

Evaluation of 257 extra pulmonary tuberculosis cases at the Tuberculosis Control Dispensary, Van, Turkey

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Abstract

Objective: To determine whether there were any changes in demographic and clinical features of extrapulmonary tuberculosis cases.

Methods: This retrospective study was conducted at Yuzuncu Yil University, Van, Turkey, and comprised records of extrapulmonary tuberculosis patients treated between January 2009 and July 2014 at the tuberculosis control dispensary. Descriptive and clinical data, including age, gender, site of involvement, diagnostic method and coexisting systemic diseases, were noted. Any changes in terms of these parameters were investigated on a year-on-year basis. SPSS 20 was used for data analysis.

Results: There were 257 cases detected. Of them, 50(19.45%) related to 2009, 61(23.75%) to 2010, 24(9.33%) to 2011, 50(19.45%) to 2012, 47(18.28%) to 2013 and 25(9.72%) to 2014. Although lymph nodes were by far most frequently affected in 2009, 2010, 2011 and 2013; pleura was most commonly involved in 2012 and 2014. Age and gender distribution displayed no changes between 2009 and 2014 ($p>0.05$). However, diagnostic method of choice and frequency of co-existent systemic disorders displayed remarkable alterations in this period ($p<0.05$).

Conclusion: Improved insight of clinicians for atypical demographic and clinical features at presentation may provide reduction of rates of morbidity and mortality due to extrapulmonary tuberculosis.

Keywords: Tuberculosis, Extrapulmonary, Epidemiology, Diagnosis. (JPMA 68: 764; 2018)

Introduction

Tuberculosis (TB) is a chronic and granulomatous infection which constitutes a major global health problem. It is caused by mycobacterium tuberculosis in the majority of cases and multisystemic involvement may be seen.^{1,2} Tuberculosis can involve any organ system in the body. Even though pulmonary TB is the most common presentation, extrapulmonary tuberculosis (EPTB) also comprises an important clinical entity. The term EPTB indicates an isolated occurrence of tuberculosis at body sites other than the lung.³

The foci of infection may stay dormant due to a functional immune system initially. However, the disease may be reactivated at anytime and anywhere in the body leading to the clinically manifest EPTB.^{3,4} Lymph nodes, pleura, skin, gastrointestinal system, bones and joints are commonly affected by EPTB.^{1,5,6} Atypical presentation, diagnostic challenges, increasing prevalence and serious sequelae and complications necessitate an insight for

timely recognition of EPTB.^{2,3} Unless diagnosis is set immediately and appropriate treatment is initiated, high rates of morbidity and mortality may be encountered.

In Germany, proportion of TB patients with extrapulmonary manifestations was found to be 21.6%. Females, children, people of African and Asian origin seemed to be more vulnerable for EPTB. Pleural TB was more likely to exist in males rather than females. Children were especially prone to develop meningeal and lymphatic involvement, while genitourinary system was more likely to be involved with advancing age.⁴

The incidence of extrapulmonary and disseminated tuberculosis (cases where pulmonary and EPTB are found in the same patient) is increasing worldwide, and this growth significantly impacts TB-related morbidity and mortality. Little is known about the host risk factors for extrapulmonary variety.⁷

The current study was planned to identify the demographic and clinical features of EPTB and to investigate whether there were any alterations in terms of these characteristics over a 6-year period.

Patients and Methods

The retrospective study was conducted at Yuzuncu Yil University, Van, Turkey, and comprised records of EPTB patients treated between January 2009 and July

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2014 at the tuberculosis control dispensary. After approval was obtained from the institutional ethics committee, sample size was calculated using the following equation; $n = [Z / 2 \times p \times (1-p)] / d^2$. Here p is proportion of the event, d is effect size and Z is critical table value for $\alpha = 0.05$. For this study, Z, p and d values were considered as 1.96, 0.5 and 0.06, respectively. Demographical and clinical data was then extracted from medical files of the relevant cases. Age, gender, site of involvement, diagnostic methods and coexistent systemic diseases (CSDs) were recorded.

Diagnosis of EPTB was established according to the definitions of World Health Organisation.^{8,9} In case fine needle aspiration (FNA) biopsy or biochemical analyses of fluid samples or other histopathological examinations yielded relevant results, diagnosis of EPTB was confirmed. Exclusion criteria comprised immune deficiency, simultaneous pulmonary involvement by TB and age less than 18 or greater than 65.

Analysis of data was done using SPSS 20. Conformability of data to normal distribution was assessed with Kolmogorov-Smirnov test. Parameters distributed normally were evaluated with parametric methods, whereas variables without normal distribution were assessed by non-parametric methods. Comparison of categorical variables was carried out using Pearson's Chi-square and Fisher's exact tests. Comparison of age groups in every year was carried out with Kruskal-Wallis test. Quantitative variables were expressed as median, interquartile

range (IQR), and range. Confidence interval (CI) was 95% and level of statistical significance was set at $p < 0.05$.

Results

There were 257 cases detected. Of them, 50(19.45%) related to 2009, 61(23.75%) to 2010, 24(9.33%) to 2011, 50(19.45%) to 2012, 47(18.28%) to 2013 and 25(9.72%) to 2014 (Table-1).

Sites of involvement between 2009 and 2014 showed remarkable statistical difference ($p < 0.001$). Lymph nodes was affected most commonly in 2009, 2010, 2011 and 2013, while pleura and joints were the most common sites of involvement in 2012 and 2014, respectively. Overall, lymph nodes and pleura constituted more than half of the organs involved (Table-2).

The median age for EPTB cases detected every year did not display any statistically significant difference ($p = 0.503$). In terms of age groups no particular group revealed any notable differences ($p = 0.431$).

Similarly, distribution of gender did not exhibit any difference ($p = 0.063$). Biopsy was the most common diagnostic method used for confirming EPTB ($p < 0.001$).

The most common CSD were diabetes mellitus (5.4%), chronic renal failure (3.1%), hypertension (1.9%) and congestive heart failure (1.5%), respectively. Distribution of EPTB patients with CSDs displayed noteworthy alterations. There were 50 patients with CSDs. Of them, 13(26%) related to 2009, 21(34.4%) to 2010, 2(8.3%) to 2011, 3(6%) to 2012, 7(14.9%) to 2013 and 4(16%) to 2014.

Table-1: Overview of demographic and clinical features of our EPTB cases between 2009 and 2014.

Variable	2009	2010	2011	2012	2013	2014	p Value	
Age (median-IQR)	36.00-27.50	36.00-21.00	32.00-21.25	29.00-17.25	31.00-20.00	31.00-34.00	0.503	
Age groups (n)							0.431	
	<31	21	24	11	29	21	11	
	31-50	15	23	11	13	13	7	
	>50	14	14	2	8	13	7	
Mode of diagnosis (n)							<0.001*	
	Biopsy	28	28	12	27	9	10	
	Clinical-radiological	11	2	2	3	7	10	
	Fluid / smear	9	13	8	16	-	3	
	Serology	-	-	2	4	1	-	
	Biopsy and clinical-radiological	1	9	-	-	1	2	
	Fluid /smear and clinical-radiological	1	9	-	-	1	-	
Gender	Male/female	24/26	29/32	15/9	23/27	30/17	7/18	0.063
CSD	Yes	13	21	2	3	7	4	0.002*
	No	37	40	22	47	40	21	

*: Statistically significant

EPTB: Extrapulmonary tuberculosis

CSD: Co-existing systemic disease

IQR: Interquartile range

n: Number of patients.

Table-2: Sites of involvement in EPTB cases between 2009 and 2014.

Site of involvement	2009	2010	2011	2012	2013	2014	n (%)
Lymph nodes	18	27	10	11	18	2	86 (33.46%)
Pleura	8	14	5	17	12	2	58 (22.57%)
Joints	8	1	1	-	1	11	22 (8.56%)
Bone	3	5	0	5	4	4	21 (8.17%)
Peritoneum	3	2	2	5	4	1	17 (6.61%)
Genitourinary	1	4	2	3	2	2	14 (5.45%)
Meninges	0	4	2	1	1	1	9 (3.50%)
Breast	0	0	1	5	1	0	7 (2.72%)
Pericardium	2	3	0	1	0	0	6 (2.33%)
Miliary	3	0	1	0	1	0	5 (1.94%)
Gastrointestinal system	2	0	0	1	2	0	5 (1.94%)
Skin	2	1	0	0	0	1	4 (1.56%)
Eye	0	0	0	1	1	1	3 (1.17%)

EPTB: Extrapulmonary tuberculosis).

Discussion

The aim of the study was to investigate the demographic and clinical characteristics of EPTB patients and to evaluate whether these features displayed variations between 2009 and 2014. Results demonstrated that site of organ involvement; diagnostic methods and rates of patients with CSDs changed significantly during the study period. On the other hand, age and gender features of EPTB patients seemed to be unchanged.

Extrapulmonary involvement either can occur in an isolated fashion or accompanied by a pulmonary focus as in the case of patients with disseminated TB. The recent human immunodeficiency virus (HIV) pandemic has resulted in changing epidemiology and has brought EPTB into focus.¹⁰ Extrapulmonary TB constitutes approximately 15-20% of TB cases in immunocompetent patients and more than 50% of cases in HIV-positive individuals.^{3,10} Lymph nodes are the most common site of involvement followed by pleural effusion and virtually every site of the body can be affected. Since EPTB mostly has an atypical clinical presentation, obtaining tissue samples for confirmation of diagnosis may be difficult and due to the poor yield of conventional diagnostic methods, the diagnosis may be delayed. Availability of more sophisticated radiological methods and endoscopic interventions have tremendously helped in the proper anatomical localisation of EPTB. However, biopsy is usually required to rule in EPTB, to initiate the appropriate treatment and to manage complications.^{3,11}

Involvement of atypical sites such as joints in conjunction with the relatively decreased proportion for lymph node involvement in the last years is another interesting finding. The most common sites of involvement for EPTB

were lymph nodes, pleura, joints, bone and peritoneum. In our series, hilar, mediastinal, cervical and axillary lymph nodes were the most frequently affected entities by EPTB. Physical findings vary with respect to the stage of the disease and enlarged lymph nodes have various sizes and are usually firm. The consistency may become cystic if necrosis and abscess formation takes place. Tenderness of lymph nodes remind the likelihood of secondary bacterial infection.^{9,11}

In contrast to the publication by Forssbohm et al., we came across no predominance of females for EPTB and both genders seemed to be affected similarly between 2009 and 2014.⁴ Neither median ages, nor age groups appeared to vary. Biopsy was by far the most useful diagnostic tool for confirming the diagnosis of EPTB. Clinical and radiological clues as well as fluid / smear analyses aided for ruling in the diagnosis of EPTB.

Females had a higher risk of developing EPTB and the risk of EPTB increased five years after the initial contact.⁶ The reason for this finding could not be elucidated yet, but endocrine factors may be responsible for this circumstance.⁴ Moreover, loss of function polymorphism in the purinergic receptor P2X7 gene increases susceptibility to EPTB in patients from Southeast Asia and it suggests that genetic factors may explain some of these differences.¹²

Even though our findings are in parallel to publications which indicate that lymph nodes were the most common sites involved in EPTB, increases in involvements of bone and joints must be noted.^{1,6,13,14} Yang et al. have suggested that bone and joints were involved more commonly in EPTB, while Noertjojo has reported that

genitourinary system and skin were affected more often than lymph nodes.^{15,16} These variations may be associated with social or environmental factors and it must be remembered that EPTB can exist at unexpected and atypical locations.

Despite the fact that fluid / smear analyses and clinical/radiological clues can be useful in EPTB, biopsy and histopathological diagnosis is usually required for ruling in EPTB.^{2,3,10,11} Improved insight must be supported by choice of appropriate diagnostic method in order to establish the diagnosis and initiate the treatment immediately.¹⁰ Even though culture for mycobacterium TB is the gold standard for establishing the definitive diagnosis, culture and other sophisticated microbiological methods have not been preferred commonly.¹³ The reason underlying this finding may be the limitation of technical facilities.

Limitations of the present study include its retrospective design, relatively small sample size and lack of elimination of socio-economical, ethnic or environmental factors prone to affect the results. Children, elderly (<65 years) and immunocompromised patients were excluded from the study. Attributed to the retrospective design, some critical data, including nutritional status, smoking habit or alcohol consumption, may not be obtained precisely from the medical files. Therefore, extrapolation of our results must be made carefully to larger populations.

Conclusion

EPTB was found to have a broad clinical spectrum with nonspecific symptoms that could involve all organs and systems. In case of doubt, EPTB diagnosis can be omitted. Diagnosis and delays in treatment cause an increase in mortality and morbidity.

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Conflict of Interest: None.

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