

Transudates in Malignancy: Still a Role for Pleural Fluid

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Abstract

Introduction: The aims of this study were to determine the distribution of transudates and exudates among pathologically proven malignant pleural effusions, and to demonstrate the necessity for cytologic studies in patients with a transudative effusion. **Materials and Methods:** This study is a retrospective review of all subjects diagnosed with malignant or paramalignant pleural effusion over a 10-year period at a tertiary hospital. The study included 67 subjects with malignant mesothelioma, 45 subjects with metastatic disease, and 36 subjects with paramalignant effusions. **Results:** There were 55 female and 93 male subjects; the mean age of the sample was 62 years. Malignant pleural effusions were transudative in 1.5% of malignant mesotheliomas, 6.8% of metastatic diseases, and 11.1% of paramalignant effusions. **Conclusions:** Cytological examination of pleural fluid in patients with unexplained transudative effusion is essential to rule out malignant processes.

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Key words: Biochemical criteria, Pleural malignancy, Pleural neoplasms

Introduction

According to Light's criteria, an exudate is defined by at least one of the following: a total protein pleural fluid to serum ratio greater than 0.5, an lactate dehydrogenase (LDH) pleural fluid to serum ratio greater than 0.6, or an absolute pleural fluid LDH greater than 2/3 of the upper normal limit of the normal serum LDH value. A transudate is any pleural effusion that does not meet the aforementioned criteria.¹ Although some authors report that malignant pleural effusions may be transudative in 1% to 10% of patients,² it is not known what proportion of these patients have transudates. Additionally, no data exist regarding the frequency of transudative effusions associated with malignant pleural mesothelioma. This study was conducted to determine the distribution of transudates and exudates in pleural effusions associated with malignant disease.

Materials and Methods

A retrospective review of 10 years' worth of patient data from the Department of Chest Diseases at a tertiary care hospital, identified 455 consecutive subjects with pleural effusions, of which 150 (33%) were associated with malignancy. All patients underwent thoracentesis and venepuncture for pleural fluid and serum biochemistry measurements to separate transudates from exudates by Light's criteria. This included 67 subjects with malignant

mesothelioma, 45 subjects with metastatic disease, and 36 subjects with paramalignant effusions. For the present study, malignant pleural effusion was defined as the presence of malignant cells in pleural fluid or pleural tissue. Paramalignant effusion was defined as a pleural effusion occurring in a patient with known neoplasia but without evidence of malignancy in pleural fluid or pleural tissue. We used repeated negative cytology, negative closed biopsy and absence of pleural metastasis on computed tomography (CT) for the diagnosis of paramalignant pleural effusions. Nine patients were excluded from the study because the distinction between primary and secondary tumour of pleura could not be made.

A diagnosis of malignant pleural mesothelioma was made by the panel composed of the following antibodies in pleural tissue or fluid: calretinin, epithelial membrane antigen (EMA), thrombomodulin, human mesothelial antigen (HBME)-1, CD15, B72.3, and carcinoembryonic antigen (CEA). Patient age, sex, type of malignant tumour, and serum biochemical values on the day of pleural specimen procurement were recorded. For each subject, clinical, laboratory, and radiological findings were reviewed and the presence of coexisting congestive heart failure, liver cirrhosis, chronic renal failure, or nephrotic syndrome was determined.

Chi-square test was used in the analysis of categorical

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data for the frequency of each disease in both sexes. Independent samples *t*-test was used for matched total leukocyte counts in blood or pleural fluid.

Results

Fifty-five female and 93 male subjects met the eligibility criteria for this study. The mean age of the subjects was 62 years, with a range of 23 to 85 years. All subjects had blood chemistry values available to calculate Light's criteria for transudative or exudative effusions. Diagnosis of malignant mesothelioma was by pleural biopsy for 48 subjects (71.5%), thoracotomy for 8 subjects (12.0%), pleural fluid cytology for 6 subjects (9.0%), transthoracic biopsy for 4 subjects (6.0%), and thoracoscopy in 1 subject (1.5%). The distribution of metastatic tumours is presented in Table 1. Female subjects were more likely to have malignant mesothelioma (54%) than metastatic disease (34%, $P < 0.05$) or paramalignant effusion (11%, $P < 0.01$). Characteristics of the study groups are presented in Table 2. The biochemical criteria for distinguishing between transudates and exudates are presented in Table 3.

Exudates were demonstrated in 66 of 67 patients with malignant mesothelioma, 42 of 45 patients with pleural metastasis, and 32 of 36 patients with paramalignant effusions. One patient with malignant mesothelioma did not have congestive heart failure, renal disease, or any other known cause that would account for the transudate. The 3 patients with pleural metastasis and transudative effusions had pulmonary adenocarcinoma, renal cell carcinoma, and stomach cancer. Two of these patients (1 with renal cell carcinoma and 1 with stomach cancer), also had congestive heart failure.

All transudative malignant pleural effusions were right-

sided and seen only in men. In contrast, malignant exudative effusions were left-sided in 50.5%, right-sided in 43%, and bilateral in 6.5% of the subjects. In the setting of malignant pleural effusions, patients with transudates were significantly older than those with exudates (70.0 ± 2.4 vs. 58.7 ± 1.3 , $P = 0.01$).

In the setting of paramalignant effusion, transudate was observed only in lung cancer patients. Three subjects had non-small cell lung cancer without evidence of congestive heart failure, hypoalbuminaemia, superior vena cava syndrome, renal or hepatic disease. One patient with small-cell lung cancer also had congestive heart failure.

Nine patients, excluded from the study because the differential diagnosis between malignant mesothelioma and carcinoma could not be performed, had exudates. There were no significant differences in pleural fluid characteristics between primary thoracic tumours (mesothelioma or lung) and distant metastases.

Discussion

In our series, the nearly equal frequency of mesothelioma in both genders suggested the environmental but not occupational exposure of mineral fibres such as asbestos or erionite. It has been previously reported that 10% to 20% of mesotheliomas do not cause exudates.³ In the present study, however, we found only 1 (1.5%) transudate among 67 subjects with pleural effusion and mesothelioma. No alternative explanations for the transudate (such as congestive heart failure, hypoalbuminaemia, superior vena cava syndrome or pulmonary embolism) could be determined for this subject. One potential explanation for the transudative effusion was related to a trapped lung experienced by this subject.

Table 1. Spectrum and Diagnostic Tools of Secondary Cancers of the Pleura

Origin of primary tumour	Total no. of cases	Diagnostic procedures			
		Pleural fluid cytology	Closed needle biopsy	Pleural cytology + closed needle biopsy	Thoracotomy
Lung	14	9	3	2	-
Gastrointestinal	9	8	1	-	-
Breast	3	3	-	-	-
Lymphoma	3	2	-	-	1
Prostate	2	2	-	-	-
Ovary	2	1	1	-	-
Kidney	1	1	-	-	-
Adrenal	1	1	-	-	-
Tongue	1	1	-	-	-
Myeloma	1	1	-	-	-
Unknown	8	5	3	-	-

Table 2. Clinical and Laboratory Parameters of Malignancy-Associated Pleural Effusions (mean $\pm$ SE)

Parameter	Malignant mesothelioma n = 67	Metastatic disease n = 45	Paramalignant effusion n = 36
(Men %)*	46%	66%	89%
Age	59.1 $\pm$ 1.5	61.3 $\pm$ 1.9	61.3 $\pm$ 1.9
Involvement (right/left/bilateral)	29 / 38 / 0	19 / 18 / 7	16 / 17 / 3
History of diuretic usage (n, %)	15 (22%)	15 (34%)	4 (11%)
Chest pain (n, %)	50 (75%)	21 (48%)	19 (53%)
Breathlessness (n, %)	58 (87%)	38 (86%)	31 (86%)
Fever (n, %)	9 (13%)	9 (21%)	8 (22%)
Cough (n, %)	42 (63%)	30 (68%)	30 (83%)
Weight loss (n, %)	33 (50%)	37 (84%)	22 (63%)
Transudates/exudates	1/66	3/42	4/32
% Neutrophilic effusion	60	70	64

*P < 0.05

Table 3. Biochemical Parameters Used for the Differentiating Exudates (mean $\pm$ SE for levels and mean for ratios)

Parameters	Malignant mesothelioma n = 67	Pleural metastases n = 45
Fluid total protein concentration (g/L)	45.7 $\pm$ 1.5	43.2 $\pm$ 0.2
Fluid albumin concentration (g/L)	27.5 $\pm$ 0.9	24.0 $\pm$ 0.1
Fluid LDH concentration (IU/L)	784 $\pm$ 73	716 $\pm$ 99
Fluid/serum total protein	0.66	0.65
Fluid/serum LDH	2.25	1.74

Transudates were observed in 4 (3.6%) of the 112 subjects with malignant pleural effusion (includes malignant mesothelioma and metastatic disease). This figure is consistent with reports of 1% to 10.7% in the literature.^{1,4-10} Transudative malignant effusions are generally due to early stages of mediastinal node involvement, atelectasis, or concomitant congestive heart failure.⁴ Of those with metastatic disease and transudative effusions, 1 subject had pulmonary adenocarcinoma and 2 had malignant disease from other sites. The latter 2 had concomitant congestive heart failure. For the patient with pulmonary adenocarcinoma, the cause of transudate was unclear. However, it is possible for malignant cells to be present in the pleural space without producing an effusion. The original study of Light and colleagues⁴ involved 43 malignant effusions, 1 of which was classified as a transudate. This single subject had both breast cancer and congestive heart failure.

In the setting of paramalignant effusions, 1 patient with small cell lung cancer had congestive heart failure. A second patient had non-small cell lung cancer with hypoalbuminaemia and free peritoneal fluid. Two others

had atelectasis due to central airway obstruction. The high rate of exudates (32/36) in the setting of paramalignant effusion may be due to obstructive pneumonia. Despite thoracenteses and pleural biopsy, some patients with malignant pleural effusions may be falsely classified as paramalignant.

Table 3 shows that malignant mesothelioma is more strongly associated with exudation than is metastatic disease. This is due to the intense inflammatory reaction during a primary malignant process, which results in increased microvascular permeability. We found only 1 study that compared the biochemical characteristics of malignant pleural mesothelioma and secondary pleural tumours.¹¹ The results of this study also support our findings.

In this study, exudative pleural effusions occurred most often in association with malignant mesothelioma compared to metastatic diseases of the pleura. However, some subjects with primary or secondary pleural malignancies demonstrated transudative pleural effusions. To ensure that malignancies associated with pleural effusion are not overlooked, we propose that cytological examination of pleural fluid should be performed for all patients with unexplained transudates, especially for those where clinical suspicion for malignancy is high.

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