

Clinical spectrum of pulmonary and pleural tuberculosis: a report of 5,480 cases

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ABSTRACT: The aim of the present study was to investigate the epidemiological, clinical, laboratory and radiological features of patients with active pulmonary tuberculosis (TB) (with or without pleural involvement) or with pleural TB (in the absence of radiological parenchymal disease).

A systematic predetermined form, including 60 items regarding the above-mentioned features, was completed for 5,480 patients. Sputum smear and culture data, radiological findings, and additional extrapulmonary involvement were evaluated in the patients with pulmonary TB (n=5,094). Epidemiological features, and other clinical and laboratory characteristics were investigated in all patients (n=5,480).

TB was more common among persons aged 20–39 yrs, males, and those living in large urban centres in our region. There were 4,268 newly detected patients (78%), and 1,212 active ex-patients (22%) who had history of previous antituberculosis treatment. Additional extrapulmonary involvement was found in 455 patients (9%). Sputum samples were smear-positive in 3,916 (79%), and culture-positive in 3,748 cases (76%). Most common radiological patterns were parenchymal infiltrate in 5,017 (99%), and cavitation in 3,363 (66%). Unusual radiological patterns were also noted, *i.e.* lower lung field TB (LLFTB) in 317 cases (6.2%), pneumothorax in 78 cases (1.5%), and miliary pattern in 66 cases (1.3%).

In conclusion, because of the more frequent occurrence in the younger age group, it is considered that the prevalence of disease is still high and that the transmission of tubercle bacilli is not decreasing in our region. The highest risk group consisted of male subjects and those living in urban centres. The high percentage of active ex-patients suggests that new control programmes for tuberculosis are required in Turkey.

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Tuberculosis (TB) in Turkey had gradually declined due to an organized, aggressive campaign against the disease between 1950 and 1970. The involvement of 252 dispensaries throughout the country, chest disease hospitals, regional laboratories, programmes of bacille Calmette-Guérin (BCG) vaccination, tuberculin skin-testing and radiological screening, co-operative studies between universities, the Ministry of Health and the National Society against Tuberculosis were the most important steps in the struggle against TB. However, since the early 1970s, this decrease in the incidence of TB has been followed by an increase, due to an interruption in the level of the campaign [1].

Izmir is the biggest city of the Aegean region, which is one of the eight principal geographical regions of Turkey. The urban and rural populations of the city are 2.1 and 0.5 million, respectively. The Aegean region, located in West Anatolia, has a 4.0 million urban and 2.8 million rural population (population figures are from 1990) [2]. The Izmir Center for Chest Diseases and Thoracic Surgery serves mainly the city of Izmir and the surrounding Aegean region as a referral centre, with 800 beds for pulmonology and thoracic surgery. From

January 1, 1988 until December 31, 1992, 41,560 patients were admitted to the hospital because of various thoracic diseases. Among them, 5,480 cases were diagnosed as active pulmonary and/or pleural TB. Our purpose was to investigate the results of epidemiological, radiological, laboratory, and clinical features of these patients identified during 5 years. This TB population is one of the largest groups in the medical literature.

Materials and methods

Study population

Four pulmonary specialists reviewed the medical records and chest roentgenograms of 5,480 patients who had active pulmonary and/or pleural TB and were admitted to the Izmir Center for Chest Diseases and Thoracic Surgery between January 1988 and December 1992. The criteria for confirmation of TB were: 1) bacteriological proof of infection with *Mycobacterium tuberculosis*; 2) biopsy material demonstrating caseating granulomas; 3)

clinical and radiological presentation consistent with TB, with marked improvement after antituberculosis therapy; and 4) a history of contact with current disease and positive skin reaction to the 5 tuberculin unit (TU) purified protein derivative (PPD) (≥ 10 mm induration). All patients fulfilled one or more criteria.

Study design

The criteria for newly detected patients were: 1) no history of previous treatment or diagnosis of TB; or 2) a history of antituberculosis therapy for less than a month [3]. On the other hand, the criteria for active ex-patients were: 1) prior therapy of more than a month; and, subsequently, 2) retreatment due to active disease. In none of the data available during the study period, was there any historical, clinical or laboratory evidence of human immunodeficiency virus (HIV) infection. Patients were considered to have a diagnosis of diabetes mellitus if they were receiving insulin or an oral hypoglycaemic agent at the time of hospital admission, or were found to have two or more blood glucose levels greater than $140 \text{ mg}\cdot\text{dL}^{-1}$. Acid-fast smears were performed using a standard concentration method and Ziehl-Neelsen acid-fast stain. Mycobacterial cultures was performed using Löwenstein-Jensen media. Hepatotoxicity was considered present if transaminase levels exceeded by fourfold the amount measured before institution of antituberculosis drugs. On evaluation of the chest roentgenograph, airspace, mixed airspace/interstitial, interstitial, or nodular opacities were included in the same category, namely infiltration. The typical radiological appearance of pulmonary tuberculosis, including parenchymal infiltrate, cavitation, pleural thickening, fibrosis and calcification were evaluated. Less common features were also assessed, namely lower lung field TB (LLFTB), pneumothorax, pleural effusion with parenchymal involvement and miliary pattern. LLFTB was defined as TB involving the middle lobe, lingula, and one or both lower lobes.

The main treatment protocol for newly diagnosed cases in Turkey lasts 9 months and consists of two phases. During the initial intensive phase, which lasts 2 months, rifampin, isoniazid, pyrazinamide, ethambutol or streptomycin (RHZSC(E)) are given daily. Subsequently, in the continuation phase, the treatment is completed, over a further 7 months, with rifampin and isoniazid (daily (RH) or twice weekly (R_2H_2)) ($2 \text{ RHZS (E)} + 7 \text{ RH}$ or $2 \text{ RHZS (E)} + 7 \text{ R}_2 \text{ H}_2$). In old cases, the treatment is adjusted according to the result of tests for antimicrobial resistance. If these results are not available, therapy is extended to 12 months ($2 \text{ RHZE} + 2 \text{ RZE} + 8 \text{ RE}$).

For statistical analysis, a standard form including 60 items was completed for each patient. These items included age, sex, place of residence, time of diagnosis (*e.g.* newly detected or active ex-patients), contact with TB cases, alcohol consumption, associated malignant or non-malignant conditions (*e.g.* diabetes mellitus, chronic obstructive pulmonary disease (COPD), psychosis, alcoholism, narcotic abuse, bronchial carcinoma), symptomatology, tuberculin test, erythrocyte sedimentation rate (ESR), sputum smear and culture data, transaminases, usual and unusual radiological presentations, and additional extrapulmonary localizations. Among these items,

the sputum smear and culture data, radiological findings, and additional extrapulmonary localizations were investigated only for patients with pulmonary TB ($n=5,094$). Epidemiological features and other clinical and laboratory data were evaluated in all cases ($n=5,480$).

Statistical analysis

Statistical analysis of the study group was performed using a software package (Minitab Release 5.1). The Chi-squared test was also used to determine the significance of relationships between features. Data are presented as mean and SD. A p-value of less than 0.05 was considered significant.

Results

Epidemiological and clinical data

Figure 1 shows the distribution of all cases and extrapulmonary sites associated with pulmonary TB during 5 consecutive years. In the study period, there were 4,433 (81%) males (mean age 37 ± 15 yrs), and 1,047 (19%) females (mean age 35 ± 16 yrs). The mean age of all patients was 37 ± 15 yrs. Persons 20–39 yrs of age accounted for 54% of the total cases. Among all cases, 5,094 had active pulmonary TB with or without pleural disease, and 386 had pleural TB in the absence of radiological parenchymal involvement. Four thousand, one hundred and fifteen cases (75%) were concentrated in large urban areas, and 1,365 cases (25%) were from rural areas. There were 4,268 newly detected cases (78%) and 1,212 active ex-patients (22%). The history of contact with TB patients was determined in 863 cases (16%). Demographic characteristics are presented in table 1.

Only 36 patients had neither respiratory nor systemic symptoms at initial evaluation. Common symptoms were

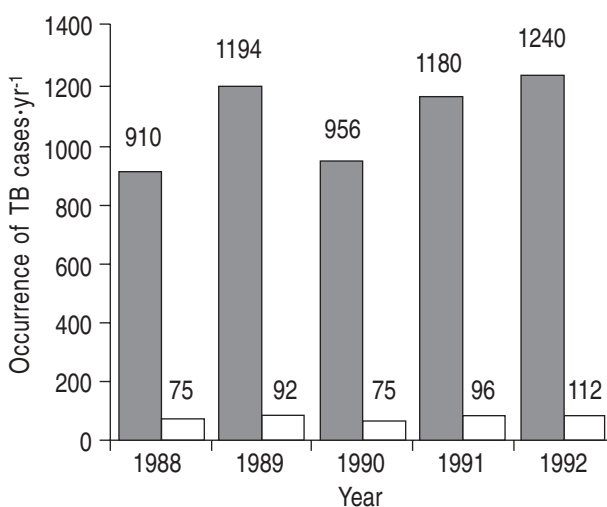


Fig. 1. – The distribution of all cases and extrapulmonary sites associated with pulmonary tuberculosis (TB) in five consecutive years. : all cases; : extrapulmonary sites.

Table 1. – Epidemiology, symptomatology, concomitant diseases, extrapulmonary localizations, and radiologic features of the patients

Age*		Newly diagnosed patients*	4268 (78)
<20 yrs	490 (9)	Active ex-patients*	1212 (22)
20–39 yrs	2936 (54)	Symptomatology*	
≥40 yrs	2054 (37)	Cough	4911 (90)
Sex*		Sputum	3544 (65)
Male	4433 (81)	Anorexia and/or weight loss	3533 (64)
Female	1047 (19)	Night sweats and/or chills	3376 (62)
Geographic location*		Chest pain	2004 (37)
Urban areas	4115 (75)	Haemoptysis	1582 (29)
Rural areas	1365 (25)	Dypnoea	1335 (24)
Concomitant malignant disease**		Concomitant nonmalignant disease**	
Bronchial carcinoma	14 (0.3)	Diabetes mellitus	428 (7.8)
Hodgkin's lymphoma	3	COPD	331 (6)
Laryngeal carcinoma	2	Psychosis and/or alcoholism and/or narcotic abuse	65 (1.2)
Non-Hodgkin's lymphoma	1	Ankylosing spondylitis	4 (0.1)
Chronic myelocytic leukaemia	1	Cirrhosis	2
Carcinoma of the colon	1	Interstitial fibrosis	1
Carcinoma of the stomach	1	Radiological features**	
Extrapulmonary localizations**		Parenchymal infiltrate	5017 (99)
Pleural	343 (6.7)	Cavitation	3363 (66)
Lymphatic	31 (0.6)	Pleural thickening	1773 (25)
Laryngeal	31 (0.6)	Fibrosis and/or calcification	1265 (25)
Genitourinary	13 (0.3)	Pleural effusion	343 (6.7)
Bone/joint	10 (0.2)	Isolated LLFTB	317 (6.2)
Meningeal	9 (0.2)	Pneumothorax	78 (1.5)
Peritoneal	7 (0.1)	Miliary pattern	66 (1.3)
Other sites#	11 (0.2)		

*: of the 5,480 patients with pleuropulmonary TB; **: of the 5,094 patients with active pulmonary TB; #: other sites include three colon, three skin and soft tissue, two pericardium, one tongue and tonsils, one auditory canal TB. Data are presented as absolute number, and percentage in parenthesis. TB: tuberculosis; COPD: chronic obstructive pulmonary disease; LLFTB: lower lung field tuberculosis.

cough (90%), expectoration of sputum (65%), anorexia and/or weight loss (64%), night sweats and/or chills (62%), chest pain (37%), haemoptysis (29%), and dyspnoea (24%). The most common nonmalignant conditions associated with pulmonary TB were diabetes mellitus in 428 patients (8%), COPD in 331 patients (6%), psychosis and/or chronic alcoholism and/or narcotic abuse in 65 patients (1.2%), ankylosing spondylitis in four patients, and cirrhosis in two patients. Twenty three patients (0.4%) had concomitant malignant diseases, including bronchogenic carcinoma in 14 patients (0.3%), and Hodgkin's lymphoma in 3 patients. Table 1 shows frequencies of malignant and nonmalignant conditions determined among all patients. Empyema and nephrotic syndrome due to TB were detected in 26 cases (0.5%) and 10 cases (0.1%), respectively. Six female patients (0.5%) were pregnant at the time of diagnosis and six patients (0.1%) died within the first 2 months of antituberculosis therapy at the hospital.

Extrapulmonary TB was found in 455 patients (9%) with active pulmonary diseases. Table 1 presents frequencies of extrapulmonary sites associated with pulmonary TB. Pleural TB without radiological parenchymal involvement was excluded from this evaluation. The most common extrapulmonary site was the pleura in 343 patients (7%). *Mycobacterium tuberculosis* was culture-positive in the urine of 10 patients, while the diagnosis of genital TB (*e.g.* prostate, scrotum and epididymis) was established *via* histopathology in three patients. The rare localizations, such as colon, skin, soft tissue, pericardium, synovia, tongue, tonsils, and auditory canal were classified as "other sites".

Laboratory findings

Among the 5,094 patients with active parenchymal TB, sputum smear and culture data of 4,929 cases are shown in table 2. The sputum specimens of the remaining 165 cases were not available. Sputum samples were smear-positive in 3,916 cases (79%), and culture-positive in 3,748 patients with active parenchymal TB (76%). The mean ESR was 71.5 ± 33.1 mm·h⁻¹. Results of tuberculin skin-testing were available for 2,603 patients (48%). Skin test reactivity was positive in 1,769 (68%) and negative in 834 cases (32%). Hepatotoxicity occurred in 276 patients (5.4%), representing 7.9% of all female cases, and 4.4% of male cases during antituberculosis therapy. There was a significant correlation between hepatotoxicity and female sex ($p < 0.005$). History of alcohol consumption was found in 865 patients (16%). There was no significant correlation between hepatotoxicity and the history of alcohol consumption.

Table 2. – Sputum smear and culture features of 5,094 patients with active pulmonary TB*

	Smear	
	+	-
Culture +	3459 (70)	289 (5.9)
Culture -	371 (7.5)	651 (1.2)
Culture NA	86 (1.7)	73 (1.5)
Total	3916	1013

*: sputum samples of 165 patients were not available. Data are presented as absolute number, and percentage in parenthesis. NA: not available; TB: tuberculosis; +: positive; -: negative.

Chest roentgenographic findings

Among 5,094 patients with pulmonary TB, radiological patterns were parenchymal infiltrate in 5,017 patients (99%), cavitation in 3,363 patients (66%), pleural thickening in 1,733 patients (35%), fibrosis and/or calcification in 1,265 patients (25%). Three hundred and forty three patients (6.7%) had pleural effusion which was on the right side in 193 patients, left side in 141 patients, and bilateral in 9 patients. Pneumothorax was present in 78 patients (1.5%). LLFTB was found in 317 cases (6.2%), representing 11.8% of female subjects and 4.4% of male subjects. There was a significant correlation between LLFTB and female sex ($p < 0.005$). LLFTB was also present in 11% of diabetic patients, and 5.3% of nondiabetic patients. There was also significant correlation between LLFTB and diabetes mellitus ($p < 0.005$). Miliary pattern was detected in 66 patients (1.3%). Table 1 shows radiological findings of 5,094 patients with active parenchymal diseases.

Discussion

The results of this study show that TB is more common among persons aged 20–39 yrs, males, and those living in large urban centres in our region of Turkey. The predominance of male patients over females has been noted in another study performed in Turkey [1]. It has also been reported that the risk of TB disease among infected females was greater than among infected males aged 15–44 yrs [4]. In that case, the risk of males being infected may be higher than that of females in our community. Rapid and unplanned urbanization, overcrowded slums associated with poor sanitation, poor economic conditions and unemployment lead to the greater concentration of cases in urban centres than in rural areas.

According to data obtained in 1982, the mean prevalence rate of TB in Turkey was estimated as 3.58 per 1,000 population, with a minimum of 1.86 per 1,000 in the Aegean region. The incidence of notified cases of TB was 44.0 per 100,000 in 1992. However, the reliability of these data is limited by the insufficiency of notification and registration systems and absence of bacteriological confirmation in some cases. On the other hand, the prevalence of infection in 1982 was found to be 25%. This rate indicates a large pool of infection which contains approximately 15 million infected persons [1]. All these results suggest that Turkey is still a country with a high prevalence of TB and a large a pool of infection, that transmission of tubercle bacilli persists, and that this issue will continue to be an important problem for a long time. The relatively high percentage of active ex-patients results mainly from inadequate patient follow-up and poor compliance with therapy, especially in patients of low socioeconomic status.

The data reported by the Ministry of Health showed that 172 acquired immune deficiency syndrome (AIDS) patients and 285 HIV-seropositive cases were diagnosed between 1985 and 1995 in Turkey. The HIV serostatus has been documented at our hospital since January 1994. After this date, no HIV-seropositive patients with pulmonary or pleural TB were found. This may, in part,

be due to the fact that our hospital is not a referral centre and has no special facilities for the treatment of patients with AIDS. Unfortunately, death from TB may occur even in newly diagnosed cases. In the ranking of causes of death in Turkey, TB decreased to 18th place after 1987 from first place in 1950. RIEDER and co-workers [5] found that the most important risk factors for mortality are advanced age and extrapulmonary sites of TB (miliary, meningeal and peritoneal). In the present study, extrapulmonary involvement with pulmonary TB was found in 8.9% of patients. Being adjacent to the lung, the pleura is the most commonly affected site. The proportion of isolated extrapulmonary TB in the United States was reported as 17.5% in 1986. The most frequent localization of isolated extrapulmonary TB is generally the lymph nodes [6].

The 79% positivity rate for sputum smears observed in our study is similar to the 74% and 81% positivity rates among non-AIDS patients reported by KIM *et al.* [7] and KLEIN *et al.* [8], respectively. There may be two main reasons for the status of sputum smear positive-culture negative (S+C-) found in 371 cases in our study: firstly, some patients had previously had therapy for TB once or more than once but had discontinued their treatment; secondly, some new patients were diagnosed and given therapy by dispensaries or other medical centres immediately before hospitalization. Among the antituberculosis drugs, rifampin and isoniazid, in particular, are known to create biochemical changes in the metabolism of the tubercle bacilli, so that they may impede the growth of the bacilli in the culture medium. KIM *et al.* [7] found that the S+C- status might appear as early as 4 weeks and as late as 20 weeks after the onset of treatment.

The tuberculin test with 5 TU PPD may be a relatively inefficient addition to the diagnosis of active TB. This status is more apparent in old patients and HIV-seropositive cases in particular [9]. Even when the skin test is applied and read with particular care in TB patients without HIV infection, only 78–90% have reactions of ≥ 10 mm to 5 TU PPD [9–11]. In the present study, the frequency of PPD negativity, which comprised 32% of patients, may result not only from factors related to the person being tested but also from incorrect administration, or reading. For this reason, it would be better to discount the results of this test in the study.

The results regarding hepatotoxicity mainly indicate elevated transaminases or disturbed liver function tests. Among them, we do not know the true frequency of clinical hepatitis. The incidence of hepatotoxicity is much higher in studies from developing countries, compared to those from developed countries, despite using similar regimens. The reported incidence in Turkey ranges 0.8–18%. Perhaps the endemic nature of viral hepatitis, poor nutrition, widespread parasitism, chronic infections, indiscriminate use of various drugs without prescription, ethnic factors and severity of the disease may play a role, individually or collectively [12]. Although the reported incidence of hepatotoxicity in the present study is not so high for a developing country, female patients in particular comprised a risk group. This may be explained by the acetylation status of women. Further prospective studies are needed to clarify this point.

Table 3. – Frequency of unusual radiographic presentations in various studies

	Reference						Aktoğ <i>et al.</i>
	[9]	[14]	[15]	[16]	[17]	[18]	
Pnx %	2.4	2	-	-	-	-	1.5
MP %	2.4	7	-	-	4.5	2.8	1.3
LLFTB %	4.9	4	7	5.1	6.8	6	6.2

Pnx: pneumothorax; MP: miliary pattern; LLFTB: lower lung field tuberculosis.

Pulmonary TB produces a broad spectrum of radiographic abnormalities. During postprimary TB, common abnormalities include parenchymal infiltration, cavitation, fibrosis, calcification and pleural thickening. Unusually, miliary pattern, isolated LLFTB, pneumothorax, masslike density resembling carcinoma, intrathoracic lymphadenopathy and normal chest radiography may be present [13, 14]. In table 3, the unusual radiographic presentations reported in the present study are compared with those of several studies which comprise patients without AIDS. The incidence of LLFTB without concomitant upper lobe disease has been reported to comprise approximately 7% of patients with active pulmonary TB [15]. Regarding isolated LLFTB, our results agree with the original observation of SOSMAN and STEIDL [19] that TB tends to occur predominantly in the lower lung fields in patients with diabetes. CHANG *et al.* [16] have also emphasized the predominance of LLFTB in women.

Although a hospital-based study can only provide limited information about the status of a disease in the community, the greater frequency of tuberculosis in the younger age group suggests that Turkey still has a high prevalence rate and that the transmission of tubercle bacilli is not decreasing. The risk group consists mainly of male subjects and those living in urban centres. On the other hand, the relative risk ratio for developing hepatotoxicity during treatment is much higher in females than males in our region. The high percentage of active ex-patients requires new tuberculosis control programmes in Turkey. It is important not only to be able to identify a sufficient level of the sources of infection, but also to be able to cure those who are diagnosed. A possible spread of human immunodeficiency virus infection in our community may add great urgency to all these measures.

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