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Atypical Pleural Fluid Profiles in Tuberculous Pleural Effusion: Sequential Changes Compared with Parapneumonic and Malignant Pleural Effusions

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Abstract

Objective Although tuberculous pleural effusion (TPE) is commonly characterized by lymphocytic predominance and high adenosine deaminase (ADA) levels, it may present with neutrophilic predominance or low ADA levels, which are more commonly found in parapneumonic effusion (PPE) or malignant pleural effusion (MPE), respectively. A few studies have observed that the atypical pleural fluid profiles of these cases of TPE may resolve at follow-up thoracentesis. However, these observations were incompletely analyzed and lacked comparison with proper control groups. Thus, limited data are available comparing the sequential pleural fluid changes between TPE and PPE or MPE with similar pleural fluid profiles.

Methods TPE, PPE, and MPE patients who underwent sequential thoracentesis were retrospectively reviewed. The sequential changes in the pleural fluid profiles were compared between neutrophilic TPE and PPE, and lymphocytic TPE and MPE with low ADA levels.

Results Twenty-three TPE patients (16 with neutrophilic exudates, seven with lymphocytic exudates), 72 cases of PPE with neutrophilic exudates, and 18 cases of MPE with lymphocytic exudates were included in the analysis. A sequential shift to lymphocytic exudates occurred significantly more often in TPE than in PPE cases. The initial and follow-up ADA levels in TPE cases with a lymphocytic shift were significantly higher than those in PPE cases with a lymphocytic shift. The ADA levels in the TPE cases with initial lymphocytic exudates and low ADA levels significantly increased at follow-up thoracentesis. For the TPE and MPE cases with initial lymphocytic exudates and ADA levels <40 U/L, the frequency of effusion with ADA levels ≥40 U/L at the second thoracentesis was significantly higher in the TPE cases.

Conclusion Follow-up thoracentesis may provide useful information for clinical decision-making in suspected atypical TPE cases with neutrophilic exudates or low ADA levels.

Key words: adenosine deaminase, tuberculous pleural effusion, parapneumonic pleural effusion, malignant pleural effusion, sequential thoracentesis

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Introduction

Tuberculous pleural effusion (TPE), parapneumonic pleural effusion (PPE), and malignant pleural effusion (MPE) are the most common causes of exudative pleural effusion in areas with a moderate to high prevalence of tuberculosis (TB) (1, 2). TPE is typically characterized by lymphocytic predominance and high adenosine deaminase (ADA) levels (3). These characteristics are helpful in the presumptive differential diagnosis of TPE, PPE, and MPE (4). However, TPE occasionally displays neutrophilic predominance like PPE does, and the ADA levels in PPE cases frequently exceed the threshold value for a diagnosis of TPE (2, 3, 5). In addition, lymphocytic exudates with low ADA levels, which are typically found in most MPE cases (6, 7), are sometimes

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observed in TPE as well (8). The differential diagnosis of atypical TPE variant cases from comparable PPE or MPE cases is challenging, because microbiological or cytological results from the pleural fluid are neither frequently positive nor rapidly obtained.

In TPE cases with these atypical pleural fluid profiles, a few previous studies have observed that neutrophilic predominance or low ADA levels in the initial pleural fluid shifted to lymphocytic predominance or increased ADA levels above the cutoff value for TPE at subsequent thoracentesis (9-12). Such findings may provide useful information for the presumptive diagnosis of TPE, based on the subsequent pleural fluid results. However, these observations were incompletely analyzed and not compared to an appropriate control group. Thus, there are limited data available comparing the sequential changes of the pleural fluid profiles in TPE, PPE and MPE cases with similar pleural fluid profiles at the initial thoracentesis.

In this study, we evaluated the sequential changes of the pleural fluid profiles of TPE patients with atypical pleural fluid findings, such as neutrophilic exudates or lymphocytic exudates with low ADA levels, and compared them with those of PPE and MPE patients with comparable pleural fluid profiles.

Materials and Methods

Subjects and study design

We retrospectively reviewed all TPE patients who underwent diagnostic thoracentesis at Kyungpook National University Hospital (KNUH), South Korea, from January 2009 to March 2014. South Korea is an area with an intermediate prevalence of active TB (13). Among these patients, only those who had undergone a second thoracentesis prior to anti-TB treatment were included in the study. A diagnosis of TPE was confirmed when one of the following criteria was met: (1) a positive culture for *Mycobacterium tuberculosis* (MTB) in pleural fluid, pleural tissue, sputum, or bronchial aspirate; (2) pathologically chronic granulomatous inflammation with either a positive MTB polymerase chain reaction, positive acid-fast bacilli (AFB) smear, or caseous necrosis in pleural biopsy tissue; and (3) chronic granulomatous inflammation alone in the pleural biopsy and pleural effusion that resolved with anti-TB treatment (11). A case of probable TPE was diagnosed when patients showed lymphocyte-predominant exudates with pleural fluid ADA levels ≥40 U/L and clinical improvement after anti-TB treatment (14). PPE patients who had two pleural fluid profiles obtained by sequential thoracentesis during the same study period were included as a control group. PPE was defined as exudative effusion associated with bacterial pneumonia, a lung abscess, or bronchiectasis (2). MPE patients who underwent sequential thoracentesis before the administration of specific chemotherapy were also included as a second control group. MPE was diagnosed when one of the following criteria was met: (1) malignant cells eventually found in pleural fluid or tissue through repeated thoracenteses or histological examination or (2) bloody effusion, increased pleural fluid tumor markers, or pleural nodularity (observed by computed tomography) identified in patients with known adjacent malignancy (15).

Data regarding the demographic and serial pleural fluid profiles [total leukocyte and differential leukocyte counts, pH, protein, glucose, lactate dehydrogenase (LDH), and ADA] were collected from patients in each group. The pleural fluid ADA activity was measured in a routine clinical setting using an automated calorimetric assay kit (Runpia Liquid ADA; Kyokuto Pharmaceutical Industrial, Tokyo, Japan). An ADA level ≥40 U/L was considered to be the threshold value for a diagnosis of TPE, as this is the most widely accepted threshold value (16). Neutrophilic effusion was defined as effusion with ≥50% neutrophils in the differential leukocyte count. Only the first and second pleural fluid profiles were used for the statistical analysis in patients with repeated thoracenteses. The time interval between the first and second thoracenteses was recorded. The study protocols were reviewed and approved by the Institutional Review Board of KNUH.

Statistical analysis

Statistical analyses were performed using the GraphPad PRISM™ software (GraphPad Software, San Diego, USA). Categorical variables were expressed as numbers and percentages, and were compared between groups using the χ^2 or Fisher's exact test. Continuous variables were expressed as the medians [interquartile range (IQR)] and differences between groups were analyzed using the Mann-Whitney U test. The Wilcoxon paired signed-rank test was used to compare data from the first and second thoracenteses in each individual. A value of $p<0.05$ was considered to be statistically significant.

Results

Patient characteristics

During the study period, 361 TPE patients who underwent diagnostic thoracentesis were reviewed. Of these, 23 TPE patients who underwent sequential thoracentesis due to atypical pleural fluid profiles at the first thoracentesis were eligible for the analysis: 16 TPE patients showed neutrophilic exudates and another seven showed lymphocytic exudates with low ADA levels (<40 U/L). The background data for the 361 patients, including the 23 atypical and 338 remaining TPE cases, and consort diagrams showing the selection of the study population with the control groups are summarized in Supplemental Table 1 and Fig. 1, respectively. These 23 TPE cases comprised 22 (96%) cases diagnosed by confirmed criteria [positive MTB culture (n=16) and histological results (n=6)] and one (4%) case met the criteria for probable TPE (Table 1).

Table 1. Characteristics of Patients with Pleural Effusion who Underwent Sequential Thoracentesis.

Characteristics	Tuberculous	Parapneumonic	Malignant
n	23	72	18
Age, yr	61 (37-73)	61 (49-68)	73 (66-78)*
Male	12 (52)	54 (75)	10 (56)
Diagnostic criteria			
Confirmed	22 (96)	24 (33)	11 (61)
Probable	1 (4)	48 (67)	7 (39)
Cellular predominance			
Neutrophil ≥50%	16 (70)	72 (100)	-
Lymphocyte >50%	7 (30)	-	18 (100)

Data are expressed as the median (IQR) or number (%).
* p <0.05 between malignant and other pleural effusions.

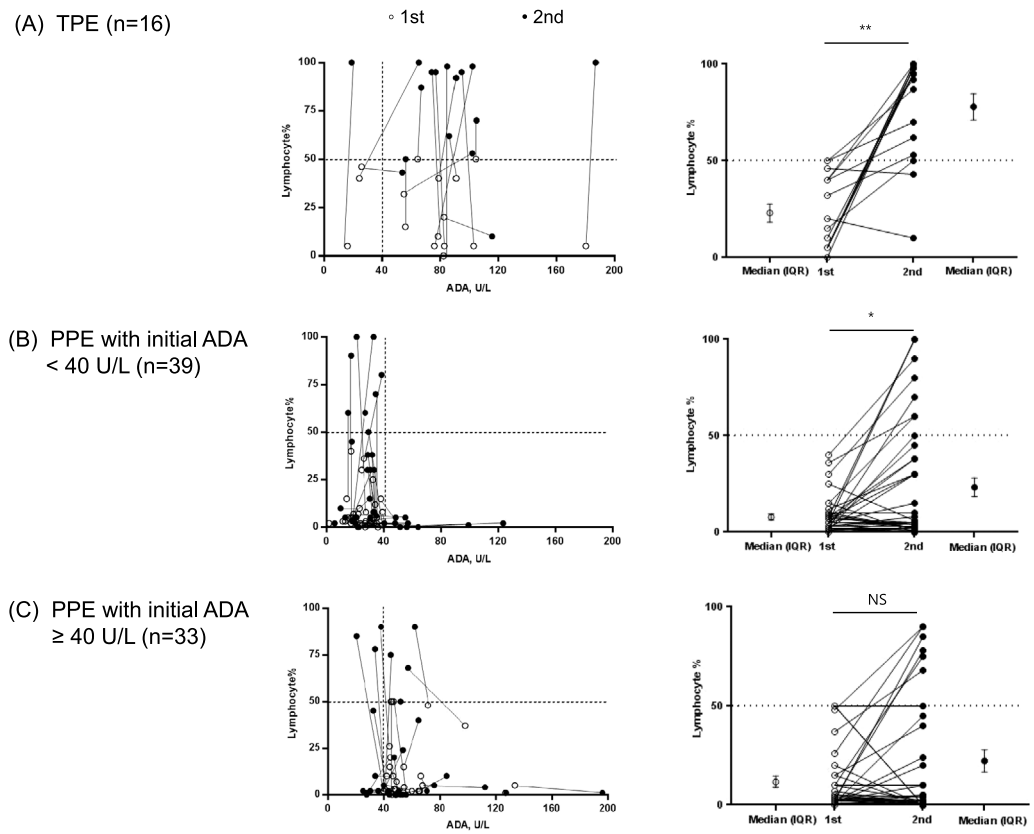

Figure 1. The changes in the pleural fluid adenosine deaminase (ADA) levels and leukocyte proportion at the follow-up thoracentesis in patients with tuberculous pleural effusion (TPE, n=16) and parapneumonic pleural effusion (PPE, n=72) with neutrophilic predominance at the first thoracentesis. The PPE groups were distinguished by the threshold value for ADA levels (40 U/L) at the first thoracentesis. The collective changes in both the ADA levels and leukocyte proportion are represented in the figures in the left column. The right column shows the changes in lymphocyte proportion in each group. Each connected pair of open and filled circles represents the first and second thoracenteses in an individual patient. The shift to lymphocytic predominance at the second thoracentesis was significantly more common in the TPE group than in the overall PPE group [13/16 (81%) vs. 13/72 (18%), p<0.001]. NS: not significant. *<0.05; **<0.001.

Seventy-two PPE patients with neutrophilic predominance underwent a second thoracentesis during the same study period. Twenty-four of these patients were diagnosed based on bacteriological results and the remaining 48 patients showed

Table 2. Comparison of Sequential Pleural Fluid Profiles between the First and Second Thoracenteses in Tuberculous and Parapneumonic Pleural Effusion Patients with Initial Neutrophilic Predominance.

Variables	Tuberculous (n=16)			Parapneumonic (n=72)		
	First	Second	p value	First	Second	p value
Time interval		3 (2-6)			3 (2-5)	0.983
Total leukocyte counts	2,850 (744-5,525)	725 (406-1,525)	0.055	4,450 (1,205-15,250)	1,075 (325-3,900)	<0.001
Neutrophil %	83 (60-95)	7 (2-45)	<0.001	95 (90-98)	95 (62-98)	0.002
Lymphocyte >50%	0 (0)	13 (81)	<0.001	0 (0)	13 (18)	0.002
pH	7.37 (7.36-7.44)	7.40 (7.37-7.42)	0.104	7.33 (7.19-7.38)	7.29 (7.09-7.43)	0.871
Protein, g/dL	5.2 (4.2-6.1)	4.7 (3.9-5.7)	0.826	4.6 (4.0-5.0)	4.3 (3.8-4.8)	0.007
Glucose, mg/dL	94 (66-141)	109 (57-137)	0.626	84 (64-125)	93 (62-121)	0.774
Lactate dehydrogenase, U/L	1,173 (574-1,198)	1,364 (491-1,774)	0.762	1,705 (1,057-2,829)	1,562 (742-3,558)	0.221
Adenosine deaminase, U/L	79 (55-89)	86 (66-102)	0.028	38 (26-48)	38 (28-56)	0.249

Data are expressed as the median (IQR) or number (%).

clinical and radiological improvement after antibiotic treatment with or without pleural space drainage.

Eighteen MPE patients with initial lymphocytic predominance and ADA levels <40 U/L had serial thoracentesis results available. Eleven of these had positive cytological and/or histological results for malignant cells, and the remaining seven were diagnosed by the presence of bloody effusion, increased carcinoembryonic antigen levels, or pleural nodularity on chest CT scans with an adjacent known malignancy [lung cancer (n=6) and hepatic cholangiocarcinoma (n=1)]. All but one of the MPE patients died of the underlying disease within six months with unresolved effusion. None of the patients with PPE or MPE had any evidence of MTB in either serial thoracenteses or sputum.

The median age was higher in the MPE group (73 years, IQR 66 - 78) than in the TPE (61 years, IQR 37- 73) and PPE (61 years, IQR 49 - 68) groups (Table 1).

The pleural fluid profiles at the first and second thoracenteses in TPE and PPE patients with initial neutrophilic predominance, and in the TPE and MPE patients with initial lymphocytic predominance and ADA levels <40 U/L are shown in Supplemental Table 2. Despite the significant differences in some variables of the pleural fluid profiles at the first thoracentesis between two groups, there were no laboratory features sufficient to make a presumptive differential diagnosis of TPE, PPE, and MPE based on these pleural fluid profiles.

Comparison of the sequential pleural fluid profiles between the first and second thoracenteses in TPE and PPE patients with initial neutrophilic predominance

Table 2 shows the sequential changes of the pleural fluid profiles between the first and second thoracenteses in TPE and PPE patients with initial neutrophilic predominance. The median time interval between the thoracenteses in both groups was three days, and it was not significantly different between the groups. In the TPE group, the neutrophil proportion had significantly decreased at the second thoracentesis (83% vs. 7%, p<0.001). The shift from a neutrophil-predominant effusion to a lymphocyte-predominant effusion occurred in 13 (81%) out of 16 TPEs (p<0.001). The total leukocyte counts and classical biochemical markers such as the pH, protein, glucose, and LDH levels were not significantly different between the first and second thoracenteses. On the other hand, the median ADA levels had significantly increased at the second thoracentesis compared to the first thoracentesis (86 vs. 79 U/L, p=0.028).

In the PPE group, the total leukocyte counts and protein levels at the second thoracentesis had significantly decreased compared to those of the first thoracentesis. Thirteen (18%) out of 72 PPE cases had shifted to lymphocytic predominance at the second thoracentesis (p=0.002). However, this was a significantly smaller proportion than that of the TPE patients who had shifted to lymphocytic predominance (18% vs. 81%, p<0.001). Other biomarkers, including the ADA levels, were not significantly different.

Fig. 1 shows the collective changes in the ADA levels and leukocyte proportion at the follow-up thoracentesis. In the 13 TPE patients with a shift to lymphocytic predominance at the second thoracentesis, the initial and follow-up median ADA levels were 79 U/L (IQR 60-97) and 86 U/L (IQR 71-102), respectively, and 12 (92%) of these TPE cases had ADA levels ≥40 U/L at the follow-up thoracentesis (Fig. 1A, left). In the 39 PPE cases with initial ADA levels <40 U/L, seven showed a shift to lymphocytic predominance at the second thoracentesis. However, their ADA levels were still below 40 U/L (Fig. 1B, left). In the 33 PPE cases with initial ADA levels ≥40 U/L, six showed a shift to lymphocytic predominance, and three had ADA levels ≥40 U/L at the follow-up thoracentesis (Fig. 1C, left). In the 13 PPE cases with a shift to lymphocytic predominance, the initial and follow-up median ADA levels were 32 (IQR 21-43) and 34 (IQR 21-42) U/L, respectively. Thus, both the initial

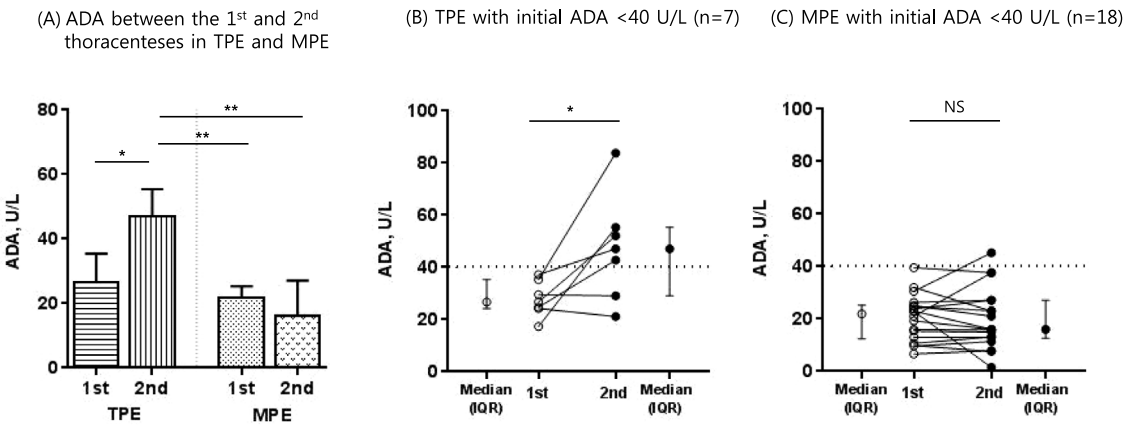

Figure 2. The changes of the pleural fluid adenosine deaminase (ADA) levels between the first and second thoracenteses in seven tuberculous pleural effusion (TPE) and 18 malignant pleural effusion (MPE) patients with lymphocytic predominance and ADA levels <40 U/L at the first thoracentesis. (A). The median ADA levels were significantly higher at the second thoracentesis in the TPE cases compared to those of the first thoracentesis in the TPE cases, as well as those of both the first and second thoracenteses of the MPE cases. (B) and (C). Each connected pair of open and filled circles represents the first and second thoracenteses in an individual patient. In the TPE group, the median ADA levels were significantly increased at the second thoracentesis compared to the first thoracentesis (47 vs. 27 U/L, p=0.039), while those of the MPE group were not significantly different between the first and second thoracenteses (22 vs. 16 U/L, p=0.556). The frequency of effusion with ADA levels ≥40 U/L at the second thoracentesis was significantly higher in the TPE group than in the MPE group [5/7 (71%) vs. 1/18 (6%), p=0.002]. NS: not significant. *<0.05; **<0.001.

and follow-up median ADA levels were significantly higher in TPE patients than in PPE patients, with a shift to lymphocytic predominance (initial: 79 vs. 32 U/L, p=0.005; follow-up: 86 vs. 34 U/L, p<0.001). In addition, the frequency of patients with ADA levels ≥40 U/L in conjunction with a shift to lymphocytic predominance at the follow-up thoracentesis was significantly higher in TPE cases than in PPE cases [12/13 (92%) vs. 3/13 (23%), p<0.001]. The right column of Fig. 1 represents the changes in the lymphocyte proportion at the follow-up thoracentesis in each group.

Comparison of the sequential pleural fluid profiles between the first and second thoracenteses in TPE and MPE patients with initial lymphocytic predominance and ADA levels <40 U/L

Fig. 2 shows the sequential changes in the pleural fluid ADA levels between the first and second thoracenteses in the seven TPE and 18 MPE patients with initial lymphocytic predominance and ADA levels <40 U/L. The median time interval between thoracenteses in the TPE group and the MPE group was four and nine days, respectively, and was not significantly different between the groups. Fig. 2A shows the median ADA levels among the first and second thoracenteses of the TPE and MPE patients. The ADA levels were significantly higher at the second thoracentesis in the TPE group compared to the first thoracentesis in the TPE group (p<0.05) and both the first and second thoracenteses in the MPE group (p<0.001, respectively). Fig. 2B presents the individual changes in the ADA levels, along with the median values at the first and second thoracentesis (27 vs. 47 U/L, p=0.039) in the TPE group. In contrast to these findings, the median ADA levels in the MPE group (Fig. 2C) were not significantly different between the first and second thoracenteses (22 vs. 16 U/L, p=0.556). The frequency of effusion with ADA levels ≥40 U/L at the second thoracentesis was significantly higher in the TPE group than in the MPE group [5/7 (71%) vs. 1/18 (6%), p=0.002].

The sequential changes of the other pleural fluid parameters in the TPE and MPE patients with initial lymphocytic predominance are shown in Supplementary Table 3. There were no significant differences between the first and second thoracenteses in either of the groups except for the pleural fluid protein and glucose levels in the MPE group, which showed considerable overlap.

Discussion

The major findings of the present study are as follows: First, most TPE patients with neutrophilic predominance shifted to lymphocytic predominance within a few days, and such shifts were significantly more common in the TPE group than in the PPE group. Second, for TPE and PPE patients with a shift to lymphocytic predominance, both the initial and follow-up ADA levels were significantly higher in the TPE patients. Third, the pleural fluid ADA levels in TPE patients with initial lymphocytic predominance and ADA levels <40 U/L significantly increased within a few days. Finally, for the TPE and MPE groups with initial lymphocytic predominance and ADA levels <40 U/L, the frequency of effusion with ADA levels ≥40 U/L at the second thoracente-

sis was significantly higher in the TPE group than in the MPE group. This study therefore indicates that the sequential pleural fluid changes of TPE patients with atypical pleural fluid finding are significantly different from those of PPE or MPE patients with comparable initial pleural fluid profiles.

TPE patients may show neutrophilic predominance, especially during the first two weeks following the onset of symptoms (17). The present study confirmed that this neutrophilic predominance usually shifts to lymphocytic predominance within a week, as shown in a few previous studies (9-11). However, the current study showed that 18% of neutrophilic PPE cases also shifted to lymphocytic predominance, although this rate was significantly lower than that of neutrophilic TPE. Under these conditions, both the initial and follow-up ADA levels of the PPE patients with a shift to lymphocytic predominance were significantly lower than those of TPE patients with a shift to lymphocytic predominance. These significant differences persisted even in comparison with the initial and follow-up ADA levels between 11 TPE cases and six PPE cases with initial ADA levels ≥40 U/L and a shift to lymphocytic predominance at the second thoracentesis (initial median, 83 vs. 43 U/L, p=0.020; follow-up median, 91 vs. 41 U/L, p<0.001). Thus, the initial and follow-up ADA levels may provide useful information for discriminating between TPE and PPE patients with a shift to lymphocytic predominance. The follow-up ADA levels of PPE patients with a shift to lymphocytic predominance were distributed at relatively low levels around 40 U/L, even in cases with initial ADA levels ≥40 U/L.

PPE typically presents with neutrophilic exudates with low ADA levels. However, high ADA levels are often observed, especially in complicated PPE (2, 18). Our PPE groups (those with initial low ADA levels and those with initial high ADA levels), showed a wide range of sequential changes in ADA levels and leukocyte proportions, with a similar frequency of shifts to lymphocytic predominance (Fig. 1B and C). These findings may reflect various clinical responses to the initial empirical antibiotic treatment. Appropriate antibiotic treatment in PPE patients might have affected the change in the lymphocytic proportion in a significant number of PPE patients. In contrast, the TPE patients showed relatively uniform changes, reflecting the inherent course of the disease, even before the initiation of anti-TB treatment (Fig. 1A). In follow-up thoracentesis, most (82%) of the PPE patients with initial ADA levels ≥40 U/L presented with persistent neutrophilic predominance (Fig. 1C), while 11 (85%) out of 13 TPE patients with initial ADA levels ≥40 U/L showed a shift to lymphocytic predominance (Fig. 1A). It is likely that these significant differences between the groups under similar conditions were mainly affected by the natural course of the disease rather than by other factors, such as the prior thoracentesis itself.

One concern regarding the usefulness of ADA as a diagnostic marker is that approximately 10% of TPE patients show low ADA levels in lymphocytic exudates (19). Lymphocytic exudate with low ADA levels <40 U/L may be more suggestive of MPE than TPE (6, 7). Interestingly, previous studies have shown that initial low ADA levels might increase above the threshold value for TPE at the subsequent thoracentesis (3, 12). However, these previous studies did not describe the leukocyte proportion in TPE patients with low ADA levels. Low ADA levels can occur in both lymphocytic and neutrophilic TPE, as shown in the current study (Fig. 1A and 2B). The low ADA levels in lymphocytic TPE might be somewhat different from those in neutrophilic TPE, which usually occur in the early stages of the disease, in terms of the host immune response. For example, patients with lymphocytic TPE with low ADA levels may have underlying problems related to pleural fluid ADA production, such as old age (20, 21), smoking (21), or a genetic defect, unlike those with early neutrophilic TPE with low ADA levels. The present study showed that the low ADA levels in lymphocytic TPE patients subsequently increased as the disease progressed, regardless of potential underlying problems associated with low ADA levels. In contrast, the ADA levels in lymphocytic MPE patients with low initial ADA levels rarely exceeded the threshold value for TPE in the follow-up thoracentesis. The present study therefore confirmed that low ADA levels, even in lymphocytic exudates, could not exclude the possibility of TPE. Thus, even where there is lymphocytic exudate with low ADA levels, if clinical suspicion exists, especially in patients with risk factors for low ADA levels, follow-up thoracentesis may be helpful in the clinical decision-making and management of pleural effusions of uncertain origin.

The appropriate time interval for follow-up thoracentesis may vary between individuals. However, it should be noted that the second thoracentesis in one of the three TPE patients with persistent neutrophilic predominance, and one of the two TPE patients with persistent low ADA levels, was performed only one day after the first thoracentesis. This may be too short of an interval to assess the changes in the pleural fluid leukocyte proportion or ADA levels in TPE patients.

The main limitations of this study were its retrospective design and small sample size. Because of the retrospective nature of the study, the timing of sample acquisition during the second thoracentesis could not be standardized. However, it is likely that a shift to lymphocytic predominance or an elevation in ADA levels will occur in most TPEs within a week. In addition, all TPE patients with initial neutrophilic exudates received empirical antibiotics, similar to the PPE patients, so we cannot completely exclude the potential impact of these antibiotics on the follow-up cellularity of the TPE patients. Finally, the current study does not provide reasons why the ADA levels were subsequently increased in the TPE patients with lymphocytic predominance and low ADA levels at the first thoracentesis. Individual differences between TPE development and ADA production may exist.

In conclusion, this study demonstrated that sequential thoracentesis may provide useful information in suspected cases

of atypical TPE with neutrophilic exudates or low pleural fluid ADA levels. In cases of pleural effusion where TPE is clinically suspected as an etiology, but when initial thoracentesis does not yield results consistent with the clinical suspicion, a follow-up thoracentesis within one week may be helpful for making further clinical decisions.

The authors state that they have no Conflict of Interest (COI).

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