Original Article

Clinical and pathological differences between polymorphonuclear-rich and lymphocyte-rich tuberculous pleural effusion

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Abstract:

OBJECTIVE: Analysis of the occurrence factors and disease characteristics of tuberculous (TB) pleural effusion (TPE) dominated by neutrophils.

METHODS: We retrospectively analyzed the clinical data of 304 patients with two types of TB pleurisy. The clinical, laboratory, and pathological features of TB pleurisy separately dominated by lymphocytes and neutrophils were analyzed.

RESULTS: Neutrophil-predominant effusion was observed in 33 (10.9%) patients. The patients with TPE with polymorphonuclear leukocytes (PMNLs) had higher fever rates and higher decortication rates than those with lymphocyte-predominant TPE. Otherwise, they had lower chest distress rates and lower positive rates of pulmonary TB and lower biopsy tissue culture-positive rates than patients with lymphocyte-predominant TPE. PMNL TPE patients had higher lactic acid dehydrogenase (LDH) (1297 vs. 410 U/l, $P < 0.001$) and adenosine deaminase (ADA) levels (54.1 vs. 42.9 U/l, $P = 0.043$) and lower pleural fluid glucose (1.92 vs. 4.70 mmol/L, $P < 0.001$) and protein (47.4 vs. 48.4 g/L, $P = 0.024$) levels than that of lymphocyte-predominant TPE. Otherwise, they had lower blood ALB levels and higher C-reactive protein levels than lymphocyte-predominant TPE. Finally, PMNL TPE patients had lower rates of granuloma formation (27.2% vs. 75.2%, $P < 0.001$) and pleural nodules than patients with lymphocyte-predominant TPE and more frequent findings of pus, caseous exudate, and necrosis.

CONCLUSION: The TB pleurisy patients dominated by neutrophils show strong inflammatory reactions and higher ADA levels in pleural effusion. These findings can significantly improve the positive rate of *Mycobacterium tuberculosis* in neutrophil-predominant TPE under thoracoscopy.

Keywords:

Adenosine deaminase, lactate dehydrogenase, thoracoscopy, tuberculous granuloma, tuberculous pleural effusions

Tuberculous (TB) pleurisy is one of the most common causes of pleural effusion in developing countries and the second most common type of extrapulmonary tuberculosis.[1,2] At present, the cause of TB pleurisy is the invasion of *Mycobacterium tuberculosis* (MTB) into the thoracic cavity and delayed-type hypersensitivity in the thoracic cavity.[3,4] The two mainstream methods for the diagnosis of pleural tuberculosis have shortcomings: one is the low positive rate and sensitivity of direct detection of acid-fast bacilli (AFB) (20%), and the other is the slow growth of MTB in pleural fluid culture. Therefore, although the presence of tuberculosis granuloma can be confirmed in up to 80% of pleural biopsy specimens,[5,6] this method is not ideal for the diagnosis of pleural tuberculosis. The increase in the number of lymphocytes in

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pleural effusion extracted from the pleural cavity is considered to be one of the diagnostic criteria of pleural tuberculosis. However, in many cases, the main type of pleural effusion is the elevation of neutrophils rather than lymphocytes. This discovery makes the diagnosis difficult and complicated. Clinically, we often see that patients with early elevated neutrophils in pleural effusion are not considered to be tuberculosis patients, resulting in delays in diagnosis and treatment. Therefore, early diagnosis and active treatment have important clinical and epidemiological significance to improve the prognosis of patients and to prevent further transmission among people. Therefore, it is very important to understand the clinical factors of TB pleurisy in patients with pleural effusion dominated by elevated neutrophils.

At present, there have been a number of studies on this subject. In a retrospective study of 354 cases of TB pleural effusion (TPE), 39 cases (11%) were rich in polymorphonuclear leukocytes (PMNLs) in pleural effusion. Weight loss, initial white blood cell (WBC) count <11 × 109/L, and poor clinical response to empirical antituberculosis therapy in the first 3 days were compared between the 39 patients with PMNL TPE and the control group with nonmycobacterial PMNL fluid. These three clinical features were independent predictors of risk for tuberculosis.[7] Light *et al*. also reported that 24 patients (11%) had higher levels of mycobacteria and pleural adenosine deaminase (ADA) in sputum and pleural fluid cultured in solid medium than those with elevated lymphocytes in pleural effusion during the first pleural puncture. Therefore, when exudate dominated by PMNL is found in the pleural effusion of patients, TPE cannot be excluded, especially when the pleural ADA activity increases; thus, more vigilance is required. For such patients, sputum and pleural effusion samples should be collected for mycobacterial culture as soon as possible, as the results of these two tests are positive in the early stage of tuberculosis, which is helpful for early diagnosis.[8]

Thus far, there have been few studies on the clinical and laboratory characteristics of neutrophil-based pleural effusion caused by MTB, especially under video-assisted thoracoscopy. In this context, the purpose of this study was to analyze the results of serum, sputum, pleural effusion, pleural biopsy, and video-assisted thoracoscopy. The pathogenic factors and disease characteristics of TPEs dominated by neutrophils were further described.

Methods

Subjects

This study has been reviewed and approved by the Medical Ethics Committee of the Shandong Provincial Chest Hospital (2019XKYYEC-14), and informed consent was deemed unnecessary. Retrospective analysis of 304 patients (age ≥8 years) with newly diagnosed TB pleurisy was performed. All patients were human immunodeficiency virus-negative and were diagnosed and treated with thoracoscopy from July 2013 to July 2018 in Shandong Provincial Chest Hospital in Jinan, PRC. All patients underwent pleural tissue inspections (including diaphragmatic pleura). These cases meet the criteria for the diagnosis of TB pleurisy, and patients were diagnosed with TB pleurisy based on the following criteria: (1) AFB smear was positive, pleural fluid was used as the source specimen, and the tuberculosis bacterium was grown in the culture medium, or the tuberculosis bacterium was detected by polymerase chain reaction (PCR); (2) In the absence of granulomatous lung disease for other reasons, a pleural biopsy revealed a granulomatous lesion with or without caseous necrosis; and (3) The sputum culture of tuberculosis was positive, and the pleural effusion improved after antituberculosis treatment. Probable pleural tuberculosis is defined as lymphocyte exudate with ADA >40 IU/L in the absence of evidence of malignancy and improves after antituberculosis treatment.[4]

When the percentage of lymphocytes or neutrophils in the total number of liquid leukocytes is greater than 50%, it is defined as a predominance of lymphocytes and neutrophils. Monocytes, basophils, and eosinophils are classified as "other" cell types.

Microbiological tests

We performed AFB staining with auramine–rhodamine fluorescent stain and then confirmed with Ziehl–Neelsen staining. We graded the staining results according to the American Thoracic Society/Centers for Disease Control and Prevention guidelines.[9] Then, specimens classified with AFB smear staining results in Grades 1–4 were defined as smear-positive. All clinical specimens were cultured on solid and liquid media for 6 weeks. We inoculated the decontaminated samples into a mycobacterium growth indicator tube (MGIT 960 system; Becton Dickinson, Sparks, MD) and inoculated onto 3% Ogawa agar (Shenyang, Seoul, Korea). All positive cultures were examined by AFB smear to confirm the presence of AFB and to rule out contamination. The Cobas TaqMan MTB test (Cobas MTB test) (Roche Diagnostics, Basel, Switzerland) is a real-time PCR method for analyzing sputum and pleural effusion samples.[9]

Data collection

Data on sex, age, clinical manifestations (fever, chest distress, chest pain, productive cough, and complications), anti-TB body test in pleural fluid and serum, microbiological tests (staining and culture of mycobacterium in sputum and pleural effusion), pleural fluid (WBC counts and differential counts, lactate dehydrogenase, ADA,

glucose and protein), pleural biopsy, and pathological results were collected under thoracoscopy. We also collected radiological data (the size of the pleural effusion, the presence of the pleural atrioventricular node, pulmonary infiltration on chest radiography); computed tomography scans were also collected if conditions permitted. Weight loss was defined as a loss of more than 10% of body weight in the past 6 months. In patients undergoing repeated thoracentesis, we used only the initial pleural effusion cell count and profiles for statistical analysis. However, pleural fluid-related clinical indicators (WBC counts and differential counts, lactate dehydrogenase, ADA, glucose, and protein) were collected in the TB pleurisy patients dominated by neutrophils undergoing repeated thoracentesis.

Statistical analysis

Continuous variables are represented by medians and interquartile ranges, and categorical variables are represented by frequencies (percentages). Due to nonnormality, continuous variables were compared using the Mann–Whitney U-test, and categorical variables were compared with Pearson's Chi-square test or Fisher's exact test. When the expected value in any cell of the contingency table was lower than five, we used Fisher's exact test instead of Pearson's Chi-square test. The Pearson test was used for correlation analysis, and the Spearman test was used for nonnormally distributed data. Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc., Chicago, Illinois, USA). $P < 0.05$ was considered statistically significant.

Results

In this study, a total of 304 TPE patients were selected consecutively: 232 (76.3%) of them were diagnosed with TB pleurisy, and the remaining 72 might have tuberculosis. A total of 33 cases (10.9%) of pleural effusion showed neutrophil infiltration [Figure 1].

Clinical characteristics analysis

Table 1 shows the demographics and clinical characteristics of the 304 patients with TB pleurisy. The clinical characteristics of TB pleurisy, mainly consisting of lymphocytes and neutrophils, were also analyzed. A total of 75.0% of participants were male. The average age was 35.08 ± 14.55 years old. The average duration of signs and symptoms of the disease at the time of thoracoscopy was 1.76 ± 2.11 months. Common symptoms included fever (76.3%), cough (75.3%), sputum production (40.0%), respiratory distress (66.4%), chest pain (60.9%), night sweats (37.5%), and debility (41.1%). Emaciation was found in 13.2%. The pleural effusions were mostly unilateral (95.1%), with bilateral effusions occurring in only 4.9%. The patients with PMNL-predominant TPE had higher high fever rates (51.5% vs. 32.4%, $P = 0.03$) and higher decortication rates (15.2% vs. 4.06%, $P = 0.007$) than those with lymphocyte-predominant TPE. In addition, the patients with PMNL-predominant TPE had lower chest distress rates (48.5% vs. 68.6%, $P = 0.021$) and lower positive rates of pulmonary TB (42.8% vs. 60.8%, $P = 0.037$).

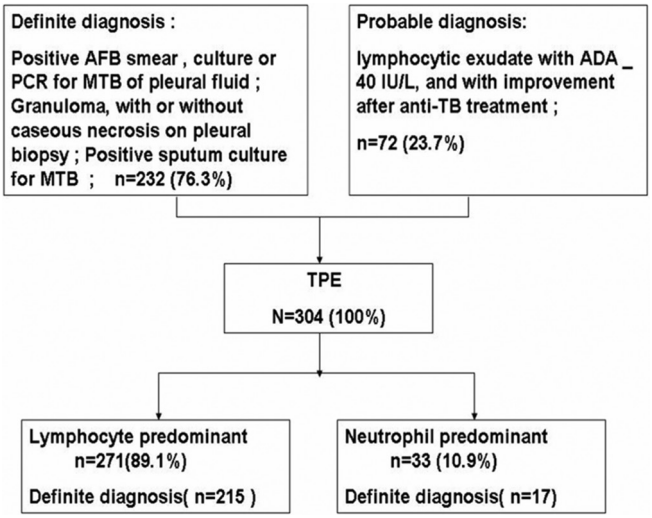

Figure 1: Groupings of the study population according to diagnostic criteria and cell type predominance

Microbiological and laboratory differences

The total positive rate of pleural biopsy tissue TB culture was 59.9%. The total positive rates of the TB antibody test in serum (26.8%) and pleural fluid (59.6%) were relatively higher. The total positive rate of pleural fluid TB smear was only 2.2%, while in pleural fluid TB culture, the positive rate was 19.9%; the total positive rate of TB in sputum smear was only 2.9%, while in sputum culture, the positive rate was 15.3% [Table 2]. Compared with healthy adults, the ADA levels in pleural effusion of both types of tuberculosis were significantly higher; elevated pleural fluid ADA >40 U/L was observed in 62.2% of patients and 71.1% of the PMNL patients. Table 2 shows the differences in microbiological and laboratory tests between patients with pleurisy dominated by lymphocytes and neutrophils. The patients with PMNL had lower biopsy tissue culture-positive rates (36.4% vs. 62.7%, $P = 0.01$) than those with lymphocyte-predominant TPE. PMNL-predominant TPE patients had higher lactic acid dehydrogenase (LDH) (1297 vs. 410 U/l, $P < 0.001$) and ADA levels (54.1 vs. 42.9 U/l, $P = 0.043$) and lower pleural fluid glucose (1.92 vs. 4.70 mmol/L, $P < 0.001$) and protein (47.4 vs. 48.4 g/L, $P = 0.024$) than patients with lymphocyte-predominant TPE. Otherwise, the patients with PMNL-predominant TPE had lower blood ALB levels (32.0 vs. 36.1 g/L, $P = 0.041$) and higher C-reactive protein (CRP) levels (27.5 vs. 12.0 mg/dL, $P < 0.001$) than patients with lymphocyte-predominant TPE.

Table 1: Comparison of clinical characteristics between lymphocyte-predominant and neutrophil-predominant tuberculous pleurisy

	Total (*n*=304)	Neutrophil-predominant (*n*=33)	Lymphocyte-predominant (*n*=271)	*P*
Age	35.08±14.55	38.70±14.04	34.64±14.58	0.131
Sex (male)	228/304 (75.0)	28/33 (84.8)	200/271 (73.8)	0.166
Cough	229/304 (75.3)	25/33 (75.6)	204/271 (75.3)	0.952
Expectoration	121/304 (40.0)	17/33 (51.5)	104/271 (38.3)	0.145
Chest distress	202/304 (66.4)	16/33 (48.5)*	186/271 (68.6)	0.021
Chest pain	185/304 (60.9)	20/33 (60.6)	165/271 (60.8)	0.975
Night sweats	114/304 (37.5)	11/33 (33.3)	103/271 (38.0)	0.601
Fatigue	125/304 (41.1)	13/33 (39.4)	112/271 (41.3)	0.831
Emaciation	40/304 (13.2)	5/33 (15.2)	35/271 (12.9)	0.720
Fever	232/304 (76.3)	27/33 (81.8)	205/271 (75.6)	0.431
High fever (≥39°C)	105/304 (34.5)	17/33 (51.5)*	88/271 (32.4)	0.030
Duration of illness (month)	1.76±2.11	2.29±1.89	1.69±2.13	0.125
Underwent decortication	16/304 (5.3)	5/33 (15.2)**	11/271 (4.06)	0.007
Pulmonary TB	180/304 (59.2)	14/33 (42.8)*	166/271 (60.8)	0.037
Confirmed diagnostic rate	232/304 (76.1)	17/33 (51.5)**	215/271 (79.3)	<0.001

Compared with the lymphocyte-predominant group. *P<0.05, **P<0.01. TB=Tuberculous

Table 2: Microbiological and laboratory differences between lymphocyte-predominant and neutrophil-predominant tuberculous pleurisy

	Total (*n*=304)	Neutrophil-predominant (*n*=33)	Lymphocyte-predominant (*n*=271)	*P*
Biopsy tissue culture positive rate	182/304 (59.9)	12/33 (36.4)*	170/271 (62.7)	0.010
Blood TB antibody positive rate	60/224 (26.8)	6/27 (22.2)	54/197 (27.4)	0.568
Pleural fluid TB antibody positive rate	164/275 (59.6)	19/31 (61.3)	145/244 (59.4)	0.842
Sputum culture	29/190 (15.3)	3/22 (13.6)	26/168 (15.5)	0.821
Sputum smear	6/210 (2.9)	1/29 (3.45)	5/181 (2.76)	0.837
Pleural fluid culture	53/267 (19.9)	8/30 (26.7)	45/237 (18.9)	0.320
Pleural fluid smear	6/270 (2.2)	1/31 (3.22)	5/239 (2.09)	0.687
Pleural fluid protein (g/L)	48.1 (44.3-51.6)	47.4 (38.5-49.3)*	48.4 (44.6-51.7)	0.024
Pleural fluid glucose (mmol/L)	4.56 (2.79-5.60)	1.92 (0.10-3.79)**	4.70 (3.09-5.67)	<0.001
Pleural fluid LDH (U/L)	446 (278-836)	1297 (542-2360)**	410 (272-746)	<0.001
Pleural fluid ADA (U/L)	43.1 (32.5-58.1)	54.1 (33.0-82.3)*	42.9 (32.1-56.8)	0.043
Blood ALB (g/L)	35.9 (31.5-38.6)	32.0 (27.5-38.8)*	36.1 (33.5-38.8)	0.041
Blood ESR (mm/h)	51.5 (27.1-67.7)	53.0 (26.8-71.1)	42.0 (21.5-63.0)	0.391
Blood CRP (mg/dL)	14.6 (8.7-24.5)	27.5 (24.0-35.0)**	12.0 (7.8-22.4)	<0.001
Blood WBC (10^9/L)	7.24 (5.47-9.10)	8.09 (6.87-10.47)*	6.96 (4.77-7.78)	0.011
Blood CD4/CD8	2.14±1.96	1.64±0.76	2.32±2.22	0.406

Compared with lymphocyte-predominant group. *P<0.05, **P<0.01. TB=Tuberculous, LDH=Lactic acid dehydrogenase, ADA=Adenosine deaminase, CRP=C-reactive protein, WBC=White blood cell, ALB=Albumin, ESR: Erythrocyte sedimentation rate

Pathological pattern data

Table 3 shows the differences in pathological changes in pleural tuberculosis patients dominated by lymphocytes and neutrophils under thoracoscopy. One or more abnormalities could be observed on the surface of the pleura under thoracoscopy in all patients. As shown in Figure 2 and Table 3, 84 cases (27.6%) of loculation of pleural fluid, 218 cases (71.7%) of pleural adhesions, 157 cases (51.6%) of pleural thickening, 127 cases (41.8%) of pleural nodules, 77 cases of pleural isolation (25.3%), 50 cases of pleural closure (16.4%) 21 cases of purulent moss (6.9%), 23 cases of caseous necrosis (7.6%), 57 cases of with a jelly-like appearance (18.8%), 106 cases of inflammation or necrosis (34.9%), and 213 cases of granuloma (70.1%) were observed. Loculation of pleural fluid was also found in the PMNL-predominant TPE (27.3%), which is similar to lymphocyte-predominant TPE. The above pleural abnormalities were widely distributed on the surface of the affected pleura. Thoracoscopic pleural biopsy showed a rate of 27.2% granuloma in the patients with PMNL-predominant TPE, which was much lower than that of lymphocyte-predominant TPE (27.2% vs. 75.2%, $P < 0.001$). In the pleural effusions dominated by neutrophils, the percentages of purulent moss, caseous necrosis, inflammation or necrosis detected by thoracoscopy were 18.1%, 27.3%, and 69.7%, respectively, which were significantly higher than those of purulent moss dominated by lymphocytes (27.3% vs. 4.43%, $P < 0.001$), caseous necrosis (18.1% vs. 6.27%, $P < 0.001$), and inflammation or necrosis (69.7% vs. 30.6%, $P < 0.001$). The positive rate of MTB detected by the noninvasive

Table 3: Thoracoscopic visual pattern differences between lymphocyte-predominant and neutrophil-predominant pleural effusions

	Total (*n*=304)	Neutrophil-predominant (*n*=33)	Lymphocyte-predominant (*n*=271)	*P*
Thoracoscopy				
Loculation of pleural fluid	84/304 (27.6)	9/33 (27.3)	75/271 (27.7)	0.961
Pleural adhesions	218/304 (71.7)	26/33 (78.7)	192/271 (70.8)	0.339
Pleural thickening	157/304 (51.6)	19/33 (57.5)	138/271 (50.9)	0.470
Pleural nodules	127/304 (41.8)	8/33 (24.2)*	119/271 (43.9)	0.031
Pleural isolation	77/304 (25.3)	12/33 (36.4)	65/271 (23.9)	0.123
Pleural shutting	50/304 (16.4)	5/33 (15.2)	45/271 (16.6)	0.832
Pus substance	21/304 (6.9)	9/33 (27.3)**	12/271 (4.43)	<0.001
Caseous exudate	23/304 (7.6)	6/33 (18.1)*	17/271 (6.27)	0.015
Gelatin content	57/304 (18.8)	7/33 (21.2)	52/271 (19.2)	0.781
Pathological type				
Inflammation or necrosis	106/304 (34.9)	23/33 (69.7)**	83/271 (30.6)	<0.001
Tuberculous granuloma	213/304 (70.1)	9/33 (27.2)**	204/271 (75.2)	<0.001

Compared with the lymphocyte-predominant group. *P<0.05, **P<0.01

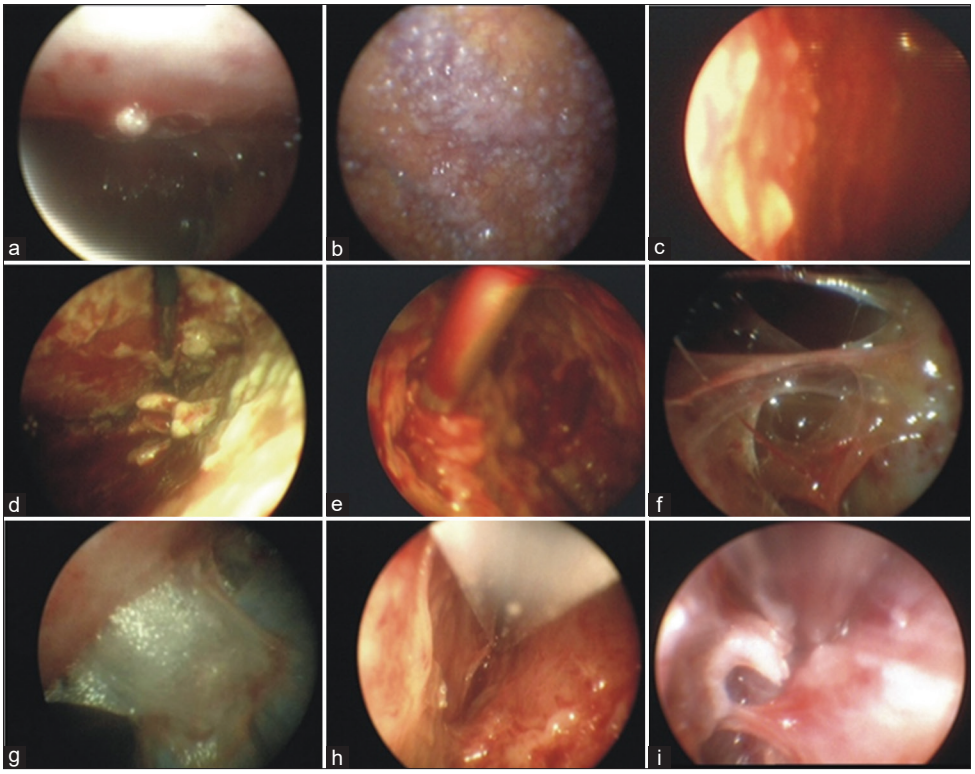

Figure 2: Thoracoscopy changes under thoracoscopy. (a-c) Pleural nodules. (d-f) Caseous necrosis and (or) purulent moss formation and fibrinous exudate. (g-i) Pleural thickening and (or) pleural atresia

method was 19.2%. In the invasive method, the positive rate of MTB in thoracoscopic tissue culture was 36.8%, and the positive rate of granuloma in pathological section was 27%.

Table 4 shows biochemical changes of sequential pleural effusions in 21 patients with PMNL-predominant TPE. In 21 patients with PMNL-predominant TPE, the median time of the second thoracotomy was 7 days (range 5–21 days), and the percentage of median lymphocytes in the hydrothorax increased (30% vs. 10%, P < 0. 001), as did the glucose level (3.49 vs. 1.92, P = 0.005) [Table 4]. The concentrations of LDH (1034 vs. 1440 U/L, P = 0.203) and ADA (46.3 vs. 54.1 U/L, P = 0.491) showed a downward trend, but there was no significant difference. In 9 (42.8%) cases, the pleural fluid was found to have changed to lymphocytic predominance after repeated thoracentesis.

Discussion

TB pleurisy is a form of extrapulmonary tuberculosis

Table 4: Biochemical changes in sequential thoracenteses of 21 patients with neutrophil-predominant pleural effusions (*n*=21)

Pleural fluid Parameter	First thoracentesis	Second thoracentesis	*P*
Lymphocytes (%)	10 (6.5-15)	30 (20-65)**	<0.001
Pleural fluid protein (g/L)	47.6 (37.2-49.4)	46.7 (43.4-51.0)	0.403
Pleural fluid glucose (mmol/L)	1.92 (0.10-3.85)	3.49 (2.77-4.57)**	0.005
Pleural fluid LDH (U/L)	1440 (524-2644)	1034 (613-1722)	0.203
Pleural fluid ADA (U/L)	54.1 (33.3-82.3)	46.3 (38.1-68.3)	0.491

Compared with the first thoracentesis group. *P<0.05, **P<0.01. LDH=Lactic acid dehydrogenase, ADA=Adenosine deaminase

that is difficult to diagnose clinically. Lymphocyte-based exudate and high ADA index have been considered to be a part of the diagnostic criteria for TB pleurisy. However, in most cases, neutrophils rather than lymphocytes are the predominant cell type of TB pleurisy exudate. The diagnosis of the disease is complicated by the different cell types in the pleural effusion. Recent studies have reported that the ratio of TPE dominated by PMNL has increased.[7,8] In our study, we found that a neutrophil-predominant effusion was observed in 33 (10.9%) TB pleurisy patients, which was consistent with the results of previous studies.[7,8] In this regard, we conducted a more detailed analysis of PMN-predominant TPE, and the results showed that patients with PMNL-predominant TPE had a higher rates of high fever and decortication than those with lymphocyte-predominant TPE. PMNL-predominant TPE fluid patients had higher LDH levels and lower pleural fluid glucose concentrations and higher blood WBC and CRP levels. PMNL-predominant TPE patients had lower rates of granuloma formation and pleural nodules and more frequent findings of pus, caseous exudate, and necrosis. These results suggest that patients with PMNL-predominant TPE have a high-intensity inflammatory response in the systemic circulation and pleural cavity compared with those with lymphocyte-predominant TPE. This is partly consistent with a previous study,[8] but we reported for the first time that patients with PMNL-predominant TPE have high-intensity inflammatory responses in the pleural space under thoracoscopy, which provides us with a more in-depth understanding of this phenomenon.

Microbiologically, our study showed that PMNL fluid had lower biopsy tissue culture-positive rates than lymphocyte-predominant TPE, and this is also the first report where patients with PMNL-predominant TPE were diagnosed by pleural biopsy. Our study found that PMNL-predominant TPE had no differences in sputum and pleural effusion cultures or in AFB-positive sputum and pleural effusion staining, inconsistent with the results of a previous study.[8] These results also demonstrated that it is difficult to diagnose PMNL-predominant TPE. The reason for the difference may be that sputum and pleural fluid were obtained at different times after TB onset. In previous studies, PMPE-predominant TPE produced MTB in sputum and pleural effusion cultures at higher levels than lymphocyte-predominant TPE because the specimen was acquired in the early stages of the disease when the infectivity was high. Accordingly, the sputum and pleural fluid used in our study were obtained relatively late, and their infectivity had weakened. Therefore, there was no difference in sputum and pleural fluid culture or in AFB-positive sputum and pleural fluid staining between neutrophil- and lymphocyte-predominant TPE. Another reason for the differences may be that in a previous study, the MTB samples were coinfected with other bacteria, making sputum and pleural fluid neutrophil-predominant. These results suggest that microbiological testing should be conducted as early as possible.

Frequently, the loculation of pleural fluid may indicate TPE, with an incidence between 22% and 32%.[10-13] In addition, Ko *et al*.[14] pointed out that it is necessary to distinguish TB pleurisy from a parapneumonic effusion (PPE). In our study, we found that pleural effusion also occurred in 27.3% of neutrophil TPE patients, as seen in lymphocyte TPEs. This finding is consistent with a previous study.[10] Even in neutral pleural effusion, ADA levels of pleural fluid are useful parameters for diagnosing TPE. In PPE, the levels rarely exceed the cutoff value of ADA in TPE unless the condition develops into an advanced form, such as a complex PPE or empyema.[15] Similar to our previous studies, in our current study, we found that the mean level of ADA was above 40 U/L in TPE patients and was markedly higher in neutrophilic pleural effusions. Therefore, a higher ADA level in neutrophilic pleural effusions indicates that these patients may have TB pleurisy. As there is an increase in the ADA level in neutrophilic pleural effusions or the cases of frequent loculation of pleural fluid, the pleural effusion dominated by neutral granules may be TB pleurisy. Therefore, ADA has been identified as a marker of cell-mediated immune responses, including delayed hypersensitivity. TB pleurisy must be included in the differential diagnosis, and a quick sputum and pleural examination of possible TB pleurisy should be performed, especially in areas with a high incidence of tuberculosis. In TPE dominated by neutrophils, we should consider TB pleurisy, and

microbiological examination should be performed. Moreover, we should take more precautionary measures to prevent the transmission of tuberculosis.

In patients with TB dominated by neutrophils in the hydrothorax, we used traditional noninvasive methods (sputum culture, sputum smear, and hydrothorax culture). Compared with invasive methods (thoracoscopic tissue culture of MTB and pathological section for granuloma), the positive rate of MTB detected by the noninvasive method was 19.2%. In the invasive method, the positive rate of MTB in thoracoscopic tissue culture was 36.8%, and the positive rate of granuloma in pathological sections was 27%. Moreover, the positive rate of MTB was 42.1% when the tissues were taken by thoracoscopy and cultured under thoracoscopy. The above results indicate that the positive rate of TB in thoracoscopic biopsies is much higher than that of traditional noninvasive methods.

According to the traditional concept of the pathogenesis of TB pleurisy, the dominant characteristics of lymphocytes and neutrophils are continuous stages in the development of TB pleurisy. In this model, early TB pleurisy is characterized by a rapid inflammatory response of neutrophils in the pleura, followed by a lymphocyte-driven immune response and pleural granuloma formation.[16] However, our results suggest that at the second pleural puncture, not all patients convert to lymphocyte-predominated pleural effusion. It has been reported that not all patients can be converted to lymphocyte-dominated pleural effusion during repeated pleural effusion analysis.[8] However, due to the lack of accurate data on the time interval between the onset of symptoms (such as chest pain) and the first pleural puncture, it is not clear whether PMNL-predominant TPE differs from the sequelae of pleural tuberculosis or represents early disease.

Conclusion

Overall, this study depicted that the TB pleurisy patients dominated by neutrophils show strong inflammatory reactions and higher ADA levels in pleural effusion. These findings can significantly improve the positive rate of Mycobacterium tuberculosis in neutrophil-predominant TPE under thoracoscopy. Meanwhile, our study also has some limitations. First, since this study is a cross-sectional retrospective clinical study, selection bias or confounding factors may influence our results. In addition, there are no accurate data on the time span between symptom onset and thoracotomy. Finally, our subjects were collected from a referral center. More clinical studies are needed to further demonstrate whether our findings can be applied to all cases of pleural tuberculosis.

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Conflicts of interest

There are no conflicts of interest.

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