Chest X-ray and bacteriology in the initial phase of treatment of 800 male patients with pulmonary tuberculosis*,**

Radiografia torácica e bacteriologia na fase inicial de tratamento de 800 pacientes masculinos com tuberculose pulmonar

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Abstract

Objective: To evaluate chest X-rays of patients with pulmonary tuberculosis and to determine whether the extent of radiographic lesions correlates with bacteriological parameters. **Methods:** In this retrospective, descriptive study, we evaluated chest X-rays, as well as AFB detection by smear microscopy and culture for *Mycobacterium tuberculosis*, initially and during the first two months of treatment, in 800 male patients hospitalized between 1995 and the present at a 250-bed hospital in northwestern Turkey. **Results:** The initial mean ESR was 58 ± 37 mm/h. Initial sputum smears and cultures were positive in 83.8% and 89.5% of the patients, respectively. After the first month of treatment, the proportion of patients with positive sputum culture was higher among those with cavitary tuberculosis than among those with non-cavitary tuberculosis (53.7% vs. 37.7%, $p < 0.001$). The number of affected zones was not correlated with age, symptom duration, contact with an active tuberculosis patient, or concomitant diabetes ($p > 0.05$ for all) but was positively correlated with the ESR ($r = 0.23$, $p < 0.001$). During the first and second months of treatment, conversion to smear-negative status was less common in patients with bilateral involvement than in those with unilateral involvement ($p < 0.001$ and $p = 0.002$ for months 1 and 2, respectively). Disease extent did not correlate with age, symptom duration, contact with an active tuberculosis patient, or concomitant diabetes but did correlate with delayed bacteriological recovery. **Conclusions:** Chest X-ray and bacteriology are valuable tools for the evaluation of pulmonary tuberculosis.

Keywords: Radiography, thoracic; Bacteriology; Tuberculosis, pulmonary/drug therapy.

Resumo

Objetivo: Avaliar radiografias de tórax de pacientes com tuberculose pulmonar e determinar se a extensão das lesões radiográficas correlaciona-se com os parâmetros bacteriológicos. **Métodos:** Neste estudo descritivo e retrospectivo; foram avaliadas radiografias de tórax, baciloscopias para BAAR e culturas de escarro para *Mycobacterium tuberculosis* no momento basal e durante os dois primeiros meses de tratamento. A amostra foi composta por 800 pacientes masculinos internados entre 1995 até o presente em um hospital com 250 leitos no noroeste da Turquia. **Resultados:** A VHS média inicial foi de 58 ± 37 mm/h. Inicialmente, a baciloscopia e as culturas de escarro tiveram resultado positivo em 83,8% e em 89,5% dos pacientes, respectivamente. Após o primeiro mês do tratamento, a proporção de culturas positivas foi maior nos pacientes com doença cavitária do que naqueles sem doença cavitária (53,7% vs. 37,7%; $p < 0,001$). Não houve correlação do número de zonas afetadas com idade, duração de sintomas, contato com paciente com tuberculose ativa, diabetes concomitante ($p > 0.05$ para todos), mas houve correlação positiva com VHS ($r = 0,23$, $p < 0,001$). Durante o primeiro e o segundo mês de tratamento, a negativação da baciloscopia foi menos frequente nos pacientes com comprometimento bilateral do que naqueles com comprometimento unilateral ($p < 0,001$ e $p = 0,002$ para os meses 1 e 2, respectivamente). A extensão da doença não se correlacionou com idade, duração dos sintomas, contato com paciente com tuberculose ativa e diabetes concomitante, mas sim com a recuperação bacteriológica atrasada. **Conclusões:** Radiografias de tórax e bacteriologia são ferramentas valiosas na avaliação de tuberculose pulmonar.

Descritores: Radiografia torácica; Bacteriologia; Tuberculose pulmonar/quimioterapia.

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Introduction

Tuberculosis is a common disease in Turkey as well as in the rest of the developing world. The 2009 World Health Organization (WHO) Tuberculosis Report estimated that the incidence of smear-positive tuberculosis cases in Turkey was 13/100,000 (≈10,000 cases) in 2007.[1]

On the chest X-rays of adult patients with pulmonary tuberculosis (PTB), infiltrates, cavities, and fibrosis are common findings. The lesions are typically seen in the apical and posterior segments of the upper lobes, as well as in the superior segments of the inferior lobes.[2-8] However, in patients with HIV infection, diabetes, silicosis or malignancy, especially in females and in the elderly, the lower lung fields can be involved.[2,4,7,9-13] Although sputum smear and culture are the main tools for the diagnosis and follow-up of PTB, clinicians frequently use chest X-ray in the differential diagnosis and the assessment of treatment responses. The WHO Expert Committee on Tuberculosis Ninth Report, issued in 1974,[14] strongly discouraged the mass screening for tuberculosis through the use of chest X-rays. However, chest X-ray, rather than sputum smear microscopy, has often been employed as an initial examination in populations considered to be at higher risk for tuberculosis, such as prisoners.[15,16]

The aim of this study was to evaluate the pre-treatment chest X-rays of patients with smear- or culture-positive PTB and to determine whether the location and extent of radiographic lesions correlated with concomitant diseases and bacteriological parameters during a two-month follow-up period.

Methods

The Ballidag Sanatorium, located in Kastamonu, Turkey, was an institution dedicated exclusively to the care of male blue-collar workers/retirees and their male family members. It was closed in 2007 and later reopened under the name Ballidag Chest Diseases Hospital.

In this retrospective, descriptive study, we evaluated hospital records and pre-treatment chest X-rays of eight hundred consecutive adult male patients with PTB who were admitted to the Ballidag Chest Diseases Hospital between January 1995 and the present. All of the patients evaluated had, initially or later, at least one AFB-positive sputum smear, at least one culture that was positive for *Mycobacterium tuberculosis* complex, or both. The duration of typical symptoms, concomitant diseases, and self-reported contact with an active tuberculosis patient had been recorded. The duration of symptoms was defined as the time elapsed (in days) from the onset of the first symptoms to the initiation of treatment. For the initial phase of the treatment, the patients had been started on one of two regimens: isoniazid/rifampin/ethambutol plus pyrazinamide; or isoniazid/rifampin/pyrazinamide/streptomycin.

In all patients suspected of having tuberculosis, at least three sputum specimens had been examined by Ziehl-Neelsen staining. In addition, at least two sputum specimens had been cultured for *M. tuberculosis* on Löwenstein-Jensen medium and the isolated strains had been subjected to testing for susceptibility to isoniazid, rifampin, ethambutol, and streptomycin. Multidrug-resistant tuberculosis (MDR-TB) was defined as infection with an *M. tuberculosis* isolate resistant to the rifampin-isoniazid combination or to the rifampin-isoniazid combination and at least one other first-line drug. Chest X-ray, smear microscopy, and culture were performed monthly during the initial intensive phase of the treatment (≈2 months), and patients had been referred to the tuberculosis dispensary nearest to their residence for further follow-up. Patients who were unable to produce spontaneous sputum samples for examination in the first or second month of therapy were not followed up by any other bacteriological method (e.g., induced sputum, gastric lavage, or bronchoscopy). Patients suspected of having primary lung cancer or pulmonary metastases, positive culture results for nontuberculous mycobacteria, or any other disease that seemed unmanageable in the hospital had been referred to a tertiary-care facility in Istanbul.

The case definitions given in the 2007 WHO Report were used for the clinical classification of PTB.[17] Patients with miliary tuberculosis, extrapulmonary tuberculosis (EPTB; including mediastinal and pleural tuberculosis without parenchymal involvement), or endobronchial tuberculosis were excluded, as were those with pneumothorax, poor quality initial chest X-ray, or radiographic findings resulting from

chest wall deformities, as well as those who had been exposed to materials known to cause pneumoconiosis, those with suspected or proven malignancy, those in whom antituberculosis drug therapy was interrupted for more than 2 weeks in the initial phase, and those who died within the first 2 weeks after admission.

Posteroanterior chest X-rays were evaluated independently by two pulmonologists, and the final decision was established by consensus at the second reading. Parenchymal infiltrates, patchy consolidations, nodular opacities, fibrotic lesions (with or without volume loss), calcified lesions, cavitations (with or without air-fluid levels), and pleural effusions or thickening with parenchymal lesions were all attributed to PTB.

The radiological classification of disease extent was as follows[18]: minimal PTB (when the lesions did not cross the area above the sternal cartilage of the second rib on one side); moderately advanced PTB (when moderately advanced lesions could be seen in one or both lungs, with disseminated lesions of low to moderate density extending throughout one lung or the equivalent in both lungs, or dense, confluent lesions limited to one-third of the volume of one lung); and well advanced PTB (when the lesions were even more extensive). On the chest X-rays, lungs were also divided into upper, middle and lower zones, which were delimited by the upper border of the second and fourth anterior ribs, and all six zones were assessed for findings indicative of tuberculosis.

The ESR was recorded at admission, after the first month of treatment, and after the second month of treatment, as were the results of sputum smear microscopy to detect AFB and culture for *M. tuberculosis*. All radiological data were evaluated for any correlation with these data.

All statistics were performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). We used Student's t-test for continuous variables and the chi-square test for categorical variables. Pearson's correlation coefficient was used in order to determine whether chest X-ray findings correlated with age, symptom duration, ESR, concomitant diabetes, or, especially, tuberculosis bacteriology. Values of $p < 0.05$ were considered statistically significant.

Results

The mean age of the patients was 39 ± 14 years (range, 16-75 years). The mean symptom duration was 113 ± 196 days (median, 120 days). The number of patients who reported close contact with an active tuberculosis patient was 193 (24.1%). The most common concomitant diseases were diabetes, reported by 81 patients (10.1%), and COPD, reported by 80 patients (10.0%). The initial mean ESR was 58 ± 37 mm/h. Initial sputum smears for AFB and cultures for *M. tuberculosis* were positive in 83.8% and in 89.5% of the patients, respectively (Table 1).

Clinical classification and drug resistance patterns are presented in Table 2. The initial chest X-ray findings are presented in Table 3. The most common radiographic finding accompanying active PTB was emphysema (in 10.0%), followed by destroyed lung (in 3.5%), pleural effusion (in 3.3%), and pleural calcification (in 2.1%). Cardiomegaly, atelectasis, bullous lung, and hilar lymphadenopathy were each seen in less than 1% of the cases.

We first evaluated the differences between unilateral and bilateral pulmonary involvement (Table 4). The number of patients with unilateral involvement (n = 399) was nearly equal to that of those with bilateral involvement (n = 400). One patient had a normal chest X-ray. There were no significant differences between the patients with unilateral involvement and those with bilateral involvement in terms of concomitant diabetes, which was observed in 46 (11.5%) and 35 (8.8%) of the patients, respectively ($p > 0.05$), contact with an active tuberculosis patient, which was reported in 96 (24.1%) and 97 (24.3%), respectively, ($p > 0.05$), or the time from symptom onset to treatment initiation (113 ± 202 days vs. 114 ± 190 days; $p > 0.05$).

Table 1 - Initial bacteriological status of the patients.

Status	Smear (–), n (%)	Smear (+), n (%)	Total
Culture (–), n (%)	82 (10.25)	2 (0.25)	84 (10.50)
Culture (+), n (%)	48 (6.00)	668 (83.50)	716 (89.50)
Total	130 (16.25)	670 (83.75)	800 (100.00)

Table 2 - Clinical classification and drug resistance patterns of patients with pulmonary tuberculosis (n = 800).

Variable	n (%)
Clinical classification	
New cases	605 (75.6)
Relapse	97 (12.1)
Re-treatment	98 (12.3)
AFB microscopy performed	
Initial	800 (100.0)
After 1 month of treatment	726 (90.8)
After 2 months of treatment	528 (66.0)
M. tuberculosis culture performed	
Initial	800 (100.0)
After 1 month of treatment	516 (64.5)
After 2 months of treatment	266 (33.3)
Drug resistance	
Any drug resistance*	359 (44.9)
Multi-drug resistance**	104 (13.0)

*Resistance to isoniazid, rifampin, ethambutol, or streptomycin. **Resistance to at least the isoniazid-rifampin combination.

However, the number of cases of re-treatment was more than twice as high among the patients with bilateral involvement. After the first month of treatment, the proportion of patients with positive cultures was significantly greater in the patients with unilateral involvement (37.3% vs. 29.1%; p = 0.01), although this difference did not retain its significance after the second month (7.3% vs. 11.8%; p = 0.037). Patients with bilateral involvement on chest X-rays were slightly older than were those with unilateral involvement (40 ± 14 years vs. 38 ± 14 years; p = 0.018) and were more likely to have previously been treated for tuberculosis (p < 0.001).

Table 3 - Initial chest X-ray findings of patients with pulmonary tuberculosis.

Chest X-ray finding	(n = 800)	
	%	%
Involvement		
None	1	0.1
Unilateral (right-sided)	245	30.6
Unilateral (left-sided)	154	19.3
Bilateral	400	50.0
Disease extent		
None	1	0.1
Minimal	111	13.9
Moderately advanced	352	44.0
Well advanced	336	42.0
Affected zones		
1	214	26.8
2	251	31.4
3	144	18.0
4	111	13.9
5 or 6	79	9.9
Cavitary lesion(s)		
Yes	575	72.0
No	224	28.0

Table 5 shows the comparison between the patients with cavitary disease and those without. After the first month of treatment, the proportion of patients with positive culture results was higher in those with cavitary disease than in those with non-cavitary disease (53.7% vs. 37.7%; p < 0.0001), as was the proportion of patients with positive smear microscopy results (36.3% vs. 24.6%; p = 0.001). After the second month of treatment, there were no differences between the two groups in terms of the culture results, although the proportion of smear-positive patients remained significantly higher in the cavitary disease group (p = 0.001).

The number of affected zones did not correlate with age, symptom duration, contact with an active tuberculosis patient, or concomitant diabetes (p > 0.05 for all) but did correlate positively with the ESR (r = 0.23; p < 0.001) and with re-treatment (r = 0.14; p < 0.001). The number of affected zones also presented significant, although weak, correlations with some bacteriological results before and after treatment: positive sputum smear at admission (r = 0.12; p < 0.001); positive smear after the second month of treatment (r = 0.15; p < 0.001); positive culture after the first month of treatment (r = 0.12; p = 0.008); and positive culture after the second month of treatment (r = 0.12; p = 0.045). Neither disease extent nor the number of affected zones correlated with resistance to any antituberculosis drug or with MDR-TB (p > 0.05 for all). Involvement of the lower lung zones was more prevalent in the patients with diabetes than in those without (30.9% vs. 24.6%; p = 0.001).

Discussion

In developing countries and countries in which the prevalence of HIV is high, PTB patients are younger, reported mean ages ranging from 28.7 to 37.7 years.[6,13,19-22] However, the mean ages reported for PTB patients treated at

Table 4 - Unilateral vs. bilateral pulmonary involvement in tuberculosis patients.

Variable	Pulmonary involvement		p
	Unilateral	Bilateral	
	(n = 399[a])	(n = 400)	
Age (years), mean ± SD	38 ± 14	40 ± 14	0.018*
Symptom duration (days) , mean ± SD	113 ± 202	114 ± 190	NS*
ESR, mean ± SD	52 ± 37	63 ± 38	< 0.001*
Diabetes, n (%)	46 (11.5)	35 (8.8)	NS**
Contact with active tuberculosis patient, n (%)	96 (24.1)	97 (24.3)	NS**
Tuberculosis classification			
New case, n (%)	324 (81.2)	280 (70.0)	< 0.0001**
Relapse, n (%)	44 (11.0)	53 (13.2)	NS**
Re-treatment, n (%)	31 (7.8)	67 (16.8)	< 0.0001**
Any antituberculosis drug resistance, n (%)	181 (45.4)	178 (44.5)	NS**
MDR-TB, n (%)	41 (10.3)	63 (15.8)	0.021**
Positive sputum smear AFB			
Initial, n (%)	325 (81.5)	345 (86.3)	NS**
After 1 month of treatment, n (%)	111 (27.8)	153 (38.3)	0.001**
After 2 months of treatment, n (%)	25 (6.3)	49 (12.3)	0.004**
Positive culture for *Mycobacterium tuberculosis* complex			
Initial, n (%)	336 (84.2)	331 (82.3)	NS**
After 1 month of treatment, n (%)	116 (29.1)	149 (37.3)	0.01**
After 2 months of treatment, n (%)	29 (7.3)	47 (11.8)	0.037**

NS: Not significant; and MDR-TB: multidrug-resistant tuberculosis. [a]In one case, the chest X-ray was normal. *Student's t-test; and **chi-square test.

tertiary-care centers in such countries, mainly in reports from Asian countries, range from 45 to 63.9 years.[2,9,23,24] Two studies conducted in Turkey reported similar mean ages: 37 years in a sample of 4,433 adult male patients with PTB[12]; and ≈37 years in a sample of 835 male patients, including children, with PTB or EPTB.[25] Therefore, the mean age of tuberculosis patients in Turkey appears to fall between that reported for developing countries and countries in which the prevalence of HIV is high and that reported for relatively developed countries.

In a study of PTB in patients with diabetes, Bacakoglu e al. reported a mean ESR of 71.5 mm/h.[10] In a sample of 109 pulmonary tuberculosis patients, 38.5% of whom were co-infected with HIV, Dominguez-Castellano e al. reported a mean ESR of ≈65 mm/h.[5] In the present study, we excluded seriously ill patients, which could explain the relatively low ESRs observed.

One group of authors studied 305 patients with PTB and reported that 15.7% were infected with strains resistant to at least one antituberculosis drug.[23] In the literature, the reported prevalence of MDR-TB ranges from 0.71% to 12.7%.[9,22] Because the history of antituberculosis treatment was self-reported in our study, the rates of relapse (12.1%) and re-treatment (12.3%) might represent underestimations. If so, this could explain the fact that the rates of resistance to any drug and multidrug resistance were higher in our study.

In the literature, the reported rates of normal chest X-rays in patients with smear- or culture-positive PTB are low,[4,11,13,22,24] except in HIV-infected patients.[8] A prevalence survey conducted in Cape Town, South Africa revealed that the presence of any abnormalities on chest X-ray has a high sensitivity for detecting subjects with smear- or culture-positive tuberculosis (0.97%; 95% CI: 0.90–1.00).[26] In our sample of 800 male patients, there was only one case of smear- or culture-positive tuberculosis and a normal chest X-ray. This suggests that all symptomatic patients had abnormal chest X-rays or that patients with normal chest X-rays are not submitted to bacteriological tests for tuberculosis, even in the presence of symptoms indicative of the infection.

The even distribution between unilateral and bilateral involvement on chest X-ray in our study is consistent with data in the literature.

Table 5 - Cavitary versus non-cavitary tuberculosis.

Variable	Non-cavitary (n = 224)	Cavitary (n = 575)	p
Age (years), mean ± SD	39 ± 14	39 ± 14	NS*
Symptom duration (days), mean ± SD	103 ± 194	117±197	NS*
Initial ESR (mm/h), mean ± SD	52 ± 37	60 ± 37	0.012*
Contact with active tuberculosis patient, n (%)	49 (21.9)	144 (25.0)	NS**
Diabetes, n (%)	17 (7.6)	64 (11.1)	NS**
Clinical classification			
New case, n (%)	175 (78.1)	429 (74.6)	NS**
Relapse, n (%)	27 (12.1)	70 (12.2)	
Re-treatment, n (%)	22 (9.8)	76 (13.2)	
Any antituberculous drug resistance, n (%)	93 (41.5)	266 (46.3)	NS**
Multi-drug resistance, n (%)	25 (11.2)	79 (13.7)	NS**
Positive sputum smear for AFB			
Initial, n (%)	168 (75.0)	502 (87.3)	< 0.0001**
After 1 month of treatment, n (%)	55 (24.6)	209 (36.3)	0.001**
After 2 months of treatment, n (%)	9 (4.0)	65 (11.3)	0.001**
Positive culture for *Mycobacterium tuberculosis* complex			
Initial, n (%)	177 (79.0)	490 (85.2)	0.03**
After 1 month of treatment, n (%)	52 (23.2)	213 (37.0)	0.0001**
After 2 months of treatment, n (%)	19 (8.5)	57 (9.9)	NS**

NS: not significant. *Student's t-test; and **chi-square test.

[3,9,23] Although culture conversion to negative was significantly less common in patients with bilateral involvement than in those with unilateral involvement after the first month of treatment, there was no such difference by the end of the second month. Among the cases of re-treatment, bilateral involvement was more common and the number of affected zones was higher. In addition, lower zone involvement was more common in patients with diabetes than in those without, as has been previously reported.[4,7,10,11]

Although cavitation is the most widely reported chest X-ray finding in patients with PTB, the reported rates range from very low (in studies involving HIV-infected or otherwise immunocompromised patients, children, or the elderly) to very high (in patients with concomitant diabetes).[7,9-11,23] Among patients with reactivation tuberculosis, cavitary lesions are reported to occur in 28-82%, the mean being 40-50%.[6,9,11,20,24] Kartaloglu e al. observed cavitary lesions in 131 (60.6%) of 216 patients with PTB.[27] Patients with cavitary PTB have higher bacterial loads than do those with non-cavitary PTB or other forms of tuberculosis.[19] Cavitary PTB patients are also at increased risk for relapse, treatment failure, and drug resistance.[20,22] Some studies have suggested that presence of cavitation increases the time to smear conversion (to negative).[23] Kim e al. found that such conversion occurred after the first month of treatment in 71% of patients with cavitary lesions and in 30% of those without.[28] Telzak e al. reported that the mean time to such conversion was 1.62 months in patients with cavitary lesions and 1.44 months in those without, although the difference was not statistically significant.[29] We found no differences between the patients with and without cavitary lesions in terms of the rates of drug resistance. However, at admission, as well as after the first and second months of treatment, the proportion of patients with AFB-positive sputum smears was higher in the patients with cavitary lesions than in those without. In addition, smear conversion rates were lower in the former group. Furthermore, the rate of culture conversion to negative after the first month of treatment was lower in the patients with cavitary lesions.

In a study involving 212 smear-positive patients, the mean time from symptom onset to treatment initiation was approximately 120 days,[30] compared with 113 days in the present

study. Our results show that symptom duration before the initiation of treatment was not correlated with disease extent on chest X-rays. Our study sample included workers who had periodic health checkups and for whom early diagnosis was therefore more likely, as well as their relatives, most of whom resided in the rural parts of the country, where there is less access to health care facilities. We can speculate that this accounted for the high standard deviation from the mean symptom duration.

It is known that ESR increases in patients with PTB, and it has been suggested that such an increase is correlated with the duration of smear negativity. However, Kartaloglu e al. found no correlation between those two entities in a study involving 216 cases, with a mean initial ESR of 57.1 mm/h.[27] In our study, we found that ESR correlated positively with the radiological extent of disease, probably in function of the high bacterial load within cavitary lesions. However, one limitation of the present study is that other possible causes of an elevated ESR, such as anemia, were not investigated.

The major limitation of the present study is its retrospective design. Because the hospital is dedicated to the care of male laborers and their male relatives, all results were derived from the records of those patients. Certain exclusion criteria based on the differential diagnoses further limited the power of the study. However, those exclusions were inevitable because the hospital has no CT unit or pathology laboratory. For technical reasons, chest X-ray represents another limitation. Chest X-ray findings were not investigated by age group. Symptoms indicative of tuberculosis were not correlated with chest X-ray findings. The number and size of cavities were not taken into account, although they might be related to the total bacterial load. In Turkey, testing for HIV cannot be performed without the permission of the patient. However, AIDS is not a prevalent disease in Turkey; between 1985 and 2009, only 3,898 cases were reported in a total population of approximately seventy million. Nevertheless, none of our patients had been tested for HIV, and, of course, the real number cannot be known without serological testing.

In conclusion, chest X-ray and bacteriology are valuable tools for the evaluation of patients with PTB.

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