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An analysis of adult patients with pulmonary and extrapulmonary tuberculosis*

Aim: In this study, it was planned to compare the features of pulmonary and extra-pulmonary tuberculosis patients over age 15 years.

Materials and methods: We compared 360 newly diagnosed pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) patients who were treated and followed up in Kahramanlar Tuberculosis Dispensary between 2000 and 2003, and were older than 15 years of age. The medical records of both patient groups were investigated in terms of age, sex, accompanying diseases, contact history and means of diagnosis.

Results: The data were compared statistically between the 2 groups. Of these patients 78.1% were diagnosed with PTB while 21.9% were diagnosed with EPTB. The proportion of male patients was 79.3% in the PTB group and 49.4% in the EPTB group ($P < 0.0001$). According to the medical histories of the patients, the mean duration between the onset of symptoms and diagnosis was 85.75 ± 77.02 (days) in PTB patients and 193.65 ± 340.40 (days) in EPTB patients ($P = 0.001$). The rates of bacteriological diagnosis of tuberculosis were 95.37% in PTB patients and 5.06% in EPTB patients, which indicated a significantly higher rate of bacteriological diagnosis in PTB patients.

Conclusion: There were statistically significant differences between the PT and EPT patients over 15 years, and EPT was found to be associated with female sex, a lower rate of bacteriological diagnosis, and delay in diagnosis.

Key words: Pulmonary tuberculosis, extrapulmonary tuberculosis, adult patient

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Onbeş yaş üzeri yeni akciğer ve akciğer dışı tüberküloz olgularının özelliklerinin karşılaştırılması

Amaç: Bu çalışmada, 15 yaş üzeri yeni akciğer tüberkülozu ve akciğer dışı tüberküloz olgularının özelliklerinin karşılaştırılması planlandı.

Yöntem ve gereçler: Bu çalışmada, Kahramanlar Verem Savaş Dispanserinde 2000-2003 yılları arasında takip ve tedavi edilen, 15 yaş üzeri yeni akciğer tüberkülozu (Akciğer TB) ve akciğer dışı tüberkülozu (ADTB) tanısı alan 360 olgunun özelliklerinin karşılaştırılmasını amaçladık. Her iki hasta grubuna ait dosyalar yaş, cinsiyet, ek hastalık, temas öyküsü, tanı şekli gibi özellikler açısından değerlendirildi.

Bulgular: Her iki hasta grubunun özellikleri istatistiksel olarak karşılaştırıldı. Olguların 281 (% 78,1)'i Akciğer TB, 79 (% 21,9)'u ADTB idi. Erkek hastaların oranı Akciğer TB'unda % 79,3 iken, ADTB olgularında bu oran % 49,4 idi ($P < 0,0001$). Anamneze göre akciğer tüberkülozlu 240 olguda semptomların başlamasından tanı konuluncaya kadar geçen ortalama süre $85,75 \pm 77,02$ iken, EPT olgularında $193,65 \pm 340,40$ idi ve aralarında anlamlı fark mevcuttu ($P = 0,0001$). Bakteriyolojik (ARB yayma ve/veya kültür pozitifliği) TB tanı konma oranları Akciğer TB olgularında % 95,37, ADTB olgularında % 5,06 olup, Akciğer TB olgularında bakteriyolojik tanı konma oranı anlamlı oranda yüksek idi ($P < 0,0001$).

Sonuç: 15 yaş üzeri erişkin PT ve EPT'lu olgular arasında, cinsiyet, bakteriyolojik tanı konma oranı, semptom ve tanıda gecikme özellikleri açısından anlamlı farklılık olduğu saptandı.

Anahtar sözcükler: Akciğer tüberkülozu, Akciğer dışı tüberküloz, erişkin hasta

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Introduction

Tuberculosis (TB) is an infectious disease that may affect almost any organ or tissue in the body, and has various clinical appearances. Of all the types of TB, the most common is pulmonary tuberculosis (PT), and it has great epidemiological significance due to its contagious nature. Extrapulmonary tuberculosis (EPT) is an important type that is difficult to diagnose. Its increasing incidence and the severe sequelae because of the delay in diagnosis leads to a significant decrease in the labor force (1,2). In Turkey, tuberculosis is an endemic disease, and its incidence is reported as 22/100,000 in the 2002 report of the World Health Organization (WHO). These figures indicate that Turkey has a moderate incidence of tuberculosis (3). A vertical structured TB control program has been put into practice in order to solve this problem in Turkey (4). This program is based on the main units as provincial health directorates, and the sub-units as tuberculosis dispensaries. There are a total of 272 tuberculosis dispensaries in Turkey, which provide free healthcare. The patients may either present to these dispensaries directly or they are referred from other health institutions. The dispensaries play a significant role in the diagnosis, screening, treatment, and follow-up of tuberculosis as well as the examination and follow-up contacts and the evaluation of epidemiological data (5).

The aim of this study was to evaluate the sociodemographical, clinical and diagnostic features of pulmonary and extra-pulmonary tuberculosis, regarding the multi-systemic nature of the disease and to compare the data of the related sub-groups.

Materials and methods

The city of İzmir (Turkey's third most populated city) has a population of 3,370,868 according to the data obtained in 2000, and there are 8 tuberculosis dispensaries in the city. Kahramanlar Dispensary is located in a region including 230,898 inhabitants, where unauthorized housing and crowded families are very common.

The study included tuberculosis patients who were registered and followed up between 2000 and 2003. Twenty-three patients were excluded, because some did not have active tuberculosis, the others' data were

not available, or the final diagnosis was not tuberculosis. Since the clinical features of tuberculosis differ between children and adults, the 0-14 age group was not included in the study. The files of the remaining 360 patients above the age of 15 and who were newly diagnosed with PT and EPT were investigated retrospectively. EPT cases were diagnosed in hospitals, and the diagnoses were supported by biopsies of the involved parts, where indicated. The patients were grouped according to the WHO criteria (6), as standard smear-positive pulmonary and extra-pulmonary new tuberculosis patients. The patients with coexistence of pulmonary tuberculosis and extrapulmonary tuberculosis were included in the pulmonary tuberculosis group (6). The data concerning the sociodemographical features of the patients, symptoms of a concomitant disease, time elapsed until diagnosis, and the rate of bacteriological diagnosis were compared and evaluated. The duration between the onset of the symptoms and first medical consultation, and the duration between the first medical consultation and the commencement of the treatment could not be determined through the information in the medical files, since the study was retrospective. However, the information obtained through the patient histories enabled the determination of the time elapsed between the onset of symptoms and diagnosis. Chi square (χ^2) test was used along with t-test for statistical analysis.

Results

In the present study, 360 newly diagnosed tuberculosis patients aged above 15 years of age were investigated over a 4-year period. Among these patients, 281 (71.8%) were PT and 79 (21.9 %) were EPT patients. Four of the pulmonary tuberculosis patients (1.4%) presented with both pulmonary and extrapulmonary tuberculosis. Three of these patients presented with pleural involvement, whereas 1 patient had lymph node involvement. The distribution of the EPT patients according to the organs involved was determined as follows: 39 (49.4%) pleural TB patients, 22 (27.8%) lymph node TB patients, 4 (5.1%) bone/joint tuberculosis patients, and 14 (17.7%) patients with other (genitourinary, gastrointestinal, central nervous system, miliary, skin/mucosa, cardiovascular) system involvement.

Table 1. Distribution of patients with pulmonary and extrapulmonary tuberculosis according to age groups and sex.

Age groups	Pulmonary tbc				Extrapulmonary tbc			
	Men	Women	Total		Men	Women	Total	
	n	n	n	%	n	n	n	%
15-24	32	18	50	17.8	7	5	12	15.2
25-34	52	15	67	23.9	9	7	16	20.3
35-44	54	5	59	21.0	9	8	17	21.5
45-54	43	6	49	17.4	5	8	13	16.4
55-64	28	5	33	11.7	2	7	9	11.4
65+	14	9	23	8.2	7	5	12	15.2
TOTAL	223	58	281	100	39	40	79	100

The distribution of the patients according to age and sex is presented in Table 1. The mean age of patients with pulmonary tuberculosis and EPT patients was 40.5 ± 15.4 and 42.5 ± 17.5 , respectively, and the difference between the 2 groups was not statistically significant ($P = 0.310$). When the distribution of PT and EPT patients was analyzed according to age and sex, it was determined that PT was observed more commonly in the 25-34 age group, whereas EPT was more commonly seen in the 35-44 age group. In men, the rate of PT was 85.1% and the rate of EPT was 14.9%, while the rates in women were 59.2% and 40.8%, respectively. These results indicated that the rate of PTB was significantly higher in men than in women, while the rate of EPT was significantly higher in women than in men ($P < 0.0001$).

The 3 principal social security institutions are the Pension Fund for Civil Servants (Emekli Sandığı), Social Insurance Institution (SSK), and Social Insurance Organization for the self-employed (Bağkur). In addition to these institutions, there is a "green card" system for the poor, which is directly funded by the Government. Thus, the number of patients without social security who benefit from the green card system was 172 (61.2%) among PT patients and 40 (50.6%) among EPT patients ($P = 0.119$).

When the educational status of both groups was considered, it was determined that 208 PT patients (74%) and 61 EPT patients (77.2%) were primary school graduates or uneducated ($P = 0.667$).

The distribution of the patients according to the accompanying diseases is presented in Table 2. At least

1 accompanying disease was present in 54 (19.2%) of the PT patients, and 13 (16.5%) of the EPT patients ($P = 0.694$). The most common accompanying disease in PTB patients was diabetes mellitus (DM) and previous gastrectomy, while hypertension and DM were the most commonly observed accompanying diseases in EPT patients. No HIV positive patient was detected in the records.

A history of contact was obtained in 32 (11.4%) of the PT patients and in 12 (15.2%) of the EPT patients ($P = 0.473$). The atypical systemic symptoms observed in both groups are presented in Table 3. It was seen that the occurrence of systemic symptoms was higher in PT patients.

In the medical records of 32 PT and 12 EPT patients, sufficient information could not be obtained to determine the time elapsed between the onset of symptoms and diagnosis. Additionally, 9 patients who were asymptomatic but were diagnosed with PT through screening were excluded from the study. The duration between the onset of symptoms and diagnosis was 85.75 ± 77.02 days in the patients with PT and 193.65 ± 340.40 days in the patients with EPT, which was significantly higher ($P = 0.0001$).

Regarding the bacteriological status of 281 patients, 258 (91.8%) were smear-positive, 18 (6.4%) were smear-negative, and a sputum examination was not performed in 5 patients (1.8%). According to the results obtained, 268 patients (95.4%) were bacteriologically positive (smear and/or culture positivity of acid resistant bacilli (ARB) of the sputum). On the other hand, the rate of

Table 2. Distribution of diseases accompanying pulmonary and extrapulmonary organ tuberculosis.*

Diseases accompanying tuberculosis	Pulmonary tbc		Extrapulmonary organ tbc	
	n	%	n	%
Diabetes mellitus	33	11.7	2	2.5
Chronic airway disease	4	1.4	1	1.3
Hypertension	3	1.1	5	6.3
Atherosclerotic heart disease	3	1.1	1	1.3
Gastrectomy	5	1.8	1	1.3
Malignancy	4	1.4	2	2.5
Peptic ulcer	3	1.1	1	1.3
Collagen tissue disease	3	1.1	-	-
Psychosis	2	0.7	-	-
Epilepsy	1	0.3	1	1.3
Cirrhosis	-	-	1	1.3
Hepatitis C	1	0.3		
Renal failure	1	0.3		
Cerebellar atrophy	1	0.3		

*More than one disease in each patient was evaluated separately. Percentage was calculated according to the total number of pulmonary and extrapulmonary patients.

bacteriological positivity was 5.06% (4 patients) in the EPT patients. Among the 2 patients with genitourinary tuberculosis (GTB), urine acid-fast bacilli were smear-positive and culture-positive in one and culture-positive in the other. Fine-needle aspiration material of an abscess was smear- and culture-positive in a patient with bone joint tuberculosis and lymph node fine-needle aspiration material of a patient with lymph node tuberculosis was smear-negative and culture-positive. When the 2 groups were compared in terms of bacteriological

positivity, the rate of bacteriological diagnosis was significantly higher in the pulmonary tuberculosis patients ($P < 0.0001$). In 56 of 58 patients (96.5%) granulomatous inflammation was detected histologically. Among these, caseous necrosis was determined in 38 patients (67.8%). The rate of bacteriological and/or histopathological (caseous necrosis) TB diagnosis was 53.2%. It was observed that the rate of diagnosing patients with pulmonary tuberculosis was significantly higher than that of the extrapulmonary cases ($P < 0.0001$) (Table 4). Lymph

Table 3. Distribution of systemic symptoms in patients with pulmonary and extrapulmonary tuberculosis.**

Symptoms	Pulmonary tbc		Extrapulmonary tbc		Statistical results	
	n	%	n	%	χ^2	P
Sweating	119	42.3	9	11.4	24.46	0.001
Weight loss	107	38.1	9	11.4	18.90	0.001
Fatigue	80	28.5	15	19	2.39	0.122
Fever	55	19.6	11	13.9	0.96	0.326
Anorexia	43	15.3	4	5.1	4.83	0.027

** More than one symptom in each patient was evaluated separately. Percentage was calculated according to the total number of pulmonary and extrapulmonary patients.

Table 4. Distribution of patients with pulmonary and extrapulmonary tuberculosis according to diagnostic methods.

Diagnostic method	Pulmonary tbc		Extrapulmonary tbc	
	n	%	n	%
ARB smear positive	258	91.8	2	2.5
ARB smear negative / culture positive	10	3.6	2	2.5
Histopathologic (with caseation necrosis)	-	-	38	48.1
Clinical + radiologic + other methods	13	4.6	37	46.8

Table 5. Histopathological biopsy results of the organs involved.

Organ involved	Caseous necrosis (n)	Granulomatous inflammation (n)	Nonspecific pleuritis (n)
Pleura (39)	17	10	2
Lymph node (22)	19	2	
Genitourinary system (3)		1	
Gastrointestinal system (3)	1	2	
Bone/joint tuberculosis (4)		2	
Skin/mucosa (2)	1	1	
Meningitis (3)			
Cardiovascular system (2)			
Miliary (2)			
Total	38	18	2

node biopsy was performed in 95% of patients (21/22), while pleura biopsy was performed in 74% (29/39) (Table 5).

Discussion

Tuberculosis is a disease that has been a threat to human health for thousands of years, and it is still prevalent in developing countries. Although the onset of tuberculosis shifts towards the older age groups in developed countries, young adults are mainly affected in developing countries (7). In this study, it was determined that both PT and EPT were most commonly seen in the 25-44 age group of young adults, which was consistent with the previous Turkish data (4,8). The studies conducted in this country also show that tuberculosis is more commonly observed in the young and middle-aged groups, and there is an obvious similarity between our

results and those of studies conducted in other developing countries, such as the overall average age of 41.3 ± 17.9 years found in South Korea (9,10).

Regarding the sex distribution according to the 2 groups, PT involvement was significantly higher in men and EPT involvement was significantly higher in women. Other studies conducted in Turkey also reported a higher incidence of tuberculosis in men (4,11). The reports of the World Health Organization show that the incidence and prevalence of tuberculosis and tuberculosis mortality were higher in men than in women (12). When the studies on extrapulmonary tuberculosis in the literature are reviewed, studies reporting a higher incidence rate of EPT in women as well as those reporting a higher or equal rate of incidence in men can be found (13,14). Although the role of sex in tuberculosis is not clearly defined yet, it has been reported that the high notification rates in men might result from factors

such as epidemiological differences in exposure and infection risk, the differences in the progression of infection to disease (15,16), geographical distribution (17), and sociocultural differences (18). Additionally, some studies report a higher rate of progression from infection to disease and a higher rate of fatality during reproductive age (15).

Tuberculosis is a disease connected with social status (19). It is reported that a great majority of tuberculosis patients in this country consist of patients with a low educational level and without social security (20). The educational level and social security status of the patients in our study are consistent with those results.

Suspecting tuberculosis is an important step in making the diagnosis while contact history serves as a clue for the diagnosis. The studies conducted in Turkey suggest that there is not a significant difference between the 2 groups in terms of contact history, and it was determined that the rate of positive contact history ranges between 12.2% and 35.3% in PT patients and 6.6% and 32.4% in EPT patients (20,21). The results of this study were similar to those in the related literature.

The rate of constitutional symptoms of tuberculosis such as weight loss, perspiration, and lack of appetite was significantly higher in the PT patients than in the EPT patients ($P < 0.01$). The studies in the literature related to this finding report that constitutional symptoms are more commonly seen in PT patients than in EPT patients, while the latter group often presents with symptoms related to the involved organs (10).

According to the data for this country, the rate of diseases accompanying tuberculosis varies between 8.5% and 15.4% in PT patients and 3.6% and 18.5% in EPT patients (11,20). Yoon et al. found an accompanying disease in 24% of patients in South Africa, while Denis Delpierre et al. reported the same result as 34% in France (10,22). Our data are similar to those reported in South Africa, but lower than those reported in France. It is suggested that this might have resulted from the higher incidence of tuberculosis in the elderly patients in developed countries. The most common accompanying diseases were DM and gastrectomy in patients with pulmonary

tuberculosis and hypertension and DM in patients with extrapulmonary tuberculosis. DM and tuberculosis have a negative reciprocal relation. It has been shown that changes occur both in the humoral and cellular immune response by DM and TB prevalence is 2- to 5-fold higher in diabetic patients than in nondiabetic patients (23).

The mean duration between the onset of symptoms and diagnosis was 193.65 ± 340.40 days in extrapulmonary tuberculosis patients and this was significantly higher than that in the pulmonary tuberculosis patients (85.75 ± 77.02) ($P = 0.0001$). The long interval between the onset of symptoms and diagnosis in extrapulmonary tuberculosis patients shows that the diagnosis of extrapulmonary tuberculosis is more difficult than the diagnosis of PT. The interval between the onset of symptoms and diagnosis is long in EPT, which follows a silent course. In various studies, the diagnosis duration ranges from 1 week to 4 years (24,25). Bobrowitz et al. (26) even stressed that the diagnosis of EPT is more difficult in living patients than from an autopsy. These results indicate that EPT should be taken in consideration to diagnosis this disease. In our study, the diagnosis duration was longer than the acceptable duration for an efficient tuberculosis control in both PT and EPT patients. The price of prolonged patient delay is the spread of infection in pulmonary tuberculosis, especially in smear-positive tuberculosis patients and severe sequelae in EPT patients (1).

The definitive diagnosis of tuberculosis can only be made through the unified evaluation of clinical and laboratory findings, and the demonstration of bacilli using direct microscopy or growth of tuberculosis bacilli in culture. Direct microscopic sensitivity in the diagnosis is 22%-80% (27). In the studies conducted in Turkey and performed in the 0-14 age group, the rate of smear positivity was determined as 14.1%-84.5% in PT patients and 0.9%-14.5% in EPT patients and the rate of bacteriological diagnosis was determined to be significantly low, as in our study (11,28). The rate of bacteriological positivity of the pulmonary tuberculosis group in our study was higher than the rates determined in other dispensaries in Turkey. This might have resulted from the following reasons: our dispensary is situated in a central location, a great majority of our patients consist of

those referred from hospitals to our dispensary for follow-up and treatment, the region's laboratory is located in our institution, and the 0-14 age group was not included in our study.

The rate of bacteriological positivity was significantly lower in the EPT patients than in the PT patients and this result was consistent with the literature (14,27). Since extrapulmonary tuberculosis is localized in the regions that are difficult to access and the disease is caused by a lower bacillus load, the sensitivity of microscopic investigation and culture is decreased (29). In patients with extrapulmonary tuberculosis, the smear positivity rate is reported as <10% in the pleural fluid, <1% in the pericardial fluid, and 5%-37% in cerebrospinal fluid, and the rates of culture positivity for these samples are reported as 12%-70%, 25%-60%, and 40%-80%, respectively (2,30). Compared to these data, the bacteriological positivity rate determined in our study was low. This might have resulted from histopathological, clinical, and radiological diagnosis making in the majority of the cases and the lack of microbiological data on the biopsy material (due to problems related to registration and/or lacking examination). Similar to

the studies conducted in Turkey and other countries, we concluded that, besides the histopathological examination, the microbiological evaluation of the biopsy samples is important and it may increase the rate of bacteriological positivity. However, histopathological findings, clinical data, and imaging results should be evaluated together with bacteriological results in the diagnosis of EPT due to the low bacteriological positivity in EPT. Additionally, in some instances, one should even await the response to the empirical treatment for the definitive diagnosis (2,30).

In conclusion, our findings showed that there were statistically significant differences between the PT and EPT patients over 15 years old, and EPT was found to be associated with female sex, a lower rate of bacteriological diagnosis, and delay in diagnosis. Extrapulmonary tuberculosis is a disease with genuine features due to its specific clinical features and its difficult diagnosis. Thus, we think that, in countries such as Turkey where tuberculosis is widespread, the consideration and the persistent and elaborate investigation of EPT in patients presenting with various symptoms would be beneficial.

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