# Neutrophilic Loculated Tuberculous Pleural Effusion: Incidence, Characteristics and Differentiation From Complicated Parapneumonic Effusion

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## ABSTRACT

**Objectives:** Tuberculous pleural effusion (TPE) is generally characterized by lymphocytic exudative effusion, either free-flowing or loculated. However, patients can also have neutrophilic loculated TPE, although little data are available concerning the incidence and characteristics of this form of TPE. It is important to differentiate between neutrophilic loculated TPE and complicated parapneumonic effusion (PPE), which also shows neutrophilic loculated effusion but needs a different management approach. The present study evaluated the incidence and characteristics of neutrophilic loculated TPE and differentiated it from complicated PPE.

**Materials and Methods:** Between 2009 and 2014, a cohort of patients with TPE was retrospectively reviewed in a South Korean referral hospital. Clinical, laboratory, computed tomography and pleural fluid findings of patients with neutrophilic loculated TPE were compared to those of patients with neutrophilic free-flowing TPE and complicated PPE, respectively.

**Results:** Neutrophilic TPE was observed in 33 (10%) out of 344 patients with TPE. Of these, 10 (30%) patients exhibited loculation of the pleural fluid. These patients showed distinct pleural fluid characteristics. The classical pleural fluid biomarker levels were more intense than those observed in 23 patients with neutrophilic free-flowing TPE, but similar to those of 54 patients with complicated PPE. A high mycobacterial burden was observed in the pleural fluid, and favorable outcomes were achieved with antituberculosis drug administration alone. Nodular parenchymal lesions and pleural fluid adenosine deaminase levels were independent discriminators of neutrophilic loculated TPE and PPE.

**Conclusions:** These results may be helpful to understand and manage patients with neutrophilic loculated TPE and differentiate them from patients with complicated PPE.

**Key Indexing Terms:** Neutrophilic tuberculous pleural effusion; Loculation; Complicated parapneumonic effusion; Adenosine deaminase. **[Am J Med Sci 2016;351(2):153–159.]**

## INTRODUCTION

Tuberculous pleural effusion (TPE) is one of the leading causes of exudative pleural effusion in areas with an intermediate-to-high prevalence of tuberculosis (TB).[1,2] Most cases of TPE are characterized by lymphocytic exudative effusion.[3,4] As with other exudative pleural effusions, TPE often manifests as loculated pleural fluid on initial radiographs. In most cases, loculated TPE also shows lymphocytic predominance.[5,6] However, TPE is not always lymphocytic. Approximately 10-15% of all TPE cases show neutrophilic exudative effusion, especially in the early stages.[7-9]

As is the case for lymphocytic TPE, neutrophilic TPE also presents with loculated pleural fluid.[10] However, neutrophilic loculated TPE has been rarely investigated, contrary to lymphocytic loculated TPE or TB empyema showing frank pus. Therefore, very little data are available on the incidence and characteristics of patients with this condition. In addition, differentiation between neutrophilic loculated TPE and complicated parapneumonic pleural effusion (PPE), which is commonly encountered in clinical practice and also shows neutrophilic loculated effusion, may be challenging. The differential diagnosis of these 2 diseases is clinically significant because they are both potentially curable but require quite different management. Thus, clinicians should be aware of the possibility of TPE in neutrophilic loculated effusion cases to avoid misdiagnosing TPE as complicated PPE, particularly in areas with an intermediate-to-high TB prevalence.

The present study investigated the incidence and characteristics of patients with neutrophilic loculated TPE, and compared the characteristics of these patients to those of patients with neutrophilic free-flowing TPE and patients with complicated PPE.

## MATERIALS AND METHODS

### Study Population and Design

All consecutive patients diagnosed with TPE between January 1, 2009 and March 30, 2014 at Kyungpook National University Hospital, South Korea, were retrospectively reviewed. In South Korea, there is an intermediate prevalence of active TB.[11] All patients with confirmed or probable TPE were included in the study and classified according to pleural fluid cellular predominance and whether the pleural fluid was free-flowing or loculated. TPE was confirmed when 1 of the following criteria was met: (1) culture positive for *Mycobacterium tuberculosis* (MTB) in the pleural fluid, pleural tissue, sputum or bronchial aspirate; (2) pathologically chronic granulomatous inflammation with either positive MTB-polymerase chain reaction (PCR), 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, which resolved with anti-TB treatment.[12] A probable case of TPE was determined when the lymphocyte-predominant exudate contained $\geq$40 U/L of adenosine deaminase (ADA) in the pleural fluid and clinical improvement was observed after anti-TB treatment.[13] Patients with neutrophilic loculated PPE were included as a control group for comparison with patients with neutrophilic loculated TPE. PPE was defined as exudative effusion associated with bacterial pneumonia, lung abscess or bronchiectasis in the absence of any evidence of MTB in the pleural fluid by serial thoracentesis or sputum.[14] Patients with pleural effusion developing during anti-TB treatment due to pulmonary or extrapulmonary TB were excluded. In addition, cases of empyema showing gross pus at thoracentesis were excluded in both the groups.

Details on patient demographics, clinical symptoms and signs, immunosuppressive conditions, laboratory and microbiological data and radiologic findings were collected. Patients with immunosuppressive conditions included those with underlying diseases such as malignancies, human immunodeficiency virus infection, end-stage renal disease or advanced chronic liver disease, those receiving immunosuppressive treatment and those who had undergone organ transplantation. Weight loss was defined as a loss of more than 10% of body weight over the past 6 months.

Lymphocytic effusion was defined as effusion with $>$50% lymphocytes in the differential leukocyte count, whereas neutrophilic effusion was defined as effusion with $\geq$50% neutrophils. Only the first pleural fluid cell counts and profiles were used for statistical analyses in patients who underwent repeated thoracentesis. AFB smears, MTB-PCR and mycobacterial cultures were performed as previously described.[15] Pleural fluid ADA activity was measured in a routine clinical setting using an automated calorimetric assay kit (Runpia Liquid ADA; Kyokuto Pharmaceutical Industrial Co., Ltd., Japan) as described in the package insert.

Chest radiographs (frontal, lateral and both decubitus views) and conventional chest computed tomography (CT) scans with 2.5 or 3 mm collimation performed before initial thoracentesis were reviewed by a board-certified radiologist and a pulmonologist, who were blinded to the patient's clinical history and final diagnosis. They independently evaluated whether the pleural effusion was free-flowing or loculated, plus the following CT findings: (1) consolidative; (2) nodular ($<$20 mm in size); (3) cavitary and (4) calcified/fibrotic lesions.[13] If a discrepancy was noted between interpretations, the images were further reviewed by another pulmonologist who was blinded to the results.

Successful treatment was defined when standard anti-TB drug administration was completed for at least 6 or 9 months with clinical and radiological improvements. The study protocols were reviewed and approved by the Institutional Review Board of the Kyungpook National University Hospital.

### Statistical Analysis

Statistical analyses were performed using the SPSS software version 19.0 (SPSS Inc, Chicago, IL). Categorical variables were expressed as numbers and percentages, and were compared between groups by $\chi^2$ test or Fisher's exact test. Continuous variables were expressed as the median (interquartile range) and differences between groups were analyzed using the Mann-Whitney $U$ test. Variables with $P < 0.05$ in univariate analysis were entered into the multivariate logistic regression analysis to identify independent predictive variables for TPE. The goodness of fit of the model was assessed with the Hosmer-Lemeshow test. A $P < 0.05$ was considered statistically significant.

## RESULTS

A total of 361 consecutive patients were diagnosed with TPE during the study period. Among these, 17 patients were excluded because of the following reasons: TPE developed during anti-TB medication ($n = 12$); frank pus was present in the pleural fluid ($n = 2$); failure of cell detection in the pleural fluid ($n = 2$) and mixed infection ($n = 1$). Finally, 344 patients were identified with TPE with nonpurulent pleural fluid before anti-TB treatment. Of these, 228 (66%) cases were confirmed and 116 (34%) cases were probable. Of 344 patients with TPE, 311 (90%) had lymphocytic effusion and 33 (10%) had neutrophilic effusion. Of 33 patients with neutrophilic TPE, 10 (30%) showed loculated pleural fluid, whereas the remaining patients (70%) showed free-flowing pleural fluid (Figure 1). Neutrophilic loculated TPE corresponded to 3% of the total TPEs. All 33 patients with neutrophilic TPE were confirmed by positive result for MTB culture ($n = 29$) and histologic results ($n = 4$).

A total of 54 consecutive patients with nonpurulent neutrophilic loculated PPE, who underwent pleural space