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ORIGINAL ARTICLE

Extrapulmonary Tuberculosis: Clinical and Diagnostic Features and Risk Factors for Early Mortality

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ABSTRACT

Objective: The aim of this study is to evaluate patients with EPTB in terms of demographics, anatomic localization, diagnosis and risk factors on early mortality.

Materials and methods: The data of 217 inpatients who were followed up with EPTB, between January 2010 and December 2020, were evaluated retrospectively. Patients were followed-up during hospital admission and early mortality was considered. Risk factors on mortality were identified in multivariate analysis using logistic regression model.

Results: The median age was 54 (IQR: 37-67) and the rate of male patients was 43.3%. 76 (35%) patients had at least one comorbidity. The most common underlying conditions were diabetes mellitus and immunosuppressive treatment. The most common forms of EPTB were lymph node, bone and CNS. Microbiological findings (ARB and/or TB-culture and/or M. tuberculosis PCR) were positive in 75 patients and histopathological findings (necrotising granuloma with/without pathological caseification) were supportive for diagnosis in 68.2%. The overall mortality rate was 8.5%. In the multivariate analysis, factors independently associated with increased risk of death included advanced age, elevated sedimentation rate above 50mmHg, miliary TB and CNS TB.

Conclusion: In conclusion, EPTB is an important health problem in developing countries with significant mortality in specific forms. The most common forms of EPTB are lymph node, bone and CNS TB. The most common underlying conditions are diabetes and immunosuppressive therapy although most patients do not have any underlying diseases. The diagnosis is forcing and a substantial proportion of patients have negative microbiological findings. The diagnosis are based on pathological, radiological and/or clinical findings in patients without definitive microbiological diagnosis. Advanced age, high sedimentation rate and severe forms such as CNS and miliary TB are associated with early mortality.

Keywords: extrapulmonary tuberculosis, mortality, risk factors.

INTRODUCTION

Tuberculosis (TB) is an ancient disease caused by *Mycobacterium tuberculosis*, which mainly affects the lungs. It is a major public health problem, with about 9 million new cases and 1-2 million deaths expected each year [1]. Although pulmonary TB accounts accounts for the majority of cases, extrapulmonary tuberculosis (EPTB) also contributes significantly to the burden of disease [2]. According to the WHO global tuberculosis report, EPTB represented 16% of the 7.1 million TB cases notified in 2019, ranging from 8% in the WHO Western Pacific Region to 24% in the Eastern Mediterranean Region. Turkey is among the countries which has the highest percentage of extrapulmonary cases among TB cases (30%) [1]. The rate of EPTB among all TB cases is increasing probably due to the rise of immunosuppressive populations [3]. In the European Union, the proportion of EPTB cases increased from 16.4% in 2002 to 22.4% in 2011 [4]. In our country, the incidence of new pulmonary and EPTB cases is decreasing, however, the decline is more prominent in pulmonary TB cases than EPTB. The proportion of new EPTB cases has risen from 28.6% in 2005 to 35.4% in 2018 [5].

EPTB can affect any organ in the body including lymph nodes, pleura, bones, joints, genitourinary system and soft tissues, therefore it can present with a wide range of symptoms and clinical findings. Invasive procedures are usually required for the diagnosis of EPTB infection [6]. These factors lead to a challenge in diagnosis and also contribute to delayed or misdiagnosis of EPTB cases. Some critical forms of EPTB, particularly meningeal and miliary forms, have a substantial morbidity and mortality. Delayed diagnosis can lead to fatal outcome. Mortality risk is also increased in patients with HIV/AIDS and underlying chronic health conditions [7].

The aim of this study is to evaluate the cases of EPTB in terms of demographics, anatomic localization, diagnosis and risk factors on mortality.

MATERIALS AND METHODS

This retrospective study was conducted on hospitalized patients with EPTB in various departments of Gazi University Hospital, between January 2010 and December 2020. The study was approved by Gazi University Ethics Committee with a decision number 10 in May 24, 2022.

Patients and data collection

All adult (≥18 years) inpatients with EPTB were consequently included in this study. In Turkey, TB is a notifiable disease and all TB cases are obligated to be reported to the health authorities with a TB surveillance form including the patients' demographics and TB status. The data of the patients were obtained from those TB forms and the electronic hospital records. Data on demographic and clinical characteristics, underlying diseases, involvement sites, laboratory and imaging findings were recorded.

All of the patients diagnosed with EPTB were treated with anti-TB drugs according to the recommendations of the national TB guideline and discharged patients were transferred to tuberculosis dispensaries to maintain antituberculosis medications [8]. Patients were only followed up during hospital admission and early mortality were assessed. Early mortality is defined as death due to any cause after TB diagnosis during hospital admission.

TB diagnosis and definitions

EPTB was classified according to the affected organs and systems. Microbiological diagnosis was defined as a positive acid-resistant bacilli (ARB) and/or TB-culture and/or *M. tuberculosis* PCR performed from specimens such as lymph node, pleural fluid, urine, cerebrospinal fluid etc. When the microbiological results were negative, TB diagnosis was based on compatible clinical findings with either histopathological findings (detection of caseating or non-caseating granulomatous inflammation in biopsy specimens obtained from extrapulmonary sites) and/or radiological findings, after the exclusion of other possible diagnosis. If both laboratory and imaging findings were negative, patients diagnosed by only clinical findings. Additional laboratory data such as adenosine deaminase (ADA) elevation in body fluids, positivity of TST (TB skin test) and/or interferon gamma release assay (IGRA) were considered. The cut off point for a positive TST was considered ≥ 15mm for patients with BCG, ≥ 10mm for patients without BCG and ≥ 5 mm for immunosuppressive patients.

Statistical analysis

Statistical analysis was performed using SPSS 20 package program. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov- Simirnov/ Shapiro-Wilk's test) to determine whether they are normally distributed. The categorical variables were expressed as a number and a percentage, continued values were presented as a mean and standard deviation (SD) or median values and an interquartile range (IQR) of 25%–75%. Comparisons between groups were made using the Chi-square test for categorical variables and the Mann-Whitney U test for numeric variables. Risk factors for mortality were identified in multivariate analysis using logistic regression model. Variables with a p-value of less than 0.20 in the univariate analysis, and not correlated with each other were included in the logistic regression model. Values with a type-I error level of below 5% were considered statistically significant.

RESULTS

A total of 217 patients included in the study. The median age was 54 (IQR: 37-67) and the rate of male patients was 43.3%. 76 (35%) patients had at least one comorbidity and the most common comorbidities were diabetes mellitus and immunosuppressive treatment. Demographics, clinical characteristics and involvement sites of EPTB cases were shown in Table 1. Demographics and clinical characteristics of EPTB cases according to involvement site were shown in Table 2.

The most common involvement site was lymph nodes (n=71, 32.7%) and the distribution of the lymph nodes were as follows: cervical (n=35, 49.3%), mediastinal (n=14, 19.7%), axillary (n=13, 18.3%), supraclavicular (n=4, 5.6%), multiple (n=3, 4.2%), intrabdominal (n=2, 2.8%), iliac (n=1, 1.4%), inguinal (n=1, 1.4%) and submandibular (n=1, 1.4%). The second common involvement site was bones. Of the 41 patients who had bone involvement, 32 (78.0%) had vertebral and 9 (22.0%) had non-vertebral involvement.

Microbiological findings were positive in 75 (34.5%) patients and histopathological findings were positive in 148 (68.2%) patients. The rates of patients with positive microbiological and histopathological findings according to involvement site were shown in Table 2. Positive microbiological and/or histopathological findings were not available for 48 (22.1%) patients.

Table 1. Demographic, clinical characteristics and involvement sites of extrapulmonary tuberculosis cases

	Total n= 217 n (%)
Age, median (IQR)	54.0 (37.0-67.0)
Gender, Male	94 (43.3)
Fever (n=202)	68 (33.7)
History of TB contact (n=123)	24 (19.5)
Previous TB infection (n=119)	15 (12.6)
Underlying diseases	
Diabetes mellitus	36 (16.6)
Immunosupressive treatment	25 (11.5)
Autoimmune disease	16 (7.3)
Malignancy	15 (6.9)
Chronic renal failure	6 (2.8)
HIV infection	4 (1.8)
At least one comorbidity	76 (35.0)
Involvement site	
Lymph node	71 (32.7)
Bone	41 (18.9)
Central nervous system	28 (12.9)
Pleura	23 (10.6)
Miliary	22 (10.1)
Genitourinary	19 (8.8)
Peritoneum	9 (4.1)
Skin	4 (1.8)
Pericardium	1 (0.5)
Nasopharynx	1 (0.5)
Eye	1 (0.5)
Laboratory findings	
Elevated sedimentation rate (≥50mmHg) (n=188)	85 (39.2)
Elevated CRP (n=184)	131 (71.2)
ARB positivity	55 (25.3)
Culture positivity	19 (8.8)
PCR positivity	26 (12.0)
Necrotising granuloma	148 (76.3)
Pathological caseification	9 (5.9)
Positive radiological findings	53 (24.4)

The diagnosis were microbiologically confirmed in 75 patients. Of these 49 patients had also positive pathological findings and 13 had positive radiological findings. 142 patients did not have

Table 2. Demographic and clinical characteristics of extrapulmonary tuberculosis cases according to involvement site

	Lymph node n=71 (%)	Bone n=41 (%)	CNS n=28 (%)	Plevra n=23 (%)	Miliary n=22 (%)	Genitourinary n=19 (%)
Age	53 (38-63)	64 (47-71.5)	52 (30-64)	42.5 (27.7-61)	61.5 (31-70.2)	59 (37-72)
Gender, Male	21 (29.6)	16 (39)	13 (46.4)	16 (69.6)	12 (54.5)	8 (42.1)
Comorbid diseases	29 (40.8)	15 (36.6)	9 (32.1)	4 (17.4)	11 (50.0)	6 (31.6)
Diabetes mellitus	14 (19.7)	11 (26.8)	6 (21.4)	2 (8.7)	3 (13.6)	1 (5.3)
Immunosuppressive treatment and autoimmune diseases	9 (12.7)	6 (14.6)	2 (7.1)	2 (8.7)	9 (40.9)	3 (15.8)
Malignancy	6 (8.5)	1 (2.4)	1 (3.6)	-	3 (13.6)	4 (21.1)
Chronic renal failure	4 (5.6)	-	-	-	-	-
HIV infection	2 (2.8)	-	1 (3.6)	-	1 (4.5)	-
Clinical and laboratory findings						
Fever	11 (17.5)	11 (28.2)	11 (39.3)	14 (60.9)	16 (72.7)	1 (6.3)
Elevated sedimentation rate						
(≥50mmHg)	20 (34.5)	19 (48.7)	8 (32.0)	14 (63.6)	12 (63.2)	5 (33.3)
Elevated CRP	32 (60.4)	28 (77.8)	15 (62.5)	20 (95.2)	18 (90.0)	9 (56.3)
Microbiological findings	20 (28.2)	16 (39.0)	5 (17.9)	3 (13.0)	15 (68.2)	12 (63.2)
ARB positivity	17(23.9)	12 (29.3)	2 (7.1)	2 (8.7)	9 (40.9)	9 (47.4)
Culture positivity	2 (2.8)	6 (14.6)	-	1 (4.3)	7 (31.8)	3 (15.8)
PCR positivity	4 (5.6)	6 (14.6)	4 (14.3)	-	8 (36.4)	4 (21.1)
Histopathological findings	68 (97.1)	25 (65.8)	7 (36.8)	9 (47.4)	17 (85.0)	11 (68.8)

a definitive microbiological diagnosis. Of these, 81 were diagnosed by positive pathological findings, 31 were radiological findings and 9 were both pathological and radiological findings. Both laboratory and imaging findings were negative in 21 patients which were diagnosed by only clinical findings.

Tuberculosis skin test (TST) records were available for 73 patients, of which 46 (63%) were positive. 28 patients had IGRA test result, and 18 (64.2%) of them were positive. ADA levels were measured in 26 patients with TB pleurisy or peritoneal TB and it was over 40 units /L in 21 of them.

The overall mortality rate was 8.5%. The median age of the deceased patients was 65.0 (IQR, 49.5-74.0) and the most frequent EPTB types were CNS and miliary TB. 2 patients with lymph node TB died during hospital admission and the mortality was associated with underlying diseases (lymphoma and AIDS) in both patients. Univariate analysis of factors associated with early mortality was shown in Table 3. Multivariate analysis revealed that advanced age (OR: 1.047, 95% CI: 1.003-1.093, p=0.038) , elevated sedimentation rate above 50mmHg (OR: 5.665, 95% CI: 1.214-26.447, p= 0.027), miliary TB (OR: 8.175, 95% CI: 1.665-40.149, p=0.010) and CNS TB (OR: 20.285, CI: 4.182-98.386, p<0.001) were the factors independently associated with increased risk of death.

DISCUSSION

In this study, we examined the distribution, diagnostic methods, comorbidities and mortality of EPTB patients. The most common types of EPTB were lymph node, bone and CNS. The most common underlying diseases were diabetes mellitus and immunosuppressive conditions, however, a majority of patients did not have any underlying diseases with an exception of miliary TB. Microbiological findings were positive in only one third of the patients and histopathological findings were helpful for diagnosis in 68.2%. The overall mortality was 8.5% and advanced age, elevated sedimentation rate above 50mmHg, miliary TB and CNS TB were associated with mortality.

The most common types of extrapulmonary TB are generally constituted of lymph node and pleural TB. A surveillance report from our country showed that lymph nodes, pleura, gastrointestinal system and vertebral bones are the most prevalent types in our country [5]. In a study examining a large series of

Table 3. Univariate analysis of factors associated with early mortality

	Survived n=200 n (%)	Died n=17 n (%)	p value
Age, median (IQR)	52.5 (36.0-65.7)	65.0 (49.5-74.0)	0.019
Gender, Male	86 (43.0)	8 (47.1)	0.802
Fever (n=202)	56 (28.0)	12 (70.6)	0.001
Underlying diseases			
Diabetes mellitus	33 (16.6)	3 (17.6)	1.000
Immunosuppressive treatment	24 (12.0)	1 (5.9)	0.700
Autoimmune disease	15 (7.5)	1 (5.9)	1.000
Malignancy	13 (6.5)	2 (5.9)	0.361
Chronic renal failure	6 (3.0)	0	N/A
HIV infection	3 (1.5)	1 (5.9)	0.280
At least one comorbidity	69 (34.5)	7 (41.2)	0.580
Involvement site			
Lymph node	69 (34.5)	2 (11.8)	0.055
Bone	41 (20.5)	0	0.047
Central nervous system	21 (10.5)	7 (41.2)	0.002
Pleura	22 (11.0)	1 (5.9)	1.000
Miliary	16 (8.0)	6 (35.3)	0.003
Genitourinary	18 (9.0)	1 (5.9)	1.000
Other	16 (8.0)	0	N/A
Laboratory findings			
Elevated sedimentation rate (≥50mmHg) (n=188)	74 (42.5)	11 (78.6)	0.009
Elevated CRP (n=184)	129 (70.1)	14 (87.5)	0.246
ARB positivity	51 (25.5)	4 (23.5)	0.858
Culture positivity	18 (9.0)	1 (5.9)	1.000
PCR positivity	23(11.5)	3 (17.6)	0.437
Positive pathology	142 (77.6)	6 (54.5)	0.135

EPTB cases from the USA reported that lymphatic, pleural and bone and/or joint involvement rates in EPTB were 40%, 19.8% and 11.3% respectively [9]. Pleural (36.7%), lymphatic (30.5) and genitourinary types (6.9%) were the most frequent ones in the European Union [4]. In our study, the most common involvement site was lymph node in line with the literature. The other common forms were were bone and CNS-TB. Rates of the EPTB types vary among different studies, regions and the healthcare facility. As we are a tertiary care center, we probably more encounter with the bone and CNS-TB both of which require advanced diagnostic facilities.

EPTB affects all age groups, both male and females and patients with and without any underlying conditions and this properties can vary with the form of EPTB and region. Lymph node and CNS TB usually affects children and young adults and a female predilection has been observed [10]. Our findings are in line with these observations. In our study, the median age was the highest in patients with bone (predominantly vertebral) TB. Previous literature mostly report younger ages for skeletal TB, however, the mean age was over 50 in a more recent large-scale study [11]. In the present study the median age of patients with bone TB were over 60 with a predominance of female patients. The median age of patients with miliary TB were also over 60 and the rate of male patients were slightly higher. Half percent of patients with miliary TB had underlying conditions mainly immunosuppression and malignancy. Several predisposing or associated conditions have also been documented in the literature [10].

Diagnosis of EPTB is challenging due to the variable and sometimes insidious clinical presentation, low bacterial burden in most EPTB cases and the difficulties in obtaining appropriate samples for

microbiological and histopathological examination [12]. Invasive procedures are generally required to take appropriate samples for microbiological and pathological diagnosis. Although this can be achieved, still, the possibility of a positive microbiological diagnosis which is the gold standard method is low. In our study, only one third of the patients had a definitive microbiological diagnosis with the highest rate of 68.2% in miliary TB and the lowest rate of 17.9% in pleural TB. Studies from our country also report low rates of positive TB-culture varying from 25% to 41% and low ARB positivity varying from 18% to 26% [12-15]. Histopathological findings provide valuable clues for diagnosis when there is a lack of microbiological findings. In our study, 76% of patients had TB-supporting histopathological findings including necrotizing/non necrotizing granulomas with/without pathological caseification. Although the contribution of histopathological findings to diagnosis is noteworthy, a number of infectious and non-infectious diseases can cause similar pathological findings [16]. Therefore, when the microbiological findings were negative, a careful differential diagnosis should be performed in order to prevent misdiagnosis. Positive microbiological and/or histopathological findings were not available for one fifth of patients in this study. This can be due to either the lack/insufficiency of tissue sampling or the paucibasillary nature of the disease leading to false negative results. These patients were diagnosed by compatible clinical or radiological findings and started anti-TB drugs empirically. TST/IGRA tests and adenosine deaminase (ADA) levels in certain body fluids can be supportive for diagnosis, however, the negative results do not exclude the TB. In our study, TST and IGRA tests were positive in 63% (n=73) and 64.2% (n=18) of patients. ADA level was over 40 and suggestive of TB in 21 of 26 patients with TB pleurisy or peritoneal TB.

Mortality rates of EPTB vary in different studies and is probably associated with the underlying HIV infection. In a study conducted in the USA where 47% of EPTB patients were HIV-positive, overall mortality and mortality in HIV-positive patients were 15% and 21%, respectively [7] . In another study in which the rate of HIV-positive patients was 62%, overall mortality and mortality in HIV-positive patients were 28% and 40%, respectively [17]. When the studies from our country where the HIV prevalence is low were examined, mortality rate was found to be between 2.7 and 8.3% [14, 18,19]. In our study, only 4 of 217 patients were HIV positive and total mortality rate was %7.8 and this low rate, in consistent with the data from our country, was attributed to the low number of HIV-positive cases in the study.

In our study advanced age, CNS TB, miliary TB and elevated sedimentation rate above 50mmHg were significantly associated with mortality. Advanced age is one of the important mortality predictors for EPTB patients [20, 21]. Studies showed that being over 40 years of age is an independent risk factor for mortality and TB mortality was about 10 times higher in the patients over 65 years [20]. Accompanying chronic illnesses and impaired immune function in the elderly patients may be the reason of both activation of latent TB infection and development of severe disease with high mortality rates. CNS-TB is a significant cause of morbidity and mortality in developing countries despite effective anti-TB treatment [22]. Mortality increases up to 50% in patients with delayed anti-TB therapy and survivors have the risk of neurological sequelae [23]. According to our findings CNS involvement, 20 times increased the risk of mortality. Miliary TB is another potentially fatal form occurring via the lymphohematogenous spread of the TB bacillary. We observed 8 times increase in mortality in patients with miliary TB patients and mortality rate was 27% which was compatible with the literature (25%-35%) [24] . The underlying comorbid diseases such as immunosuppression and malignancy is more common in miliary TB. These conditions and delayed diagnosis due to the protean and non-specific presentation of the disease may increase mortality. Sedimentation is a routine laboratory test usually performed during the diagnosis of the infection. As sedimentation rate above 50mmHg was associated with poor outcome, these patients should be followed closely in terms of mortality.

This study had several limitations. The major limitation was that we could not follow up all patients after hospital discharge. Therefore, we could not evaluate mortality at the end of TB treatment, the compliance of patients to treatment, adverse events and the effect of antituberculosis therapy on mortality. We could not evaluate how many of the patients diagnosed by radiological and/or clinical findings had good clinical response to empirical treatment. We also could not reach the drug susceptibility testing data.

In conclusion, EPTB is an important health problem in developing countries with significant mortality in specific forms. The most common forms of EPTB are lymph node, bone and CNS TB. The most common underlying diseases are diabetes and immunosuppressive therapy although most patients do not have any underlying diseases. The diagnosis is forcing and a substantial proportion of patients have negative microbiological findings. The diagnosis are based on pathological, radiological and/or clinical findings in patients without definitive microbiological diagnosis. Advanced age, high sedimentation rate and severe forms such as CNS and miliary TB are associated with early mortality.

Author contribution

Study conception and design: PAY, DK, ÖGT and MD; data collection: DK and HK; analysis and interpretation of results: PAY, DK, HSÖ and ÖGT; draft manuscript preparation: PAY, DK and HK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Gazi University Ethics Committee (Protocol no. 10 / 24.05.2022).

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] World Health Organization. Global tuberculosis report 2020. https://www.who.int/publications/i/item/9789240013131 (accessed May 2022).

[2] Ayed HB, Koubaa M, Marrakchi C, et al. Extrapulmonary tuberculosis: update on the epidemiology, risk factors and prevention strategies. Int J Trop Dis 2018; 1: 1-6.

[3] Natali D, Cloatre G, Brosset C, et al. What pulmonologists need to know about extrapulmonary tuberculosis. Breathe (Sheff) 2020; 16: 200216.

[4] Sandgren A, Hollo V, van der Werf MJ. Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002 to 2011. Euro Surveill 2013; 18.

[5] T.C. Sağlık Bakanlığı. Türkiye'de Verem Savaşı 2020 raporu. https://hsgm.saglik.gov.tr/depo/kurumsal/yayinlarimiz/Raporlar/Turkiyede_Verem_Savasi_2020_Raporu.pdf (accessed August 2022).

[6] Aisenberg G, Jacobson K, Chemaly R, et al. Extrapulmonary tuberculosis active infection misdiagnosed as cancer: Mycobacterium tuberculosis disease in patients at a Comprehensive Cancer Center (2001-2005). Cancer 2005; 104: 2882-7.

[7] Kourbatova E, Leonard MJ, Romero J, et al. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. Eur J Epidemiol 2006; 21: 715-21.

[8] T.C. Sağlık Bakanlığı. Tüberküloz tanı ve tedavi rehberi 2019. https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/haberler/Tuberkuloz_Tani_Ve_Tedavi_Rehberi_/Tuberkuloz_Tani_ve_Tedavi_Rehberi.pdf (accessed May 2022).

[9] Peto H, Pratt R, Harrington T, et al. Epidemiology of extrapulmonary tuberculosis in the United States, 1993–2006. Clin Infect Dis 2009; 49: 1350-7.

[10] Sharma SK, Mohan A, Kohli M. Extrapulmonary tuberculosis. Expert Review of Respiratory Medicine 2021; 15: 931-948.

[11] Batirel A, Erdem H, Sengoz G, et al. The course of spinal tuberculosis (Pott disease): results of the multinational, multicentre Backbone-2 study. Clin Microbiol Infect 2015; 21: 1008.e9-1008.e18

[12] Özsoy-Hitit G, Göktaş P, Erdem İ, et al. Extra-Pulmonary Tuberculosıs In Adults: An Analysıs Of 67 Cases Turkish Journal of Infection 2005; 19: 407-13.

[13] Turunç T, Habeşoğlu MA, Demiroğlu YZ, et al. Ciddi ve hafif seyirli 113 akciğer dışı tüberküloz olgusunun karşılaştırılmalı olarak değerlendirilmesi. Mikrobiyol Bul 2008; 42: 399-406.

[14] Bozca B, Özgenç O, Avcı M, et al. Altmış ekstrapulmoner tüberküloz olgusunun incelenmesi. Turkiye Klinikleri J Med Sci. 2012; 32: 66-73.

[15] Şengül A, Ogan N, Aydemir Y. Akciğer dışı tüberküloz: Kocaeli verem savaş dispanseri'nde takip edilen 331 olgunun retrospektif incelenmesi. Medical Journal of Kocaeli 2015; 4 :4-9.

[16] Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis 2017; 7: 1-12.

[17] Ohene S, Bakker M, Ojo J, et al. Extra-pulmonary tuberculosis: A retrospective study of patients in Accra, Ghana. PLoS One 2019; 14 :e0209650.

[18] Sevgi D, Derin O, Alpay A, et al. Extrapulmonary tuberculosis: 7 year-experience of a tertiary center in Istanbul. Eur J Intern Med 2013; 24: 864-7.

[19] Çakar B. Akciğer Dışı Tüberküloz Olgularının Yıllara Göre Değerlendirilmesi. Turk Toraks Derg 2014; 15: 142-9.

[20] Salvadó M, Garcia-Vidal C, Vázquez P, et al. Mortality of tuberculosis in very old people. J Am Geriatr Soc 2010; 58: 18-22.

[21] Wang C, Chen H, Yang C, et al. The impact of age on the demographic, clinical, radiographic characteristics and treatment outcomes of pulmonary tuberculosis patients in Taiwan. Infection 2008; 36: 335-40.

[22] Thwaites G, Tran T. Tuberculous meningitis: many questions, too few answers. Lancet Neurol 2005; 4: 160-70.

[23] Cherian A, Thomas SV. Central nervous system tuberculosis. Afr Health Sci 2011; 11: 116-27.

[24] Mert A. Miliary Tuberculosis: Practical Diagnostic Approach in an Endemic Area. Flora Derg 2011; 16: 141-5.