

Rarely seen extrapulmonary tuberculosis in immunocompetent adults: Experience of a tertiary hospital

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ABSTRACT

Objective: Tuberculosis (TB) is an infection that can involve all tissues and organs of the body. Although pulmonary tuberculosis (PTB) is commonly seen, extrapulmonary tuberculosis (EPTB) is still major clinical problem with an incidence of 35.1%. In recent years, there has been an increase in cases of EPTB. This retrospective study presents the clinical and laboratory characteristics of rarely seen EPTB cases.

Material and Methods: The study included rarely seen EPTB patients diagnosed and/or followed up. Cases with pleura TB and lymph node TB that are frequently seen were excluded from the study. The diagnosis of EPTB was made by clinical, microbiologic and/or histopathologic and/or radiologic findings and response to the therapy. The demographic features, clinical findings, and laboratory values were recorded from files.

Results: Fifty cases were included in the study (mean age: 34±15.8, female/male: 33/17). The most frequently involved organ was the peritoneum (n: 13, 26%). There was multi-organ involvement in 4(8%) cases. Co-existence of EPTB plus lung TB was determined in 9 (18%) cases. Of the patients, 4 had a story of TB and 14 had contact story with TB. All the cases were HIV-negative, and 1 case was HBsAg-positive. The major complaints of the patients were abdominal pain, weight loss, night sweats, fever, and cough. Lung radiology was normal in 23 of the cases. The mean length of therapy was 9 months.

Conclusion: Tuberculosis is a serious public health problem in Turkey as well as the world over. Early diagnosis and therapy have utmost importance for avoiding the serious complications of rarely seen EPTB forms.

Keywords: tuberculosis, extrapulmonary tuberculosis, adult tuberculosis

ÖZ

Immunkompetent erişkinlerde nadir görülen akciğer dışı tüberküloz: Üçüncü basamak bir hastanenin deneyimi

Amaç: Tüberküloz (TB) tüm organ ve dokuları tutabilen bir enfeksiyondür. Pulmoner tüberküloz (PTB) formu daha yaygın olarak görülmesine karşın ekstrapulmoner tüberküloz (EPTB) halen önemli bir klinik problemdir. EPTB sıklığı %35,1 olup, son yıllarda ülkemizde de EPTB olgu bildiriminde artış gözlenmektedir. Çalışmamızda nadir görülen EPTB olgularının klinik ve laboratuvar özelliklerini retrospektif olarak araştırdık.

Gereç ve Yöntem: Çalışmaya kliniğimizde tanı konulan ve/veya takip edilen nadir görülen EPTB tüberkülozlu hastalar alındı. Sık görülen plevra TB ve lenf bezi TB olguları çalışmaya alınmadı. EPTB tanısı, klinik bulgular, tedaviye yanıt ile mikrobiyolojik ve/veya histopatolojik ve/veya radyolojik bulgularla kondu. Hastaların demografik verileri, klinik ve laboratuvar değerleri dosya bilgilerinden kaydedildikten sonra EPTB açısından özellikleri değerlendirildi.

Bulgular: Çalışmaya 50 olgu alındı (yaş ort: 34±15.8 K/E: 33/17). En sık tutulum periton (n:13, %26) idi. Olguların 4 (%8) 'un de çoklu organ tutulumu saptandı. Akciğer TB ile birliktelik %18 (n:9) idi. Olguların 4'ünde geçirilmiş TB, 14'sında tüberküloz temas hikayesi mevcuttu. Olguların tümü HIV negatif olup, 1 olgu da HbsAg pozitif bulundu. En önemli başvuru yakınmaları karın ağrısı, kilo kaybı, gece terlemesi, ateş ve öksürük idi. Olguların 23'ünde akciğer grafisi normal olup, ortalama tedavi süresi 9 aydı.

Sonuç: Sonuç olarak; tedavi edilebilir bir hastalık olmasına rağmen, tüm dünyada olduğu gibi ülkemizde de ciddi bir halk sağlığı sorunu olan tüberkülozun, nadir görülen ekstrapulmoner tutulumlarında, erken tanı ve tedavi gelişebilecek ciddi komplikasyonları önlemek açısından önemlidir.

Anahtar kelimeler: tüberküloz, ekstrapulmoner tüberküloz, erişkin tüberküloz

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INTRODUCTION

Tuberculosis (TB) is a granulomatous infectious disease that can involve all tissues and organs of the body. Although it is a preventable and curable disease, it still exists as one of the major health problems in the whole world ⁽¹⁾. In Turkey, the prevalence of extra-pulmonary tuberculosis (EPTB) has been reported as 30-45% ⁽²⁻⁴⁾. Extra-pulmonary tuberculosis frequently involves lymph nodes and pleura and less frequently bones, joints, genito-urinary system, skin, and soft tissues. In recent years, there has been a rise in the number of EPTB cases ^(1,3,5-7). One should consider EPTB in the differential diagnosis of almost every infection particularly in countries where tuberculosis is endemic.

The ratio of EPTB to pulmonary tuberculosis (PTB) changes according to geographic, social, ethnic, and economic parameters ⁽⁸⁻¹⁰⁾.

EPTB develops as a result of lympho-hematogenous dissemination of the primary infection and subsequent latency of the disseminated tuberculosis bacilli which then may acquire reactivation in case of lowered body resistance or increased susceptibility. The disease may occur in any stage of life and involve any organ ⁽⁴⁻¹¹⁾. The period of latency in different organs ranges from 6 to 600 months ⁽⁴⁾. It is not yet completely clear why tuberculosis bacilli show reactivation in lungs in some cases and in other organs in some other cases ^(4,8). Female gender, story of contact with TB, smoking, and end-stage renal disease has been implicated as factors affecting reactivation in organs ^(4,12).

Studies on rare cases of EPTB are limited in number ⁽¹³⁻¹⁹⁾. In this context, different clinical courses of TB in terms of different involved organs and rarity of EPTB render diagnostic difficulties. Difficulty in diagnosis results in delayed therapy, therapeutic problems, and increased costs as well as in increased morbidity and mortality.

The purpose of this study was to determine the demographic and clinical features of rarely seen EPTB cases, to show that possible complications of EPTB can be prevented by early diagnosis and therapy, and to underline that EPTB should be considered among other disorders in differential diagnosis.

MATERIAL and METHODS

Study Design, Setting and Population

We designed a retrospective study of EPTB cases diagnosed and/or followed up in a tertiary teaching hospital for chest diseases and thoracic surgery center.

The study was approved by the local Ethics Committee of the Institution and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Since our study was retrospective, patient consent forms were not obtained. On the condition that the patients' identities would remain confidential, the use of the data was permitted by the academic committee of the hospital.

The study included cases with EPTB followed up in our clinic. The criteria for exclusion from the study were the following: 1) Immunosuppression, 2) Presence of malignancy, 3) Pleural TB, 4) Lymph node TB, 5) Age under 18.

Data Source

The clinical and laboratory data of EPTB cases hospitalized in our clinic were retrospectively obtained from patients' files.

Additional covariate

The cases with EPTB were evaluated in terms of age, gender, contact with TB, co-morbidities, coupling with lung TB, story of contact with TB, tuberculin skin test (TST), radiologic and bacteriologic findings, diagnostic and therapeutic features, and extrapulmonary organ involvement.

Definitions

The cases receiving the final diagnosis of EPBT had at least one of the diagnostic criteria stated below ⁽²⁰⁾:

- 1) Determination of the presence of acid-fast bacteria in direct microscopic examination and/or culture of the biopsy material obtained from extrapulmonary organs;
- 2) Presence of necrotizing granulomatous inflammation in biopsy material;
- 3) As compatible with TB, TST positivity and re-

sponse to antituberculosis therapy;

- 4) Clinical picture: Cough, expectoration, night sweats, weight loss, malaise, fever.

The tuberculin skin test was accepted as positive when induration diameter was 10 mm and over in patients without BCG eschar, and 15 mm and over in patients with BCG eschar ⁽²¹⁾.

Statistical analysis

A descriptive analysis was performed to evaluate patient demographics and data.

RESULTS

The study included 50 cases with EPTB. Of the cases, 69% were females and mean age was 34±15.8. Four (0.8%) cases had the story of past TB and 16 (31%) of contact with TB. The demographic features of the cases are summarized in Table 1. All the cases were HIV-negative, and 1 case was HBsAg-positive. Co-infection with PTB was present in 8 (16%) of the patients. 3 of 8 cases had acid-fast bacilli-positive sputum and 5 of 8 cases had culture positive for tuberculosis. In 23 of the cases, lung radiology was normal. The mean length of therapy was 9 months; in the first 2 months the patients were put on a HREZ regimen and in the rest 7 months on a HR regimen.

Table 1. Demographic features of the extrapulmonary tuberculosis cases.

	n (%)
Number of cases	50
Gender	
Female	33 (66)
Male	17 (34)
Mean age	34±15.8
Story of smoking	
Smoker	36 (72)
Non-smoker	11 (22)
Ex-smoker	3 (6)
TST* (Tuberculin skin test)	24
Positive	14 (28)
Negative	10 (20)
Past tuberculosis	4 (8)
Story of contact with tuberculosis	14 (28)
Additional disease	
Hypertension	4 (8)
Diabetes mellitus	1 (2)

The most frequent symptoms were abdominal pain and weight loss followed by cough, fever, night

sweats, expectoration, chest pain, and anorexia as expected in tuberculosis. Distribution of the symptoms on referral to the hospital is shown in Table 2.

Table 2. Symptoms of the extrapulmonary tuberculosis cases on referral to hospital.

	n (%)*
Abdominal pain	17 (34%)
Weight loss	17 (34%)
Night sweats	14 (28%)
Cough	14 (28%)
Fever	12 (24%)
Expectoration	11 (22%)
Chest pain	9 (18%)
Anorexia	8 (16%)
Malaise	6 (12%)
Other**	7 (14%)

*There were cases with more than one complaint.

**Other; hoarseness, mass in breast, mass in testis, ulcer in tongue, pain in knee, ulcer in skin, diarrhea, menstrual irregularity

The diagnosis of EPTB has been histological mostly. In 92% of our cases EPTB was histopathological and in 8 cases with co-presence of PTB smear/culture was also positive in addition to histopathological positivity. No culture was made from biopsy specimens.

In our EPTB cases, gastrointestinal system was the most frequently involved. The distribution of cases according to organ involvement is shown in Table 3.

Table 3. Distribution of the extrapulmonary tuberculosis cases according to organ involvement.

Extrapulmonary involvement	n	%
Peritoneum	13	26
Peritoneum + Pleura	3	6
Intestines + Lung	3	6
Tongue + Lung	3	6
Peritoneum + Lung	2	4
Intestines	2	4
Liver	2	4
Larynx + Lung	2	4
Larynx	2	4
Breast	2	4
Endometrium	2	4
Peritoneum + Spleen	1	2
Peritoneum + Miliary	1	2
Lip + Lung	1	2
Epiglottis + Lung	1	2
Chest wall	1	2
Peritoneum + Vertebra + Lung	1	2
Pericardium	1	2
Knee joint	1	2
Skin	1	2
Parotid gland	1	2
Peritoneum + Pericardium + Pleura	1	2
Thyroid	1	2
Testis + Vertebra + Psoas abscess	1	2
Liver + Spleen + Lung + Lymph node	1	2

DISCUSSION

Extrapulmonary tuberculosis causes diagnostic and therapeutic difficulties because it presents different clinical course in different organs. The consequences of this situation are delayed therapy and cost problems as well as increase in morbidity and mortality. In our group of EPTB cases; most of the cases were females; there was the story of contact with TB in 28% of the cases; although the symptoms changes according to the involved organ, also classical TB symptoms like weight loss, fever, night sweats were frequently present; the most frequently involved was the gastrointestinal system; and the most frequently used diagnostic method was histopathological examination.

The incidence of EPTB has been reported to be 4.5 to 53% in studies (2,3,5,9,22). This variable incidence of tuberculous organ involvement is related to geographic, social, ethnic, and economic parameters. The disease is more frequent in females than in males (4,6,9,10). Also in our study, female cases predominated. Although the role of gender in EPTB has not been fully clarified, cellular immunity, hormonal changes, and socio-economic and cultural status are thought to be related to this difference (12,23,24). Extrapulmonary tuberculosis is most frequent at the 30-58 age range (3,5,6,10,12). The mean age of our cases was compatible with this age range. Lin et al. (12) have reported the prevalence rate of EPTB at ages <24 as 5.9% and at ages >60 as 54.9%. This difference in prevalence rates may be related to changes in the immune system with aging.

Kollappan et al. (25) in their study on the association of smoking with TB have reported that the rate of TB increases parallel to the number of cigarettes smoked and length of smoking period. On the other hand, EPTB is more frequent in non-smokers (4,26). Lin et al. (12) have reported a negative correlation between smoking habit and EPTB. In our group of patients, 72% of the cases were smokers, a finding that may be related to high rate of smoking in Turkey.

The important clue in the diagnosis of EPTB is the story of patient's former contact with TB. Musellim et al. (4) have reported an EPTB rate of 76.6% within 5 years after contact with TB. According to another study, there is no significant difference between PTB and EPTB in terms of contact story with TB, rate of

contact is 8.9% and 8.4%, respectively (9). Our 2 cases with breast TB were sisters with the story of PTB in their family (27). Cases of PTB under therapy and included in the screening program for TB in the family should also be carefully examined for the possible presence of EPTB.

Co-morbidities such as long-term corticosteroid use, chronic obstructive pulmonary disease, alcoholism, diabetes mellitus, chronic renal failure, malignancies, and immunosuppression enhance the development of TB (28). Lin et al. (12) have found that the presence of co-morbidity is insignificant in terms of development of EPTB and PTB. On the other hand, Gonzelaz et al. (29) have reported hepatic cirrhosis to be a risk factor for the development of EPTB. In our group of patients, there was only 1 case with diabetes mellitus.

The symptoms and findings in EPTB vary according to the involved organ and co-presence of PTB. In our group of patients; the frequent symptoms were cough, expectoration, weight loss, night sweats, and anorexia accompanied by organ-specific symptoms in most cases, compatible with data in relevant studies (3,6,9,12). The variety of systemic or pulmonary symptoms leads the patients to doctors in various medical branches which results in diagnostic difficulties and delayed therapy unless TB is suspected. Demiralay et al. (9) have reported that the time between start of symptoms and establishment of EPTB diagnosis is 154+39.2 days. The duration of diagnosis in EPTB is shortest in pleural TB and longest in skeletal system TB (9,29). This finding can be related to more frequency of pleural TB which is early suspected and thus early diagnosed.

Mycobacterium tuberculosis culture is the gold standard in the diagnosis of TB (1). The diagnosis of EPTB is more difficult than the diagnosis of PTB. Histopathological examination and culture of biopsy material are important for the diagnosis of EPTB (5,8). In our group of patients, no culture was made from biopsy specimens, and this situation was associated with no consideration of EPTB in differential diagnosis in the preoperative period. Clinical suspect of EPTB is an important step in diagnosis after which diagnosis can be established by using a proper diagnostic method. Delay in diagnosis can result in serious morbidities and mortality. One of our cases who received a

late diagnosis of testis TB had additionally vertebra and psoas involvement at the time of diagnosis⁽³⁰⁾. In our group of patients; gastrointestinal system was the most frequently involved. Sreeramareddy et al. in their comparative study of PTB and EPTB on a total of 474 cases (48.5% EPTB and 51.5% PTB) have reported that of their EPTB cases 42.6% had lymph node, 14.8% peritoneal and/or intestinal, and 12.4% bone and/or joint involvement. As rare EPTB cases; 7.2% had miliary, 7.2% meningeal/brain, 4.8% skin, 2.9% genital, and 2.4% laryngeal involvement⁽¹¹⁾. The rate of EPTB is variable^(3,4,9-11). This variation may be related to social and environmental factors as well as with the center where the study is made. Our study was conducted in a center for chest diseases where there is a frequent referral of PTB cases. This may be the cause of our limited number of EPTB cases.

The rate of co-presence of PTB and EPTB has been reported to range from 16 to 34%^(3,6,11,12). This rate was 16% in our study. It has been reported that treatment longer than 9 months has no additional advantage and that long-term therapy decreases patient compliance and increases costs^(31,32).

Our study has some limitations: The data was obtained retrospectively from patient files. The data on life style of some cases were incomplete. Thus, in some cases it was not possible to study the effects of social, ethnic, economic, and environmental factors and so reasons of delayed therapy. Also, since this study was conducted on a small group of cases and in a tertiary hospital, it does not reflect the situation in the whole population. Prospective future studies are required to overcome these limitations.

In conclusion, as seen in our group of patients, TB is a systemic infection that can involve any organ in the body. Delayed diagnosis and therapy of TB result in serious morbidity and mortality. We think that in cases with no PTB, EPTB is not considered and so missed. In cases with no specific symptoms and findings, suspecting EPTB is the most important step toward final diagnosis. In our group of patients; the cases showed organ-specific symptoms frequently along with symptoms expected in TB. Particularly in female patients, the presence of these symptoms with story of contact with TB and TST-positivity should lead the clinician to suspect TB even in the absence

of PTB. The suspicion of TB would lead to early diagnosis by diagnostic algorithm and therapy which would decrease costs, mortality and morbidity.

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