DIFFERENCES IN CLINICAL MANIFESTATIONS AND PLEURAL FLUID CHARATERISTICS BETWEEN TUBERCULOUS AND MALIGNANT PLEURAL EFFUSIONS

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Abstract. Tuberculous and malignant pleural effusions share similar clinical and radiographic findings and both may produce lymphocytic-predominant exudative effusions. This study aimed to determine distinguishing clinical features between the two diseases. We conducted a retrospective study among 47 patients with tuberculous pleural effusions (TBPE) and 73 with malignant pleural effusions (MPE). Demographic data, clinical features, pleural fluid characteristics, and radiographic findings were obtained for each patient and the 2 groups were compared. Sixty-nine (57.5%) patients were males. The mean (±SD, range) age was 60.2 (±16.9, 19 - 94) years. Mean (± SD) symptom duration was 31.6 (± 51.6) days. Univariate analysis identified 20 clinical, pleural fluid and radiological differences between the two groups. Multivariate logistic regression analysis revealed 3 independent predictors of TBPE: fever (OR=8.2; 95% CI: 1.9 - 35.9; p=0.005), having a non-serosanguinous effusion (OR=6.1; 95% CI: 1.1 - 33.6; p=0.038), and a fluid adenosine deaminase level > 30 U/l (OR=86.7; 95% CI: 4.3 -1735; p=0.004). Fever, non-serosanguinous pleural effusions and high adenosine deaminase levels were suggestive of a TBPE and could be clinically useful when evaluating a pleural effusion of unknown etiology.

Keywords: adenosine deaminase, malignancy, pleural effusion, tuberculosis

INTRODUCTION

Pleural effusions can pose a serious respiratory problem. The two leading causes of exudative pleural effusions are tuberculosis (TB) and malignancy (Valdes *et al*, 1996; Liam *et al*, 2000a; Kalaajieh, 2001). Tuberculous pleural effusions (TBPEs) and malignant pleural effusions (MPEs) are lymphocytic predominant (lymphocyte count >50% of the total white blood cells count) and both are exudates according to Light's criteria (Light *et al*, 1972). Distinguishing between the two groups is challenging because they share a number of common clinical and radiological characteristics (Nyman *et al*, 1996; Porcel and Vives, 2003b; Antonangelo *et al*, 2007; Kim *et al*, 2014).

Studies have evaluated a variety of models to distinguish between TBPEs and MPEs but the results have been inconsis-

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tent (Porcel and Vives, 2003a; Neves *et al*, 2007; Porcel *et al*, 2008; Valdes *et al*, 2010).

One study from Malaysia found patients with TBPEs were younger, had larger effusions, a higher lymphocyte percentage, a lower red blood cell count and a higher protein content in pleural fluid than patients with MPEs (Liam *et al*, 2000b). A study from Korea found more nodular pleural thickening on chest computed tomography (CT) scan among patients with MPEs than with TBPE (Kim *et al*, 2014).

In Thailand there have been no study of the clinical characteristics that could be used to distinguish between TBPEs and MPEs; therefore we determined to accomplish this with our study.

MATERIALS AND METHODS

Study population and design

We conducted this retrospective case study at Thammasat University Hospital, a 540-bed tertiary care teaching hospital in Thailand, among all patients aged ≥ 15 years admitted with a diagnosis of TBPEs or MPEs between January 2007 and December 2012.

Ethics

This study was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University, Thailand (IRB No. MTU-EC-IM-1-099/55).

Data sources and definitions

Eligible patients were identified by using the International Classification of Diseases, 10th revision (ICD-10) codes associated with tuberculous pleurisy, confirmed bacteriologically and histologically (A15.6), tuberculous pleurisy, without mention of bacteriological or histological confirmation (A16.5), malignant neoplasm of the pleura (C38.4), and secondary malignant neoplasm of the pleura (C78.2). Chart reviews were conducted to verify the diagnosis, sex, age, smoking status, co-morbid diseases, clinical features, pleural fluid characteristics, and radiographic findings. The data were recorded on a standard case record form (CRF).

Pleural effusions were classified as an exudate using Light's three criteria of at least one of the following criteria: a pleural fluid to serum protein ratio >0.5, a pleural fluid to serum LDH ratio >0.6, and a pleural fluid LDH >2/3 the upper limit of normal for the serum LDH (Light *et al*, 1972) and described by their gross appearance as being purulent, serosanguinous or hemorrhagic.

Studied patients had diagnostic thoracentesis for cell count, cell differential, cytology, Gram stain, Ziehl-Neelsen stain, and bacterial and TB cultures, and protein and lactate dehydrogenase (LDH) levels. Their sera were also checked for protein and LDH levels. Patients with an exudate also had a closed percutaneous pleural biopsy with an Abrams needle. None of the patients underwent thoracoscopy.

The diagnostic criteria for TBPEs and MPEs are shown in Tables 1 and 2, respectively.

On chest radiograph at presentation, a pleural effusion was considered small if the costophrenic angle was obliterated, moderate if the lower zone was completely opaque, large if the lower and middle zones were opaque and massive if all three zones were opaque. For patients with bilateral effusions, the size of the larger effusion was used for categorization. Other abnormal chest findings on plain film radiography and CT scans were recorded.

Statistical analysis

Comparisons between TBPEs and

Table 1
Diagnostic methods of tuberculous pleural effusions (*n*=47).

Criteria for diagnosis	Number of patients (%)
Positive AFB staining of pleural fluid (*n*=47)	1 (2.1)
Mycobacterium tuberculosis identified by PCR testing and culture of the pleural fluid (*n*=8)	1 (12.5)
Mycobacterium tuberculosis identified by PCR testing of the pleural fluid (*n*=15)	2 (13.3)
Mycobacterium tuberculosis identified by culture of the pleural fluid (*n*=16)	2 (12.5)
Caseous granuloma on pleural biopsy with a positive culture for *Mycobacterium tuberculosis* (*n*=9)	1 (11.1)
Caseous granuloma on pleural biopsy with a negative stain for AFB, PCR testing and culture (*n*=17)	8 (40.0)
Clinical and radiological evidence of TB in the absence of any other cause of pleural effusion and clinical improvement with anti-tuberculosis treatment (*n*=47)	32 (68.1)

AFB, acid-fast bacilli; PCR, polymerase chain reaction.

Table 2
Diagnostic methods and types of malignant pleural effusions (*n*=73).

Diagnostic methods and types of cancer	Number of patients (%)
Criteria for diagnosis	
Cytological evidence of malignancy from pleural fluid	59 (80.8)
Histological evidence of malignancy from pleural biopsy	2 (2.7)
Cytological and histological evidence of malignancy from pleural fluid and pleural biopsy	12 (16.4)
Types of cancer	
Lung cancer	37 (50.7)
Lymphoma	7 (9.6)
Breast cancer	4 (5.5)
Ovarian cancer	1 (1.4)
Prostate cancer	1 (1.4)
Colorectal cancer	1 (1.4)
Cholangiocarcinoma	1 (1.4)
Chronic lymphocytic leukemia	1 (1.4)
Malignant paraganglioma	1 (1.4)
Osteosarcoma	1 (1.4)
Cancer of unknown primary origin	18 (24.6)

MPEs were made using the chi-square test for categorical data and unpaired *t*-test for continuous data. A two-side p-value < 0.05 was considered statistically significant. Logistic regression was used to assess independent predictors for TBPEs using a backward-stepwise selection using p-value < 0.05 as significant. The program

Table 3
Clinical features and radiographic findings of patients with tuberculous and malignant pleural effusions.

Characteristics	Total (*N*=120) *n* (%)	TBPEs (*N*=47) *n* (%)	MPEs (*N*=73) *n* (%)	*p*-value[a]
Male	69 (57.5)	29 (61.7)	40 (54.8)	0.45
Age, years[b]	60.2 ± 16.9	51.1 ± 17.8	66.0 ± 13.5	<0.001
Smoking	45 (37.5)	14 (29.8)	31 (42.5)	0.16
History of TB contact	3 (2.5)	2 (4.3)	1 (1.4)	0.32
Previous history of TB	2 (1.7)	1 (2.1)	1 (1.4)	0.75
Comorbid diseases	63 (52.5)	22 (46.8)	41 (56.2)	0.32
HIV infection	5 (4.2)	4 (8.5)	1 (1.4)	<0.001
Malignancy	16 (13.3)	1 (2.1)	15 (20.5)	0.004
Others	42 (35.0)	17 (36.2)	25 (34.2)	0.21
Duration of symptoms in days[b]	31.6 ± 51.6	17.0 ± 15.3	41.0 ± 63.4	0.004
Dyspnea	89 (74.2)	22 (46.8)	67 (91.8)	<0.001
Fever[c]	46 (38.8)	37 (78.7)	9 (12.3)	<0.001
Chest pain	45 (37.5)	27 (57.4)	18 (24.7)	<0.001
Cough	85 (70.8)	32 (68.1)	53 (72.6)	0.59
Hemoptysis	3 (2.5)	2 (4.3)	1 (1.4)	0.32
Weight loss	55 (45.8)	21 (44.7)	34 (46.6)	0.84
Chest radiographic findings				
Mediastinal lymphadenopathy	31 (25.8)	3 (6.4)	28 (38.4)	<0.001
Lung mass	21 (17.5)	1 (2.1)	20 (27.4)	<0.001
Lung nodules	3 (2.5)	1 (2.1)	2 (2.7)	0.83
Reticulonodular infiltration	3 (2.5)	2 (4.3)	1 (1.4)	0.32
Lung cavity	2 (1.7)	2 (4.3)	0 (0)	0.15
Bronchiectasis	1 (0.8)	0 (0)	1 (1.4)	1.0
Pleural nodules	21 (17.5)	0 (0)	21 (28.8)	<0.001
Pleural thickening	4 (3.3)	1 (2.1)	3 (4.1)	1.0
Loculated pleural effusion	3 (2.5)	2 (4.3)	1 (1.4)	0.56
Pericardial effusion	6 (5.0)	1 (2.1)	5 (6.8)	0.40

[a]Comparison between TBPEs and MPEs; [b]Mean ± SD.
[c]Defined as body temperature more than 37.8°C.
TBPEs, tuberculous pleural effusions; MPEs, malignant pleural effusions; TB, tuberculosis; HIV, human immunodeficiency virus.

SPSS version 16 (SPSS, Chicago, IL) was used for statistical calculations.

RESULTS

One hundred twenty patients were included in the study; 47 (39.2%) had TBPEs and 73 (60.8%) had MPEs. The most common cause of MPEs was lung cancer (Table 2). Males comprised 57.5% and the mean [± standard deviation (SD), range] age was 60 (± 16, 19 - 94) years. The most common criteria (68.1%) for diagnosing a TBPE were clinical and radiological evidence of TB without findings consistent with other

Table 4
Pleural fluid characteristics of patients with tuberculous and malignant pleural effusions.

Characteristics	Total (*N*=120) *n* (%)	TBPEs (*N*=47) *n* (%)	MPEs (*N*=73) *n* (%)	*p*-value[a]
Affected side of pleural effusion				
Right	75 (62.5)	31 (66.0)	44 (60.3)	0.53
Left	35 (29.2)	13 (27.7)	22 (30.1)	0.77
Both	10 (8.3)	3 (6.4)	7 (9.6)	0.53
Size of pleural effusion				
Small	30 (25.0)	19 (40.4)	11 (15.1)	0.002
Moderate	49 (40.8)	22 (46.8)	27 (37.0)	0.28
Large	18 (15.0)	4 (8.5)	14 (19.2)	0.11
Massive	23 (19.2)	2 (4.3)	21 (28.8)	0.001
Pleural fluid color				
Serosanguinous	44 (36.7)	6 (12.8)	38 (52.1)	< 0.001
Straw	53 (44.2)	25 (53.2)	28 (38.4)	0.11
Yellowish	22 (18.3)	16 (34.0)	6 (8.2)	< 0.001
Milky	1 (0.8)	0 (0)	1 (1.4)	0.42
Red blood cell count, cells/μl[b]	48,500 ± 124,683	8,731 ± 13,455	74,100 ± 154,543	0.004
White blood cell count, cells/μl[b]	1,793 ± 2,138	2,467 ± 2,370	1,359 ± 1,865	<0.001
Lymphocyte percentage[b]	77.0 ± 16.9	82.8 ± 18.0	73.2 ± 15.2	0.002
Neutrophil percentage[b]	22.8 ± 16.9	16.8 ± 17.9	26.7 ± 15.2	0.002
Lymphocyte-predominant pleural effusion[c]	117 (97.5)	46 (97.9)	71 (97.3)	0.83
LDH concentration, U/l[b]	1,588 ± 4,672	2,379 ± 7,275	1,078 ± 1,265	0.05
Pleural fluid/serum LDH ratio[b]	2.70 ± 6.60	3.99 ± 10.11	1.87 ± 2.22	0.06
Fluid:serum ratio > 0.6	103 (85.8)	41 (87.2)	62 (84.9)	0.79
Protein concentration, g/dl[b]	4.7 ± 1.8	5.1 ± 1.7	4.5 ± 1.9	0.001
Pleural fluid/serum protein ratio	0.68 ± 0.32	0.69 ± 0.22	0.69 ± 0.37	0.11
Fluid:serum ratio > 0.5	102 (85.0)	42 (89.4)	60 (82.2)	0.43
Glucose concentration, mg/dl[b]	109 ± 60	96 ± 41	117 ± 69	0.06
ADA concentration, U/l[b]	30.1 ± 25.1	51.0 ± 21.7	12.2 ± 8.4	<0.001

[a]Comparison between TBPEs and MPEs; [b]Mean ± SD; [c]defined as lymphocyte count more than 50% of the total white blood cells count.
TBPEs, tuberculous pleural effusions; MPEs, malignant pleural effusions; LDH, lactate dehydrogenase; ADA, adenosine deaminase.

diagnoses and clinical improvement with anti-TB treatment (Table 1). The mean duration of symptoms was 31 days. The most common presenting symptoms were dyspnea, cough and weight loss. Mediastinal lymphadenopathy, lung mass, pleural nodules, predominant right-sided pleural effusion, and small to moderate size of pleural effusion were the more frequent radiographic findings (Table 3). The most common pleural fluid finding was straw colored or serosanguinous appearance. The pleural fluid findings and laboratory test results are shown in Table 4. The most striking difference between the TBPEs and MPEs groups was the average adenosine

Table 5
Logistic regression analysis of significant differences in characteristics of patients with tuberculous compared with malignant pleural effusions.

Characteristics	Adjusted odds ratio (95% CI)	*p*-value
Fever[a]	8.2 (1.9 - 35.9)	0.005
Non-serosanguinous pleural effusions	6.1 (1.1 - 33.6)	0.038
ADA > 30 U/l	86.7 (4.3 - 1,735)	0.004

[a]Defined as body temperature more than 37.8°C.

deaminase level in the TBPE group was 4 times that in the MPE group.

On bivariate analysis, there were a number of significant differences between the TBPEs and MPEs groups (Tables 3 and 4). However, on logistic regression analysis, 3 characteristics were significant different between TBPEs and MPEs: fever, non-serosanguinous pleural fluid, and an ADA level > 30 U/l were also more common in the TBPE group (Table 5).

DISCUSSION

In this study we found a low TB diagnostic yield with TB culture, PCR and histology. We also found a low diagnostic yield for MPEs with histology but pleural fluid cytology had a higher sensitivity. The most common malignancy in our study was lung cancer.

We found three independent predictors of TBPEs: fever, non-serosanguinous pleural effusions and an ADA level >30 U/l.

Fever was a common presentation with TBPEs in our study (about 80%). Its value as an independent predictor of TB has been found in several studies (Liam *et al*, 2000b; Porcel *et al*, 2008; Valdes *et al*, 2010; Sarker *et al*, 2011). Valdes *et al* (2010) found 4 predictors of TB among patients aged <40 years: pleural fluid ADA, lymphocytes, fever and cough.

A serosanguinous effusion is associated with an acute inflammatory reaction, vascular dilatation and proliferation in the pleura or underlying pulmonary parenchyma (Broghamer *et al*, 1984) and having increased levels of vascular endothelial growth factor and angiopoietin-2 (Tomimoto *et al*, 2007). In our study, a serosanguinous effusion was much less common in TBPEs than MPEs (12.8% *vs* 52.1%, $p<0.001$) similar to a previous study (11.5% *vs* 50.7%, $p<0.001$) (Antonangelo *et al*, 2007).

ADA, a T-cell enzyme, is a well-established biomarker for diagnosing TBPEs (Light, 2010). ADA levels increased when there is T-cell activation. Diagnostic cut-off values for ADA have varied by study, ranging from 20-71 U/l (Liang *et al*, 2008; Zaric *et al*, 2008; Valdes *et al*, 2010). Studies from Thailand found similar ranges (range: 17.5-60 U/l) (Riantawan *et al*, 1999; Reechaipichitkul *et al*, 2001; Khow-Ean *et al*, 2013). In the present study, we used an ADA cut-off level of 30 U/l because it gave the highest sensitivity (85.4%) and specificity (97.9%) with area under the ROC curve of 0.918. Furthermore, this cut-off value was significant on multivariate logistic regression. Given its high diagnostic value, measuring pleural fluid ADA is essential. This is supported by a meta-

analysis by Liang *et al* (2008) who found it gave an overall sensitivity of 92% and a specificity of 90% for diagnosing TBPEs.

Our findings suggest 3 factors are suggestive of TBPEs: fever, a non-serosanguinous pleural effusion and an ADA level >30 U/l. A prospective study is required to verify these factors as part of a predictive model.

A limitation of this study was its retrospective nature and the relatively small number of patients. The data were more likely to be incomplete than a prospective study. The small sample size could limit the sensitivity in detecting factors significantly associated with TBPEs.

In summary, factors significantly associated with TBPEs were fever, a non-serosanguinous pleural effusion and a high ADA level. These may assist physicians in clinically differentiating TBPEs from MPEs in high TB prevalence areas.

ACKNOWLEDGEMENTS

This study was funded by the Faculty of Medicine, Thammasat University. The authors gratefully acknowledge Dr Bob Taylor who assisted with the English version of the manuscript. The authors declare that they have no conflicts of interest.

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