ORIGINAL ARTICLE

https://doi.org/10.4046/trd.2017.80.1.35
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2017;80:35-44

Loculated Tuberculous Pleural Effusion: Easily Identifiable and Clinically Useful Predictor of Positive Mycobacterial Culture from Pleural Fluid

Yousang Ko, M.D.[1,2,*], Changhwan Kim, M.D., Ph.D.[3,*], Boksoon Chang, M.D., Ph.D.[4], Suh-Young Lee, M.D.[1,2], So Young Park, M.D.[1,2], Eun-Kyung Mo, M.D., Ph.D.[1,2], Su Jin Hong, M.D., Ph.D.[5], Myung Goo Lee, M.D., Ph.D.[2,6], In Gyu Hyun, M.D., Ph.D.[2,7] and Yong Bum Park, M.D.[1,2]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, [2]Lung Research Institute, Hallym University College of Medicine, Chuncheon, [3]Department of Internal Medicine, Jeju National University Hospital, Jeju, [4]Department of Pulmonary and Critical Care Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, [5]Department of Radiology, Hallym University Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, [6]Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, [7]Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea

Background: Isolation of *M. tuberculosis* (MTB) is required in cases of Tuberculous pleural effusion (TBPE) for confirming diagnosis and successful therapy based on drug sensitivity test. Several studies have focused on predictors of MTB culture positivity in TBPE. However, the clinical role of loculated TBPE as a predictor of MTB cultivation from TBPE remains unclear. The aim of this study was to examine possible predictors including loculation of TBPE of MTB culture positivity in TBPE.

Methods: We retrospectively examined associations between clinical, radiological, microbiological, and laboratory characteristics and positive MTB culture from TBPE to determine a potent predictor of culture positivity.

Results: From January 2011 to August 2015, 232 patients with TBPE were identified. Of these, 219 were finally analyzed. Among them, 69 (31.5%) were culture positive for MTB in TBPE and 86 (39.3%) had loculated TBPE. In multivariate logistic regression analysis, the loculation of TBPE was independently associated with culture positivity for MTB in TBPE (adjusted odds ratio [OR], 40.062; 95% confidence interval [CI], 9.355–171.556; p<0.001). In contrast, the lymphocyte percentage of TBPE (adjusted OR, 0.934; 95% CI, 0.899–0.971; p=0.001) was inversely associated with culture positivity for MTB in TBPE.

Conclusion: In clinical practice, identification of loculation in TBPE is easy, reliable to measure, not uncommon and may be helpful to predict the possibility of positive mycobacterial culture.

Keywords: Tuberculosis; Pleural Effusion; Pleurisy

Address for correspondence: Yong Bum Park, M.D.
Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, 150 Seongan-ro, Gangdong-gu, Seoul 05355, Korea
Phone: 82-2-2224-2561, **Fax:** 82-2-488-6925, **E-mail:** bfspark2@gmail.com
*Yousang Ko and Changhwan Kim contributed equally to this work.
Received: Jul. 29, 2016, **Revised:** Aug. 30, 2016, **Accepted:** Sep. 1, 2016

Introduction

Extrapulmonary tuberculosis (EPTB) is defined as tuberculosis (TB) involving organs other than the lungs[1,2]. Of 5.4 million new TB cases in 2014, 0.8 million were classified and notified as EPTB according to the revised World Health Organization (WHO) definition[2]. Among EPTB, tuberculous pleural effusion (TBPE) is one of the most common forms[1,3].

The definitive diagnosis of TBPE is detection or isolation of *Mycobacterium tuberculosis* (MTB) in respiratory specimens, pleural fluid, or pleural biopsy specimens, or histological demonstration of caseating granuloma in the pleura[1,4,5]. But, in actual clinical practice of areas with intermediate-to-high prevalence of TB, the diagnosis of TBPE is frequently established on the basis of a lymphocyte-predominant exudate and a high adenosine deaminase (ADA) level in the pleural fluid[1,4,6,7]. However, it should be noted that because drug-resistant TB is more common in areas with an intermediate-to-high burden[2,8], it is necessary to isolate and identify MTB even in a patient with TBPE to allow definitive diagnosis and successful therapy based on a drug sensitivity test (DST).

Recent advances in culture techniques, including the use of liquid media, have improved sensitivity[1,4,9-11], while from a clinical point of view, several studies have attempted to identify predictors for cultivation of MTB from TBPE[10-13].

Loculation of pleural effusion is generally the result of intense intra-pleural inflammation and organization, and can occur in association with various clinical conditions including parapneumonic effusion, empyema, malignant pleural effusion (PE), hemothorax, and TBPE[14,15].

In TBPE, the pathogenesis is now considered as a result of direct pleural infection of MTB and followed with an immunologic response such as delayed hypersensitivity according to recent advance of culture technique[1,4]. Assuming that pleural inflammation is associated with the amount of MTB into the pleural space, the presence of loculation may be an important predictor of a high probability of cultivation of MTB from a TBPE. However, there are no data concerning the clinical role of loculated TBPE as a predictor of the cultivation of MTB from TBPE.

In this study, we hypothesized that loculation is an important predictor of a positive MTB culture in TBPE. We undertook this study to compare the clinical, radiological, serological, and pleural fluid characteristics of patients with positive and negative TBPE cultures to determine the predictors of a positive MTB culture in TBPE.

Materials and Methods

1. Study population and design

We retrospectively reviewed the records of all consecutive patients diagnosed with TBPE who underwent diagnostic thoracentesis between January 2011 and July 2015 at Hallym University Kangdong Sacred Heart Hospital (Seoul, Korea), which is situated in an area of intermediate TB burden with a reported estimated prevalence of 143/100,000 persons in 2013[2]. Patients who had received any anti-TB treatment before diagnostic thoracentesis, or patients who had been previously treated for pulmonary tuberculosis (PTB) or TBPE, were excluded because these conditions can result in pleural adhesions that mask the loculation of TBPE. The protocol for this study was approved by the Institutional Review Board of Hallym University Kangdong Sacred Heart Hospital (IRB 2015-12-013). Informed consent was waived because of the retrospective nature of the study.

2. Diagnosis of TBPE

A diagnosis of TBPE was made based on the following criteria: (1) positive culture for MTB in pleural fluid or pleural tissue; (2) granulomatous inflammation in biopsy tissue of parietal pleura; (3) positive culture for MTB in a respiratory specimen such as sputum or lower respiratory tract specimen obtained via bronchoscopy, and a PE that resolved with anti-

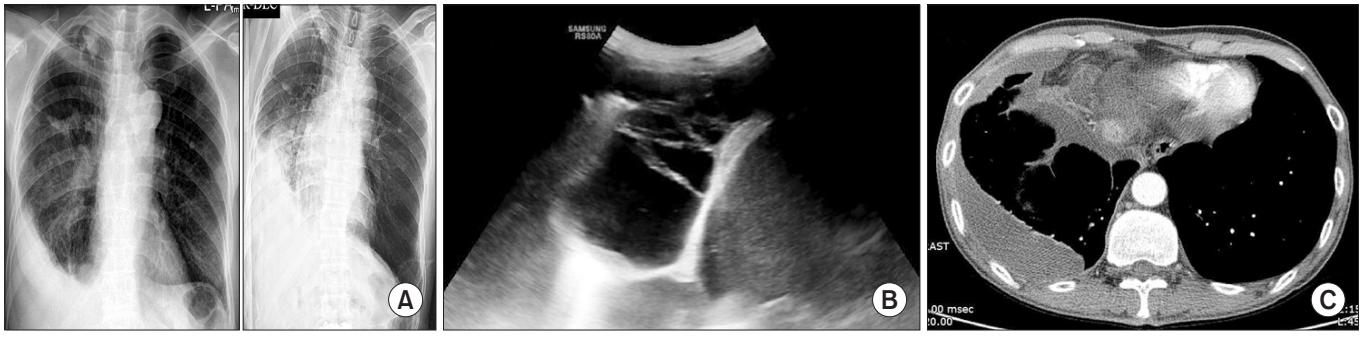

Figure 1. The representative radiographic finding of loculated tuberculous pleural effusion. (A) Chest plain X-ray shows no shifting of pleural fluid on decubitus film, as compared with chest posteroanterior view. (B) Thoracic real-time sonography shows complex septated pleural effusion. (C) Chest computed tomography shows loculated pleural fluid, accumulated in nondependent portion.

TB treatment; (4) lymphocytic exudates from the first or subsequent thoracentesis, high ADA levels (>40 U/L) in pleural fluid, negative cytological results, and effusions that resolved in response to anti-TB treatment[1,16].

3. Definition of loculation and classification of the amount of TBPE

Loculated TBPE was defined as PE that did not shift on decubitus film and/or loculation on chest computer tomography and/or real-time chest ultrasonography[17,18]. The absence or presence of loculation of TBPE was classified based on radiologic data before pleural aspiration. The radiographic finding of loculated TBPE are shown in Figure 1.

The amount of TBPE was classified as small, moderate, or large scale based on the chest radiographs before pleural tapping: (1) small: a level of TBPE that blunted the costophrenic angle but did not obscure the entire diaphragm; (2) moderate: a level that obscured the entire diaphragm but was below the hilum; and (3) large: a level up to and above the hilum[19,20].

Table 1. Clinical and radiological characteristics of 219 patients diagnosed with TBPE

Characteristic	All patients (n=219)	Positive culture (n=69)	Negative culture (n=150)	p-value
Age, yr	51.0 (32.0–69.0)	52.0 (31.5–66.0)	49.0 (33.5–70.0)	0.998
Male	141 (64.4)	42 (60.9)	99 (66.0)	0.544
PTB*	102 (46.6)	32 (46.4)	70 (46.7)	>0.990
Comorbidity				
COPD and asthma	7 (3.2)	2 (2.9)	5 (3.3)	0.504
Chronic liver disease	12 (3.0)	2 (2.9)	10 (6.7)	0.348
Diabetes	23 (6.0)	6 (8.7)	17 (11.3)	0.372
Cerebrovascular disease	5 (2.3)	1 (1.4)	4 (2.7)	>0.990
Hypertension	45 (20.5)	16 (23.2)	32 (21.3)	0.861
ESRD	2 (0.5)	0	2 (1.3)	1.000
Rheumatic disease	2 (0.5)	1 (1.4)	1 (0.7)	0.532
Thyroid disease	3 (0.8)	0	3 (2.0)	0.553
Malignancy†	1 (0.3)	1 (1.4)	0	0.315
Radiological feature				
PTB in CT‡	83 (37.9)	28 (40.6)	55 (36.7)	0.653
PTB in CXR	77 (35.2)	26 (37.7)	51 (34.0)	0.649
Pleural effusion				
Loculation§	86 (39.3)	59 (85.5)	27 (18.0)	<0.001
Amount				0.201
Small	52 (23.7)	18 (26.1)	34 (22.7)	
Moderate	130 (59.4)	44 (63.8)	86 (57.3)	
Large	37 (16.9)	7 (10.1)	30 (20.0)	
Effusion site				0.240
Right	126 (57.5)	44 (63.8)	82 (54.7)	
Left	93 (42.5)	25 (36.2)	68 (45.3)	

Values are presented as number of patients (%) or median (interquartile range).
*Pulmonary involvement of tuberculosis was determined based on radiologic studies, either chest X-ray or chest CT. Among 142 patients with no evidence of pulmonary involvement on CXR, 17 cases of pulmonary involvement were detected on chest CT. †Malignancy was prostate cancer. ‡Chest CT was performed in 177 patients (80.8%). §Loculation of TBPE was determined based on radiologic studies, either CXR, chest CT, and/or sonography. CXR with decubitus view was conducted in all 219 cases and classified as loculation (75/86, 87.2%). Chest CT was conducted in 177 cases and classified as loculation (86/86, 100%). Thoracic sonography was conducted in 109 cases, via pigtail insertion for drainage and/or fibrinolysis, and classified as loculation (38/86, 44.2%).
TBPE: tuberculous pleural effusion; PTB: pulmonary tuberculosis; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; CT: computed tomography; CXR: chest X-ray.

Radiologic studies were reviewed independently by a pulmonologist and a radiologist. If a discrepancy was noted between their interpretations, the image was reviewed further by another pulmonologist blinded to the results.

4. Microbiologic examination of respiratory and pleural fluid specimens

Pleural fluid specimen were obtained during thoracentesis and transported to the laboratory. It was concentrated but not decontamination then inoculated for MTB culture in the laboratory as recommended[21]. The acid-fast bacilli (AFB) smears were examined after auramine–rhodamine fluorescence staining. All specimens including pleural fluid were simultaneously cultured on both solid and liquid media, 3% Ogawa medium (Eiken Chemical, Tokyo, Japan) using the mycobacteria growth indicator tube 960 system (Becton Dickinson, Mountainview, CA, USA). TB polymerase chain reaction was performed using the AdvanSure TB/NTM RT-PCR kit (LG Life Sciences, Seoul, Korea) according to the manufacturer's protocol.

5. Statistical analysis

The data are presented as medians and interquartile range (IQR) for continuous variables and number (percentage) for categorical variables. The data were compared using the Mann-Whitney U test for continuous variables and Pearson's chi-square test or Fisher exact test for categorical variables. Multiple logistic regression analysis was used to identify independent predictors of cultivation of MTB, as measured by the estimated odds ratios (OR) with 95% confidence intervals (CI), including variables with a p-value <0.2 on univariate analysis[22]. To reduce the risk of multicollinearity, one closely correlated variable was a candidate for inclusion in the final model. All tests were two-sided, and a p-value of less than 0.05 was considered to indicate statistical significance. Data were analyzed using IBM SPSS Statistics version 19 (IBM Corp., Armonk, NY, USA).

Results

During the study period, 232 consecutive patients diagnosed with TBPE were screened for this study. Of these, 13 were excluded: nine because they received anti-TB therapy before thoracentesis and four because of a previous history of PTB; thus 219 were finally analyzed. The demographic and radiologic characteristics of the 219 patients with TBPE are summarized in Table 1. There were 141 males (64.4%) with a median age of 51.0 (IQR, 32.0–69.0) years. Of these, 117 patients (53.4%) had only TBPE based on radiologic studies and 102 had PTB with concurrent TBPE. Loculated TBPE was identified in 86 cases (39.3%).

Table 2 shows the microbiological and laboratory data for these patients, of whom 69 (31.5%) were culture positive for MTB in the pleural fluid and 150 were culture negative. There were no case with TB empyema, defined as the presence of frank pus or smear positive for AFB on pleural aspiration. Of the 150 patients with negative pleural culture for MTB, 50 had a positive culture from a respiratory specimen and had PE that resolved with anti-TB treatment, and 100 were clinically diagnosed based on lymphocytic exudates, high ADA levels in the pleural fluid, negative cytological results, and effusions that resolved in response to anti-TB treatment.

Among the 146 TBPE patients in whom MTB was not isolated from a respiratory specimen, it was possible to cultivate MTB in the pleural fluid of 46 patients. The combination of both respiratory specimen and pleural fluid culture showed a diagnostic sensitivity of 54.3% (119/219). There were nine patients (median neutrophil %, 70.5; IQR, 55.0–85.0) with neutrophil-predominant TBPE, all of whom were culture positive for MTB, two of whom were positive for MTB by polymerase chain reaction of TBPE, and six of whom had loculated TBPE.

1. Comparison of clinical, radiological, microbiological, and laboratory findings

Univariate comparisons of the clinical, radiological, microbiological, and laboratory characteristics of MTB culture-positive and culture-negative patients are presented in Tables 1 and 2. There were no significant differences between the groups of patients who were culture-positive and culture-negative for MTB in the pleural fluid with regard to age, sex, underlying disease, frequency of TBPE combined with PTB, and radiological findings, except for loculation. Compared with the patients with TBPE that was culture-negative for MTB, the patients with TBPE that was culture-positive for MTB had a lower lymphocyte percentage, pH, and glucose level in their TBPE. In addition, the culture-positive group had a higher neutrophil percentage, higher protein and lactate dehydrogenase (LDH) levels in their TBPE and a higher C-reactive protein (CRP) level in their blood than the culture-negative group.

2. Predictors of MTB culture positivity in patients diagnosed with TBPE

To identify clinical predictors suggestive of culture positivity for MTB in TBPE, eight variables that were significantly different between the two groups in univariate analysis were further analyzed using multivariate logistic regression. After adjusting for potential confounding factors, the loculation of TBPE was independently associated with culture positivity for MTB in TBPE (adjusted OR, 40.062; 95% CI, 9.355–171.556; p<0.001). In contrast, the lymphocyte percentage of TBPE (adjusted OR, 0.934; 95% CI, 0.899–0.971; p=0.001) was inversely associated with culture positivity for MTB in TBPE (Table 3).

Table 2. Microbiological and laboratory characteristics of 219 patients diagnosed with TBPE

Characteristic	All patients (n=219)	Positive culture (n=69)	Negative culture (n=150)	p-value
Respiratory specimen*				
AFB smear positive	22 (10.0)	6 (8.7)	16 (10.7)	0.810
AFB culture positive	73 (33.3)	23 (33.3)	50 (33.3)	>0.990
MTB-PCR positive	35 (16.0)	13 (18.8)	22 (14.7)	0.552
Pleural fluid exam				
AFB smear positive	0	0	0	NA
MTB culture positive†	69 (31.5)	69 (100)	0	NA
MTB-PCR positive	5 (2.3)	3 (4.3)	2 (1.3)	0.181
Color				0.804
Brown	4 (1.8)	1 (1.4)	3 (2.0)	
Reddish	21 (9.6)	5 (7.2)	16 (10.7)	
Yellow	192 (87.7)	62 (89.9)	130 (86.7)	
Turbid	2 (0.9)	1 (1.4)	1 (0.7)	
WBC (total cells)	1,920.0 (830.0–3,960.0)	1,920.0 (760.0–5,120.0)	2,080.0 (1,050.0–3,680.0)	0.815
Lymphocyte, %	80.0 (65.0–90.0)	70.0 (55.0–87.0)	85.0 (70.0–92.0)	<0.001
Neutrophil, %	9.0 (2.0–20.0)	15.0 (4.0–30.0)	6.0 (1.0–15.0)	0.001
pH	7.36 (7.32–7.41)	7.341 (7.286–7.406)	7.374 (7.325–7.414)	0.006
Glucose	90.0 (73.0–108.0)	82.0 (58.5–95.0)	96.0 (77.8–110.2)	<0.001
Protein	5.2 (4.7–5.6)	5.4 (4.8–5.8)	5.2 (4.7–5.5)	0.034
Albumin	2.9 (2.6–3.2)	2.9 (2.6–3.2)	2.9 (2.5–3.2)	0.329
LDH	552.0 (350.0–834.0)	628.0 (492.0–932.0)	500.5 (290.0–751.8)	0.001
ADA	90.4 (74.7–105.6)	89.8 (74.7–105.0)	90.8 (74.8–106.2)	0.941
CRP‡	26.8 (14.0–36.9)	29.1 (23.1–37.4)	23.1 (13.2–36.3)	0.132
Serum exam				
WBC	6,490.0 (5,350.0–7,900.0)	6,480.0 (5,190.0–7,900.0)	6,505.0 (5,525.0–7,907.5)	0.543
Platelet	325 (255–410)	296.0 (231.5–408.0)	331.5 (265.0–415.0)	0.057
CRP	48.7 (32.2–78.5)	67.4 (42.4–89.9)	39.9 (22.9–74.2)	<0.001
Protein	6.7 (6.3–7.2)	6.9 (6.5–7.4)	6.7 (6.3–7.2)	0.120
Albumin	3.6 (3.2–3.9)	3.6 (3.2–3.9)	3.6 (3.2–3.9)	0.848
LDH	222.0 (185.0–261.0)	229.0 (186.5–266.5)	220.5 (185.0–261.5)	0.611

Values are presented as number of patients (%) or median (interquartile range).
*Respiratory specimens include bronchoalveolar lavage (8, 3.7%), bronchial washing (21, 9.6%), and sputum (190, 86.8%). †MTB culture in TBPE were positive on both media (28/69, 40.6%), liquid media alone 40 (58.0%) and solid media alone 1 (1.5%), respectively. ‡CRP in pleural fluid was determined in 129 patients (58.9%, 38 in culture-positive group, 91 in culture-negative group).
TBPE: tuberculous pleural effusion; AFB: acid-fast bacilli; MTB: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; NA: not applicable; WBC: white blood cell; LDH: lactate dehydrogenase; ADA: adenosine deaminase; CRP: C-reactive protein.

3. Comparison of clinical, radiological, microbiological, and laboratory parameters in patients with loculated and free-flowing TBPE

Table 4 compares the characteristics of patients with loculated and free-flowing TBPE. The median values of the white blood cell count, lymphocyte percentage, pH, and glucose level in patients with loculated TBPE were lower than their median values in patients with free-floating TBPE. However, the neutrophil percentage, LDH levels in TBPE, and blood levels of CRP were higher in patients with loculated TBPE.

https://doi.org/10.4046/trd.2017.80.1.35

Table 3. Predictors of MTB culture positivity in patients diagnosed with TBPE

Characteristic	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Loculated TBPE	26.878 (12.209–59.172)	<0.001	40.062 (9.355–171.556)	<0.001
Blood				
CRP	0.992 (0.985–0.998)	0.011	-	-
Platelet	1.002 (0.999–1.005)	0.130	-	-
Protein	0.695 (0.449–1.075)	0.102	-	-
Pleural fluid				
MTB-PCR positive	3.364 (0.549–20.606)	0.190	-	-
Lymphocyte, %	0.956 (0.937–0.976)	<0.001	0.934 (0.899–0.971)	0.001
Neutrophil, %	1.041 (1.024–1.059)	0.001	-	-
pH	0.002 (0.000–0.064)	0.001	-	-
Glucose	1.017 (1.007–1.027)	0.001	1.019 (0.997–1.041)	0.084
Protein	0.690 (0.472–1.008)	0.055	-	-
LDH	1.000 (0.999–1.000)	0.246	-	-
CRP	0.999 (0.973–1.008)	0.286	-	-

MTB: *Mycobacterium tuberculosis*; TBPE: tuberculous pleural effusion; OR: odds ratio; CI: confidence interval; CRP: C-reactive protein; PCR: polymerase chain reaction; LDH: lactate dehydrogenase.

Discussion

To our knowledge, this is the first study to evaluate the clinical role of loculated TBPE as a predictor of culture positivity for MTB in TBPE. This study aimed to identify clinically useful factors that predict cultivation of MTB in patients with TBPE. The results showed that loculation of TBPE was an independent positive predictor of culture positivity for MTB in TBPE, while a high lymphocyte percentage in TBPE was inversely associated with MTB culture positivity in TBPE.

It is known that concurrent PTB and TBPE is not as uncommon as previously believed, and PTB can be diagnosed by induced sputum in approximately 52% of cases of TBPE[23-25]. However, in the remaining cases of TBPE, it is necessary to cultivate the MTB in the TBPE rather than in respiratory specimens to identify it as the pathogen. Thus, cultivation of MTB from TBPE should not be overlooked in the diagnostic process. Furthermore, it can allow targeted therapy according to the DST[1,4].

Although previous few studies reported that drug-resistant TB occurs less frequently in EPTB than in PTB[26,27], there is no theoretical reason for a difference in drug-resistance between PTB and EPTB. The reason is that TB is an infectious disease and the proportion of drug-resistant strains of MTB in a community similarly affects both PTB and EPTB[28,29]. Moreover, the proportion of EPTB is increasing among new cases according to the WHO global TB report[2,30]. Therefore, it is necessary to isolate the MTB even in EPTB and verify whether actually drug-resistant or not. In our study, MTB was isolated only in the TBPE (46/146, 31.5%), not in respiratory specimen. Furthermore, among these 46 cases identified only by TBPE, two had multidrug-resistant TB, one was resistant to isoniazid and para-aminosalicylic acid, and one was resistant to streptomycin.

Until a recent day, the pathogenesis of TBPE were considered largely as delayed hypersensitivity response of tuberculous protein into the pleural space for most, according to experimental study of guinea pigs and negative cultivation of MTB in patients with TBPE[1,4,31]. However, the TBPE is now believed to be the consequence of direct infection of the pleural space by paucibacillary MTB related to serial immunologic responses by various pro-inflammatory cytokines based on recent studies[1,31-34]. After inoculation of MTB into pleural space, TBPE is initially developed as a result of rapid neutrophilic inflammatory reaction and followed by a $CD4^+$-lymphocyte driven immunologic response of delayed hypersensitivity response over time[1,31]. Actually, automated liquid culture systems, now widely used, provide a higher yield of positive cultures, with up to 75% in human immunodeficiency virus (HIV)–positive TBPE patients and up to 60% in HIV-negative TBPE patients, unlike solid media culture at past.

Based on the mechanism of TBPE, from a clinical point of view, it is necessary to identify possible predictors of positive mycobacterial culture in TBPE. Previous studies focused on this point and demonstrated that a low lymphocyte percentage, a high neutrophil percentage, a low protein level, a low

Table 4. A comparison of the clinical characteristics of patients with loculated TBPE and without loculated TBPE

Characteristic	Loculated TBPE (n=86)	Non-loculated TBPE (n=133)	p-value
Age, yr	48.5 (31.0–62.5)	54.0 (34.0–73.0)	0.139
Male	54 (62.8)	87 (65.4)	0.773
PTB*	37 (43.0)	65 (48.9)	0.409
Radiological feature			
PTB in CT†	35 (40.7)	48 (36.1)	0.569
PTB in CXR	30 (34.9)	47 (35.3)	>0.990
Pleural effusion			
Amount			0.943
Small	21 (24.4)	31 (23.3)	
Moderate	50 (58.1)	80 (60.2)	
Large	15 (17.4)	22 (16.5)	
Effusion site			0.332
Right	53 (61.6)	73 (54.9)	
Left	33 (38.4)	60 (45.1)	
Respiratory specimen			
AFB smear positive	8 (9.3)	14 (10.5)	0.480
AFB culture positive	59 (85.5)	10 (14.5)	<0.001
MTB-PCR positive	16 (18.6)	19 (14.3)	0.451
Pleural fluid exam			
AFB smear positive	0	0	
MTB culture positive	59 (68.6)	10 (7.5%)	<0.001
MTB-PCR positive	4 (4.7)	1 (0.8)	0.079
Color			0.881
Brown	1 (1.2)	3 (2.3)	
Reddish	7 (8.1)	14 (10.5)	
Yellow	77 (89.5)	115 (86.5)	
Turbid	1 (1.2)	1 (0.8)	
WBC (total cells)	1,600.0 (460.0–3,520.0)	2,240.0 (1,300.0–3,960.0)	0.026
Lymphocyte, %	80.0 (60.0–88.5)	82.0 (70.0–92.0)	0.037
Neutrophil, %	12.0 (2.0–24.0)	6.0 (1.5–15.0)	0.026
pH	7.339 (7.267–7.398)	7.389 (7.331–7.417)	<0.001
SG	1.038 (1.036–1.042)	1.038 (1.035–1.040)	0.087
Glucose	82.0 (59.8–99.3)	96.0 (78.5–113.0)	<0.001
Protein	5.3 (4.7–5.7)	5.2 (4.7–5.6)	0.310
Albumin	2.9 (2.6–3.2)	2.9 (2.5–3.2)	0.374
LDH	634.0 (437.5–893.5)	494.0 (279.5–727.0)	<0.001
ADA	89.1 (75.7–106.3)	91.3 (72.3–105.5)	0.818
CRP‡	28.9 (17.7–37.4)	26.3 (13.2–36.8)	0.315
Serum exam			
WBC	6,180.0 (5,190.0–7,757.5)	6,760.0 (5,575.0–7,980.0)	0.174
Platelet	311.5 (229.0–414.3)	328.0 (265.5–409.0)	0.219
CRP	61.3 (39.3–87.4)	42.2 (22.9–75.0)	0.005
Protein	6.9 (6.4–7.3)	6.7 (6.3–7.2)	0.525
Albumin	3.7 (3.2–3.9)	3.5 (3.2–3.9)	0.250
LDH	219.0 (184.8–265.0)	224.0 (185.0–260.0)	0.777

Values are presented as number of patients (%) or median (interquartile range).
*Pulmonary involvement of tuberculosis was determined based on radiologic studies, either CXR or chest CT. Among 142 patients with no evidence of pulmonary involvement on CXR, 17 cases of pulmonary involvement were detected on chest CT. †Chest CT was performed in 177 patients (80.8%). ‡CRP in pleural fluid was determined in 129 patients (58.9%, 51 in loculated TBPE group, 78 in non-loculated group).
TBPE: tuberculous pleural effusion; PTB: pulmonary tuberculosis; CT: computed tomography; CXR: chest X-ray; AFB: acid-fast bacilli; MTB: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; WBC: white blood cell; SG: specific gravity; LDH: lactate dehydrogenase; ADA: adenosine deaminase; CRP: C-reactive protein.

glucose level, low pH and high LDH level of TBPE, cancer as an underlying disease, and lack of a radiologically detectable lung infiltrate may be predictors for positive mycobacterial culture[10-13]. Unfortunately, these studies did not demonstrate any predictors that were markedly superior compared with others.

However, there were interesting finings observed in previous studies. It is that higher neutrophil percentage and lower lymphocyte percentage is associated with a high frequency of positive MTB cultures[10-13]. It can be explained that higher neutrophil percentage and lower lymphocyte percentage indicate more severe intra-pleural inflammation such as TB empyema or early phase of mycobacterial infection before immunologic response of anti-mycobacterial activity[10,11]. The current study cohort also demonstrated a similarly high culture frequency, but the proportion with a high neutrophil percentage in the TBPE was relatively low, with only 4.1% in this study cohort compared with 11.0%–17.0% in previous studies[11,13,35,36].

Loculation of pleural fluid is not an uncommon feature of inflammatory exudates including TBPE and parapneumonic PE, and is considered to be an intense intra-pleural inflammation resulting in fibrin deposit and subsequent adhesions in the pleural space[15,33]. In TBPE, this may be caused by elevation of the release of pro-inflammatory cytokines such as tumor necrosis factor α, interleukin 1β, transforming growth factor β1, and vascular endothelial growth factor in response to pleural infection with MTB[33,37]. Since it was demonstrated that loculated TBPE causes pulmonary impairment by residual pleural thickening, most studies have concentrated on reducing the sequelae of TBPE.

However, we focused on the predictive power of loculation of TBPE for cultivation of MTB based on the pathogenesis. The analysis of our study cohort demonstrated that compared with other factors, the loculation of TBPE is potent predictor for positive mycobacterial culture. It has been suggested that loculation of TBPE indicates intense intra-pleural inflammation caused by pleural invasion of more bacillary, with not yet effective immune-clearance system[1,4,10,11,31]. In our study, loculated TBPE group has higher neutrophil percentage and higher LDH level of pleural fluid, while it has lower lymphocyte percentage, lower glucose and pH level (Table 4). Moreover, loculation of TBPE is not uncommon and easily identifiable by the clinician. Features of loculation are shown by 22.4%–68.8% of TBPE patients, with 39.3% in this study cohort[13,17,20,38].

There are several limitations to this study. First, it was a retrospective hospital patient-based study. Second, the rate of culture-positive TBPE in this study cohort, despite using both solid and liquid media, was relatively low compared with that in previous studies (31.5% vs. 41.3%–63.1%)[10,11,39]. Third, this study was conducted in an area with intermediate TB and low HIV infection burden, and there were no HIV-infected patients in this study cohort. Fourth, the discrepancy of classification of loculated TBPE may have impacted result of this study. Among 219 cases, 177 case were underwent chest computed tomography. Of these, there were no discrepancy between interpretations. Other 42 cases were only underwent chest plain X-ray without thoracic sonography and two cases were classified as loculation group by one pulmonologist but not radiologist. However, that cases finally were classified as non-loculated group by other pulmonologist. Thus, the effect of loculation of TBPE as a predictor of positive mycobacterial culture may not be generalizable to other clinical situations.

In conclusion, our study demonstrates that loculation of TBPE is clinically useful predictor of MTB culture positivity in TBPE. The radiological identification of loculation in TBPE is easy, reliable to measure in existing practice, not uncommon and may be used in clinical practice to help to predict the possibility of positive mycobacterial culture.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

The authors thank Ms. Youn Jung Lee for her help in data collection.

References

1. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CF. Tuberculous pleural effusions: advances and controversies. J Thorac Dis 2015;7:981-91.
2. World Health Organization. Global tuberculosis report 2014. Geneva: World Health Organization; 2014.
3. Ogawa K, Koga H, Hirakata Y, Tomono K, Tashiro T, Kohno S. Differential diagnosis of tuberculous pleurisy by measurement of cytokine concentrations in pleural effusion. Tuber Lung Dis 1997;78:29-34.
4. Light RW. Update on tuberculous pleural effusion. Respirology 2010;15:451-8.
5. Udwadia ZF, Sen T. Pleural tuberculosis: an update. Curr Opin Pulm Med 2010;16:399-406.
6. Lee J, Lee SY, Lim JK, Yoo SS, Lee SY, Cha SI, et al. Radiologic and laboratory differences in patients with tuberculous and parapneumonic pleural effusions showing non-lymphocytic predominance and high adenosine deaminase levels. Infection 2015;43:65-71.
7. Gui X, Xiao H. Diagnosis of tuberculosis pleurisy with adenosine deaminase (ADA): a systematic review and meta-analysis. Int J Clin Exp Med 2014;7:3126-35.
8. Gandhi NR, Nunn P, Dheda K, Schaaf HS, Zignol M, van

Soolingen D, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010;375:1830-43.
9. Luzze H, Elliott AM, Joloba ML, Odida M, Oweka-Onyee J, Nakiyingi J, et al. Evaluation of suspected tuberculous pleurisy: clinical and diagnostic findings in HIV-1-positive and HIV-negative adults in Uganda. Int J Tuberc Lung Dis 2001;5:746-53.
10. Lee BH, Yoon SH, Yeo HJ, Kim DW, Lee SE, Cho WH, et al. Impact of implementation of an automated liquid culture system on diagnosis of tuberculous pleurisy. J Korean Med Sci 2015;30:871-5.
11. Ruan SY, Chuang YC, Wang JY, Lin JW, Chien JY, Huang CT, et al. Revisiting tuberculous pleurisy: pleural fluid characteristics and diagnostic yield of mycobacterial culture in an endemic area. Thorax 2012;67:822-7.
12. Liu SF, Liu JW, Lin MC. Characteristics of patients suffering from tuberculous pleuritis with pleural effusion culture positive and negative for *Mycobacterium tuberculosis*, and risk factors for fatality. Int J Tuberc Lung Dis 2005;9:111-5.
13. Bielsa S, Palma R, Pardina M, Esquerda A, Light RW, Porcel JM. Comparison of polymorphonuclear- and lymphocyte-rich tuberculous pleural effusions. Int J Tuberc Lung Dis 2013;17:85-9.
14. Mason RJ, Broaddus VC, Martin TR, King TE Jr, Schraufnagel DE, Murray JE, et al. Murray and Nadel's textbook of respiratory medicine. Philadelphia: Saunders Elsevier; 2010.
15. Idell S. The pathogenesis of pleural space loculation and fibrosis. Curr Opin Pulm Med 2008;14:310-5.
16. Joint Committee for the Development of Korean Guideline for Tuberculosis; Korean Centers for Disease Control and Prevention. Korean guidelines for tuberculosis. 2nd ed. Cheongwon: Korean Centers for Disease Control and Prevention; 2014.
17. Chung CL, Chen CH, Yeh CY, Sheu JR, Chang SC. Early effective drainage in the treatment of loculated tuberculous pleurisy. Eur Respir J 2008;31:1261-7.
18. Kwak SM, Park CS, Cho JH, Ryu JS, Kim SK, Chang J, et al. The effects of urokinase instillation therapy via percutaneous transthoracic catheter in loculated tuberculous pleural effusion: a randomized prospective study. Yonsei Med J 2004;45:822-8.
19. Kwon JS, Cha SI, Jeon KN, Kim YJ, Kim EJ, Kim CH, et al. Factors influencing residual pleural opacity in tuberculous pleural effusion. J Korean Med Sci 2008;23:616-20.
20. Cases Viedma E, Lorenzo Dus MJ, Gonzalez-Molina A, Sanchis Aldas JL. A study of loculated tuberculous pleural effusions treated with intrapleural urokinase. Respir Med 2006;100:2037-42.
21. Bae E, Im JH, Kim SW, Yoon NS, Sung H, Kim MN, et al. Evaluation of combination of BACTEC mycobacteria growth indicator tube 960 system and Ogawa media for mycobacterial culture. Korean J Lab Med 2008;28:299-306.
22. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125-37.
23. Conde MB, Loivos AC, Rezende VM, Soares SL, Mello FC, Reingold AL, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med 2003;167:723-5.
24. Kim HJ, Lee HJ, Kwon SY, Yoon HI, Chung HS, Lee CT, et al. The prevalence of pulmonary parenchymal tuberculosis in patients with tuberculous pleuritis. Chest 2006;129:1253-8.
25. Ko JM, Park HJ, Kim CH. Pulmonary changes of pleural TB: up-to-date CT imaging. Chest 2014;146:1604-11.
26. Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of extrapulmonary tuberculosis in the United States, 1993-2006. Clin Infect Dis 2009;49:1350-7.
27. Lai CC, Liu WL, Tan CK, Huang YC, Chung KP, Lee MR, et al. Differences in drug resistance profiles of *Mycobacterium tuberculosis* isolates causing pulmonary and extrapulmonary tuberculosis in a medical centre in Taiwan, 2000-2010. Int J Antimicrob Agents 2011;38:125-9.
28. Lee HY, Lee J, Lee YS, Kim MY, Lee HK, Lee YM, et al. Drug-resistance pattern of *Mycobacterium tuberculosis* strains from patients with pulmonary and extrapulmonary tuberculosis during 2006 to 2013 in a Korean tertiary medical center. Korean J Intern Med 2015;30:325-34.
29. Baumann MH, Nolan R, Petrini M, Lee YC, Light RW, Schneider E. Pleural tuberculosis in the United States: incidence and drug resistance. Chest 2007;131:1125-32.
30. World Health Organization. Global tuberculosis report 2013. Geneva: World Health Organization; 2013.
31. Ferreiro L, San Jose E, Valdes L. Tuberculous pleural effusion. Arch Bronconeumol 2014;50:435-43.
32. Chen WL, Sheu JR, Chen RJ, Hsiao SH, Hsiao CJ, Chou YC, et al. *Mycobacterium tuberculosis* upregulates TNF-alpha expression via TLR2/ERK signaling and induces MMP-1 and MMP-9 production in human pleural mesothelial cells. PLoS One 2015;10:e0137979.
33. Chung CL, Chen CH, Sheu JR, Chen YC, Chang SC. Proinflammatory cytokines, transforming growth factor-beta1, and fibrinolytic enzymes in loculated and free-flowing pleural exudates. Chest 2005;128:690-7.
34. Jeon D. Tuberculous pleurisy: an update. Tuberc Respir Dis 2014;76:153-9.
35. Jolobe OM. Atypical tuberculous pleural effusions. Eur J Intern Med 2011;22:456-9.
36. Lin MT, Wang JY, Yu CJ, Lee LN, Yang PC; TAMI Group. *Mycobacterium tuberculosis* and polymorphonuclear pleural effusion: incidence and clinical pointers. Respir Med 2009;103:820-6.
37. Bien MY, Wu MP, Chen WL, Chung CL. VEGF correlates with inflammation and fibrosis in tuberculous pleural effusion. ScientificWorldJournal 2015;2015:417124.
38. Han DH, Song JW, Chung HS, Lee JH. Resolution of residual

pleural disease according to time course in tuberculous pleurisy during and after the termination of antituberculosis medication. Chest 2005;128:3240-5.
39. von Groote-Bidlingmaier F, Koegelenberg CF, Bolliger CT, Chung PK, Rautenbach C, Wasserman E, et al. The yield of different pleural fluid volumes for *Mycobacterium tuberculosis* culture. Thorax 2013;68:290-1.