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Original Article

Clinical Features of Pleural Tuberculosis

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Purpose: Pleural tuberculosis is a common and important disease in Taiwan. Previous studies have not focused on the sex differences of pleural tuberculosis. The purpose of the study was to elucidate the clinical features and sex difference in the presentation of pleural tuberculosis.

Method: We retrospectively reviewed the medical records of patients with pleural tuberculosis who initiated therapy at a regional hospital in northern Taiwan between January 2003 and March 2008. The identified characteristics were analyzed and compared in males and females.

Results: Thirty-three patients (24 males and 9 females) with a mean age of 65.8 ± 20.8 years were enrolled into our study. There was a much higher proportion of right pleural involvement than the left and bilateral cases (66.7% vs. 24.2% vs.9.1%), especially in females (88.9% vs. 11.1% vs. 0.0%). More male than female patients were former or current smokers (58.3% vs. 11.1%, p = 0.021), had concurrent pulmonary tuberculosis (37.5% vs. 0.0%, p = 0.039), and weakness (58.3% vs. 11.1%, p = 0.021). The neutrophil count was higher in males (6.0 ± 2.9 vs. 4.3 ± 1.4 × 10^9/L, p = 0.033). The creatinine level was also higher in males (107 ± 40 vs. 77 ± 19 μmol/L, p = 0.006).

Conclusion: Our study expands the knowledge of the clinical features of pleural tuberculosis. The patients with pleural tuberculosis are male-predominant and older in Taiwan. There are indeed sex differences in the presentation of pleural tuberculosis in Taiwan.

Key words: clinical feature, pleural tuberculosis, pulmonary tuberculosis, sex difference

Introduction

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*, remains an enormous global health problem. One-third of the world's population is estimated to be latently infected with *Mycobacterium tuberculosis*, and the majority of these cases and deaths occur in Asia[1]. Approximately 10% of those infected will develop active disease at some time in their life[2]. Tuberculosis is highly prevalent in Taiwan where the annual incidence of tuberculosis is 72.47 per 100000 population[3]. Tuberculosis is transmitted by coughed aerosol and usually presents with respiratory symptoms. However, it can produce disease in any organ system. Dissemination from the site of initial infection in the lung can take place at the time of primary infection or years later, when immunologic containment fails[4].

Extrapulmonary tuberculosis constitutes about 15-22% of all tuberculous cases[5,6]. In Taiwan, the

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extrapulmonary tuberculosis accounts for 23.0-27.0% of tuberculous cases[6]. Pleural tuberculosis is one of the leading two types of extrapulmonary tuberculosis[3,5,7]. It makes up about 59.5% of the extrapulmonary tuberculosis cases in Taipei[3,6]. Pleural tuberculosis arises from the rupture of the subpleural caseous foci in the lung into the pleural space within 6 to 12 weeks after a primary tuberculous infection[8,9], but it can occur years later with reactivation of the disease[7]. The common symptoms of pleural tuberculosis are fever, cough, pleuritic chest pain, and dyspnea [10]. The complications of pleural tuberculosis include pseudochylothorax, bronchopleural fistula, tuberculous empyema, and fibrothorax[10-12]. The patients with tuberculous empyema may require serial thoracocentesis, extrapleural pneumonectomy, or thoracoscopy[11].

Because pleural tuberculosis is an important common disease, we conducted a retrospective study to elucidate the clinical features of pleural tuberculosis. The previous studies have not investigated sex difference of pleural tuberculosis. Therefore, our study also intends to determine if there are sex differences in this disease.

Materials and Methods

In this single hospital-based and retrospective study, we reviewed medical records of all patients with pleural tuberculosis seeking care in a regional hospital in northern Taiwan between January 2003 and March 2008. The disease was diagnosed based on suspected symptoms of pleural tuberculosis and various diagnostic tests showing the characteristics of tuberculous infection. The criteria of diagnostic tests included pleural exudative effusion with lymphocyte predominance, pleural effusion culture yielding *Mycobacterium tuberculosis*, positive smear results for acid-fast bacilli, granulomatous inflammation in pleural biopsies, or adenosine deaminase levels higher than 40 U/L in pleural effusion. Only the patients initiating antituberculous therapy here were enrolled into our study. Those receiving initial treatments at other hospitals were excluded. We identified and analyzed basic characteristics, underlying diseases, the laterality, symptoms, laboratory data, diagnostic methods, and the treatments of the patients. All characteristics of males and females were compared.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 12.0.1 version. The difference of continuous variables between two groups was analyzed using independent samples t-test. The Chi-square test or the Fisher's exact test was used to evaluate the associations of categorical variables. A p value of less than 0.05 was considered significant. Continuous variables were presented as mean ± standard deviation.

Results

Thirty-three patients with the mean age of 65.8 ± 20.8 years (range 24 to 97 years) were enrolled into our study. Twenty four patients were males (72.7%) and 9 patients were females (27.3%). There were many more males than females in our study. The characteristics of our patients and the comparison of males and females are presented in Table 1. There was a significantly higher proportion of the former or current smoking in males than in females (58.3% vs. 11.1%, p = 0.021). The most common underlying diseases were hypertension (33.3%), heart disease (24.2%), and old cerebrovascular accidents (24.2%). The prevalence rates of underlying diseases other than chronic liver diseases and cerebrovascular accidents were higher in males than in females. There was no statistical significance in the prevalence differences between males and females. Nineteen male patients and 5 female patients had at least one kind of underlying disease (79.2% vs. 55.6%, p = 0.212). Four male patients had history of tuberculosis, and the sex difference was insignificant (16.7% vs. 0.0%, p = 0.555).

The presentations of our patients by male and female are presented in Table 2. Among our patients, the proportion of the right pleural involvement was much higher than the left and bilateral involvement (66.7% vs. 24.2% vs. 9.1%). The predominance of right pleural involvement was higher in females than in males, though the sex

Table 1. The characteristics of patients with pleural tuberculosis and the comparison of males and females

	All patients (n = 33)	Male (n = 24)	Female (n = 9)	p value
Basic characteristic				
Age (year)	65.8 ± 20.8	67.5 ± 18.6	61.1 ± 26.6	0.441
Body mass index (kg/m^2)	23.3 ± 4.3	23.7 ± 4.3	22.3 ± 4.2	0.428
Ever smoking	15 (45.5%)	14 (58.3%)	1 (11.1%)	0.021
Ever habitual drinking	8 (24.2%)	7 (29.2%)	1 (11.1%)	0.394
Underlying disease				
Hypertension	11 (33.3%)	9 (37.5%)	2 (22.2%)	0.681
Diabetes mellitus	6 (18.2%)	6 (25.0%)	0 (0.0%)	0.156
Dyslipidemia	5 (15.2%)	4 (16.7%)	1 (11.1%)	1.000
Hyperuricemia	7 (21.2%)	6 (25.0%)	1 (11.1%)	0.642
Heart disease	8 (24.2%)	6 (25.0%)	2 (22.2%)	1.000
Chronic obstructive pulmonary disease	5 (15.2%)	5 (20.8%)	0 (0.0%)	0.290
Chronic liver disease	3 (9.1%)	2 (8.3%)	1 (11.1%)	1.000
Renal disease	3 (9.1%)	3 (12.5%)	0 (0.0%)	0.545
Cerebrovascular accident	8 (24.2%)	5 (20.8%)	3 (33.3%)	0.651
History of tuberculosis	4 (12.1%)	4 (16.7%)	0 (0.0%)	0.555

difference was not significant (88.9% vs. 58.3%, p = 0.212). The most common symptoms were dyspnea (78.8%), cough (69.7%), and sputum (51.5%) in our patients with pleural tuberculosis. Twenty- four patients (72.7%) had constitutional symptoms, the most common being fever (51.5%), weakness (45.5%), and anorexia (36.4%). Significantly more male patients suffered from weakness than females (58.3% vs. 11.1%, p = 0.021). Nine male patients were identified as having concurrent active pulmonary tuberculosis. The prevalence rate of concurrent pulmonary tuberculosis was significantly higher in males than in females (37.5% vs. 0.0%, p = 0.039).

The laboratory data were analyzed by gender. The leukocyte count was not different between males and females (7.9 ± 3.0 vs. 6.7 ± 2.6 × 10^9/L, p = 0.310), but the neutrophil count was significantly higher in males than in females (6.0 ± 2.9 vs. 4.3 ± 1.4 × 10^9/L, p = 0.033). The creatinine level was also significantly higher in males than in females (107 ± 40 vs. 77 ± 19 μmol/L, p = 0.006). Other

Table 2. The presentations of patients with pleural tuberculosis and the comparison of males and females

	All patients (n = 33)	Male (n = 24)	Female (n = 9)	p value
Side				0.232
Only right side	22 (66.7%)	14 (58.3%)	8 (88.9%)	0.212
Only left side	8 (24.2%)	7 (29.2%)	1 (11.1%)	0.394
Bilateral sides	3 (9.1%)	3 (12.5%)	0 (0.0%)	0.545
Symptom				
Dyspnea	26 (78.8%)	19 (79.2%)	7 (77.8%)	1.000
Cough	23 (69.7%)	16 (66.7%)	7 (77.8%)	0.686
Sputum	17 (51.5%)	13 (54.2%)	4 (44.4%)	0.708
Chest pain	8 (24.2%)	7 (29.2%)	1 (11.1%)	0.394
Chest tightness	6 (18.2%)	5 (20.8%)	1 (11.1%)	1.000
Fever	17 (51.5%)	12 (50.0%)	5 (55.5%)	1.000
Weakness	15 (45.5%)	14 (58.3%)	1 (11.1%)	0.021
Anorexia	12 (36.4%)	9 (37.5%)	3 (33.3%)	1.000
Dizziness	3 (9.1%)	3 (12.5%)	0 (0.0%)	0.545
Weight loss	2 (6.1%)	2 (8.3%)	0 (0.0%)	1.000
Active pulmonary tuberculosis	9 (27.3%)	9 (37.5%)	0 (0.0%)	0.039

laboratory data were not significantly different in males and females patients.

The diagnosis of pleural tuberculosis was based on clinical features and the analysis of pleural effusion in 16 cases (48.5%), including 10 males and 6 females. Typical pathological findings of pleural biopsy for tuberculosis were found in 9 males (37.5%) and 3 females (33.3%). Positive finding for *Mycobacterium tuberculosis* culture, acid-fast bacilli, and adenosine deaminase measure were found in 5 males, 2 males, and 2 males in our study, respectively. The sex difference in positive results of the various diagnostic tools used in this study was insignificant.

Eighteen patients (54.5%) and 15 patients (45.5%) received 4 and 3 kinds of antituberculous drugs as initial therapy, respectively. Isoniazid, rifampicin, pyrazinamide, and ethambutol were prescribed to 100%, 97.0%, 81.8%, and 75.8% of our patients, respectively. The antituberculous therapy was continued for 7.9 ± 2.7 months (range 6 to 14 months). Acute hepatitis associated with antituberculous drugs was seen in one female patient. There was no sex difference in the treatment and the incidence rate of antituberculous drug-related hepatitis.

Discussion

The patients with pleural tuberculosis in our study are male-predominant (72.7%) and old (65.8 ± 20.8 years). Wang's epidemiologic study also revealed that males account for 64.5% of pleural tuberculous cases in Taipei[3]. However, the study of Valdes et al. about pleural tuberculosis conducted in Spain shows a much lower mean age (34.1 ± 18.1 years) and a lower male proportion (60.2%) [9]. The patients in the study of Ilgazli et al. are even younger (28.4 ± 14.4 years) and less male-predominant (54.2%) in Turkey[13]. One Brazilian study also documents the predominance of males (2:1)[14]. We confirm that pleural tuberculosis is more prevalent in males and the sex difference is more obvious in Taiwan than in Spain and Turkey, and possibly than Brazil. The different sex and age distribution of pleural tuberculosis in Taiwan and other countries is difficult to explain and needs further study to confirm. The diagnosis of pleural tuberculosis in older individuals can be problematic because these patients tend to have other conditions, such as pleural malignancy, that could be responsible for their pleural effusions [11]. For all patients in our study, change of diagnosis did not happen after the initial diagnosis of pleural tuberculosis.

The prevalence of smoking is much higher in males than in females in Taiwan. Thus, the finding that more male patients have former or current smoking than females (58.3% vs. 11.1%) in our study is not surprising. The prevalence of pulmonary tuberculosis is also higher in males than in females in Taiwan. In one single hospital-based study in Taiwan, the males accounted for 74.7% of patients with pulmonary tuberculosis[15]. The male-predominance in patients with pulmonary tuberculosis in our study may suggest that co-existing pulmonary tuberculosis is more prevalent in males than in females (37.5% vs. 0.0%).

In cases of pleural tuberculosis, chest radiography typically reveals unilateral pleural effusion in small-to-moderate amount[10]. Among our patients, the right pleural tuberculous involvement was much more prevalent than the left and bilateral involvement (66.7% vs. 24.2% vs.9.1%). The predominance of right pleural involvement was higher in females than in males (88.9% vs. 58.3%). Our finding differs from the observation of Valdes et al., who reported 55.9%, 42.5%, and 1.6% of pleural tuberculosis were on the right side, on the left side, and on both sides, respectively[9]. In Turkey, a study of Ilgazli et al. reported that 51.5%, 47.5%, and 1.0% of pleural tuberculosis were on the right side, on the left side, and on bilateral sides, respectively[13]. Why more cases of pleural tuberculosis are on the right and bilateral in Taiwan is difficult to explain and needs further studies to confirm.

In our study, the most common symptoms related to the pleural and pulmonary involvement of tuberculosis are dyspnea, cough, and sputum. The most common constitutional symptoms are fever, weakness, and anorexia. More male patients have weakness than females (58.3% vs. 11.1%). The incidence rate of concurrent pulmonary

tuberculosis was also significantly higher in males than in females (37.5% vs. 0.0%). The sex differences in suffering from weakness and concurrent pulmonary tuberculosis in pleural tuberculous cases is not seen in literature.

Pleural tuberculosis is not always easy to diagnose because the criteria of common diagnostic tools are not invariably satisfied[9,16-18]. Multiple diagnostic tests are administrated concurrently to improve the diagnostic efficiency, but diagnosis is still sometimes difficult[9]. In our study, the diagnosis of pleural tuberculosis depended on the physician considering the possibility of tuberculosis in patients at risk and submitting material for mycobacterial culture and pathological examination. The diagnostic tools used for our patients include pleural fluid examination, pleural biopsy, mycobacterial culture, smear for acid-fast bacilli, and adenosine deaminase, in frequency of the number of positive yields. Those other than the pleural fluid examination were not administered extensively in our study. Tuberculosis is highly prevalent and pleural tuberculosis is the most common type of extrapulmonary tuberculosis in Taiwan. Tuberculosis is frequently seen by physicians and usually one of the leading differential diagnoses in many situations in Taiwan, especially in a regional hospitals like ours. This is why the diagnosis of pleural tuberculosis is often made with only clinical features and pleural fluid analysis.

In patients with untreated pleural tuberculosis, the pleural effusion may spontaneously resolve in 4 to 16 weeks, but active pulmonary or extrapulmonary tuberculosis may develop in 43 to 65% of cases over the next several years[19,20]. These findings emphasize the importance of proper diagnosis and treatment of pleural tuberculosis[21]. A six- to nine-month regimen with all of isoniazid, rifampin, pyrazinamide, and ethambutol as initial therapy is recommended for pleural tuberculosis[10]. In our study, 45.5% of patients received only three kinds of antituberculous drugs as initial therapy. Isoniazid, rifampicin, pyrazinamide, and ethambutol were prescribed to 100%, 97.0%, 81.8%, and 75.8% of our patients initially, respectively. The incomplete adherence of guidelines suggesting all four drugs as initial therapy might be attributed to the limited types of combo drugs. In our hospital, one available combo drug contains isoniazid, rifampicin, and pyrazinamide, and the other contains only isoniazid and rifampicin. In our observation, physicians preferred to prescribe combo drugs because the treatment regimens containing combo drugs can decrease the number of pills and improve the compliance of patients. The limited contents of available combo drugs may result in the less prescription of pyrazinamide and ethambutol in our study. Thus, we look forward to the development of combo drugs containing the above 4 drugs.

The low incidence rate of pleural tuberculosis makes the single hospital-based study difficult. The main limitation of our study is the small sample size. We could identify only 33 patients with pleural tuberculosis who initiated treatment at this regional hospital in a period of 5 years and 3 months. The small sample size may limit the statistical power of our data. Future prospective and maybe multi-center based studies are needed to expand the sample size and further explore the clinical features of pleural tuberculosis and the sex difference.

In conclusion, our study expands our knowledge about the clinical features of pleural tuberculosis. There is indeed sex difference in pleural tuberculosis. The patients with pleural tuberculosis are male-predominant and older in Taiwan. The right pleural involvement was much more prevalent than left and bilateral involvement, especially in females. More male patients have former or current smoking, concurrent pulmonary tuberculosis, and weakness than females. The neutrophil count and the creatinine level are also higher in males.

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Original Article

肋膜結核之臨床特徵

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目的：肋膜結核是台灣的盛行及重要疾病，以往的研究並未探討肋膜結核的性別差異性。本研究的目的在探討肋膜結核的臨床特徵與性別差異性。

方法：我們回溯式檢視2003年一月至2008年三月間北台灣某區域醫院肋膜結核病患的病歷，分析病患的臨床特徵與性別差異性。

結果：本研究共回顧33位病患（24位男性與9位女性）的病歷，其平均年齡為65.8 ± 20.8歲。右側肋膜侵犯的比率遠高於左側及兩側侵犯（66.7% vs. 24.2% vs.9.1%），尤其是女性病患（88.9% vs. 11.1% vs. 0.0%）。男性病患比女性病患較常有吸煙史（58.3% vs. 11.1%，p = 0.021）、並存的肺結核（37.5% vs. 0.0%，p = 0.039）、以及虛弱無力的症狀（58.3% vs. 11.1%，p = 0.021）。男性病患的嗜中性白血球數目（6.0 ± 2.9 vs. 4.3 ± 1.4 × 10^9/L，p = 0.033）及肌酸酐（107 ± 40 vs. 77 ± 19 μmol/L，p = 0.006）比女性病患高。

結論：本研究增加了對於肋膜結核臨床特徵的認識，台灣的肋膜結核病患以男性為主且年紀較大，肋膜結核存在著性別差異性。

關鍵詞：臨床特徵、肋膜結核、肺結核、性別差異性

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