

Dr. Mamata Tiwari designed the study, collected and interpreted the data, drafted the manuscript, and revised it. Dr. Sushna Maharjan and Dr. Sabin Ranabhat took part in data collection and critically revision of the manuscript. Final manuscript was approved by all authors.

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