

The Diagnostic Yield of Pleural Fluid Cytology in Malignant Pleural Effusions

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ABSTRACT

Background: The development of a pleural effusion in a patient with a known malignancy often raises the possibility that the effusion is due to malignant involvement of the pleura. Accurate diagnosis of the cause of the pleural effusion in such a patient is essential as the treatment and prognosis may vary. Currently, thoracentesis and cytologic analysis of pleural fluid cytology is usually the initial diagnostic step.

Aim: To assess the diagnostic yield of pleural fluid cytologic examination in patients with suspected malignant pleural effusions seen at our centre.

Methods: Retrospective review of the results of pleural fluid cytologic examination performed on 103 patients who presented with suspected malignant pleural effusions.

Results: The underlying malignancies in these patients were as follows: bronchogenic carcinoma (51.5%), breast carcinoma (29.1%), hepatocellular carcinoma (1.9%), carcinoma of the stomach (1.9%), malignant mesothelioma, nasopharyngeal carcinoma, renal cell carcinoma, carcinoma of the oesophagus, lymphoma, carcinoma of the colon (1% each), unknown (9.7%). Initial pleural fluid cytology was positive for malignancy in 48.5% of patients. The yield of this diagnostic procedure was improved with repeated pleural fluid cytologic specimens and when combined with a percutaneous pleural biopsy. There was no statistically significant difference in the clinical features and pleural fluid characteristics of patients with malignant pleural effusions and those in whom the pleural effusions were paramalignant.

Conclusion: Pleural fluid cytologic examination is a useful initial step in the diagnostic work-up of patients with suspected malignant pleural effusions. The diagnostic yield of such examination is improved with repeated pleural fluid cytologic specimens and when combined with a percutaneous pleural biopsy. Clinical presentation and pleural fluid characteristics were inadequate in differentiating between malignant and paramalignant effusions.

Keywords: thoracentesis, paramalignant pleural effusions, cell blocks, cytologic examination, pleural biopsy

INTRODUCTION

Malignant disease involving the pleura is common. It is the second leading cause of exudative pleural effusions after parapneumonic effusions⁽¹⁾ and approximately 50% of all patients with metastatic cancer develop malignant pleural effusions⁽²⁾. Malignant pleural effusions result from malignancy directly involving the pleura or secondary to pleural metastases. However not all pleural effusions in patients with known cancers are malignant. Malignant disease can also cause pleural effusions without direct pleural involvement or metastases. This may occur as a result of bronchial occlusion leading to decreased pleural pressure, thoracic duct or lymph node involvement with decreased pleural lymphatic drainage, hypoproteinaemia, post obstructive pneumonitis and pulmonary emboli.

Accurate evaluation of the aetiology of pleural effusions in patients with known cancers is important as the prognosis and subsequent treatment of these patients may be different. However, the evaluation of such patients is often limited because the desire for a definitive diagnosis often conflicts with the goal of optimising quality of life in a terminally ill patient and the least invasive methods are preferred. Thoracentesis and evaluation of pleural fluid cytology is currently the most common method used to distinguish malignant pleural effusions from other causes. Previous studies have shown that the accuracy of pleural fluid cytology in diagnosing malignant pleural effusions varies from centre to centre and has been reported to be between 40% and 87%⁽³⁻⁷⁾. We conducted a study to assess the yield of pleural fluid cytology evaluation in diagnosing malignant effusions at our centre. We also suggest ways to improve the diagnostic value of thoracentesis in the diagnosis of malignant pleural effusions.

METHODS

Study population

Between 1994 and 1997, all patients admitted or referred to the Department of Respiratory & Critical Care Medicine of Singapore General Hospital for suspected malignant pleural effusions received thoracentesis as an initial step in the evaluation. Inclusion criteria were as follows: (1) hospitalisation

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during the study period with a pleural effusion and (2) presence of a known or suspected malignancy. Patients with pleural effusions not suspected to be malignant in nature were excluded. Departmental protocol for thoracentesis requires the removal of at least 20 mL of pleural fluid (whenever possible) for cytologic analysis. The total protein and LDH levels of the pleural fluid and serum were determined simultaneously. Percutaneous pleural biopsies were performed with the Abrams needle following a technique described previously⁽⁸⁾.

Pleural effusion criteria

Light's criteria⁽⁹⁾ were used to define an exudative effusion: a) Pleural fluid protein divided by serum protein greater than 0.5; b) Pleural fluid LDH divided by serum LDH greater than 0.6, or c) Pleural fluid LDH greater than 200 IU/L.

For the purpose of this study, the following definitions were used: Malignant effusion – An effusion associated with malignancy in the pleural space as demonstrated by cytologic study or pleural biopsy. (Pleural fluid specimens showing cellular atypia or mesothelial hyperplasia without obvious features of malignancy were considered negative for malignancy.) Paramalignant effusion – A pleural effusion occurring in a patient with known malignancy but in whom the pleural fluid cytologic study or pleural biopsy did not demonstrate malignancy and for whom there was no alternative diagnosis. Size of pleural effusions: This is determined by the extent of opacification of the hemithorax on frontal chest radiographs and are classified as follows: a) small – less than one-third opacification b) moderate – greater than one-third but less than two-thirds opacification c) large – greater than two-thirds opacification

Decisions to obtain repeated pleural fluid cytologic samples and/or to perform pleural biopsies in the diagnostic workup of suspected malignant pleural effusions were made by the attending care-providers.

Laboratory methods

Pleural fluid preparation: Each pleural fluid specimen was sent to the laboratory in a clean container within 4 hours of the thoracentesis. Ten millilitres of the fluid was transferred into a centrifuge tube and spun for 10 minutes at 1500 – 2000 rpm. The supernatant was decanted and the sediment smeared to make 4 slides. These slides were fixed in 95% ethyl alcohol and stained with Papanicolaou stain. The pleural fluid was examined together with the pleural biopsy whenever it was available. Pleural biopsy: Each biopsy specimen was fixed in formalin, processed and stained with hematoxylin-eosin. Special stains and immunohistochemical studies were performed when indicated.

Statistical methods

For data analysis, patients with malignant pleural effusions were compared to those with paramalignant pleural effusions. Comparisons between groups were done with Student's *t* tests for normally distributed

continuous variables and Mann-Whitney *U* tests for those not normally distributed. Chi-square analysis was used for comparison of proportions. A *p* value < 0.05 was interpreted to indicate statistical significance.

RESULTS

A total of 103 patients were evaluated. Fifty-eight (56.3%) of these patients had positive pleural fluid cytology. Initial pleural fluid cytology was positive in 50 patients (48.5%). In patients with negative cytology in the first sample of pleural fluid, 38 had a second repeat study and 6 (15.8%) of these were positive in the second sample. Of those who had negative first and second samples, a third specimen was obtained in 13 patients and of these, 2 (15.4%) were positive in the third sample.

Pleural biopsies were performed in 26 patients. Fourteen patients (53.8%) had positive pleural biopsies. Malignancy was detected in the pleural biopsy but not in the pleural fluid cytologic specimen in 6 patients. Therefore, pleural biopsies can potentially increase the diagnostic rate of pleural fluid cytologic examination by an additional 23.1% had they been performed in all patients with negative pleural fluid cytologic studies.

The underlying malignancies in these 103 patients were as follows: bronchogenic carcinoma (51.5%), breast carcinoma (29.1%), hepatocellular carcinoma (1.9%), carcinoma of the stomach (1.9%), malignant mesothelioma, nasopharyngeal carcinoma, carcinoma of the oesophagus, renal cell carcinoma, lymphoma and carcinoma of the colon (1% each). The malignant pleural effusions due to an unknown primary occurred in 9.7% of patients.

Thirty-nine patients had paramalignant pleural effusions. There was no statistically significant difference in the clinical features of patients with malignant pleural effusions and those in whom the pleural effusions were paramalignant. The performance status of patients according to the clinical scale developed by the Eastern Cooperative Oncology Group (ECOG) was also not significantly different. Likewise, the radiological site and size of the pleural effusions were also not significantly different among patients with malignant and paramalignant pleural effusions. None of the cases had bilateral pleural effusions. The clinical and radiological features of patients in the 2 groups are shown in Table I.

The pleural fluid characteristics of malignant and paramalignant pleural effusions were also studied and shown in Table II. Malignant pleural effusions tended to have predominance of lymphocytes compared to paramalignant effusions which were more likely to be non-lymphocytic, ie. neutrophilic or eosinophilic in nature. The difference in the proportions of patients with lymphocytic and non-lymphocytic pleural effusions in the 2 groups was statistically significant. Otherwise, there was no significant difference between the two groups with regards to other characteristics of pleural fluid viz haemorrhagic vs. non-haemorrhagic and exudative vs. transudative.

Table I – Comparison of clinical features in patients with malignant and paramalignant pleural effusions*

	Malignant (n = 64)	Paramalignant (n = 39)	p value
Age, yr	59.5 ± 2.0	62.2 ± 1.8	0.3186
Male, %	42.2	47.6	0.6748
ECOG** score, %			0.9477
0	5.26	9.38	
1	56.26	37.5	
2	23.68	28.13	
3	10.53	12.5	
4	5.26	12.5	
Primary malignancy			0.8101
a) Bronchogenic cancer, %	50.0 (32)	53.8 (21)	
b) Other, %	39.7 (25)	38.5 (15)	
c) Unknown, %	12.1 (7)	7.7 (3)	
Site of effusion, %			0.0807
left	46.3 (30)	35.9 (14)	
right	53.7 (34)	64.1 (25)	
Size of effusion, %			0.2311
small	4.7 (3)	2.6 (1)	
moderate	53.1 (34)	41.0 (16)	
large	42.1 (27)	56.4 (22)	

* Continuous variables expressed as means ± standard deviations; number of patients shown in parentheses

** ECOG = Eastern Cooperative Oncology Group

Table II – Comparison of the pleural fluid characteristics of malignant vs paramalignant pleural effusions*

	Malignant	Paramalignant	p value
Amount of fluid obtained	33.5 ± 5.1	33.5 ± 4.1	0.9948
Haemorrhagic, %			0.0839
Yes	36.5	63.5	
No	49.3	50.7	
Major cellular yield, %			0.001
lymphocytic	62.4	37.6	
non-lymphocytic	2.5	97.5	
Exudate, %	100	97.8	

* Continuous variables expressed as means ± standard deviations

DISCUSSION

Pleural effusions occurring in patients with known primary cancers may be malignant, paramalignant, or nonmalignant in origin. Malignant effusions are due to pleural metastases and most commonly occur with primary malignancies of the lung and breast^(10,11). Paramalignant effusions are not associated with pleural metastases or direct pleural involvement by the malignancy. Obstruction of the lymphatics by enlarged mediastinal lymph nodes, atelectasis and pneumonia from a tumour obstructing a bronchus, and a chylothorax due to invasion of the thoracic duct are some instances where paramalignant effusions may occur⁽²⁾. Nonmalignant effusions are unrelated to the primary malignancy. Differentiation of these 3 forms of pleural effusions is important as the treatment and prognosis of the patient may vary. Malignant pleural effusions generally portend a poor prognosis with the

average survival time following diagnosis of a malignant pleural effusion being 3 to 6 months⁽¹²⁾. Effusions due to nonmalignant causes, on the other hand, may be potentially treatable.

The present study shows that, in patients with known primary cancers, there are no reliable means of differentiating malignant from paramalignant pleural effusions without cytologic analysis of pleural fluid. Massive pleural effusions are suggestive of but not specific for malignancy. The size of the pleural effusion was previously found to provide a diagnostic clue in that, if the effusion is massive (opacification of the entire hemithorax), then it is likely due to malignant disease. Maher and Berger⁽¹³⁾ reviewed 46 patients with massive pleural effusions and found that 31 (67%) of the effusions were due to malignant disease, the remaining being secondary to non-malignant conditions. As shown in Table I, there was no significant difference in the proportions of patients with large effusions among patients with malignant and paramalignant effusions in our study. However the statistical power of the present study in detecting the difference in the proportions of patients with large pleural effusions in the two groups is low (0.29). Nonetheless, we do not recommend using the size of the pleural effusion to predict the likelihood of malignancy in patients suspected to have malignant pleural effusions.

Haemorrhagic pleural effusions are more likely to be malignant based on a previous study⁽¹⁴⁾ which reported that 55% of bloody pleural effusions were due to malignant disease. However, the same study showed that a pleural effusion that is not bloody is still likely to be malignant as 50% of malignant pleural effusions have relatively low pleural fluid red blood cell counts⁽¹⁴⁾. As can be seen from Table II, a malignant cause for the pleural effusion should not be inferred based upon whether the pleural fluid is haemorrhagic or not and whether it is exudative or not as there is no significant difference in the proportions of patients with these 2 pleural fluid characteristics among patients with malignant and paramalignant effusions. This study is again limited in its ability to detect the differences in proportions of haemorrhagic effusions between the two groups because of a lack of statistical power (0.50). Malignant pleural effusions are often lymphocyte-predominant but this finding by itself is not specific as tuberculous pleural effusions also tend to have lymphocytes as the major cellular yield.

Pleural fluid cytologic examination is indicated in the initial work-up of suspected malignant pleural effusions. The percentage of cases in which cytologic study of the pleural fluid establishes the diagnosis of a malignant pleural effusion ranges from 40% – 87%^(3,4,7). The percentage of positive results of initial cytologic examination in the present study is 48.5%. This is significantly less when compared to that of the study by Light⁽¹⁴⁾ in which 77% of proven malignant pleural effusions had positive cytological results. Several factors influence the percentages in the various reports. Firstly, the diagnostic yield of pleural fluid cytology differ depending on the

percentage of pleural effusions resulting from malignant, paramalignant and nonmalignant causes in the various studies. Secondly, the frequency of positive cytologic results depends upon the tumour type. For example, it is unusual for the results of pleural fluid cytology to be positive in patients with squamous cell carcinoma^(10,14,15) of the lung which tend to be central in location. The pleural effusions associated with such tumours are usually due to bronchial obstruction or lymphatic blockade and rarely due to direct involvement of the pleura. The cytologic test is also more frequently positive with adenocarcinomas than other tumours⁽¹⁵⁾. Thirdly, the accuracy depends on the way in which the specimens are examined. If both cell blocks and smears are prepared and examined, the percentage of positive diagnoses will be greater than if only one method is used^(5,16). However, it is not cost-effective to routinely obtain cell blocks in addition to smears on all cases of suspected malignant pleural effusions⁽¹⁷⁾. Lastly, the greater the number of separate specimens submitted for cytologic examination, the higher will be the percentages of positive reports⁽¹⁴⁻¹⁹⁾. Not only do multiple specimens allow examination of more material, pleural fluid which has recently accumulated following a thoracentesis is likely to contain freshly shed and better preserved cells⁽¹⁸⁾. In the study by Light⁽¹⁴⁾, if 3 separate specimens are submitted, the diagnostic yield increased from an initial 60% to nearly 80%. Even though the number of repeated pleural fluid specimens in the present study was small, positive diagnoses were made in 8 additional patients (7.8%).

Besides pleural fluid cytologic examination, another procedure commonly used in the initial work-up of patients with suspected malignant pleural effusions is pleural biopsy. The incidence of positive pleural biopsies in patients with malignant pleural effusions ranges from 39% to 75%^(7,18,20-24). In general, cytologic study of the pleural fluid establishes the diagnosis more frequently than pleural biopsy⁽¹⁾. This is because the costal parietal pleura is not involved in about 50% of patients with malignant pleural disease⁽²⁵⁾. Nonetheless, tumour cells will be present in the pleural fluid only if the tumour involves the pleural surface. Subserosal tumours often have negative cytology⁽²⁶⁾ but may be detected by pleural biopsy. Hence the combination of cytology and pleural biopsy can increase the rate of definitive diagnosis from 73% to 90%⁽²⁾. This is similar to the diagnostic rate of 80% by obtaining 3 separate pleural fluid cytologic examination as mentioned above. The choice between repeated thoracentesis or pleural biopsy in addition to thoracentesis should therefore be made clinically, based on the fitness of the patient to undergo each procedure and the operator's expertise.

Several ancillary tests may be performed on the pleural fluid in addition to cytologic examination to aid the diagnosis of malignant pleural effusions. The use of monoclonal antibodies directed against various antigens appears to be useful in distinguishing malignant from benign pleural effusions⁽²⁷⁻²⁹⁾. The

quantification of tumour markers in pleural fluid has also been reported to be useful in establishing the diagnosis of malignant pleural effusions. The tumour marker most commonly measured in pleural fluid is carcinoembryonic antigen (CEA). Approximately 30% – 40% of patients with malignant pleural effusions have positive pleural fluid CEA levels that exceed 10 ng/mL and only a rare benign effusion has levels that exceed this value⁽³⁰⁾. However, since most patients with an elevated CEA level also have positive pleural fluid cytology⁽³¹⁾, the performance of this measurement is not routinely recommended. The routine use of flow cytometry for the differentiation between benign and malignant effusions is also currently not recommended. It is helpful mainly in the diagnosis of pleural lymphomas and are recommended in lymphocytic pleural effusions in which the diagnosis of lymphoma is a consideration⁽³²⁾.

CONCLUSIONS

Pleural fluid analysis is mandatory in the evaluation of a pleural effusion in a patient with malignant disease. This is because clinical and/or radiological features cannot reliably differentiate malignant effusions from paramalignant ones in such patients.

The percentage of positive initial pleural fluid cytologic examination performed in cases with suspected malignant pleural effusions at our centre is 48.5%. The diagnostic yield of such examination is improved with repeated pleural fluid cytologic specimens and when combined with a percutaneous pleural biopsy.

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