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Extrapulmonary Tuberculosis Cases: Five Years Experience

Ekstrapulmoner Tüberküloz Olguları: Beş Yıllık Deneyim

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Abstract

Introduction: Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*, which can affect any organ. The incidence of TB has increased due to the increase in the number of diseases and drugs that cause immunosuppression. The diagnosis of extrapulmonary TB (EPTB) is mostly clinical, histopathologic, radiologic, less frequent microbiological diagnosis. In our study, it was aimed to reveal the data helpful in the diagnosis by retrospectively examining the demographic and clinical data of the patients with EPTB.

Materials and Methods: The patients who had a diagnosis of EPTB and were followed up between January 2012 and March 2017 in Fırat University Hospital, Department of Infectious Diseases and Clinical Microbiology were included in the study. Data were analyzed using Statistical Packages for the Social Science 22 statistical program.

Results: The study included 125 patients, 28.8% were male and 71.2% were female. The mean age was 46.3±17 years. Of the patients with EPTB diagnosed; 49% had lymphadenitis, 14% musculoskeletal system involvement, 3% miliary involvement, 10% genitourinary system involvement, 4% central nervous system involvement, 5% gastrointestinal system involvement, 5% mastitis, and 9% had other organ involvements. Patients most frequently presented with complaints of swelling, sweating and fever. Tuberculin skin test (TST) was positive in 61.1% of the patients and quantiferon test was positive in 71% of the patients. Growth in mycobacterial culture was found in 12.8% of our patients, polymerase chain reaction positivity in 6.4%, and acid-resistant staining positivity in 16.8%. Granuloma structures were seen in 81.9% of the patients who underwent histopathological examination, and caseification necrosis was detected in 64.7% of the granuloma structures.

Conclusion: Tuberculosis must be considered in the differential diagnosis of infectious diseases in which no etiology is detected in areas where TB is common, such as our country. It is thought that none of the EPTB diagnostic methods have the sensitivity and specificity that can be used alone, and that the evaluation of TST or quantiferon can still be used for diagnosis. There is a need for new tests that have high sensitivity and specificity for the diagnosis of EPTB.

Keywords: Extrapulmonary tuberculosis, epidemiology, tuberculin skin test, quantiferon

Öz

Giriş: Tüberküloz (TB), *Mycobacterium tuberculosis*'in etken olduğu, her organı tutabilen bir hastalıktır. İmmün sistemi baskılayan hastalıklar ve ilaç kullanımının artışıyla bağlı olarak TB insidansı artmaktadır. Ekstrapulmoner TB (EPTB) tanısı çoğunlukla klinik, histopatolojik, radyolojik, daha az oranlarda mikrobiyolojik olarak konulmaktadır. Çalışmamızda EPTB'li olguların demografik, klinik verileri, retrospektif olarak incelenerek, tanıya yardımcı verilerin ortaya çıkarılması amaçlandı.

Gereç ve Yöntem: Fırat Üniversitesi Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı'nda, Ocak 2012 ve Mart 2017 yılları arasında EPTB tanısı ile takip edilen hastalar çalışmaya dahil edildi. Veriler Statistical Packages for the Social Science 22 istatistik programı kullanılarak analiz edildi.

Bulgular: Çalışmaya dahil edilen 125 hastanın %71,2'si kadın, %28,8'i erkek ve yaş ortalaması 46,3±17 idi. EPTB tanısı konulan hastaların %49'u lenfadenit, %14'ü kas iskelet sistemi, %3'ü miliyer, %10'u genitoüriner sistem, %4'ü santral sinir sistemi, %6'sı gastrointestinal sistem, %5'i mastit ve %9'u diğer organ tutulumu gösterdi. Hastalar en sık şişlik, terleme ve ateş şikayetleri ile başvurdu. Hastaların %61,1'inde tüberkülin deri testi (TDT),

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%71'inde quantiferon testi pozitif olarak saptandı. Hastalarımızın %12,8'inde mikobakteri kültüründe üreme, %6,4'ünde polimeraz zincir reaksiyonu pozitifliği, %16,8'inde de aside dirençli boyama pozitifliği tespit edildi. Histopatolojik inceleme yapılan hastaların %81,9'unda granülom yapıları görüldü ve bunların %64,7'sinde kazeifikasyon nekrozu saptandı.

Sonuç: Ülkemiz gibi TB'nin endemik görüldüğü yerlerde birçok hastalığın ayırıcı tanısında TB düşünülmelidir. EPTB'de kullanılan tanı yöntemlerinin hiçbirinin yeterli duyarlılık ve özgüllüğe sahip olmadığı, TDT ya da quantiferon testlerinin tanıyı destekleyici testler olarak kullanılabileceği düşünüldü. EPTB tanısı için duyarlılık ve özgüllüğü yüksek yeni testlere ihtiyaç vardır.

Anahtar Kelimeler: Ekstrapulmoner tüberküloz, epidemiyoloji, tüberkülin deri testi, quantiferon

Introduction

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*, which can affect every organ, especially the lung. Extrapulmonary TB (EPTB) is TB of various tissues and organs with extrapulmonary involvement. Tuberculosis is a treatable and preventable disease. Despite this, it is still an important health problem in developing countries^[1]. About 1/3 of the entire world population is infected with TB bacillus. Of infected people 5–10% have the disease at some point in their lives^[2].

According to the World Health Organization Global Tuberculosis Report 2020, mortality, incidence and prevalence rates of TB are decreasing worldwide. It is estimated that 10 million people worldwide were infected with TB in 2019^[3]. In Turkey, 12,046 patients with TB were registered in TB dispensaries in 2017. It was observed that 60.9% of the patients had lung involvement, 33.9% had extrapulmonary organ involvement, and 5.3% had both pulmonary and extrapulmonary involvement^[4].

The TB bacillus is usually first localized in the lung tissue. From here, the bacilli may spread to an extrapulmonary organ via the lymphohematogenous route or contiguous path and may remain dormant there. As a result of suppression of the immune system for any reason, the disease occurs as a result of the re-activation of dormant bacilli years later. If reactivation occurs in foci outside the lung, EPTB types emerge^[5]. Patients with EPTB present with non-specific complaints such as fever, weight loss, anorexia, and fatigue, and symptoms and findings specific to the anatomical location of the involved organ^[6].

In our study, it was aimed to analyze the demographic and clinical data of patients with EPTB retrospectively and to reveal the data helpful for the diagnosis.

Materials and Methods

This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Firat University Faculty of Medicine (date: 05.03.2016/meeting no: 5, decision no: 15).

One hundred and twenty five patients who were diagnosed as having EPTB and started treatment between January 2012 and March 2017 in Firat University Hospital, Department of

Infectious Diseases and Clinical Microbiology were included in the study. The clinical forms, diagnostic methods and demographic characteristics of the patients were evaluated retrospectively.

Exclusion Criteria

Patients under the age of 18, patients with a diagnosis of pulmonary TB, patients for whom anti-TB treatment was started preemptively and then it was discontinued due to a different diagnosis.

Tuberculin Skin Test

Tuberculin skin test positivity was accepted as ≥ 15 mm in those without risk factors and those with BCG vaccination, >10 mm in those without BCG vaccination, and >5 mm in those with risk factors. The following conditions were considered as risk factors:

- Use of 15 mg/day prednisolone or equivalent dose of steroids or other immunosuppressive drugs for more than two to four weeks,
- Those with immunosuppressive disease: Malnutrition, diabetes mellitus, chronic kidney disease, HIV positivity, oncological, hematological or reticuloendothelial system malignancies (leukemia, lymphoma, etc.).

Statistical Analysis

The IBM Statistical Package for the Social Sciences (SPSS) Statistics version 22 package program (SPSS inc., Chicago, IL, USA) was used for statistical analysis. The conformity of the quantitative data to the normal distribution was examined using the Shapiro-Wilk test. Mean $\pm$ standard deviation was used for normally distributed continuous variables. Data for categorical variables were given as frequency and percentage. Fisher Exact test and Pearson's chi-square test were used to compare the ratios in different groups. A $p<0.05$ was considered statistically significant.

Results

One hundred and twenty-five patients were included in our study. Of the patients, 89 (71.2%) were female, 36 (28.8%) were male, and the mean age was 46.3 ± 17 years.

When the histories of the patients were examined, 53 (44.4%) patients had at least one additional disease: hypertension in 20 (16%) patients, diabetes mellitus in 15 (12%), ischemic heart disease in 12 (9.6%) patients, chronic renal failure in five (4%), and malignancy in five (4%) patients. There were three (2.4%) patients with a diagnosis of chronic hepatitis B and one (0.8%) patient with a diagnosis of chronic hepatitis C. There was no human immunodeficiency virus (HIV) positivity. Seven (5.6%) patients had a history of TB and 31 (24.8%) had a family history of TB.

The distribution of patients with EPTB by clinical types is given in Figure 1. One (0.8%) patient had pleural, one had pericardium, one had tonsil, one had cartilage tissue, one had maxillary sinus, and two (1.6%) had soft tissue involvement.

The most common clinical type was lymphadenitis with 61 (49%) patients. Of the patients with lymphadenitis, 49 (80.3%) were female and 12 (19.7%) were male ($p=0.028$). The mean age of female patients was 50.2 ± 16.25 , and the mean age of male patients was 35.2 ± 13 ($p=0.05$).

The most common involvement was found in the cervical region in patients with lymphadenitis ($n=46$, 75.4%). Of the patients 13.3% had single axillary, 4.9% cervical and axillary, 3.2% axillary and inguinal, 1.6% intra-abdominal and inguinal, 1.6% thoracic and intra-abdominal lymph node involvement. Fistulized lymphadenitis was detected in 10 (16.3%) patients, eight of whom were cervical, two were axillary, and one was inguinal.

The patients most frequently presented with complaints of fever, swelling in different parts of the body, sweating, anorexia, weakness and weight loss. The complaints of the patients according to the clinical types of EPTB are presented in Table 1.

Diagnosis was made microbiologically in 27% of the patients, histopathologically in 60%, and clinically and radiologically in 6.4%. The number of samples taken according to clinical types and the number of culture positive, acid resistant bacillus (ARB) positive, TB polymerase chain reaction (PCR) positive patients are given in Table 2.

Samples taken from 104 patients were examined histopathologically. Pathology results according to clinical types are presented in Table 3.

Tuberculin skin test (TST) results were obtained in 103 of the patients, and 61.1% were found to be positive (Table 4). Tuberculin skin test was found to be anergic in 15 patients. Of the patients with anergic TST result, two had malignancy, one had chronic renal failure, three had diabetes mellitus, and one had sarcoidosis. Quantiferon test was positive in 71% of 31 patients whose quantiferon test was studied (Table 4). Tuberculin skin test was positive in 10 (45.4%) and negative in nine (40.9%) of

Figure 1. Distribution of patients with extrapulmonary tuberculosis by clinical types

the patients with positive quantiferon test ($p=0.391$). Tuberculin skin test results of three (13.6%) patients could not be obtained.

Discussion

Although TB is treatable, it remains an important health problem. It is estimated that 10 million people worldwide were infected with TB in 2019. Extrapulmonary TB accounts for 16% of patients^[3]. While a decrease is observed in the total number of new patients, the rate of patients with EPTB is increasing. It has been shown in patients with EPTB that lymph nodes are involved in 28.5%, pleura in 23.4%, musculoskeletal system in 7%, gastrointestinal system in 5.4%, genitourinary system in 4.9%, miliary system in 2.8%, central nervous system (CNS) in 3.5%, and other organs in 14.3%^[4]. In the United States, involvement of lymph nodes were found in 35.2% of the patients with EPTB, pleura in 17.2%, musculoskeletal system in 9.6%, peritoneum in 6.2%, genitourinary system in 4.5%, CNS in 4.5%, and other organs in 22.8%^[7]. Extrapulmonary TB is more common in women^[4]. In a study, the mean age of patients with EPTB was found to be 37 ± 15 ^[8]. In our study, the female/male ratio was 2.47 and the mean age of the patients was 46.3 ± 17 . The most common site of involvement was lymph node in our study.

The most common form of EPTB is lymphadenitis^[6,7]. While pulmonary TB is more common in males and advanced age groups; TB lymphadenitis is more common in women and younger age groups^[1]. Dandapat et al.^[9] attributed this to the fact that women in male-dominated communities were exposed to worse living conditions and generally noticed changes in the body earlier. In our study, the most common form of EPTB was lymphadenitis and it was more common in women. Tuberculosis lymphadenitis mostly involves the cervical lymph nodes^[10]. In

Table 1. Complaints of patients with extrapulmonary tuberculosis at admission

	Lymphadenitis n (%)	Musculoskeletal n (%)	GUS n (%)	GIS n (%)	Mastitis n (%)	CNS n (%)	Miliary n (%)	Other n (%)	All patients n (%)
Swelling	56 (91.8)	2 (11.8)	1 (8.3)	-	6 (85.7)	-	1 (25)	3 (27.3)	69 (55.2)
Sweating	25 (41)	9 (52.9)	4 (33.3)	7 (87.5)	-	3 (60)	3 (75)	7 (63.6)	58 (46.4)
Fever	13 (21.3)	8 (47.1)	3 (25)	7 (87.5)	-	4 (80)	3 (75)	8 (72.7)	46 (36.8)
Anorexia	18 (29.5)	8 (47.1)	3 (25)	8 (100)	1 (14.3)	1 (20)	2 (50)	5 (45.5)	46 (36.8)
Weakness	14 (23)	6 (35.3)	-	7 (87.5)	-	3 (60)	3 (75)	7 (63.6)	40 (32)
Weight loss	11 (18)	5 (29.4)	5 (41.7)	6 (75)	-	1 (20)	1 (25)	5 (45.5)	34 (27.2)
Cough and phlegm	5 (8.2)	2 (11.8)	3 (25)	3 (37.5)	-	-	4 (100)	3 (27.3)	20 (16)
Nausea	2 (3.3)	1 (5.9)	2 (16.7)	6 (75)	-	3 (60)	-	2 (18.2)	16 (12.8)
Stomachache	2 (3.3)	-	3 (25)	6 (75)	-	-	-	2 (18.2)	13 (10.4)
Joint pain	2 (3.3)	5 (29.4)	1 (8.3)	-	-	-	1 (25)	3 (27.3)	12 (9.6)
Waist, back, neck pain	-	10 (58.8)	-	-	-	-	2 (50)	-	12 (9.6)
Vomiting	-	1 (5.9)	-	4 (50)	-	3 (60)	-	1 (9.1)	9 (7.2)
Burning in urination	-	-	6 (50)	-	-	-	2 (50)	-	8 (6.4)
Headache	1 (1.6)	-	-	-	-	4 (80)	-	2 (18.2)	7 (5.6)
Shortness of breath	1 (1.6)	-	1 (8.3)	2 (25)	-	-	1 (25)	1 (9.1)	6 (4.8)
Chest pain	-	1 (5.9)	1 (8.3)	-	-	-	1 (25)	2 (18.2)	5 (4)
Muscle pain	1 (1.6)	1 (5.9)	-	1 (12.5)	-	-	1 (25)	1 (9.1)	5 (4)
Urinary incontinence	-	-	3 (25)	-	-	-	1 (25)	-	4 (3.2)
Pain in the groin	-	-	3 (25)	-	-	-	-	-	3 (2.4)
Infertility	-	-	3 (25)	-	-	-	-	-	3 (2.4)
Clouding of consciousness	1 (1.6)	-	-	-	-	-	1 (25)	1 (9.1)	3 (2.4)
Walking problem	-	3 (17.6)	-	-	-	-	-	-	3 (2.4)
Dizziness	-	-	-	-	-	2 (40)	-	-	2 (1.6)
Flank pain	-	-	2 (16.7)	-	-	-	-	-	2 (1.6)
Scrotal pain	-	-	2 (16.7)	-	-	-	-	-	2 (1.6)
Contraction	-	-	-	-	-	-	-	2 (18.2)	2 (1.6)
Ear pain	-	-	-	-	-	-	-	1 (9.1)	1 (0.8)

GUS: Genitourinary system, GIS: Gastrointestinal system, CNS: Central nervous system

approximately 8-10% of patients, the lymph node is drained^[11]. Patients usually present with a mass complaint^[12]. Consistent with the literature in our study, most of the patients presented with mass complaints and cervical lymphadenitis was the most common. The lymph node was drained in 16.3% of our patients. The gold standard in the diagnosis of TB lymphadenitis is the demonstration of the TB bacillus and the growth of TB bacillus in culture. However, growth in mycobacterial culture was reported at a rate of 10-69%^[12], and ARB positivity was reported at a rate of 34.4-52.9%^[12,13]. Another diagnostic method in TB is histopathological examination of tissue biopsy. The sensitivity and specificity of the biopsy were 88% and 96%, respectively^[13]. In one study, caseified granulomatous lymphadenitis was found in 80% of patients in histopathological examination^[9]. Tuberculin skin test was positive in 64.4-100% of patients^[10,14]. In our study, the rate of growth in mycobacterial culture, and

ARB and TB PCR positivities was found to be low. This might be due to the low re-sampling after a negative result. Tuberculin skin test positivity was detected in 56.5% of our patients and 73.8% of them were diagnosed histopathologically.

Musculoskeletal TB accounts for 7% of patients with EPTB^[3,4]. It most commonly involves the vertebral region and accounts for approximately one-third of patients with musculoskeletal TB^[15,16]. In TB arthritis, the most common involvement is the hip (12.3%), followed by the knee (7%). The first symptom that occurs in patients is local pain, followed by non-specific complaints such as weight loss, fever and sweating^[15,16]. In our study, musculoskeletal TB (14%), TB spondylitis (58.8%) and TB arthritis (11.8%) were observed at similar rates. Pain was the first symptom in most of our patients, and as in other studies, patients presented with non-specific complaints. In the study of Chen et al.^[15], the rate of bacteriological diagnosis (19%) was

Table 2. Number of culture positive, acid resistant bacillus positive and tuberculosis polymerase chain reaction positive patients by clinical types

	Culture (+) n/N (%)	ARB n/N (%)	PCR n/N (%)
Lymphadenitis	6/26 (23)	10/29 (34.4)	4/7 (57.1)
GUS	2/7 (28.5)	3/7 (42.8)	-
Pyelonephritis	1/1 (100)	1/1 (100)	-
Endometritis	1/1 (100)	0/1 (0)	-
Cystitis	0/2 (0)	2/2 (100)	-
Prostatitis	0/2 (0)	0/2 (0)	-
Orchitis	0/1 (0)	0/1 (0)	-
GIS	1/4 (25)	1/4 (25)	0/2 (0)
Peritonitis	1/4 (25)	1/4 (25)	0/1 (0)
Ileitis	-	-	0/1 (0)
Musculoskeletal	4/10 (40)	3/10 (30)	1/3 (33.3)
Spondylodiscitis	1/3 (33.3)	1/3 (33.3)	-
Synovitis	0/1 (0)	0/1 (0)	-
Psoas abscess	1/1 (100)	1/1 (100)	-
Osteomyelitis	1/1 (100)	0/1 (0)	-
Fasciitis	1/1 (100)	0/1 (0)	1/1 (100)
Bursitis	0/1 (0)	0/1 (0)	-
Arthritis	0/2 (0)	1/2 (50)	0/2 (0)
Mastitis	0/2 (0)	0/2 (0)	0/2 (0)
Miliary	2/2 (100)	1/2 (50)	-
CNS	0/3 (0)	1/4 (0)	2/3 (66.6)
Other			
Maxillary sinus	1/1 (100)	1/1 (100)	-
Soft tissue	-	1 (100)	-
Pericarditis	0/1 (0)	0/1 (0)	1/1 (100)
Pleura	0/1 (0)	0/1 (0)	-

n: number of positive patients, N: number of samples taken, GUS: Genitourinary system, GIS: Gastrointestinal system, CNS: Central nervous system, PCR: Polymerase chain reaction, ARB: Acid resistant bacillus

reported to be low. In our study, bacteriological diagnosis was made in 23.5% of the patients. In one study, similar to our study, TST was reported positive in 89.8% and quantiferon test was reported positive in 82.1% of the patients^[16].

Genitourinary system TB constitutes 20-40% of patients with EPTB and the kidneys are most frequently affected^[17-19]. In females, genital TB is often located in the endosalpinx. It is observed that the patients present with local symptoms such as infertility, menstrual disorders and abdominal pain. It is frequently seen in women of reproductive age (15-45 years)^[20]. It may occur with symptoms resembling endometrial malignancy such as bleeding in the postmenopausal period. All of our patients who were in the reproductive age were admitted with the complaint of infertility. Although the production of the agent in the diagnosis of TB is the gold standard, culture sensitivity in urinary TB has been reported as 10.7-80% and ARB sensitivity at a rate of 37.1-52.1%^[19]. Acid resistant bacillus and culture positivity in genital TB are 1.3-1.8% and 3.3-8.8%^[21,22]. The low rates of ARB and culture positivities may be due to the fact that only the fallopian tubes are infected, sampling may be from the uninfected area, the number of microorganisms is low, and the endometrium is periodically shed^[21]. There was growth in mycobacteria culture of one patient with genital TB in our study. Tuberculin skin test was positive in 50% of our patients. The sensitivity and specificity of the urine PCR method were reported as 95.6% and 98.1%^[23]. Tuberculin skin test is positive at the rate of 42.6%. In our study, growth in mycobacterial culture and ARB positivity for urinary TB were detected at similar rates, and TB PCR was not studied.

Gastrointestinal TB accounts for 11% of patients with EPTB and the ileum and cecum are the most frequently involved areas. Patients usually present with abdominal pain, weight loss, loss of appetite, constipation, fever and diarrhea. In the study of

Table 3. Pathology results according to clinical types

	Lymphadenitis n (%)	Musculoskeletal n (%)	GUS n (%)	GIS n (%)	Mastitis n (%)	CNS n (%)	Miliary n (%)	Other n (%)	All patients n (%)
Caseified granulomatous	35 (61.4)	5 (41.7)	5 (50)	4 (50)	-	1 (100)	1 (33.3)	4 (66.7)	55 (53)
Non-caseified granulomatous	15 (26.3)	1 (8.3)	4 (40)	2 (25)	7 (100)	-	-	1 (16.7)	30 (28.9)
Chronic inflammatory infiltration	-	3 (25)	-	1 (12.5)	-	-	2 (66.7)	-	6 (5.9)
Necrotic foci, chronic inflammatory infiltration	2 (3.5)	1(8.3)	1 (10)	-	-	-	-	-	4 (3.8)
Acute inflammatory reaction	-	1(8.3)	-	-	-	-	-	1 (16.7)	2 (1.9)
Leukocytes	1 (1.8)	1(8.3)	-	-	-	-	-	-	2 (1.9)
Necrotic foci	2 (3.5)	-	-	-	-	-	-	-	2 (1.9)
Lymphocytes	-	-	-	1 (12.5)	-	-	-	-	1 (0.9)
Histiocytes	1 (1.8)	-	-	-	-	-	-	-	1 (0.9)
Caseification necrosis	1 (1.8)	-	-	-	-	-	-	-	1 (0.9)
Total	57 (100)	12 (100)	10 (100)	8 (100)	7 (100)	1 (100)	3 (100)	6 (100)	104 (100)

GUS: Genitourinary system, GIS: Gastrointestinal system, CNS: Central nervous system

Table 4. Tuberculin skin test and quantiferon results by clinical type

Clinical type	TST		Quantiferon	
	Positive (%)	Negative (%)	Positive (%)	Negative (%)
Lymphadenitis	26 (56.5)	20 (43.5)	12 (92.3)	1 (7.7)
Musculoskeletal	11 (73.3)	4 (26.7)	3 (75)	1 (25)
GUS	8 (66.7)	4 (33.3)	4 (100)	0 (0)
GIS	5 (62.5)	3 (37.5)	1 (50)	1 (50)
Mastitis	1 (20)	4 (80)	0 (0)	4 (100)
Miliary	4 (100)	0 (0)	0 (0)	0 (0)
CNS	1 (20)	4 (80)	0 (0)	1 (100)
Other	7 (87.5)	1 (12.5)	2 (66.7)	1 (33.3)
Total	63 (61.2)	40 (38.8)	22 (71)	9 (29)

TST: Tuberculin skin test, GUS: Genitourinary system, GIS: Gastrointestinal system, CNS: Central nervous system

Fillion et al.^[24], similar to our study, the most frequently involved area was the peritoneum with 67%. Granuloma structures can be seen in 81–94.7% of the histopathological examinations^[24]. Granulomatous inflammation was detected in 75% of our patients. The rates of growth in mycobacterial culture and ARB positivity were low in our study, which was consistent with the literature^[25]. Growth was detected in 83% of mycobacterial cultures made with one liter of acidic fluid^[26]. Therefore, searching for ARBs in larger amounts of acidic fluid and culturing mycobacteria increase the probability of diagnosis. Although quantiferon test and TST positivities were found to be lower in our study, in a meta-analysis, the sensitivity of the quantiferon test was 74% and the specificity 87% in differentiating between Crohn's disease and intestinal TB^[27].

Breast TB is a rare form and accounts for 4% of patients. It is usually observed in women of reproductive age (20–40 years). It is reported that patients most frequently present with breast swelling and pain in the breast. On physical examination, lymphadenopathy (LAP) may be seen with a breast mass in patients^[28]. In our study, TB mastitis was seen in 5%. Of the patients 85.7% were admitted with the complaint of breast swelling and LAP was detected in 42.5%. Although the gold standard for the diagnosis of TB mastitis is ARB positivity or its production in mycobacteria culture, positivity is rare. Histopathological examination is the most common diagnostic method. In some studies, ARB positivity was not reported in any of the patients with TB mastitis^[29,30]. In our study, all patients were diagnosed histopathologically. Acid resistant bacillus positivity and TB PCR positivity were not detected in any patient, and there was no growth in mycobacterial culture. The low number of patients with TB mastitis and the inability to diagnose bacteriologically may be due to the fact that the mammary gland tissue is resistant to the proliferation of bacilli and the infection occurs with a small amount of bacillus.

Central nervous system TB accounts for approximately 1% of all

patients with TB and is important because of its high mortality and morbidity rate. According to Centers for Disease Control and Prevention data, CNS TB constitutes 4.5% of patients with EPTB^[7]. It was observed that the patients were most frequently admitted with the complaints of fever, headache, nausea-vomiting and confusion. Neck stiffness was found in 86.7% of the patients, Kernig and Brudzinski phenomenon in 40%, and cranial nerve paralysis in 33.3% of the patients^[31]. In our study, CNS TB constituted 4% of patients with EPTB. In a study conducted in our country, ARB positivity was found in 20.9% of CSF samples, *M. tuberculosis complex* growth in CSF culture in 82.9%, and DNA positivity of *M. tuberculosis* in 44.4% by PCR method^[32]. Acid resistant bacillus positivity was found in 50% of our patients, and TB PCR positivity was found in 33.3% of our patients, but there was no growth in mycobacterial culture. Tuberculin skin test positivity was found in 10–67.8% of patients in different studies^[33,34]. In our study, this rate was found to be 20%.

Miliary TB develops by lympho-hematogenous dissemination of *M. tuberculosis* and is a rare form of TB. It constitutes 1% of all patients with TB in the USA. Patients may present with various symptoms and signs. It is difficult to diagnose even in endemic regions, since classical miliary changes do not always occur on chest radiography and atypical involvements are common^[35]. A high clinical suspicion and a systematic approach to diagnostic tests are required to diagnose miliary TB. Patients usually present with complaints of fever, weakness, weight loss and night sweats. In our study, miliary TB was seen in 4% of our patients and our patients were admitted with non-specific complaints. Histopathological demonstration of granulomas in two of the organs such as the lung, liver, bone marrow and lymph nodes is helpful in the diagnosis of miliary TB. In one study, 75% of granuloma structures were detected in histopathological examination^[36]. In our study, granuloma structures were detected in the pleura and urinary system in one patient. Growth was detected in the culture of mycobacteria

in the other two patients. Anergic incidence of TST in patients with a diagnosis of miliary TB is higher than in patients with pulmonary TB and EPTB^[35]. Tuberculin skin test positivity was found in all of our patients.

Pleural TB is a common (20%) clinical type of EPTB and is the most common cause of pleural effusion^[37]. We had one (0.8%) patient who was diagnosed as having pleural TB because the patients with pulmonary TB and pleural effusion were followed up mainly in the chest diseases clinic in our hospital.

Tuberculous pericarditis accounts for approximately 1% of all patients with TB^[38]. It was found in one patient in our series.

Tuberculous sinusitis, cutaneous TB, thyroid TB, tonsillar TB, and TB chondritis are rare clinical forms and in our case series, cutaneous TB was seen in two patients and the other forms were seen in one patient each.

The limitation of our study was that it was a retrospective study.

Conclusion

In conclusion, TB is an important health problem that can affect all organs and tissues and can be seen in different age groups and in both genders. The incidence of TB is increasing due to the increase in the number of geriatric patients, increasing diabetes mellitus and chronic kidney disease incidences, increasing HIV incidence, and widespread use of immunosuppressive therapies in many areas. It should not be forgotten that existing latent TB infection may be activated in patients with risk factors. Tuberculosis should definitely be considered in the differential diagnosis of infectious diseases in which etiology cannot be determined, especially in endemic regions. Microscopy and culture methods have high specificity but low sensitivity. Although the search for *M. tuberculosis* DNA by PCR is an expensive method, it is considered an ideal method because of its rapid results in TB diagnosis, detection of resistance genes, and high sensitivity and specificity. In accordance with the literature, it is seen in our study that none of the diagnostic methods in EPTB have the sensitivity and specificity that can be used alone. New tests with high sensitivity and specificity are needed for the diagnosis of EPTB.

Ethics

Ethics Committee Approval: This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Firat University Faculty of Medicine (date: 05.03.2016/meeting no: 5, decision no: 15).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.A.B., A.S.T., A.A., K.D., Concept: İ.A.B., Design: İ.A.B., A.S.T., Data Collection or Processing: İ.A.B., Analysis or Interpretation: İ.A.B., A.S.T., A.A., K.D., Literature Search: A.S.T., A.A., Writing: İ.A.B.

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