

Demographic and microbiological characteristics of tuberculous lymphadenitis and other extrapulmonary tuberculosis cases

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ABSTRACT

Objective: Tuberculosis (TB) is a significant public health problem that remains important worldwide. This study aimed to examine the demographic characteristics and clinical features of patients with extrapulmonary tuberculosis (EPTB) and also identify the comorbidities of EPTB. Our secondary aim was to compare tuberculous lymphadenitis (TBL) with other forms of EPTB.

Patients and Methods: This single-center, retrospective, observational study was conducted on patients diagnosed with EPTB in a training hospital in Turkey between January 1, 2011 and December 31, 2020. The demographic characteristics and clinical features of the patients were examined. TBL cases were compared with other forms of EPTB cases.

Results: The most common clinical form was TBL. Fever, night sweats, and accelerated erythrocyte sedimentation rate were significantly more common in the other forms of the EPTB group compared to TBL. The rate of tuberculin skin test positivity was significantly higher in patients with TBL. The complication rate was 3%, and mortality rate was 4% among all patients.

Conclusions: Extrapulmonary tuberculosis should be considered in the differential diagnosis by evaluating the medical history of patients who present with organ-specific symptoms, especially in TB endemic countries. The clinic may differ according to the organ involvement. TBL may be seen with milder symptoms compared to other clinical forms.

Keywords: Extra pulmonary tuberculosis, Tuberculous lymphadenitis, Mycobacterium tuberculosis

1. INTRODUCTION

Tuberculosis (TB) is a crucial infectious disease that causes mortality and morbidity all around the world, especially in developing countries. According to the World Health Organization (WHO) global report, TB is the 13th cause of death worldwide [1]. In 2020, approximately 10.4 million new TB cases and 1.4 million deaths were reported globally, especially in low and middle-income countries [2]. This rate is equivalent to 127 cases per 100,000 people all around the world. TB is an endemic disease in our country. According to the Turkish Ministry of Health, the total number of cases in our country is 14.4 per 100,000 people [3].

Tuberculosis may appear as a multisystemic disease and pulmonary tuberculosis (PTB) is the most common clinical form. Moreover, TB affects other systems with the hematogenous

and lymphomatous spread [4,5]. Although the exact cause is unknown, the number of extrapulmonary tuberculosis (EPTB) cases are increasing. It might be due to increased risk factors such as human immunodeficiency virus (HIV) positivity, anti-tumor necrosis factor alfa therapies, foreign-born status [6,7]. Earlier studies have shown a high proportion (20%-53%) of cases presenting with EPTB in all TB cases [8-11]. In our country, the rate of EPTB has been found as 34.3% in all TB patients [3]. The most common form of EPTB is tuberculous lymphadenitis (TBL) in countries with a low TB prevalence, while it is tuberculous pleurisy in countries with a high prevalence [12].

Nonspecific symptoms such as fever, night sweats, and a wide spectra of clinical manifestations are seen in EPTB. These patients usually receive treatments for alternative diagnoses

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on their first visit to the primary care setting. The difficulty of sampling specimens and the low rate of microbiological positivity cause delayed diagnosis or misdiagnosis of EPTB patients.

Gold standard diagnostic laboratory tests are microscopic identification of acid-fast mycobacteria from any body fluid by acid-resistant bacilli (ARB) staining or TB polymerase chain reaction (PCR) or mycobacterial culture. Also, tuberculin skin test (TST) demonstrates cellular immunity against mycobacteria and delayed-type hypersensitivity reactions against mycobacterial antigen [12,13].

This study aimed to examine the demographic characteristics and clinical features of patients with EPTB. We also examined the differences between TBL and the other forms of EPTB such as bone/joint, gastrointestinal, genitourinary, meningeal, skin, breast, and eye.

2. PATIENTS and METHODS

Study design

The study was conducted in an 805-bed training and research hospital in Turkey, between January 1, 2011 and December 31, 2020. Older than 18 years old patients were included in the study. TBL cases were compared with other forms of EPTB. Demographic and clinical characteristics of the patients (age, gender, and nationality) were collected from the hospital database. The systemic symptoms such as fever, night sweats, loss of weight, and previous TB histories of the patients and their families were recorded.

To confirm the diagnosis of EPTB, appropriate clinical samples (cerebrospinal fluid, urine, peritoneal fluid, etc.) and biopsy materials were examined histopathologically and microbiologically (ARB staining or TB PCR or mycobacterial culture).

The obtained specimens were cultured in solid (Lowenstein-Jensen, Salubris inc, Istanbul Turkey) and liquid (Becton Dickinson / BD BACTEC MGIT 960, Sparks MD, USA) media. Real-time PCR (GenXpert Ultra, Cepheid) was used for quantitative PCR. In histological examination, necrotizing granulomatous lesions were interpreted as tuberculosis specific. Tuberculin skin test ≥ 10 mm was considered as skin test positive.

Patients with a diagnosis of PTB or coexistence of pulmonary with EPTB were excluded.

The ethics committee of the Health Sciences University of Turkey, Research and Training Hospital approved the study on June 17, 2021, with decision number 191.

Statistical Analysis

Analyzes were performed with Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 21. software statistical programs. Normality control of the tests was done with Kolmogorov Smirnov. Since the distribution of the data was not normal, the values were given as median and 25%-75%. Non-parametric measurement data were compared with

the Mann-Whitney U test in independent groups. Demographic characteristics of the patients were evaluated with the chi-square test. $P < 0.05$ was considered significant.

3. RESULTS

Characteristics of the study patients

A total of 110 patients, (76 (69 %) female), were included in this study and the mean age was 42.8 ± 6.3 . Seven of the patients were non-Turkish citizens. Sixteen patients (15 %) had a history of previously treated tuberculosis. Fifteen patients (14 %) had a family history of tuberculosis. The most common comorbidity was malignancy (n:6, 6 %), followed with hypertension (n:3, 3 %), diabetes mellitus (n:3, 3%), anti-HIV positivity (n:3, 3 %), and chronic renal failure (n:1, 1 %) (Table I).

Of the 110 EPTB, the most commonly seen form was TBL (n:63; 57 %), followed by bone/joint tuberculosis (n: 13; 12 %), gastrointestinal tuberculosis (n:12; 11 %), genitourinary tuberculosis (n:12; 11 %), meningeal tuberculosis (n:7; 6 %), skin tuberculosis (n:1; 1 %), breast tuberculosis (n:1; 1 %), and eye tuberculosis (n:1; 1 %).

While the diagnosis was confirmed histologically in 85 (77%) cases, the number of microbiologically confirmed cases was 63 (57%). Twenty (18%) of microbiologically confirmed cases were culture positive, nine of them (8%) were ARB positive, and 37 (34%) were tuberculosis PCR positive in tissue. TST was positive in 42 cases (38%).

We did not detect any multidrug-resistant isolates. While in the TBL group, only one patient had streptomycin resistance, one patient had streptomycin, and one had pyrazinamide resistance in the other EPTB group.

Among all patients, three patients with tuberculous meningitis and one patient with bone/joint tuberculosis died in the follow-up. Chronic renal failure has been developed in one patient, and infertility has been developed in two patients as a complication of genitourinary tuberculosis. Relapse occurred in a patient with bone/joint tuberculosis. The mortality rate of our study was 4%, and the complication rate was 3% in all patients.

Patients diagnosed with tuberculous lymphadenitis and other extrapulmonary tuberculosis

The TBL and the other EPTB cases were compared. There was no difference in the gender, incidence of malignancy (6 % versus 4 %, $p < 0.39$), diabetes mellitus (0 % versus 3 %, $p < 0.07$), hypertension (3 % versus 0 %, $p < 0.25$), chronic renal failure (0 % versus 1 %, $p < 0.427$), previously treated for tuberculosis (16 % versus 13 %, $p < 0.85$), and family history of tuberculosis (14 % versus 13 %; $p = 1$) between both of two groups.

In other forms of EPTB patients, fever (36% versus 8 %, $p < 0.001$), night sweats (36 % versus 13 %, $p < 0.007$), accelerated ESR (49 versus 29, $p < 0.00$) were significantly more common compared to TBL. TST positivity rate was significantly higher in patients with TBL (46 % versus 28 %; $p < 0.002$) (Table I).

Table I. Demographic characteristics of all patients

	Total	Tuberculous Lymphadenitis (n %)	Other extrapulmonary tuberculosis (n %)	P
Gender				
Female	76 (69)	46 (73)	30 (64)	0.302
Male	34 (31)	17 (27)	17 (36)	
Mean age	42.8±6.3	45±17.1	39.9±17.5	
Nationality				
Turkish citizen	103 (94)	61 (97)	42 (89)	0.135
Comorbidities				
Malignancy	6 (6)	4 (6)	2 (4)	0.391
Diabetes mellitus	3 (3)	0 (0)	3 (6)	0.075
Hypertension	3 (3)	3 (5)	0 (0)	0.259
Chronic renal failure	1 (1)	0 (0)	1 (2)	0.427
Anti-HIV				
Positive	3 (3)	1 (2)	2 (4)	0
Complaint				
Fever	22 (20)	5 (8)	17 (36)	0.001
Weight loss	8 (7)	3 (5)	5 (11)	0.283
Night sweats	25 (23)	8 (13)	17 (36)	0.007
Previously treated for tuberculosis	16 (15)	10 (16)	6 (13)	0.854
Family history of tuberculosis	15 (14)	9 (14)	6 (13)	1
Tuberculin skin test positive	42 (38)	29 (46)	13 (28)	0.002
Accelerated ESR	57 (52)	29(15-40)	49(27-63)	0.003
Mycobacterial PCR				
Positive	37 (33.6)	18 (29)	19 (40)	0.664
Pathology				
Tuberculosis specific histology	85 (77)	55 (87)	30 (64)	1
Mycobacterial culture				
Positive	20 (18)	6 (10)	14 (30)	0.228

ESR: Erythrocyte sedimentation rate, PCR: Polymerase Chain Reaction

4. DISCUSSION

Most of the patients in our study were diagnosed with TBL and were female. Fever, night sweats, and accelerated ESR were significantly common in the other forms of the EPTB group compared to TBL. TST positivity rate was significantly higher in patients with TBL.

In the developing countries, TB is an important disease that may affect all tissues and organs. Although, it varies according to the development levels of the countries, the incidence of EPTB is increasing worldwide [2]. The diagnosis of EPTB is more difficult than PTB because of the nonspecific symptoms and clinical findings.

Previous studies have demonstrated the risk factors for TB. These risk factors included; born in high prevalence countries, poverty, crowded living conditions, undernourishment, low levels of education, use of glucocorticoids, malignancy, smoking, and genetic predisposition [14-18].

Sreeramareddy et al., have found that female patients were more likely to have EPTB in Nepal, a developing country [19]. Also, Djannah et al., have shown that the incidence of EPTB in women is higher than in men in Indonesia [20]. In our study, the female gender is dominant at the rate of 69%. Our study is in line with other studies [21-24]. On the contrary, some articles have shown that being male is a risk factor for EPTB [25-27]. The reason for this gender difference is unclear in different cities and countries. These may be associated with the variability among male-dominant communities where women experience worse living conditions.

Although, there is no consensus on the possible effect of aging, it has been found that younger age may be an independent risk factor for EPTB [19,28]. Other studies have also demonstrated that EPTB is more common in the younger age groups of patients [19,29]. The mean age was 42.8±6.3 in our study and it was similar to other studies from Turkey [28,29]. Older people are more prone to EPTB than the youngsters. This result may be associated with the altered immune function of the body of older people, or it could be due to differences in the prevalence of host-related factors.

In previous studies, extrapulmonary involvement was most common in the lymph nodes 12%, 49%, 26.5%, and 40%, respectively [7,21,25,30]. In our study, the most frequent form was TBL (57%), followed by bone/joint (12%), gastrointestinal (11%), and genitourinary TB (11%). Also, some studies have shown that a common form of EPTB is bone/joint TB, genitourinary TB, or meningeal TB [28,31,32]. The difference may be associated with dietary habits, developing levels, and social restrictions between populations [25].

In a large-scale study, diabetes mellitus, hypertension, anti-HIV positivity, and using immunosuppressive drugs have been found associated with different sites of EPTB [21]. Also, Oztop et al., found that the most common accompanying diseases were diabetes mellitus, and hypertension [24]. The immunosuppressive conditions such as anti-HIV positivity, and using immunosuppressive drugs were known to be associated with EPTB, however little is known about the epidemiological or clinical relationship between malignancy and EPTB. In our study, malignancy was the most common comorbid disease (6%); followed by diabetes mellitus, hypertension, anti-HIV positivity (3%), and chronic renal failure (1%) with EPTB.

Since, the organ-specific symptoms are predominant and variable in each case, the constitutive symptoms are less common in EPTB. In a study from Iran, fever, fatigue, and night sweats were the most common complaints of the patients [33]. Bal et al., found that common symptoms in our country were fever, night sweats, and weight loss [30]. With this finding, most TBL (up to 57%) present with no systemic symptoms and manifest with local symptoms like mass lesions [34]. A small number of

the TBL patients presented with low-grade fever, weight loss, fatigue, and less frequent night sweats [35, 36]. TB bacilli spread via the lymphatics to the lymph nodes initially. Because of the limited disease, patients may not become aware of the illness, and immunity may restrict it. After this period, some bacilli may spread to organs and may be clinically symptomatic with uncontrolled multiplication of TB bacilli [37]. In our study, the major clinical features of all EPTB were night sweats, fever, and the loss of weight. Similar to the other studies, we found that systemic symptoms such as fever and night sweats were less common in the TBL group with statistical significance, respectively ($p=0,001$; $0,007$).

Erythrocyte sedimentation rate is an acute phase reactant widely used in the initial diagnosis of TB. In the study of Mandal et al., in patients with PTB and EPTB, the mean ESR was 67.6 mm/hr. Also, there was no statistically significant difference between the two groups in terms of ESR value [38]. We found that ESR was elevated in 52% of patients, and the median ESR level was significantly higher in the other forms of EPTB than in TBL (49% versus 29%; $p=0,003$). Moreover, we did not evaluate nutritional status, hemoglobin, albumin levels, or other infectious diseases, which may also raise the ESR.

When TB is suspected, it is important to ask about previous contact, treatment, or family history of patients. In studies conducted in Turkey, TB contact history has been reported between 5.1% and 65.8% [39]. Previous articles showed that 25–65.8% of patients had a history of contact with a case of TB [29,40]. In this study, 15% of all patients have been treated for previous TB and 14% had a family history, and there was no difference between TBL and other forms.

Although, the site of the TST in infection is debated, it is used for diagnostic purposes [34]. Test values may be affected by BCG vaccination, other infections, malnutrition, malignancy, immunosuppression, older age, or improper test application [34,38]. Previous studies have shown that the TST positivity rate in TBL is higher than in other forms of EPTB [41,42]. Similarly, in our study, the TST positivity rate was significantly higher in the TBL group (46% versus 28%; $p < 0.02$). However, we did not evaluate the BCG vaccination status, which could affect the test positivity of the patients.

In TB cases, providing appropriate and sufficient tissue materials is essential for diagnosis. Histopathology is an essential part of the diagnosis for all forms of TB. Sinna et al., found that the rate of classified epithelioid granuloma with fine-needle aspiration was 71.3%, and the rate of ARB positivity with smear was 39.8% [43]. Also, Güler et al., established the diagnosis as pathological in 73.8% of the cases, and found the ARB positivity rate was 30.3% [25]. In previous studies, ARB positivity was shown to range from 23% to 45%, and culture positivity from 20.8% to 83% [44]. In the present study, the diagnosis was confirmed in 77% of cases by histopathological examination, 57% with culture, and 34% with ARB positivity, similar to previous studies. Also, we found that histopathological confirmation of tissue material was higher in TBL than in other EPTB (87 % versus 64 %; $p=1$)

This is the first study that investigated the differences between TBL and other forms of EPTB. In addition, it reflects ten years of data about patients with EPTB. In our study, the most common clinical form was TBL. No significant difference was found between TBL and other EPTB groups in gender, age, comorbid factors, and laboratory tests except for TST and ESR. Symptoms such as fever, and night sweats were more common in the other forms of EPTB. This can be explained by the fact that the other forms of TB are more likely to present with active symptoms with hematogenous spreads to organs. Also, median ESR levels were higher in the other forms of the EPTB, and the TST positivity rate was higher in the TBL group, statistically.

Our research was a single-center observational study in a TB endemic country with a limited number of patients. We did not evaluate nutritional status, hemoglobin, albumin levels, or other infectious diseases which may also raise the ESR, and the BCG vaccination status, which could affect the TST positivity of the patients. We observed that multicenter, randomized controlled studies with large populations are needed to investigate the differences between TBL and other forms of EPT.

In conclusion, EPTB should be considered in the differential diagnosis by evaluating the medical history of patients, especially in TB endemic countries. It is essential to obtain sufficient tissue material for both pathological and microbiological analysis to confirm the diagnosis and early treatment of the patients. The organ involvement may lead to different clinical findings. Nonspecific symptoms in TBL may be seen as milder than in other clinical forms.

Compliance with Ethical Standards

Ethical Approval: The ethics committee of Umraniye Health Sciences University of Turkey, Research and Training Hospital approved the study on June 17, 2021, with decision number 191.

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