ORIGINAL ARTICLE

Differences in Pleural Fluid Characteristics, White Cell Count and Biochemistry of Tuberculous and Malignant Pleural Effusions

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Summary

Tuberculosis and malignancy are two common causes of exudative pleural effusions. In this retrospective study of 52 patients with tuberculous pleural effusions and 32 patients with malignant effusions, the median age of patients with malignant effusions (68.5 years) was older than that of patients with tuberculous effusions (34.5 years) ($p<0.001$). Both types of effusion occurred more frequently on the right side and there was no difference between them in terms of right-sided dominance. A higher percentage of patients with malignant pleural effusions (44%) presented with large effusions than patients with tuberculous effusions (12%) ($x^2=11.33$, $p=0.001$). A higher proportion of patients with tuberculous effusion had lymphocyte predominant effusions and tuberculous effusions had higher lymphocyte percentage, lower red cell count, and higher protein content. However, there was considerable overlap of these characteristics of both types of effusions.

Key Words: Malignancy, Pleural effusion, Tuberculosis

Introduction

The distinction between malignant and non-malignant pleural effusions is often difficult in medical practice as it is not always possible to demonstrate the presence of malignant cells in malignant effusions. Closed needle biopsy of pleural is a well established method in the evaluation of unexplained pleural effusion[1-3]. However, compared to pleural fluid cytology, needle pleural biopsy has an even lower yield for the diagnosis of malignant pleural disease because of a problem in sampling[4-6].

The development of pleural effusions is associated with an influx of inflammatory cells into the pleural space[7]. Different disease entities are associated with the presence of particular types of leucocytes in the pleural fluid[8-11]. In malignant and tuberculous pleural effusions, lymphocytes predominate[8-12]. In Malaysia, tuberculous pleuritis is rather common, and the differential diagnosis between tuberculous and nontuberculous causes of lymphocyte-rich exudative pleural effusions is an important clinical problem. The diagnosis of tuberculous pleuritis is considered when epithelioid granuloma exists in the pleural biopsy specimen. However, epithelioid granulomas are scattered throughout the parietal pleura and the pleural tissue between granulomas shows a non-specific histology[1,2]. As a result, some of the closed needle biopsy specimens of tuberculous pleuritis reveal only non-specific findings[13]. Pleural fluid culture for *Mycobacterium tuberculosis* has a sensitivity of only 20 to 30% and the long culture periods required means that clinical decisions are often made before culture results become available[14,15].

When the initial evaluation fails to clarify the cause of an exudative pleural effusion rich in lymphocytes and a needle biopsy of the pleura shows only non-specific histological findings, we always face the problem of whether the effusion is caused by tuberculosis (TB) or malignancy. Anti-tuberculosis therapy may be tried in such a patient. However, this may result in delay in the diagnosis of other causes of lymphocyte-rich pleural effusion, particularly neoplasm. Thoracoscopy or open pleural biopsy may be considered but these invasive procedures entail morbidity, lengthen hospital stay, and on rare occasions result in mortality. Even though recent reports[16] have shown the utility of measuring pleural fluid adenosine deaminase levels combined with differential leucocyte counts in the differentiation of tuberculous from neoplastic pleural effusions, the former test is not widely available.

The objective of this study was to assess whether patient demographics, pleural fluid characteristics and simple pleural fluid analysis: cell counts, differential leucocyte counts, protein level and glucose concentration help to distinguish two of the most common causes of exudative pleural effusions - tuberculous pleurisy and malignancy[17-20].

Materials and Methods

This is a retrospective review of patients who were diagnosed to have pleural effusions due to tuberculous pleurisy and malignancy at the University of Malaya Medical Centre, Kuala Lumpur, Malaysia from January 1995 to June 1998.

Pleural effusions were diagnosed to be due to pleural TB if (i) pleural fluid was culture positive for *Mycobacterium tuberculosis*; or (ii) histological examination of pleural biopsy specimens showed the presence of epithelioid granulomas with or without caseating necrosis and the presence of acid-fast bacilli (AFB) on Ziehl-Neelsen staining; or (iii) the presence of epithelioid granulomas with or without caseating necrosis in pleural biopsy specimens plus the presence of positive direct smear for AFB and/or positive culture for *Mycobacterium tuberculosis* from respiratory tract specimens which included sputum, bronchoalveolar lavage, or bronchial biopsy specimen; or (iv) the presence of epithelioid granulomas with or without caseating necrosis in pleural biopsy specimens with clinical and radiological response to anti-tuberculosis chemotherapy.

Malignant or neoplastic pleural effusions were confirmed by (i) positive pleural biopsy and/or (ii) positive pleural fluid cytology.

The size of the pleural effusion seen on chest radiograph at presentation was graded as small when the costophrenic angle was obliterated but the hemidiaphragm was not covered, as medium when it filled up to half of the hemithorax, or as large when it filled up more than half of the hemithorax.

Patients who presented with pleural effusions routinely underwent diagnostic thoracentesis to obtain pleural fluid specimens for cell count, biochemistry, cytology and microbiology. As a routine, a sample of pleural fluid was sent to the medical microbiology laboratory for bacterial and tuberculosis culture. Cell counts were performed by placing a drop of undiluted pleural fluid in a counting chamber. The cells were concentrated by centrifugation of the pleural fluid, followed by resuspension of the sediment in 1ml of pleural fluid. Then one drop of the concentrated specimen was placed on a cover slip, spread evenly and stained with Field's stain. The differential white cell count was reported as percentages. Patients were considered to have lymphocyte-predominant pleural effusions when lymphocytes constituted more than 50% of white blood cells in the pleural fluid. Total protein levels were obtained for both serum and pleural fluid specimens to distinguish exudates from transudates according to Light's criteria[21]. Total protein level in pleural fluid was measured by turbidimetry using a spectrophotometer at wavelength 420 nm (Jenway, UK). Pleural fluid glucose concentration was estimated using a glucose analyser (Beckman Glucose Analyser 2, USA).

Patients with pleural effusions too haemorrhagic for analysis were excluded from this study. For patients in whom more than one thoracentesis was performed, the biochemical and cell count results of only the first thoracentesis specimens were reported and used for statistical analysis.

Table I
Basis for Diagnosis of Tuberculous Pleural Effusion

Criteria for Diagnosis of Tuberculous Pleural Effusion	No. of Patients
Pleural fluid culture positive for *Mycobacterium tuberculosis*	2
Presence of epithelioid cell granulomas with/without caseating necrosis and positive staining for AFB in pleural biopsy specimens	13
Presence of epithelioid cell granulomas with/without caseating necrosis in pleural biopsy specimens plus positive AFB and/or *Mycobacterium tuberculosis* isolated from respiratory tract specimens	4
Presence of granulomas with/without caseating necrosis in pleural biopsy specimens plus clinical and radiological response to anti-tuberculosis chemotherapy	33
Total	52

AFB = acid-fast bacilli

Data and statistical analysis

Results are expressed as median (range). To analyse continuous variables, the Mann-Whitney *U* test was used for data that were not normally distributed. Categorical variables were compared using the chi-square (x^2) method with Yates' correction or Fisher's exact test when appropriate. The correlation between two continuous variables was tested with the Pearson's correlation coefficient. A p value of less than 0.05 for a two-tailed test was considered statistically significant.

Results

During the period of study, there were 52 patients with pleural effusions due to tuberculous pleurisy and 37 patients with malignant pleural effusions. Five patients with malignant pleural effusions which were too haemorrhagic for analysis were excluded from the study. The criteria for the diagnosis of pleural effusions due to tuberculous pleurisy are shown in Table I. The methods of confirming malignant pleural effusions are shown in Table II. All cases of malignant pleural effusions except one were due to lung cancer (Table III).

Table IV summarises the differences in demographic and clinical features of patients with tuberculous and malignant pleural effusions. The male to female ratios were not significantly different. Patients with malignant pleural effusions were significantly older with a median age double that of patients with tuberculous effusions. Almost all the patients with pleural effusions due to tuberculosis had fever but none of those with malignant effusions had this symptom. The majority of patients with both conditions suffered weight loss. A history of tuberculosis contact was infrequently present in patients with tuberculous effusions and none of the patients with

Table II
Confirmation of Malignant Pleural Effusions

Method of Confirmation	No. of Patients
Positive histology on pleural biopsy	7
Positive histology on pleural biopsy and positive pleural fluid cytology	8
Positive pleural fluid cytology only	17
Total	32

Table III
Neoplasms Causing Malignant Pleural Effusions

Type of Malignancy	No. of Patients
Adenocarcinoma of lung	21
Undifferentiated carcinoma of lung	5
Small cell lung cancer	3
Squamous cell carcinoma of lung	1
Adenosquamous carcinoma of lung	1
Mesothelioma	1
Total	32

Table IV
Differences Between Demographic and Clinical Features of Patients with Tuberculous and Malignant Pleural Effusions

Demographic and Clinical Features	Tuberculous Pleural Effusion (n = 52)	Malignant Pleural Effusion (n = 32)	*P* value
Male to female ratio	2.7	1.7	0.439
Median age (years)	34.5 (19 - 83)	68.5 (31 - 87)	<0.001
Proportion of patients with fever	50/52	0/32	<0.0001
Proportion of patients with weight loss	40/52	25/32	0.898
Proportion of patients with tuberculosis contact	4/52	0/32	0.140
Median erythrocyte sedimentation rate (mm/hr)	72.5 (2 - 133)	39 (3 - 150)	<0.016

The values in parentheses are the ranges

malignant effusions gave such a history. Patients with tuberculous effusions had significantly higher erythrocyte sedimentation rates (ESR) than those with malignant effusions.

Table V shows the comparison between the pleural fluid characteristics of patients with pleural effusions due to tuberculosis and that of those due to malignancy. Both types of effusion occurred more frequently on the right side and there was no difference between them in terms of right-sided dominance of their occurrence. A significantly higher percentage of patients with malignant pleural effusions presented with large effusions than patients with tuberculous effusions (x^2=11.33, p=0.001). The median red blood cell count in malignant pleural effusions was significantly higher while there was no difference in the median white cell count between the two types of pleural effusions. The median lymphocyte percentage was higher and conversely, the polymorphonuclear leucocyte percentage was lower in tuberculous pleural effusions. A significantly higher proportion of patients with tuberculous effusions had lymphocyte-predominant pleural fluids than those with malignant effusions.

While the median protein concentration of tuberculous effusions was significantly higher than that of malignant effusions there was no difference in the sugar concentration between the two types of effusion. The pleural fluid protein concentration was greater than 50g/L in 39 (75%) patients with tubercuous effusions and in 11 (34.4%) patients with malignant effusions (x^2=11.936, p=0.001). The pleural fluid sugar level was less than 3.3mmol/L in eight (15.4%) patients with tuberculous effusions and in eight (25%) patients with malignant effusions (p=0.422). There was no correlation between pleural fluid protein and sugar in the case of tuberculous effusions (r=-0.0318, p=0.823) or in the case of malignant effusions (r=-0.2567, p=0.156).

Discussion

The median age of our patients with tuberculous pleural effusion was 34.5 years. This is in agreement with the findings in other developing countries where the average age of patients with pleural TB remains much lower[22,23] compared to the average age of such patients in developed countries which has steadily increased[14,24-26]. As malignancy tends to occur in an older population it is not surprising that patients with malignant pleural effusions were much older than those with tuberculous pleural effusions in Malaysia. However, there is considerable overlap between the age range of patients with tuberculous pleurisy (19 - 83 years) and that of patients with malignant effusions (31 - 87 years). Therefore, age alone cannot be used to predict whether a

Table V
Differences between Tuberculous and Malignant Pleural Effusions

Characteristics	Tuberculous Pleural Effusion (n = 52)	Malignant Pleural Effusion (n = 32)	*P* value
Side of pleural effusion (no. of patients)			
Right	34 (65%)	23 (72%)	0.706
Left	14 (27%)	9 (28%)	
Bilateral	4 (8%)	-	
Size of pleural effusion (no. of patients)			
Large	6 (12%)	14 (44%)	0.001
Medium	34 (65%)	13 (41%)	
Small	12 (23%)	5 (15%)	
Median pleural fluid red cell count ($x10^6$/L)	1885 (0 - 55,000)	4880 (340 - 625,000)	0.002
Median pleural fluid white cell count ($x10^6$/L)	1660 (120 - 5,750)	1080 (45 - 7,500)	0.343
Median pleural fluid lymphocyte percentage (%)	92.5 (0 - 100)	70.0 (0 - 100)	0.003
Median pleural fluid polymorphonuclear leucocyte percentage (%)	7.5 (0 - 100)	30.0 (0 - 100)	0.002
Proportion of patients with lymphocyte -predominant pleural effusion	48 of 52 (92%)	21 of 32 (66%)	0.003
Median pleural fluid protein concentration (g/L)	55 (25 - 68)	45.5 (26 - 97)	<0.0001
Median pleural fluid sugar concentration (mmol/L)	4.8 (0.6 - 19.4)	5.2 (0.2 - 17.6)	0.778

The values in parentheses are the ranges

pleural effusion is due to tuberculosis or malignancy. However, fever is a useful differentiating feature; it being present in almost all patients with tuberculous pleural effusions and not present in those with malignant effusions. The ESR of patients with pleural effusions due to tuberculosis tended to be higher than those with malignant effusions but the considerable overlap of the ESR ranges in the two conditions means that ESR alone cannot be relied upon to distinguish one condition from the other.

In keeping with reports in the literature[17,27], carcinoma of the lung was the most common tumour to cause malignant pleural effusion in our patients. The right-sided dominance of tuberculous pleural effusion in our patients is in keeping with the observations by others[15,28]. The reason for this predilection is not known. Although other authors do not find a preference of neoplastic effusions for any particular side[17], malignant pleural effusions in our patients occurred 2.6 times more commonly on the right side than the left. That the

majority of massive pleural effusions are due to malignancy[29] is evident from our results which showed that the proportion of patients with large effusions was higher among our patients with malignant pleural effusions than those with TB.

Only two of our cases of tuberculous pleural effusion were diagnosed on the basis of a positive pleural fluid culture for *Mycobacterium tuberculosis*. The mycobacterial population in tuberculous pleural effusion is generally small and AFB are demonstrated on smear in less than 10% of patients[30] and cultures of the pleural fluid specimens are generally positive in only up to about 30% of cases[14,15]. Bacteriological confirmation is, therefore, often not achieved in tuberculous pleurisy. The presence of granulomatous inflammation on histological examination of pleural biopsy specimens is frequently used as a diagnostic criterion for pleural TB[31,32]. AFB was stained positive in granulomas of pleural biopsy specimens of 25% of our patients with tuberculous effusions. This is within the range of about 20 to 40% described in the literature[31,33,34].

In malignant and tuberculous effusions, the white blood cell count generally ranges between 500 to 2500 x $10^3/L^1$. The differential white cell counts often provide more insight into the cause of the pleural effusion than do total counts. More than 90% of our patients with tuberculous pleurisy had lymphocyte-predominant pleural effusions. This compares favourably with what is reported in the literature, that is, 60 to 90%[14,15,25]. A predominance of lymphocytes is also found in effusions due to malignancy[8-12]. This feature of pleural effusion, therefore does not help to distinguish between these two causes of exudative pleural effusions. However, lymphocyte-predominant pleural effusions were more commonly seen in our patients with tuberculous pleurisy than in those with neoplastic pleural disease. Even though the pleural fluid lymphocyte percentage of the total white blood cell was higher in our patients with tuberculous pleurisy than in those with malignant effusions, the overlap between the ranges of pleural fluid lymphocyte percentage in the two types of effusion renders this characteristic useless as a distinguishing feature. It is important to note that about a third of our patients with malignant effusions were polymorphonuclear predominant though this type of pleural effusion is generally lymphocyte-rich. Therefore, polymorphonuclear predominance does not rule out the possibility of an effusion being of malignant etiology.

The total protein content of pleural fluid tends to be quite high in tuberculous pleurisy and values above 50g/L suggest a tuberculous etiology[30]. Three quarters of our patients with tuberculous pleural effusions had pleural fluid protein greater than 50g/L. While tuberculous effusions in our patients had higher protein levels than malignant effusions there was no difference in the sugar concentration between the two types of effusion. Apart from empyema and rheumatoid pleurisy, low pleural fluid glucose concentration is found in tuberculous pleurisy and carcinomatous effusions[28]. There was also no correlation between pleural fluid protein and glucose levels in the two types of effusion although a high pleural fluid protein concentration is said to be found in effusions with a low glucose level[6].

In conclusion, although there are similarities between tuberculous and malignant pleural effusions in terms of their right-sided dominance and lymphocyte-rich characteristics there are significant differences between them. Malaysian patients with tuberculous pleural effusions are much younger than those with malignant effusions. A higher proportion of patients with tuberculous effusion have lymphocyte predominant effusions and tuberculous effusions are less likely to be large at presentation and have higher lymphocyte percentage, lower red cell count, and higher protein content. However, the considerable overlap of these characteristics of both types of effusions means that they cannot be used to distinguish one from the other in the individual patient who presents with an exudative pleural effusion.

References

1. Kinasewitz GT, Fishman AP. Pleural dynamics and effusions. In: Fishman AP (ed). Pulmonary diseases and disorders. 2nd ed. New York: McGraw Hill, 1989; 2117-138.
2. Poe RH, Israel RH, Utell MJ, Hall WJ, Greenblatt DW, Kallay MC. Sensitivity, specificity and predictive values of closed pleural biopsy. Arch Intern Med 1984; 144: 325-28.
3. Abrams LD. A pleural punch biopsy. Lancet 1958; 1: 30-31.
4. Salyer WR, Eggleston JC, Erozan YS. Efficacy of pleural needle biopsy and pleural fluid cytopathology in the diagnosis of malignant neoplasm involving the pleura. Chest 1975; 67: 536-39.
5. Prakash UBS, Beiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. Mayo Clin Proc 1985; 60: 158-64.
6. Sahn SA. Malignant pleural effusions. In: Fishman AP (ed). Pulmonary diseases and disorders. 2nd ed. New York: McGraw Hill, 1989; 2159-170.
7. Antony VB, Godbey SW, Kunkel SL, *et al.* Recruitment of inflammatory cells to the pleural space: chemotactic cytokine, IL-8, and monocyte chemotactic peptide-1 in human pleural fluids. J Immunol 1993; 151: 7216-223.
8. Light RW, Erozan YS, Ball WC Jr. Cells in pleural fluid: their value in differential diagnosis. Arch Intern Med 1973; 132: 854-60.
9. Yam LT. Diagnostic significance of lymphocytes in pleural effusions. Ann Intern Med 1967; 66: 972-82.
10. Light R. Parapneumonic effusions and infections of the pleural space. In: Light RW, ed. Pleural diseases. 2nd ed. Philadelphia: Lea & Febiger, 1990; 129-49.
11. Sahn SA. State of the art: the pleura. Am Rev Respir Dis 1988; 138-234.
12. Albera C, Mabritto I, Ghio P, Scagliotti GV, Pozzi E. Lymphocyte subpopulations analysis in pleural fluid and peripheral blood in patients with lymphocytic pleural effusions. Respiration 1991; 58: 65-71.
13. Leslie WK, Kinasewitz GT. Clinical characteristics of the patients with nonspecific pleuritis. Chest 1988; 94: 603-08.
14. Moudgil H, Sridhar G, Leitch AG. Reactivation disease: the commonest form of tuberculous pleural effusion in Edinburgh, 1980-1991. Respir Med 1994; 88: 301-04.
15. Berger HW, Mejia E. Tuberculous pleurisy. Chest 1973; 63: 88-92.
16. Burgess LJ, Maritz FJ, Le Roux I, Taljaard JJF. Combined use of pleural adenosine deaminase with lymphocyte/ neutrophil ratio: increased specificity for the diagnosis of tuberculous pleuritis. Chest 1996; 109: 414 -19.
17. Valdes L, Alvarez D, Valle JM, Pose A, San Jose E. The etiology of pleural effusions in an area with high incidence of tuberculosis. Chest 1996; 109: 158-62.
18. Fontan Bueso J, Verea Hernando H, Perez Garcia-Beula J, *et al.* Diagnostic value of simultaneous determination of pleural adenosine deaminase and pleural lysozyme/serum lysozyme ratio in pleural effusions. Chest 1988; 93: 303-07.
19. Storey DD, Dines DE, Coles DT. Pleural effusion: a diagnostic dilemma. JAMA 1976; 236: 2183-186.
20. Peterman TA, Speicher CE. Evaluating pleural effusions: a two-stage laboratory approach. JAMA 1984; 252: 1051-053.
21. Light RW, MacGregor I, Luchsinger PC, *et al.* Pleural effusion: the diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77: 507-13.
22. Sinha PK, Sinha BB, Sinha AR. Diagnosing tuberculous pleural effusion: comparative sensitivity of mycobacterial culture, histopathology and adenosine deaminase activity. J Assoc Phys India 1985; 33: 644-45.
23. Arriero JM, Romero S, Hernandez L, *et al.* Tuberculous pleurisy with or without radiographic evidence of pulmonary disease. Int J Tuberc Lung Dis 1998; 2: 513-17.
24. Seibert AF, Haynes J, Middleton R, Bass JB. Tuberculous pleural effusion: twenty-year experience. Chest 1991; 99: 883-86.
25. Epstein DM, Kline LR, Albelda SM, Miller WT. Tuberculous pleural effusions. Chest 1987; 91: 106-09.
26. Dutt AK, Moers D, Stead WW. Tuberculous pleural effusion: 6-month therapy with isoniazid and rifampin. Am Rev Respir Dis 1992; 145: 1429-432.
27. Hausheer FH, Yarbro JW. Diagnosis and treatment of malignant pleural effusions. Semin Oncol 1985; 12: 54-75.

28. Sahn SA. Pleural manifestations of pleural disease. Hosp Pract 1981; 16: 73-89.

29. Maher GG, Berger HW. Massive pleural effusion: malignant and non-malignant causes in 46 patients. Am Rev Respir Dis 1972; 105: 458-60.

30. Winterbauer RH. Nonneoplastic pleural effusions. In: Fishman AP (ed). Pulmonary diseases and disorders. 2nd ed. New York: McGraw Hill, 1989; 2139-157.

31. Scharer L, McClement JH. Isolation of tubercle bacilli from needle biopsy specimens of parietal pleura. Am Rev Respir Dis 1968; 97: 466-68.

32. Levine H, Metzger W, Lacera D, Kay L. Diagnosis of tuberculous pleurisy by culture of pleural biopsy specimens. Arch Intern Med 1970; 126: 269-71.

33. Kirsh CM, Kroe DM, Jensen WA, Kagawa FT, Wehner JH, Campagna AC. A modified Abrams needle biopsy technique. Chest 1995; 108: 982-86.

34. Centres for Disease Control. Tuberculosis and human immunodeficiency virus infection: recommendations of the Advisory Committee for the Elimination of Tuberculosis. MMWR 1989; 34: 236-50.