The profile of pleural tuberculosis patients in Turkey

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Abstract

Tuberculosis is the leading cause of exudative pleural effusion. The present study was designed to evaluate the patient profile in a 3-year cohort of pleural tuberculosis patients. A total of 174 patients with pleural tuberculosis (mean age was 36.1 years, 64.9% were male) followed up in our clinic from 2004 to 2007 were included in this study. Data on diagnostic methods, pleural fluid findings and clinical features of patients were recorded based on retrospective evaluation of the medical records. Diagnostic thorasynthesis was performed in patients with pleural effusion. Concomitant analysis of pleural fluid and blood biochemistry (glucose, LDH, protein levels), ADA values and cytology of pleural fluid were performed. Tuberculosis patients were categorized and treated in accordance with WHO guidelines. Patients were invited to attend monthly visits for the cohort analysis after discharge. The frequency of patients below and above 35 years of age was 51.1 and 48.9%, respectively. Parenchymal lesion was evident in 22.4% of patients while pleural fluid was detected in 50.6% of patients within right hemithorax and in 47.1% within the left hemithorax. Lymphocytic fluid was detected in 98%. Mean level for ADA in the pleural fluid was 76.9 U/L. Pleural biopsy revealed granulomatous infection in 53.8% and chronic pleuritis in 46.2% of patients. There was a significant relation of age over 35 years to presence of chronic infection in pleural biopsy (OR: 3.11) and co-morbid disorder (OR: 23.53). Pleural biopsy was performed in 38.2% of patients who were younger than 35 years while in 51.7% of patients who were older than 35 years. The frequency of granulomatous infection diagnosis was significantly higher in patients younger than 35 years when compared to older patients (54.8% vs. 45.2 %; p=0.02). In our study including homogenous distribution of patients in terms of being younger and older than 35 years of age, pleural biopsy was performed more commonly in older patient in order to eliminate possible underlying malignancy. However the diagnostic power of pleural biopsy was determined to be poor. Accordingly, after elimination of other causes of the exudate development, initiation of tuberculosis treatment based on ADA and cell count results seems reasonable.

Key words: pleural tuberculosis; patients profile; Turkey

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Introduction

Tuberculosis is the most common reason for the exudative pleural effusions. The worldwide ratio of detection of tuberculosis in the pleural fluids is 30-60% [1]. Extrapulmonary tuberculosis (XPTB) constitutes 20-25% of overall tuberculosis cases in immuno-competent persons while the frequency of the disease reaches up to 60% in severely immune-compromised patients with HIV infection [2]. Lymphatic, pleural, and bone or joint forms are the most common specific types of XPTB that is specifically seen among elderly in developed countries with low incidence of tuberculosis whereas at younger ages in developing countries with high tuberculosis incidence [1,3].

Pleuritis/effusion complicating primary pulmonary tuberculosis, pleuritis/effusion complicating reactivation-type pulmonary tuberculosis, effusion associated with extrapulmonary tuberculosis and chronic emphysema associated with pneumothorax are the principle mechanism underlying the development of disease [4].

The present study was designed to evaluate the patient profile in a 3-year cohort of pleural tuberculosis patients.

Methods

Of 1443 tuberculosis patients followed up at our clinic from 2004 to 2007, 200 (13.9%) patients having the diagnosis of pleural tuberculosis were enrolled in the present study while 174 patients (mean age was 36.1 (SD 17.3) years, 64.9% were males) were determined to be eligible for the analysis. Data on diagnostic methods, pleural fluid findings and clinical features of patients were recorded based on retrospective evaluation of the medical records. Diagnostic thorasynthesis was performed in patients with pleural effusion. Concomitant analysis of pleural fluid and blood biochemistry (glucose, LDH, protein levels) as well as cell count, ADA values and cytology of pleural fluid were performed. Differentiation of transudate and exudate was made via Light criteria by analysis of levels of protein and LDH in the pleural fluid and in the serum. Determination of pleural fluid /serum protein > 0.5, pleural fluid /serum LDH >0.6 or pleural fluid LDH >2/3 upper normal serum limit was considered for the evidence of exudative effusion.

In patients with congestive heart failure or cirrhosis, serum-pleural fluid protein gradient was considered to be >3.1 [1].

In patients with exudative pleural fluid, pleural biopsy was performed under local anesthesia via Cope or Brahms biopsy set. Sputum smear was analyzed in patients with parenchymal lesion. Pleural fluid ARB analysis was not performed routinely. Serum collagen tissue markers were measured in patients with clinical features compatible with the rheumatological disease.

Diagnosis of pleural tuberculosis was confirmed based on detection of adenosine deaminase (ADA) levels of 40U/L, lymphocyte-predominant exudate and/or granulamatous inflammation in pleural biopsy. In patients with advanced age with malignancy suspicion, thoracic CY and FOB were performed.

Tuberculosis patients were categorized and treated in accordance with WHO guidelines [5]. New smear-negative PTB patients with less severe forms of EPTB were considered to be in category III. TB treatment regime included 2-month initial phase isoniasid, rifampicin, pyrazinamide, ethambutol and 4-month continuation phase with isoniasid and rifampicin. Initial phase of the treatment was administered in hospital under direct surveillance while via self administration after discharge. Patients were discharged after evaluation of clinical and radiological treatment response. Medications supply and controls were performed by related tuberculosis dispensaries. Patients were also invited to attend monthly visits for the cohort analysis while the data of patients who did not attend to control visits were obtained by direct phone calling of tuberculosis dispensaries.

Patients were classified as below and over 35 years of age and evaluated in terms of pleural biopsy findings, ADA values, cell counts, gender, parenchymal involvement, localization and co-morbid disorders.

Statistical analysis

Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). Data were analyzed by Chi-square (χ^2) test and logistic regression analysis. Data were

expressed as "mean (standard deviation; SD)", minimum-maximum and percent (%) where appropriate. $p<0.05$ was considered statistically significant

Results

Demographic and clinical features and pleural fluid analysis in pleural tuberculosis patients

A total of 174 patients (mean age: 36.1 (SD 17.3) years) were included in the present study. Females composed 35.1% (mean age: 33.0 (SD 17.0) years) of the population while males 64.9% (mean age:37.9 (SD 17.4) years). The frequency of patients below 35 years of age was 51.1% while patients older than 35 years composed 48.9% of patients.

Parenchymal lesion was evident in 22.4% of patients, while pleural fluid was detected in 50.6% of patients within the right hemithorax and in 47.1% of patients within the left hemithorax (Table 1).

Biochemical analysis of pleural fluid revealed mean levels for LDH to be 691.5 (SD 487.9) IU/L, glucose to be 79.4 (32.5) and protein to be 5.5(1.1) g/dl.

Cellular distribution was evaluated in 89.7% of patients while lymphocytic fluid was detected in 98%. Neutrophil predominance was detected in 3 patients (0.02%). Pleural fluid ADA level was evaluated in 136 patients (75.9%) revealed mean ADA level to be 76.9 (SD 41.2) U/L with levels below 40 U/L in 18.1% and above 40 U/L in 81.9% of patients (Table 1).

Co-morbid disorders were identified in 17.8% including diabetes mellitus, hypertension, malignancy (bladder, breast, and thyroid), and gastrointestinal disorders (gastritis, ulcer) (Table 1).

Pleural biopsy performed in 44.8% of patients (n=78) revealed granulomatous infection in 53.8% and chronic pleuritis in 46.2% (Table 1).

Table 1. Demographic and clinical features and pleural fluid analysis in pleural tuberculosis patients

	Mean (SD)
Age (years)	36.1 (17.3)
15-34	89(51.1)
≥35	85(48.9)
Gender	**n(%)**
Female	61(35.1)
Male	113(64.9)
Cell count	
None	18(10.3)
Lymphocyte	153(87.9)
Neutrophil	3(1.7)
Parenchymal lesion	
Absent	126(72.4)
Present	48(27.6)
Right hemithorax	88(50.6)
Left hemithorax	82(47.1)
ADA level (U/L)	
<40	24(12.6)
>40	108(62.6)
None	42(24.7)
Pleural biopsy findings	
Performed	78 (44.8)
Chronic infection	36(46.2)
Granulomatous	42(53.8)
Not performed	96(55.2)
Co-morbid disorders	
Hypertension	14(45.2)
Diabetes mellitus	9(29)
Gastrointestinal disorders	4(16.2)
Malignancy	3(9.6)

Distribution of tuberculosis patients with or without diagnosis via pleural biopsy in terms of age and pleural fluid properties

Of 132 patients lacking biopsy directed confirmation of tuberculosis diagnosis, 66 (50.0%) of whom were over 35 years old, ADA levels were determined to be over 40 U/L in 64.4% while lymphocyte predominance was identified in 87.1% (Table 2).

Table 2. Distribution of tuberculosis patients with or without diagnosis via pleural biopsy in terms of age and pleural fluid properties

	Chronic pleuritis or without pleural biopsy	Granulomatous infection	Total
Age (years)	n(%)	n(%)	n(%)
<35 years	66 (50)	23 (54.8)	89(51.1)
≥35 years	66 (50)	19 (45.2)	85(48.9)
ADA level (U/L)	n(%)	n(%)	
None or <40	47 (35.6)	19 (46.3)	66 (37.9)
>40	85 (64.4)	22 (53.7)	108 (62.1)
Predominant cell type	n(%)	n(%)	
Lymphocyte	115 (87.1)	38 (90.4)	153(87.9)
None or neutrophil	17 (12.9)	4 (9.6)	21(12.1)
Total	132	42	174

Relation of age distribution to gender and clinical features

There was a significant relation of increased age (≥35 years) to having male gender (p=0.039), chronic infection in pleural biopsy (p=0.02) and co-morbid disorder (p=0.000; Table 3).

Pleural biopsy was performed in 38.2% of patients who were younger than 35 years while in 51.7% of patients who were older than 35 years. The frequency of granulomatous infection diagnosis was significantly higher in patients younger than 35 years when compared to older patients (54.8 %vs. 45.2 %; p=0.02; Table 3).

Table 3. Relation of age distribution in pleural tuberculosis patients to gender and clinical features

	Age		Total	p value (chi-square)
Co-morbid disorder	**<35 years**	**≥35 years**		
Absent	87 (60.8)	56 (39.2)	143(100.0)	**0.000**
Present	2 (6.5)	29 (93.5)	31 (100.0)	
Localization				
Right	45(51.1)	43(48.9)	88 (100.0)	0.563
Left	43 (52.4)	39 (47.6)	82 (100.0)	
Bilateral	1(25.0)	3 (75.0)	4 (100.0)	
Parenchymal lesion				
Absent	67 (53.6)	58 (46.4)	125(100.0)	0.317
Present	22 (44.9)	27 (55.1)	49 (100.0)	
Gender				
Female	38 (62.3)	23 (37.7)	61 (100.0)	**0.039**
Male	51 (45.1)	62 (54.9)	113(100.0)	
Pleural biopsy finding				
Chronic infection	11 (30.6)	25 (69.4)	36(100.0)	**0.02**
Granulomatous	23 (54.8)	19 (45.2)	42(100.0)	
None	55 (57.3)	41 (42.7)	96(100.0)	
ADA level (U/L)				
<40	9 (37.5)	15 (62.5)	24(100.0)	0.150
>40	54 (50.0)	54 (50.0)	108(100.0)	
None	26 (61.9)	16 (38.1)	42(100.0)	
Total	**89 (51.1)**	**85 (48.9)**	**174 (100.0)**	

Table 4. Logistic regression analysis of age distribution in relation to pleural biopsy and co-morbid disorders

	OR	%95CI	p
Pleural biopsy	3.1	1.3; 7.2	0.008
Co-morbid disorder	23.5	5.3; 103.9	0.000

OR: Odds ratio; CI : confidence interval

As shown in Table 4, logistic regression analysis revealed significant relation of age over 35 years to presence of chronic infection in pleural biopsy (OR: 3.11 (1.33-7.23)) and co-morbid disorder (OR: 23.53 (5.33-103.93)).

Discussion

Globally, extrapulmonary cases without concurrent pulmonary involvement were reported to comprise 14% of newly notified or relapsed cases in 2007 [3]. Epidemiologically, pleural tuberculosis has been accused for a major portion of XPTB morbidity in the United States [4]. In the United Kingdom, pleural disease is traditionally not included within XPTB since it is considered as a pulmonary disease [6].

Pleural disease constituted 26.5% of the XPTB in the United States during a 5 year period from 1969 to 1973 while the pleural component of XPTB was reported to reduce to 20% by 1997 [7]. Studies from Northern Spain and Saudi Arabia demonstrated that tuberculosis was the mostly encountered reason for the pleural effusions accounting for 25% and 37% of all pleural effusions [8,9]. Based on data from past studies indicating higher percentage of pleural effusion in patients with thoracic tuberculosis accompanied with HIV-positivity, the incidence of pleural effusions seems to be higher in patients with AIDS [10-12].

Evaluation of annual distribution of pulmonary and non-pulmonary tuberculosis cases in Turkey revealed the incidence of non-pulmonary tuberculosis to range from 27.0 to 30.6% between 2005-2008 years [13]. Tuberculosis incidence in our country was reported to be 26/100000 [13]. In this regard of 1443 tuberculosis patients diagnosed and treated at our clinic from 2004 to 2007, 200 (13.9%) patients were identified to have the diagnosis of pleural tuberculosis.

Past studies concerning age distribution of tuberculosis patients in Turkey revealed that 56.4% of patients to be <30 years old [14], 77.6% to be <45 years old [15] and 55% to be 20-39 years old [16]. Accordingly in our population the frequency of patients below 35 years of age was 51.1% while patients older than 35 years composed 48.9% of the population.

Chest radiography usually demonstrates only the pleural fluid, but approximately 20% of patients are also known to have tuberculosis related parenchymal infiltrate [17]. In our study, 48 of 174 cases (27.6%) had parenchymal lesion on chest radiography while 50.6% of patients had right hemithorax pleural effusion and 47.1%) had left hemithorax pleural effusion. In our study, thoracic CT was not performed routinely but offered only for patients with malignancy suspicion.

The diagnosis of pleural tuberculosis depends on demonstration of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimen or the demonstration of granulomas in the pleura [1].

Pleural fluid analysis is useful in the diagnosis of pleural tuberculosis The fluid is invariably exudate. In most patients, differential white blood cell (WBC) count in the pleural fluid reveals more than 50% small lymphocytes. In patients with symptoms of less than 2 weeks duration, the pleural fluid differential WBC may reveal predominantly polymorphonuclear leukocytes [1]. In our study, 156 cases had pleural cell count, 153 (98%) of 156 cases had pleural fluid lymphocytes and only 3 (1.7%) of 174 cases had neutrophils in the pleural fluid.

Biochemical analysis of pleural fluid in our population revealed findings frequently reported in these patients including pleural fluid protein level of > 5 g/dl, pleural fluid LDH level of 500-1,500 IU/L and pleural fluid glucose level which is typically slightly below the serum concentration [1,4].

Demonstration of elevated pleural fluid ADA level is useful in establishing the diagnosis of pleural tuberculosis. In patients with lymphocytic pleural effusion, demonstration of ADA level above 40 U/L is strongly suggestive of the diagnosis since ADA level is almost always below 40 U/L in lymphocytic pleural effusions due to reasons other than tuberculosis [1].

Prospective average 5 year follow up of 40 patients with undiagnosed pleural effusions by Fever et al [18] revealed pleural fluid ADA level to be <43 U/L and development of tuberculosis in none of the patient within the follow up period. Lymphocytic pleural effusions not due to pleural tuberculosis usually have pleural fluid ADA levels below 40 U/L. Lee et al. [19] measured the pleural fluid ADA in 106 patients with non-tuberculous lymphocytic pleural effusion and reported that only 3 of the 106 fluids (3%) had ADA levels above 40 U/L. Likewise, Castro et al.

[20] measured the pleural fluid ADA levels in 410 lymphocytic non-tuberculous pleural fluids and showed ADA levels above 40 U/L only in 7 (1.7%) of patients. In our study population, pleural fluid ADA level was evaluated in 136 patients (75.9%) and revealed mean (SD) ADA level to be 76.9(41.2) U/L with levels below 40 U/L in 18.1% and above 40 U/L in 81.9% of patients.

According to latest data from tuberculosis patients in 2008 in Turkey, the percentage of male and female patients was documented to be 62.2% and 37.8%, respectively. In line with due to higher numbers of beds reserved for males in our hospital, most of our population was male patients (64.9%).

For the last 40 years, the diagnosis of pleural tuberculosis has been based on pleural needle biopsy via demonstration of granuloma in the parietal pleura which suggests pleural tuberculosis. The clinical and laboratory differences have been shown between pleural tuberculosis developed as a complication of reactivation type pulmonary tuberculosis or of the primary infection. The granuloma in the pleural tissue was reported to occur in 25% of cases in reactivation type pleural tuberculosis, while in 72% of cases in the primary infection dependent pleural tuberculosis [21]. In our study, while pleural biopsy was performed only in 44.8% of the population, the diagnosis of granulamatous infection was determined to be more likely in patient younger than 35 years of age (67.6 vs. 43.2%). This may indicate the increased likelihood of primary infection in these patients.

Cultures of the biopsy were positive in approximately 55% of our cases while the cultures of the fluid itself were positive in 35%. In this regard, the culture of the biopsy per se seems to provide an additional positive culture in only 20% of the patients [1]. Pleural fluid or tissue samples were not evaluated in terms of bacteriological parameters in our population.

The management of pleural tuberculosis aims to prevent subsequent development of active tuberculosis, to relieve the patient's symptoms and to prevent the development of fibrothorax. While spontaneous recovery is evident in many cases with primary infection dependent pleural tuberculosis, the development of active tuberculosis in 65% of these cases within 5 years has been documented [21,22]. In our pleural tuberculosis patients, treatment was administered in

accordance with WHO guideline for six months. Corticosteroid treatment the role of which in the treatment of tuberculous pleurisy is controversial was not used in our cases. If the patient had dyspnea and massive effusion, therapeutic pleural thorasynthesis was performed. Radiological and clinical improvement was evaluated in patients during hospitalization and routine controls performed following discharge.

The major limitation of the present study was change in health policies regarding follow up of tuberculosis patients since 2005 in accordance with the health reform program. Accordingly routine control and medication supply of tuberculosis patients have been executed by tuberculosis dispensaries. Therefore patients were also asked to attend control visits performed in and for patients did not attend to these visits, data were obtained by direct phone calling of the dispensaries. However since radiological evaluation of treatment response was not possible in all of our patients, we couldn't evaluate the pleural thickening. Secondly, while routine bacteriological work up was performed in patients with parenchymal lesions, pleural fluid and pleural biopsy tissue samples were not evaluated in this manner.

In conclusion, pleural tuberculosis is one of the leading causes of exudative pleural fluid particularly in young patients in Turkey. In our study including homogenous distribution of patients in terms of being younger and older than 35 years of age, invasive procedures such as pleural biopsy was performed more commonly in older patient in order to eliminate possible underlying malignancy. However the diagnostic power of pleural biopsy was determined to be poor. Accordingly, after elimination of other causes of the exudate development, initiation of tuberculosis treatment based on ADA and cell count results seems reasonable.

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