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ARAŞTIRMA / RESEARCH

Epidemiological profile of extrapulmonary tuberculosis cases: 4 year-experience

Ekstrapulmoner tüberküloz olgularının epidemiyolojik profili: 4 yıllık deneyim

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Abstract

Purpose: The aim of this study was to examine the demographic features, organ and tissue distribution, diagnostic methods and treatment outcomes of extrapulmonary tuberculosis cases who were registered to the Adana Tuberculosis Dispensary.

Materials and Methods: 400 cases, who were diagnosed with extrapulmonary tuberculosis, treated and followed up between 2014 and 2017, were examined and analyzed retrospectively. Their demographic characteristics, drug susceptibility tests, follow-ups and treatment outcomes were reviewed. Individual data for extrapulmoary tuberculosis cases were collected from tuberculosis registers, tuberculosis medical personal files and treatment cards.

Results: In total, 400 cases of extrapulmoary tuberculosis were recorded. Patients were within the range of 0 to 87 years old (mean age: 41.19±19.97 years), and 245 of them (61.2%) were female. Tuberculosis most frequently affected lymph nodes (38.8%), followed by pleura (17.8%) and gastrointestinal tract (9.0%). None of the cases had multidrug-resistant tuberculosis. Treatment completion rates were high and reached 95.8%.

Conclusion: The present findings provide information about the epidemiology of extrapulmonary tuberculosis in Adana during the 4-year period. The occurrence of cases at the most productive age is important to show the degree of economic loss in Turkey. Tuberculosis is a contagious illness that mainly affects the lymph nodes rather than the lungs. Investigations into epidemiological and clinical characteristics of extrapulmonary tuberculosis in large number of cases might be crucial to early diagnosis and therapy in endemic countries such as Turkey.

Keywords:. Epidemiology, extrapulmonary tuberculosis, treatment outcome, Turkey

Öz

Amaç: Bu çalışmada Adana Verem Savaş Dispanserine kayıtlı ekstrapulmoner tüberküloz olgularının demografik özelliklerinin incelenmesi, organ ve doku yerleşimleri açısından dağılımı, tanıda kullanılan yöntemlerin belirlenmesi ve tedavi sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2014-2017 yılları arasında ekstrapulmoner tüberküloz tanısı ile tedavi ve takip edilen 400 olgu geriye dönük olarak incelendi ve analiz edildi. Olguların demografik özellikleri, ilaç duyarlılık testleri, takip ve tedavi sonuçları değerlendirildi. Akciğer dışı tüberküloz vakaları için veriler tüberküloz kayıtları, tedavi kartları ve kişisel tıbbi dosyalarından toplandı.

Bulgular: Çalışmaya alınan olguların yaşı 0-87 yıl arasında değişmekte olup (ortalama yaş: 41,19±19,97 yıl), 245 (%61,2)'i kadındır. En sık tutulan bölgenin lenf nodu (%38,8) olduğu, bunu %17,8'lik oranla plevra ve %9,0'luk oranla gastrointestinal tutulumun izlediği belirlenmiştir. Yapılan ilaç duyarlılık testi sonucunda, çok ilaca dirençli tüberküloza rastlanmamıştır. Tedavi tamamlama oranı %95,7'dir.

Sonuç: Bu çalışmanın sonuçları, Adana'da 4 yıllık dönemde akciğer dışı tüberküloz epidemiyolojisi hakkında bilgi vermektedir. Olguların en üretken yaşlarda görülmesi ülkemizin ekonomik kaybının boyutlarını göstermesi açısından önemlidir. Tüberküloz akciğer dışında en sık lenf düğümlerini tutmakla birlikte tüm organ ve dokuları tutabilen bir enfeksiyon hastalığı oldugu gösterilmiştir. Ülkemiz gibi tüberküloz açısından endemik olan ülkelerde, ekstrapulmoner tüberküloz olgularının epidemiyolojik ve klinik özelliklerinin daha geniş seriler ile araştırılmasının, hastalığın erken tanı ve tedavisi açısından önemli olduğu düşünülmüştür

Anahtar kelimeler: Epidemiyoloji, ekstrapulmoner tüberküloz, tedavi sonucu, Türkiye

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INTRODUCTION

Tuberculosis (TB) is a major global health concern and may emerge as a disease that influences many systems with myriad presentations[1]. The World Health Organization (WHO) is projected to rise to 10.4 million incident cases of TB and 1.67 million deaths of TB in 2017[2]. Tuberculosis, caused by the *Mycobacterium tuberculosis* complex, is a chronic necrotizing bacterial infection characterized by the presence of granulomatous lesions[3]. It has been well known that TB generally affects the lungs. However, it can also have an effect on other organs, a form known as extrapulmonary tuberculosis (EPTB). EPTB most commonly affects anatomic sites such as lymph nodes, pleura, urogenital tract bones, joints and meninges. Some types of EPTB, such as tuberculous meningitis and miliary TB, are responsible for a considerable number of diseases and deaths in various populations[4]. About 10%–50% of EPTB patients suffer from accompanying pulmonary involvement. Thus, all suspected cases of EPTB need to be assessed in terms of accompanying pulmonary TB (PTB) to detect whether the case is contagious and to assist in diagnosis[5].

The number of EPTB cases have recently increased. The differential diagnosis of almost every infection should be focused on EPTB particularly in countries where TB is endemically seen. The rate of EPTB to PTB varies according to social, ethnic, geographical and economic parameters. EPTB emerges as a result of lympho-hematogenous spreading of the primary infection and subsequent latency of the spreading TB bacilli, which may then reactivate in the event of increased susceptibility or reduced body resistance. The disease might appear in any stage of life and may affect any organ[6]. 6.3 million new cases of TB were officially recognized by WHO in 2017, 16% of which were cases of EPTB. Its incidence varied from 8% in the Western Pacific Region to 24% in the Eastern Mediterranean Region[2]. The incidence of EPTB has been reported to be 30-45% in Turkey[6].

In the last few decades, studies of high-income countries have demonstrated that cases of EPTB constitute a rising rate of total cases of TB[4]. However, the cause of this increase remains so elusive. Missing cases and difficulties in diagnosing EPTB show most likely that real rate of EPTB was much greater than that was reported[5]. Despite these data, research on EPTB is scarce, perhaps as EPTB is less transitable than PTB[4].

In fact, this study aimed to identify demographic factors, the diagnostic strategies, as well as treatment outcomes of patients who were diagnosed with EPTB in Adana, Turkey, to develop preferable control strategies of TB and to extend the knowledgebase of EPTB. To the best of our knowledge, any study has not been reported from this region.

MATERIALS AND METHODS

Records of the patients with EPTB followed up by tuberculosis dispensary between 2014 and 2017 were investigated, retrospectively. According to Turkish legislation, patients diagnosed with TB in hospitals were referred to the regional dispensary for the treatment of TB[7]. Tuberculosis dispensary is an official place in healthcare system where TB patients are followed up for therapy, treatment outcomes are reported and TB drugs are distributed to the patients for free. Adana, located in south-central Anatolia, is the sixth most populous province with a population of 2.20 million in Turkey. There are 4 tuberculosis dispensaries in Adana and its districts.

In this study, the EPTB patients registered to these dispensaries were retrospectively examined in terms of socio-demographic information (age, gender, country of birth), history of anti-tuberculosis treatment, presence of HIV infection, microbiology of biological samples, involvement sites and response to treatment. The underlying concepts and definitions used here were based on the "T.R. Ministry of Health Tuberculosis Diagnosis and Treatment Guidelines 2019"[8].

Definition of EPTB

EPTB is described as the involvement of organs such as lymph nodes, genitourinary tract, gastrointestinal tract, abdomen, pleura, skin, joints, bones, meninges and others other than the lung parenchyma[3]. Diagnosis needs to be based upon at least one specimen with confirmed *M. tuberculosis* or strong clinical or histological evidence consistent with active EPTB, followed by a clinician's decision to treat with a full course of tuberculosis chemotherapy[9]. Generally, due to difficulties in gaining access to and providing specimens from different biological sites, EPTB treatment is initiated depending on symptoms and other circumstantial evidence that supports radiographic abnormalities and laboratory investigations. Where possible, the collected

specimens need to be sent for bacteriological investigation (standard culture or molecular tests or direct microscopy examination). These specimens are also examined by pathology laboratories. With regard to record, patients with TB in both pulmonary and extrapulmonary sites are classified as "PTB"[10]. The case definition of an EPTB case with affected several sites (e.g., lymph nodes and pleural effusion), is dependent on the site showing the most severe form of disease[9].

Pilot studies have been performed by the Ministry of Health for the Directly Observed Therapy Short-Course (DOTS) strategy since 2003 in Turkey. Tuberculosis Control Program was combined with the health care system in 2006, and DOTS strategy expanded. The guidelines of the Ministry of Health pursued for the diagnosis and treatment of TB in all the tuberculosis dispensaries[3].

Patients who had no previous tuberculosis treatment or who had received tuberculosis treatment for less than one month were defined as "new cases"[8]. Patients who were previously diagnosed as having tuberculosis, completed treatment succesfully and once again developed ARB positivity and clinical and radiological findings were defined as "recurrence cases"[8].

Procedure

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was received for this study from the ethics committee of Cukurova University School of Medicine (document no: 2018/82/37, date: 02.10.2018).

Records of medical history and physical examination details were investigated for all compatible patients who met EPTB definition during analyzing period. Definitive diagnosis was established by histopathologically, bacteriological, radiological methods and clinical evidence. Clinical evidence was described as the patient's presenting signs and symptoms, as well as radiographic or tisue sample analysis supporting the diagnosis of EPTB. Cases with missing or insufficient data in their records were excluded. Patients with concomitant pulmonary and extrapulmonary TB were left out of the present study.

Radiologic evaluation

The radiologic imagings of all patients at baseline and at the end of treatment were evaluated by a radiologist. Patients with EPTBC were screened in terms of tuberculosis-specific radiologic findings by infection site. Although it is not appropriate to diagnose tuberculosis by radiology alone without clinical and bacteriological findings[8].

Histopathologic evaluation

Suitable biopsy samples were submitted to the laboratory for histopathologic examination. For histopathological diagnosis, presence of granulomatous reaction, caseous necrosis have been commonly used to define a positive test[5,8]. In addition, the granulomas could also observe in nontuberculous mycobacteria disease, brucellosis, syphilis or fungal infections. Therefore, it should be cautious about interpreting them[5].

Microbiologic evaluation

Suitable specimens by the infection sites were gathered from patients and submitted to microbiology laboratory. Cerebrospinal fluid specimens obtained through lumbar puncture in appropriate cases, aspirates and biopsies of lymph nodes and other sites and urine, peritoneal fluid, pleural fluid and tissue samples obtained from the organs involve, were used for microbiologic tests.

In direct smears, ARB was explored and cultures were studied. Samples were cultured on Mycobacterium Growth Indicator Tube (MGIT) (Becton Dickenson, USA) and Lowenstein-Jensen medium. AFB staining was applied together with Ziehl–Neelsen acid fast staining. Drug susceptibility tests (DST) for four first-line drugs were performed on the isolate of *M. tuberculosis* from apropriate patients. The diagnosis of tuberculosis was made by detecting the agent in culture and/or presence of histopathologic, clinical, and radiologic findings.

Statistical analysis

The Statistical Package for the Social Science (SPSS) statistical program was used for statistical analyses (Version 21 for windows, Chicago, IL, USA). Qualitative measurements are expressed as numbers and percentages. The relationships between different sites of extrapulmonary tuberculosis cases and epidemiological characteristics and also involment site distribution of the cases according to years were performed Chi-square tests. P value less than 0.05 was deemed statistically significant.

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Table 1. Epidemiological characteristics in relation to the different sites of extrapulmonary tuberculosis cases, Adana, 2014-2017.

		Lymph nodes		Pleura		Gastrointestinal		Spine		Genitourinary		Central Nervous System		Bone and Joint Involvement		Other		Total		
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	p value
Age, year	0-14	22	14.2	0	0.0	2	5.6	1	4.0	0	0.0	4	22.2	1	11.1	3	4.8	33	8.3	<0.001
	15-24	18	11.6	22	31.0	6	16.7	0	0.0	0	0.0	2	11.1	0	0.0	7	11.1	55	13.8	
	25-39	30	19.4	24	33.8	8	22.2	5	20.0	10	43.5	3	16.7	1	11.1	18	28.6	99	24.8	
	40-64	56	36.1	17	23.9	18	50.0	10	40.0	10	43.5	8	44.4	4	44.4	27	42.9	150	37.5	
	≥65	29	18.7	8	11.3	2	5.6	9	36.0	3	13.0	1	5.6	3	33.3	8	12.7	63	15.8	
Gender	Male	44	28.4	43	60.6	13	36.1	10	40.0	8	34.8	8	44.4	6	66.7	23	36.5	155	38.8	0.001
	Female	111	71.6	28	39.4	23	63.9	15	60.0	15	65.2	10	55.6	3	33.3	40	63.5	245	61.3	
Country of birth	Born in Turkey	148	95.5	64	90.1	34	94.4	25	100.0	22	95.7	18	100.0	9	100.0	61	96.8	381	95.3	0.417
	Born abroad	7	4.5	7	9.9	2	5.6	0	0.0	1	4,3	0	0.0	0	0.0	2	3.2	19	4.7	
Patient category	Relaps	6	3.9	2	2.8	4	11.1	2	8.0	0	0.0	1	5.6	0	0.0	5	7.9	20	5.0	0.401
	New	149	96.1	69	97.2	32	88.9	23	92.0	23	100.0	17	94.4	9	100.0	58	92.1	380	95.0	
Smear result	Could not be made	139	89.7	57	80.3	33	91.7	19	76.0	17	73.9	14	77.8	6	66.7	50	79.4	335	83.8	<0.001
	Negative	16	10.3	14	19.7	3	8.3	2	8.0	4	17.4	3	16.7	1	11.1	7	11.1	50	12.5	
	Positive	0	0.0	0	0.0	0	0.0	4	16.0	2	8.7	1	5.6	2	22.2	6	9.5	15	3.8	
Culture result	Could not be made	142	91.6	63	88.7	34	94.4	19	76.0	17	73.9	16	88.9	8	88.9	55	87.3	354	88.5	0.001
	Contamination	3	1.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	0.8	
	Negative	7	4.5	8	11.3	2	5.6	1	4.0	1	4.3	1	5.6	0	0.0	4	6.3	24	6.0	
	Positive	3	1.9	0	0.0	0	0.0	5	20.0	5	21.7	1	5.6	1	11.1	4	6.3	19	4.8	
Treatment outcome	Death	5	3,2	2	2.8	1	2.8	1	4.0	0	0.0	2	11.1	0	0.0	4	6.3	15	3.8	0.012
	Treatment Completion	150	96.8	68	95.8	35	97.2	24	96.0	23	100.0	16	88.9	8	88.9	59	93.7	383	95.8	
	Default	0	0,0	1	1.4	0	0.0	0	0.0	0	0.0	0	0.0	1	11.1	0	0.0	2	0.5	
HIV status	Unknown	19	12.3	6	8.5	1	2.8	1	4.0	2	8.7	3	16.7	0	0.0	7	11.1	39	9.8	0.507
	Negative	136	87.7	65	91.5	35	97.2	24	96.0	21	91.3	15	83.3	9	100.0	56	88.9	361	90.3	
Total		155	100.00	71	100.0	36	100.0	25	100.0	23	100.0	18	100.0	9	100.0	63	100.0	400	100.0	

RESULTS

According to Dispensary records, in the period 2014–2017, 400 cases were diagnosed as EPTB and included in the study. Table 1 shows the epidemiological characteristics of EPTB cases. The mean age of the patients with EPTB was 41.19±19.97 years (range 0-87). Among the various age groups studied the age group 40-64 years had the highest proportion of EPTB cases 150 (37.5%). Next most affected was 25-39 years 99 (24.8%), which is the economically productive population of the society. 63 (15.8%) patients were older than ≥65 years. The lowest proportion 33 (8.3%) was observed in 0-14 years age group. The overall 61.3% of the patients, were female, and the female/male ratio was 1.58. A decrease by gender indicated that rates of EPTB in women were greater than those in men.

According to dispensary records, 381 cases were born in Turkey (95.3%), the rest of them were born in five different countries (Afghanistan, Azerbaijan, Bangladesh, Somali, Syria). The difference was not statistically significant (p=0.417). Three hundred eighty patients (95.0%) were classified as new patient, twenty patients (5.0%) were classified as relapse (p=0.401). Information on HIV status was available for 361 (90.3%) patients; all of these had anti-HIV negative. HIV serology records were not present in about 9.8% of patients. There was no either HIV associated manifestations or obvious risk factors for HIV infection during the treatment.

EPTB diagnosis was confirmed by a positive culture in only 19 (4.8%) of the cases. Also, 15 (3.8%) of the EPTB cases had Ziehl-Neelsen acid fast bacilli smear positive. Both cultures and smears of 8 (2.0%) patients were positive at the same time.

For as many as 78.9% of the culture-positive EPTB cases, DST was performed. Nine (60.0%) were susceptible to all the drugs tested. Isoniazid monoresistance was identified in 2 (13.3%) cases, streptomycin monoresistance in 1 (6.6%) cases and 3 (20.0%) of the cases had isoniazid and ethambutal resistance. None of the cases had multidrug-resistant TB (MDR-TB).

Treatment outcome was documented for all EPTB patients. Among 400 patients with EPTB, the treatment completion was 95.8% (383/400). However, 0.5% of the patients had defaulted treatment. Among EPTB patients, the overall mortality rate was 3.8%. There was an underlying disease in the patients who died such as chronic renal failure, lymphatic cancer, heart failure, stomach cancer.

Table 2. Involment site distribution of the cases according to years, Adana, 2014-2017

	2014		**2015**		**2016**		**2017**		**Total**		
Site	n	%	n	%	n	%	n	%	n	%	p
Lymph Node	46	40.0	39	41.5	38	39.6	32	33.7	155	38.8	0.013
Pleural Cavity	23	20.0	22	23.4	15	15.6	11	11.6	71	17.8	
Gastrointestinal	7	6.1	10	10.6	14	14.6	5	5.3	36	9.0	
Spine	13	11.3	2	2.1	5	5.2	5	5.3	25	6.3	
Genitourinary	5	4.3	5	5.3	6	6.3	7	7.4	23	5.8	
Central Nervous System	3	2.6	6	6.4	4	4.2	5	5.3	18	4.5	
Bone and Joint Involvement	3	2.6	1	1.1	3	3.1	2	2.1	9	2.3	
Other*	15	13.0	9	9.6	11	11.5	28	29.5	63	15.8	
	115	100.0	94	100.0	96	100.0	95	100.0	400	100.0	

* pericardial, skin, eye, ovary, pancreas, larinx, fallopian tubes and breast

Information on the disease site was present in all of 400 cases of EPTB. Table 1 shows that involvement of the lymph node was found in 155 (38.8%) of the cases. Pleural cavity was found in 71 (17.8%) which is the second most common site. Rest of the cases were found in decreasing order with gastrointestinal 36 (9.0%), spine 25 (6.3%), genitourinary 23 (5.8%), central nervous system 18 (4.5%), bone and joint involvement 9 (2.3%). Sixty-three patients (15.8% of EPTB cases) constituting the category "other" had various sites affected including pericardial, eye, ovary, pancreas, larinx, fallopian tubes, skin, and breast. The rates of different types of EPTB showed a statistically significant difference among gender (p = 0.001), age

groups ($p < 0.001$), treatment outcome ($p=0.012$). There were no statistically significant differences seen with regard to the proportions of different types of EPTB among country of birth ($p=0.417$), patient category ($p=0.401$) and HIV status ($p=0.207$) (Table 1). When the patients were grouped years (classified according to when the patient file was opened), 115 patients were diagnosed from 2014, 94 from 2015, 96 from 2016 and 97 from 2017. Involment site distribution of the cases according to years are shown in table 2.

DISCUSSION

In Turkey, the incidence of tuberculosis was reported as 15.3/100,000 in the Tuberculosis Control Report 2018. In all cases, extrapulmonary organ involvement is found with a rate of around 35%[2,8]. The role of sex in TB has not yet been clearly clarified. However, extrapulmonary involvement was found to be more common among women in Turkey[8]. Series studies of America, Nepal and Turkey showed that males were also more frequently diagnosed with EPTB [12,13,14]. A recent study from Western India out of 492 patients, 66.0% were males and 34.1% were females. Male to female ratio was 1.9:1[15]. Nevertheless, a recent observational study of EPDR-TB in India, the female preponderance was observed[16]. Findings reported from Hong-Kong and Germany indicated that females predominate in cases of EPTB[17,18]. A population-based case control study in the United States found that 16.9% of female patients had extrapulmonary disease when compared to 9.3% of male patients[19]. A study from Afghanistan, the female to male ratio of EPTB cases was 2.03:1[20]. In consonance with other studies, our study found the proportion of female patients was higher compared with the male patients. Male to female ratio was 1.58. While the reasons for this finding have not been evidently elucidated, it is suggested that genetic factors, increase of females' participation in social life and work life and improved access to health services possibly are the linking factors[21,7].

The age distribution of tuberculosis patients is also an important indicator in determining the changes in TB's epidemiology. In developed countries TB is encountered in elderly ages and mostly results from the reactivation of a previous primary infection; however, in developing countries, TB affects all age groups, especially youth and young adults[7]. As the report of the EU/EEA countries between January 2002 and December 2011, 36.7% of the EPTB cases were 25 to 44 years of age[22]. A national study from Spain analysis that 15-44-year age group exhibited the highest percentage of cases[10]. Velingker et al. reported that in India, majority of cases (47.35%) cases belonged to 30-50 years of age[15]. Similar reports of high prevalence of EPTB in this age group are reported in other studies from India and Ethiopi[23,24]. A study carried out in Turkey majority of the cases were in the 15-44-year ages[7]. In our study, the majority of the patients were in the 40-64 year age group, who are adult and working individuals, highlighting the socio-economic burden of EPTB. Children (<15 years) represented 8.3% (33/400) of all EPTB cases diagnosed. Our study is similar to in line with nationwide studies of Turkey and other studies in different countries, the proportion of pediatric age group was lower[7,10].

A large-scale study conducted in Oman from 2006 to 2015 showed that the HIV infection was a significant risk factor for EPTB. This finding is rationalized by the negative effect of HIV on the immune system[25]. Another study conducted in Brazil reported that HIV co-infection was one of the key factors related with EPTB. A relationship between HIV co-infection and EPTB has been expected, since occurrence of EPTB increases in frequency when cellular immune function is impared. HIV is also a known risk factor for progression of *M. tuberculosis* infection to active tuberculosis disease and rises the risk by 20-fold[26]. Since Nepal has high HIV prevalence, strong association was found between HIV seropositvity and EPTB[13]. A study from Turkey reported that HIV seropositivity was detected in one patient [27]. In another study in Turkey, anti-HIV was found to be negative in all patients[9]. In our study population, HIV screening was not performed routinely. Thus, we did not provide enough data to carry out a useful analysis association between HIV enfection and EPTB. In screened patients, HIV seropositivity was not detected. Although Turkey has a low prevelance of HIV, it is important to screen HIV patients for tuberculosis.

An EU study has indicated that the rate of previously treated patients is very low (5.1%). Indeed, moreover, Culqui-Lévano et al. reported that this rate was 3.7%, which is even less than the EU average[22,28]. In an earlier study carried out on 168 patients in Istanbul region of Turkey, proportion of relaps was 1.1%[3]. Of the 400 cases included in the present study, proportion of relaps was 3.1%. We think that the high rate of relaps in our study was due to the higher

number of study population compared to the other studies in Turkey.

The distribution of different forms of EPTB differs among studies performed in different populations, including different regions of Turkey[11]. Gunal et al. reported wide range of EPT cases that were officially recorded by tuberculosis dispensaries in Turkey. This report shows that the most common involment was genitourinary (27.2%) tuberculosis, followed by meningeal (19.4%) and joint/bone infection (10%). This report also found that rate of EPTB constituted 26% of all tuberculosis cases[11]. In contrast, a previous study in other region of Turkey showed that the most frequently forms of EPTB were meningites (23%) and lymphadenitis (21%) and did not find any association between EPTB sites and gender [27]. The present results are similary with two previous findings, which have found that lymph nodes are implicated in almost half of the EPTB cases. Guler et al[3] in Turkey and Holden et al.[29] in Denmark have reported that lymphadenitis was the most frequent type of EPTB, followed by pleural TB. According to tuberculosis report 2018 in Turkey, extrathoracic lymph nodes (27.8%) and pleura (23.4%) involvement were found to be the most common in EPTB cases [30]. Our results are also compatible with this report showing the data of our country. In our study population, lymph nodes and pleural cavity was the most common involment sites of EPTB including 38.8% and 17.8% respectively. Lymphatic TB was found to be high among female patients, while male patients exhibited a predominance of pleural TB and bone/joint involvement. However, the distribution of the sites affected by EPTB across gender does not seem to pursue a clear pattern as many studies indicate similar or slightly different gender predominance in one site or the other [21,31]. The predominance of males among those with pleural TB in the present study has also been found by other researchers[21,10].

The difficulty in diagnosing EPTB is well known. It is due to the lower bacilary counts present in almost all EPTB cases and the problems related with getting valid samples for analysis[27]. *M. tuberculosis* culture is the accurate method of diagnosing an active infection and should be performed whenever possible. In clinical practice, a positive culture is received in fewer than half of the EPTB cases[3]. Sevgi et al. reported that diagnosis established in culture was (86/113), by histological analysing (55/75) and both culture and histological analysing (34/45)[7]. Güler et al. reported that the diagnosis of EPTB was made according to the evaluation of histopathologic samples (124 cases) derived from pleural fluid examination, or pleural biopsy (32 cases), fine-needle aspiration cytology (39 cases) and total excision (53 cases). AFB and culture positivity were detected %34.8 and 0.2% respectively[3]. A previous study in China have shown that diagnosis was validated by a positive culture in 12.8% (758/5,910) of EPTB cases. AFB positivity was also 4.2% (174/5,574). Of 758 culture-positive EPTB cases, 483 (63.7%) cultures yielded DST results. Of note, they identified MDR-TB in 17.2% (83/483)[4]. Khan et al. reported that around, 330 (27%) of patients had AFB smear positive and 687 (56.2%) culture positive. However, 360 patients (29.5%) were diagnosed via pathology alone and 43 (3.5%) were confirmed on polymerase chain reaction (PCR). Among the culture confirmed EPTB patients, 1.5% of cases were resistant to single first line drugs[32]. In our study culture positivity was detected 4.8% of the cases. Also, 3.8% of the cases had Ziehl-Neelsen acid fast bacilli smear positive. Among the DST performed none of the cases had MDR-TB.

Anti-TB treatment is the main factor in the administration of EPTB[5]. Khan et al. reported that 67.6% of the patients successfully completed treatment[32]. A previous study conducted in Benin reported that, treatment results of EPTB patients were satisfying, although the high loss-to-follow-up in the Atlantique region of the country needs to be rectified[10]. The overall treatment success rate was 70.1% for the EPTB cases in Ohane's study report. A study in DR-EPTB cases in Mumbai showed a treatment completion rate was 81.6% [16]. The treatment completion incidance for EPTB cases in our study was higher than these reports (95.8%). This result is an indication that the treatment is implemented well in our region.

This study has some limitations. Selected site encompasses one geographic region and hence cases from these facilities might have a different profile from cases residence in other parts of the country. At the same, due to the retrospective nature of the study, it was not possible to show detailed clinical properties of the EPTB patients, which might play a notable role in indicating the overall profile of the patients. Smokers, alcoholics, previous contact with EPTB, hypertension, chronic obstructive pulmonary disease and underlying disease (cancer, etc) patients have an advanced incidence of EPTB in many studies[6,13,32]. Ours being retrospective data drawn from records

this particular status could not be studied due to its non availibility.

In conclusion, the present study provides an insight into the epidemiologic characteristics of EPTB cases in Adana, Turkey. Timely diagnosis and initiation of appropriate treatment are important to reduce morbidity and mortality in cases with EPTB[3]. Among the EPTB cases highlights the importance of DST in successful development of effective treatment regimens[4]. Also, EPTB cases should remain to be assessed in following studies using different inhabitants-based or randomly chosen samples[1]

Yazar Katkıları: Çalışma konsepti/Tasarımı: PE, ATA; Veri toplama: PE, ATA; Veri analizi ve yorumlama: PE, ATA; Yazı taslağı: PE; İçeriğin eleştirel incelenmesi: PE, ATA; Son onay ve sorumluluk: PE, ATA; Teknik ve malzeme desteği:ATA; Süpervizyon: PE; Fon sağlama (mevcut ise): yok.
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