ORIGINAL ARTICLE

DOI: 10.4274/eamr.galenos.2017.05925
Eur Arch Med Res 2019;35(3):115-9

Rare Extrapulmonary Tuberculosis in Immunocompetent Adults: Experience of a Tertiary Hospital

Sinem Güngör, Özlem Soğukpınar, Murat Yalçınsoy, Bilgen Begüm Afşar Dönmez, Olga Akkan, Esra Akkütük Öngel, Esra Usta Bülbül, Esen Akkaya

İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pulmonary Diseases, İstanbul, Turkey

Abstract

Objective: Tuberculosis (TB) is an infection that can involve all tissues and organs. Although pulmonary TB (PTB) is more common, extrapulmonary TB (EPTB) is still a major clinical problem. The incidence of EPTB is 35.1% and in recent years; there has been an increase in EPTB case reporting in our country. In this study, we retrospectively investigated the clinical and laboratory characteristics of rare EPTB cases.

Methods: The study included rare EPTB patients diagnosed and/or followed up in our clinic. Cases with pleural TB and lymph node TB were excluded from the study. The diagnosis of EPTB was made by clinical, microbiological and/or histopathological and/or radiological findings and response to treatment. The demographic features, clinical findings and laboratory values were recorded from patient files, and were evaluated in terms of EPTB.

Results: Fifty patients were included in the study (mean age=34±15.8 years, female/male=33/17). The most frequently involved organ was peritoneum (n=13, 26%). There was multi-organ involvement in 4 cases (8%). Co-existence of EPTB with PTB was determined in 9 cases (18%). Four patients had a history of TB and 14 had a history of contact with TB. All the cases were human immunodeficiency virus-negative, and one case was hepatitis B surface antigen positive. The major complaints were abdominal pain, weight loss, night sweats, fever, and cough. Twenty-three patients had normal chest radiographs and the mean duration of treatment was 9 months.

Conclusion: TB is a serious public health problem in Turkey as well as all over the world. Since it is a treatable disease, early diagnosis and treatment have utmost importance for avoiding the serious complications of rare EPTB forms.

Keywords: Tuberculosis, extrapulmonary tuberculosis, adult tuberculosis

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 world (1). In Turkey, the incidence of extrapulmonary TB (EPTB) has been reported as 30-45% (2-4). EPTB frequently involves lymph nodes and pleura, and less frequently includes bones, joints, genitourinary system, skin and soft tissues. In recent years, there has been an increase 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 TB is endemic. The ratio of EPTB to pulmonary TB (PTB) changes according to geographical, 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 TB bacilli, which then may acquire reactivation in case of reduced body resistance or increased susceptibility. The disease may occur in any stage of life and may involve any organ (4-11). The latency period in different organs ranges from 6 to 600 months (4). It is not yet clear why TB bacilli show reactivation in the lungs in some cases and in other organs in other cases (4,8). Female gender, history of contact with TB, smoking and end-stage renal disease have been implicated as factors affecting reactivation in organs (4,12). Studies on rare EPTB cases are limited (13-19). In this context, different clinical courses of TB render diagnostic difficulties in terms of different involved organs and rarity of EPTB. Difficulty

Address for Correspondence: Sinem Güngör, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pulmonary Diseases, İstanbul, Turkey
Phone: +90 532 591 33 76 **E-mail:** sinematikgungor@yahoo.com **ORCID ID:** orcid.org/0000-0002-1163-125X

Received: 29.03.2017
Accepted: 10.11.2017

Cite this article as: Güngör S, Soğukpınar Ö, Yalçınsoy M, Afşar Dönmez BB, Akkan O, Akkütük Öngel E, Usta Bülbül E, Akkaya E. Rare Extrapulmonary Tuberculosis in Immunocompetent Adults: Experience of a Tertiary Hospital. Eur Arch Med Res 2019;35(3):115-9

in diagnosis results in delayed treatment, therapeutic problems, and increased costs as well as increased morbidity and mortality. The purpose of this study was to determine the demographic and clinical features of rare 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.

METHODS

Study Design, Setting and Population

We designed a retrospective study of EPTB cases diagnosed and/or followed up in a tertiary training hospital for chest diseases and thoracic surgery. 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. The data was authorized by the hospital's academic committee, provided that the patient's identity remained confidential. The study included EPTB cases followed up in our clinic. The criteria for exclusion were as follows: 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 obtained from patient files retrospectively.

Additional Covariate

The EPTB cases were evaluated in terms of age, gender, contact with TB, co-morbidities, concurrent PTB, history of contact with TB, tuberculin skin test (TST), radiological and bacteriological findings, diagnostic and therapeutic features and extrapulmonary organ involvement.

Definitions

There was at least one of the following diagnostic criteria in cases with definitive diagnosis of EPBT (20):

- Determination of the presence of acid-fast bacteria in the direct microscopic examination and/or culture of biopsy material obtained from extrapulmonary organs,

- Presence of necrotizing granulomatous inflammation in the biopsy material,

- Consistent with TB, TST positivity and response to anti-TB treatment,

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

TST was accepted as positive when the induration diameter was ≥10 mm in patients without Bacillus Calmette-Guérin (BCG) scar, and ≥15 mm in patients with BCG scar (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 female and the mean age was 34±15.8 years. Four cases (0.8%) had a history of TB and 16 (31%) had contact with TB. The demographic features of the cases are summarized in Table 1. All cases were human immunodeficiency virus negative and one case was hepatitis B surface antigen positive. Concurrent PTB was present in eight patients (16%). Three of eight cases had acid-fast bacilli-positive sputum and five of eight cases had positive culture for TB. Pulmonary radiology was normal in 23 patients. The mean duration of treatment was 9 months, including isoniazid, rifampicin, ethambutol, pyrazinamide (HREZ) regimen in the first 2 months and isoniasid, rifampicin (HR) regimen in the remaining 7 months. The most frequent symptoms were abdominal pain and weight loss followed by cough, fever, night sweats, expectoration, chest pain, and anorexia as expected in TB. The distribution of symptoms on admission is shown in Table 2. The diagnosis of EPTB was mostly histological. In 92% of our

Table 1. Demographic features of the extrapulmonary tuberculosis cases

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

*Tuberculin skin test was available in 24 cases. Rest of the data is missing

cases, EPTB was diagnosed histopathologically and in eight cases with concurrent 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 system. The distribution of cases according to organ involvement is shown in Table 3.

DISCUSSION

EPTB causes diagnostic and therapeutic difficulties because it has different clinical courses in different organs. The consequences of this situation are delayed treatment and cost problems, as well as increased morbidity and mortality. In our study, most cases were female, there was a history of contact with TB in 28% of the cases, classical TB symptoms like weight loss, fever, night sweats were frequently present although the symptoms changed according to the involved organ, the most frequently involved system was the gastrointestinal system, and the most frequently used diagnostic method was histopathological examination. The incidence of EPTB has been reported to be 4.5-53% (2,3,5,9,22). This variable incidence of TB is related to geographical, social, ethnic, and economic parameters. The disease is more frequent in women than in men (4,6,9,10). Similarly, we had more female patients in our study. Although the role of gender in EPTB is not fully clarified, cellular immunity, hormonal changes and socio-economic and cultural status are thought to be related to this difference (12,23,24). EPTB is most common in the 30-58 age range (3,5,6,10,12). The mean age of our patients was consistent with this age range. Lin et al. (12) reported the prevalence rate of EPTB as 5.9% at ages ≤24 and as 54.9% at ages ≥60. This difference in prevalence may be related to changes in the immune system with aging. In their study on the association of smoking with TB, Kolappan et al. (25) reported that the rate of TB increased 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) reported a negative correlation between smoking habit and EPTB. In our patient group, 72% were smokers, indicating a finding that might be related to high rate of smoking in Turkey.

An important clue in the diagnosis of EPTB is the history of patient's previous contact with TB. Musellim et al. (4) reported an EPTB rate of 76.6% within 5 years after contact with TB. According to another study, there was no significant difference between PTB and EPTB in terms of contact history with TB (8.9% vs. 8.4%, respectively) (9). Two patients with breast TB in our study were sisters with a family history of PTB (27). Cases of PTB under treatment and included in the screening program for TB in the family should also be carefully examined for the possible presence of EPTB.

Table 2. The symptoms of extrapulmonary tuberculosis patients referred 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%)
Others**	7 (14%)

*There were cases with multiple complaints,
**Others include hoarseness, breast mass, testicular mass, tongue ulcer, knee pain, skin ulcer, diarrhea, menstrual irregularity

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

Co-morbidities such as long-term corticosteroid use, Chronic Obstructive Pulmonary disease, alcoholism, diabetes mellitus, chronic renal failure, malignancies, and immunosuppression increase the development of TB (28). Lin et al. (12) found that the presence of co-morbidity is insignificant for the development of EPTB and PTB. On the other hand, Gonzalez et al. (29) reported hepatic cirrhosis as a risk factor for the development of EPTB. In our patient group, there was only one case with diabetes mellitus. The symptoms and findings in EPTB vary according to the involved organ and concurrent PTB. In our patient group, the most common symptoms were cough, expectoration, weight loss, night sweats, and anorexia accompanied by organ-specific symptoms in most cases, consistent with data from relevant studies (3,6,9,12). The diversity of systemic or pulmonary symptoms leads patients to admit doctors in various medical branches, resulting in diagnostic difficulties and delayed treatment unless TB is suspected. Demiralay (9) reported that the time between the onset of symptoms and establishment of EPTB diagnosis was 154±39.2 days. The diagnosis time in EPTB is shortest in pleural TB and longest in skeletal system TB (9,29). This finding may be related to a higher incidence of pleural TB, which is suspected and therefore diagnosed earlier. *Mycobacterium* TB 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 patient group, no culture was made from biopsy specimens, and this was related to the fact that EPTB was not considered in differential diagnosis in the preoperative period. The clinical suspicion of EPTB is an important step in diagnosis, leading to establishment of diagnosis by using a proper diagnostic method. Delay in diagnosis may result in serious morbidity and mortality. One of our patients with late testicular TB had additional vertebral and psoas involvement at the time of diagnosis (30). In our patient group, gastrointestinal system was the most frequently involved system. In a comparative study of PTB and EPTB on a total of 474 cases (48.5% EPTB and 51.5% PTB), Sreeramareddy et al. (11) reported that patients with EPTB had 42.6% lymph node involvement, 14.8% peritoneal and/or intestinal involvement, and 12.4% bone and/or joint involvement. Some rare EPTB cases had 7.2% 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 to the center where the study is conducted. Our study was conducted at a chest diseases center where PTB cases are frequently referred. This may be the cause of our limited number of EPTB cases. The rate of co-existence 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 treatment reduces patient compliance and increases costs (31,32). Our study has some limitations: The data were obtained retrospectively from patient files. Some patients lacked data on lifestyle. Thus, in some cases, it was not possible to study the effects of social, ethnic, economic, and environmental factors and therefore the reasons for delayed treatment. In addition, since this study was conducted on a small group of cases and at a tertiary hospital, it does not reflect the situation in the whole population. Prospective future studies are required to overcome these limitations.

CONCLUSION

In conclusion, as seen in our patient group, TB is a systemic infection that can involve any organ in the body. Delayed diagnosis and treatment of TB result in serious morbidity and mortality. We think that EPTB is overlooked in cases with no PTB. In cases without specific symptoms and findings, suspicion of EPTB is the most important step toward definitive diagnosis. In our patient group, patients exhibited organ-specific symptoms, frequently along with symptoms expected in TB. Particularly in female patients, the presence of these symptoms with a history of contact with TB and TST-positivity should lead the clinician to suspect TB even in the absence of PTB. The suspicion of TB will lead to early diagnosis with diagnostic algorithm and treatment that decreases costs, mortality and morbidity.

Ethics

Ethics Committee Approval: Ethics committee approved. (İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, 13.11.2015/7).

Informed Consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., M.Y., E.A., Concept: S.G., Ö.S., Design: S.G., B.B.A.D., Data Collection or Processing: O.A., E.A.Ö., Analysis or Interpretation: S.G., M.Y., Literature Search: S.G., E.U.B., Writing: S.G., M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2014. Available from: URL: http://www.who.int/tb/publications/global_report/gtbr14_main_text.pdf?ua=1.
2. The ministry of health of Turkey health. Tuberculosis Report 2012. URL: www.tuberkuloz.thsk.gov.tr.
3. Guler SA, Bozkus F, Inci MF, Kokoglu OF, Ucmak H, Ozden S, et al. Evaluation of Pulmonary and Extrapulmonary Tuberculosis in Immunocompetent Adults: A Retrospective Case Series Analysis. Med Princ Pract 2015;24:75-9.
4. Musellim B, Erturan S, Sonmez Duman E, Ongen G. Comparison of extrapulmonary and pulmonary tuberculosis cases: factors influencing the site of reactivation. Int J Tuberc Lung Dis 2005;9:1220-3.
5. Sunnetcioglu A, Sunnetcioglu M, Binici I, Baran AI, Karahocagil MK, Saydan MR6. Comparative analysis of pulmonary and extrapulmonary tuberculosis of 411 cases. Ann Clin Microbiol Antimicrob 2015;14:34.
6. Tavusbay N, Aksel N, Özsöz A. Epidemiologic, clinical and laboratory features of cases with extrapulmonary tuberculosis. İzmir Göğüs Hastanesi Dergisi 2008;22:27-34.
7. Turunç T, Habeşoğlu MA, Demiroğlu YZ, Karataşli M, Sen N, Ermiş H, et al. Comparative evaluation of 113 cases with severe and mild forms of extrapulmonary tuberculosis. Mikrobiyol Bul 2008;42:399-406.
8. Antony SJ, Harrell V, Christie JD, Adams HG, Rumley RL. Clinical differences between pulmonary and extrapulmonary tuberculosis: a 5-year retrospective study. J Natl Med Assoc 1995;87:187-92.
9. Demiralay R. Comparison of the Clinical and Epidemiological Characteristics of Pulmonary and Extrapulmonary Tuberculosis. Tuberk Toraks 2002;50:264-71
10. Fader T, Parks J, Khan NU, Manning R, Stokes S, Nasir NA. Extrapulmonary tuberculosis in Kabul, Afghanistan: a hospital-based retrospective review. Int J Infect Dis 2010;14:e102-10.
11. Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis in Nepal - a hospital-based retrospective study. BMC Infect Dis 2008;8:8.
12. Lin JN, Lai CH, Chen YH, Lee SS, Tsai SS, Huang CK, et al. Risk factors for extrapulmonary tuberculosis compared to pulmonary tuberculosis. Int J Tuberc Lung Dis 2009;13:620-5.
13. Sherif MM, Schauer CK. Multifocal Cutaneous and Osseous Tuberculosis. Int J Infect Dis 2015;37:11-3.
14. Sharma V, Chhabra P, Rana SS, Bhasin DK. Pancreatic tuberculosis: Look at the kidney! Dig Liver Dis 2015;47:e1.
15. Lombardi R, Pelusi S, Airaghi L, Fargion S. Extrapulmonary tuberculosis: an unusual presentation in an immunocompetent patient. BMJ Case Rep 2015;2015.
16. Lee KJ, Yoo JS, Jeon H, Cho SK, Lee JH, Ha SS, et al. A Case of Splenic Tuberculosis Forming a Gastro-splenic Fistula. Korean J Gastroenterol 2015;66:168-71.
17. Gupta N, Dass A, Goel N, Tiwari S. Tuberculous Otitis Media Leading to Sequentialib Bilateral Facial Nerve Paralysis. Iran J Otorhinolaryngol 2015;27:231-7.
18. Pandit VR, Shubha S, Rohit V, Vikas M, Vandana KE, Ashwini K, et al. Pott's spine with 'bird nest' appearance. Int J Infect Dis 2010;14 Suppl 3:e390-1.
19. Karan MA, Erten N, Taşçıoğlu C, Kazancıoğlu R, Kaysı A. Extrauplmonary Tuberculosis: 5 case report. Klimik Derg 1995;8:68-70.
20. Organization WH. World Health Organization. Diagnostic and Treatment Delay in Tuberculosis. 2006. URL: http://applications.emro.who.int/dsaf/dsa710.pdf.
21. Menzies D. Interpretation of repeated tuberculin tests. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 1999;159:15-21.
22. Gunal S, Yang Z, Agarwal M, Koroglu M, Arıcı ZK, Durmaz R. Demographic and microbial characteristics of extrapulmonary tuberculosis cases diagnosed in Malatya, Turkey, 2001-2007. BMC Public Health 2011;11:154.
23. Chan-Yeung M, Noertjojo K, Chan SL, Tam CM. Sex differences in tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2002;6:11-8.
24. Borgdorff MW, Nagelkerke NJ, Dye C, Nunn P. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. Int J Tuberc Lung Dis 2000;4:123-32.
25. Kolappan C, Gopi PG. Tobacco smoking and pulmonary tuberculosis. Thorax 2002;57:964-6.
26. Leung CC, Yew WW, Chan CK, Tam CM, Lam CW, Chang KC, et al. Smoking and tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2003;7:980-6.
27. Akbaba B, Baran A, Yalçinsoy M, Güngör S, Akkaya E. [Two sisters with breast tuberculosis]. Tuberk Toraks 2007;55:395-9.
28. The ministry of health of Turkey health. Tuberculosis diagnosis and treatment Guideline 2011. URL: www.tuberkuloz.thsk.gov.tr.
29. Gonzalez OY, Adams G, Teeter LD, Bui TT, Musser JM, Graviss EA. Extrapulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis. Int J Tuberc Lung Dis 2003;7:1178-85.
30. Yalçınsoy M, Güngör S, Akkaya E, Bilgin S, Akkütük E, Sırmalı M, et al. [Progress of treatment delayed testicular tuberculosis: one case]. Tuberk Toraks 2013;61:255-7.
31. Syed FF, Mayosi BM. A modern approach to tuberculous pericarditis. Prog Cardiovasc Dis 2007;50:218-36.
32. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.