Correlation between pleural fluid cytology and magnitude of pleural invasion in patients with malignant pleural mesothelioma

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Introduction Malignant pleural mesothelioma (MPM) is an aggressive tumor commonly triggered by exposure to asbestos, and commonly presented with unilateral pleural effusion. Pleural fluid cytological assessment is often the first diagnostic step that leads to a confirmed diagnosis in a relatively small percentage of cases. Medical thoracoscopy is considered as the procedure of choice to achieve a definite diagnosis and evaluate the extent of the disease.

Aim of the study The aim of this study was to assess the correlation between pleural fluid cytological yield and the invasion of different pleural surfaces detected by means of medical thoracoscopy.

Patients and methods In this retrospective study, the medical records of all patients with confirmed MPM who underwent medical thoracoscopy at the Chest Department of Ain Shams University Hospitals from May 2012 to May 2016 were analyzed. Patients were included only if the results of pleural fluid cytology were available, as well as the detailed reports of medical thoracoscopy.

Results We included 85 patients with MPM in this study, 71 male and 14 female, with a mean age of 61.56±8.75 years. Types of MPM were epitheliod type (64.7%), biphasic type (23.5%), and sarcomatoid type (11.8%). Positive pleural fluid cytology was found in 24 patients (28.2%). Medical thoracoscopy demonstrated parietal pleural invasion in all patients (100%) and visceral pleural invasion in 26 patients (30.5%). Visceral pleural invasion was found in 83.3% of patients with positive pleural fluid cytology. Our results demonstrated that the presence of visceral pleural invasion could predict a positive pleural fluid cytology with a sensitivity of 79.17%, specificity of 88.52%, positive predictive value of 73.08%, and negative predictive value of 91.83. The pattern of visceral pleural invasion had no impact on the results of pleural fluid cytology ($P>0.05$).

Conclusion The results of our study showed that the overall diagnostic yield of pleural fluid cytology in MPM is 28.2%. Positive pleural fluid cytology results were found to be significantly higher in cases with visceral pleural invasion, and, as visceral pleural invasion indicates a more advanced disease, the positive pleural fluid cytological results may be considered an indicator for advanced MPM.

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Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive tumor arising from the mesothelial cells lining the pleura. Asbestos exposure is the principal risk factor involved in the pathogenesis [1]. MPM is not a rare tumor nowadays; its incidence is still increasing, and it is expected to peak in the next 5 years [1]. A long latent period usually exists between the exposure to asbestos and the development of the disease. The diagnosis may be late in many cases because symptoms are nonspecific, and they may appear late in the course of the disease [2]. The presentation of MPM is frequently in the form of unilateral pleural effusion; therefore, cytological analysis of the pleural fluid is usually the first diagnostic procedure that should be performed [3]. The sensitivity of pleural fluid cytology for MPM varies widely in the literature for an unclear reason; it goes from 4 to 77% [1]. Recently, it is well recommended that a cytological suspicion of MPM has to be followed by tissue biopsies for histopathological confirmation [4]. Medical thoracoscopy is the procedure of choice in the investigation of patients with suspected MPM; it allows large biopsies to be taken, proper assessment of the pleural surfaces to be carried out, and it gives the possibility to perform pleurodesis through talc poudrage [5]. Optimal therapeutic strategies for MPM are not yet clearly defined, and usually patients have poor outcome. However, it is reported that early diagnosis and management may have a positive influence on the outcome, and it may improve the patients' survival [4].

Aim of the study

The aim of this study was to determine whether there is a correlation between pleural fluid cytological yield and the magnitude of pleural invasion detected by means of medical thoracoscopy.

Patients and methods

We reviewed the medical records of patients with confirmed MPM, diagnosed at the Chest Department

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of Ain Shams University Hospitals during the period from May 2012 to May 2016. Patients were included only if they had undergone thoracocentesis and medical thoracoscopy. The reports of pleural fluid cytology evaluated by a cytopathologist, as well as the detailed reports of medical thoracoscopy procedures should be available for patient's inclusion. Eighty-five patients fulfilled the inclusion criteria, and their data were analyzed. Ethical committee approval was obtained.

Standard medical thoracoscopy procedure

In all patients, apart from fasting for at least 6 h, no other special preoperative preparations were required. The procedure was performed in the lateral decubitus position with the affected side upwards under general analgesia using a combination of inhalation anesthetic (isoflurane) and intravenous anesthetic (propofol), with monitoring blood pressure, pulse, ECG, and pulse oximetry. Skin sterilization, followed by incision and blunt dissection in the appropriate intercostal space, was carried out. Thereafter, a 7-mm trocar was inserted, and a 0° telescope was inserted through it and connected to a video camera. The pleural space was carefully inspected through the thoracoscope (Richard Wolf rigid thoracoscopy; Germany). Abnormal areas were biopsied. Following the procedure, a chest tube (24–28 Fr) was inserted through the same incision and was connected to an underwater sealed chamber. The chest tube was left in place until less than 100 ml of fluid drained in 24 h, and then it was removed.

Statistical analysis

Data were tabled and statistically analyzed using SPSS version 15 (Chicago, Illinois). Parametric data were expressed as minimum, maximum, and mean and SD. Nonparametric data were expressed as number and percentage. Comparison of parametric data between more than two groups was made using the one-way analysis of variance test. The χ^2-test was used to study the difference between two or more groups as regards nonparametric data. Sensitivity, specificity, positive predictive value, and negative predictive value as well as disease prevalence are expressed as percentages for ease of interpretation. Their confidence intervals are 'exact' Clopper–Pearson confidence intervals. Two-tailed *P* value was considered nonsignificant if greater than 0.05 and significant if less than or equal to 0.05.

Results

This retrospective study reviewed the medical records of 85 patients with MPM to determine whether there is a correlation between pleural fluid cytological yield and the extent of pleural invasion detected by means of medical thoracoscopy. Among the 85 studied patients, there were 71 male and 14 female patients. The age of the studied patients ranged from 41 to 82 years, with a mean of 61.56±8.75 years.

The histological subtype of MPM was epitheliod in 55 patients (64.7%), biphasic in 20 patients (23.5%), and sarcomatoid in 10 patients (11.8%). No significant relation was detected between the age of the patients and the final histological subtype (P=0.5).

Medical thoracoscopy demonstrated parietal pleural invasion in all patients. Visceral pleural invasion was found in 26 patients (30.5%): 10 patients with biphasic mesothelioma (50%) and 16 patients with epitheliod mesothelioma (29.1%). The visceral pleural invasion was in the form of nodules, masses, and thickening. A significant relation was found between the type of mesothelioma and both the presence and the type of visceral pleural invasion (P<0.05) (Table 1). Visceral pleural invasion was significantly associated with biphasic mesothelioma. Pleural thickening was significantly associated with epithelioid type, pleural nodules with biphasic type, and pleural masses were significantly associated with biphasic type (Table 1). Adhesions between the visceral and the parietal pleura were found in 16 patients (17.6%): 11 patients (20%) with epithelioid type, two patients (10%) with biphasic, and two patients (20%) with sarcomatoid.

Table 1 Relation between thoracoscopic findings and type of mesothelioma

Thoracoscopic findings	Biphasic mesothelioma (n=20) [n (%)]	Epithelioid mesothelioma (n=55) [n (%)]	Sarcomatoid mesothelioma (n=10) [n (%)]	χ^2	P
Parietal pleura invasion	20 (100)	55 (100)	10 (100)	0	1
Visceral pleura invasion	10 (50)	16 (29.1)	0	8.01	0.01*
Pleural adhesions	2 (10)	11 (20)	2 (20)	1.05	0.5
Pattern of visceral pleura invasion			0	13.6	0.001*
Nodule	6 (60)	3 (18.75)		4.6	0.03*
Thickening	1 (10)	13 (81.25)		12.57	0.0004*
Masses	3 (30)	0		5.42	0.01*

*P<0.05.

There was a nonsignificant relation between the type of mesothelioma and the presence of pleural adhesions ($P>0.05$) (Table 1).

Positive pleural fluid cytology was found in 24 patients. A nonsignificant relation was found between the type of mesothelioma and the positivity of pleural fluid cytology ($P>0.05$) (Table 2 and Fig. 1). Visceral pleural invasion was present in 20 patients with positive cytology (83.3%). The relations between different thoracoscopic findings and pleural fluid cytological results are demonstrated in Table 3 and Fig. 2. We studied the relation between the extent of pleural invasion detected by means of medical thoracoscopy and positive pleural fluid cytology, and we found that the presence of visceral pleural invasion could predict positive cytology results with a sensitivity of 79.17%, specificity of 88.52%, positive predictive value of 73.08%, and negative predictive value of 91.83 (Table 4). However, the presence of parietal pleural invasion has a sensitivity of 100%, specificity of 0, positive predictive value of 28.24%, and no negative predictive value, and the presence of pleural adhesions had a sensitivity of 4.17%, specificity of 77.05%, positive predictive value of 6.67%, and negative predictive value of 67.14% (Table 4).

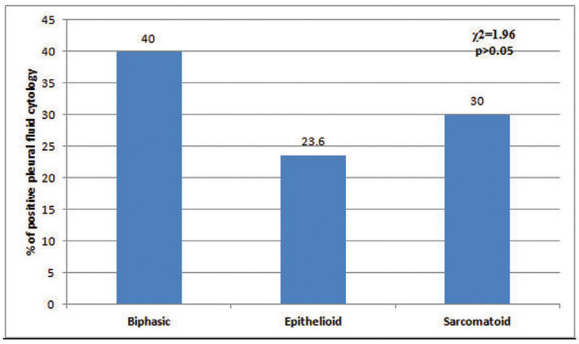
Positive pleural fluid cytology was found in 76.9% of patients with visceral pleural invasion, and there were only 6.7% of patients without visceral pleural invasion.

A nonsignificant relation was found between the pattern of visceral pleural invasion and the results of pleural fluid cytology ($P>0.05$) (Table 5).

Table 2 Relation between pleural fluid cytology and subtype of malignant pleural mesothelioma

Pleural fluid cytology	Biphasic (n=20) [n (%)]	Epithelioid (n=55) [n (%)]	Sarcomatoid (n=10) [n (%)]	χ^2	P
Positive cytology	8 (40)	13 (23.6)	3 (30)	1.96	0.3

Figure 1



Relation between positive pleural fluid cytology and the type of mesothelioma.

Table 3 Relation between thoracoscopic findings and pleural fluid cytology

Thoracoscopic findings	Pleural fluid cytology		χ^2	P
	Positive	Negative		
Parietal pleura invasion				
Positive	24 (TP)	61 (FP)	–	–
Negative	0 (FN)	0 (TN)		
Visceral pleura invasion				
Positive	19 (TP)	7 (FP)	37.17	0.0001*
Negative	5 (FN)	54 (TN)		
Pleural adhesions				
Positive	1 (TP)	14 (FP)	4.18	0.04*
Negative	23 (FN)	47 (TN)		

FN, false negative; FP, false positive; TN, true negative; TP, true positive. *$P<0.05$.

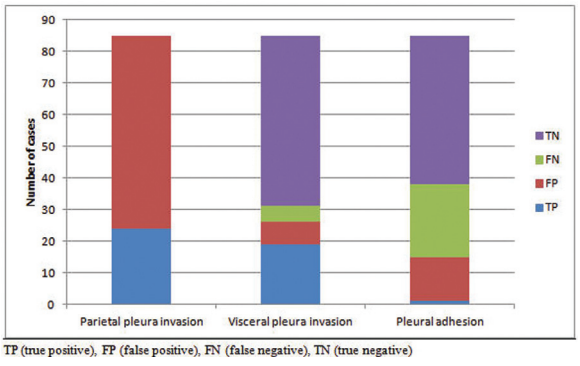
Discussion

MPM is a highly aggressive malignant neoplasm affecting the pleural cavity. The disease initially affects the parietal pleura, and then it spreads to invade the visceral pleural surfaces. Therefore, visceral pleural affection represents a more advanced disease, and it may be considered as an important prognostic factor [4].

Unilateral pleural effusion is usually the first presentation of the disease, and therefore thoracocentesis with cytological examination of the pleural fluid is the primary diagnostic procedure performed [3].

For an unclear reason, there is a very wide variation in the diagnostic yield of pleural fluid cytology, ranging from 4 to 77%. The suggested explanations for such a variation may be the difference in the cytologist's experience, or difference in sample handling [4,5].

Figure 2



Relations between thoracoscopic findings and cytological results.

Table 4 Sensitivity, specificity, positive and negative predictive values of thoracoscopic findings in relation to positive pleural fluid cytology

Thoracoscopic findings	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)
Parietal pleura invasion	100 (85.75–100)	0 (0–5.87)	28.24 (19–39.04)	–
Visceral pleura invasion	79.17 (57.85–92.87)	88.52 (77.78–95.26)	73.08 (52.21–88.43)	91.53 (81.32–97.19)
Pleural adhesion	4.17 (0.11–21.12)	77.05 (64.5–86.85)	6.67 (0.17–31.95)	67.14 (54.88–77.91)

Table 5 Relation between pattern of visceral pleura invasion and pleural fluid cytology

Pattern of visceral pleura invasion	Pleural fluid cytology		χ^2	P
	Positive	Negative		
Masses	2	1	1.76	0.4
Nodules	8	1		
Thickening	9	5		

The present study was aiming to correlate between the pleural fluid cytological yield and the pattern of invasion of the pleural surfaces detected through medical thoracoscopy.

Our results showed that the sensitivity of pleural fluid cytology to diagnose MPM in general was 28.2%. An evident relation was found between positive pleural fluid cytology and visceral pleural invasion. Positive pleural fluid cytology was found in 76.9% of patients with visceral pleural invasion, and the prevalence was as low as 6.7% in patients without visceral pleural invasion. The presence of visceral pleural invasion could predict positive pleural fluid cytology with a sensitivity of 79.17%, specificity of 88.52%, a positive predictive value of 73.08%, and a negative predictive value of 91.83.

The study of Pinelli *et al.* [6] reviewed the medical records of 75 patients with epithelioid MPM who underwent thoracocentesis followed by medical thoracoscopy; they reported that visceral pleural invasion could predict positive pleural fluid cytology with a sensitivity of 84.1%, which is nearly similar to our results. However, the sensitivity of pleural fluid cytology in patients without visceral pleural invasion was 18%, which is higher than that reported in our study, in which it was only 6%. This difference may be attributed to the inclusion of all types of MPM in our study, whereas the study of Pinelli *et al.* [6] included only epithelioid type. Another possible reason may be cytologist's experience.

Renshaw *et al.* [7] reviewed the medical records of 29 patients with MPM who underwent pleural fluid cytological examination. The reported sensitivity of cytological examination of the pleural fluid for the diagnosis of MPM was 32%, which is comparable to our results (28.2%). The authors of this study also recommended immediate pleural biopsies for patients with suspected MPM and negative pleural fluid cytology. They also reported that patients with positive or suspected cytological results were found to have a shorter duration from initial presentation to diagnosis.

Other authors [8] reviewed the cytological findings of 234 patients with MPM diagnosed between 2001 and 2008, and they stated that the cytological examination was diagnostic, or contributory to the diagnosis in about half of the cases (51.3%), which is higher than that in our results (28.2%). They also reported that epithelioid mesothelioma showed the highest sensitivity, whereas sarcomatoid mesothelioma showed the lowest sensitivity.

The visceral pleural invasion was in the form of nodules, masses, or thickening. A significant relation was found between the type of mesothelioma and both the presence and type of visceral pleural invasion ($P<0.05$). Visceral pleural invasion was significantly associated with biphasic type, pleural thickening with epithelioid type, pleural nodules with biphasic type, and pleural masses were significantly associated with biphasic type. However, there was a nonsignificant relation between the pattern of visceral pleural invasion and the results of pleural fluid cytology ($P>0.05$). These results are in accordance with the results of Pinelli *et al.* [6], who reported that the pattern of pleural invasion did not influence the results of pleural fluid cytology.

It has been previously demonstrated that the staging of MPM is important to define the prognosis [9–11]. The assessment of the pleural cavity is an important step in the staging procedure, and the involvement of the visceral pleura is clearly associated with a more advanced disease, and therefore a worst prognosis [11–13].

Conclusion

The overall diagnostic yield of pleural fluid cytology in MPM in our study was 28.2%. From our results we conclude that positive pleural fluid cytology results are found to be significantly higher in cases with visceral

pleural invasion, and, as visceral pleural invasion indicates more advanced disease, the positive pleural fluid cytological results may be considered an indicator for advanced MPM and therefore an indicator for poor outcome. Thoracocentesis with pleural fluid cytology should be performed as the first step in the diagnosis of patients with suspected MPM; medical thoracoscopy should be performed subsequently, either to diagnose suspected cases with negative cytological results or to confirm the diagnosis and stage the disease.

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Conflicts of interest
There are no conflicts of interest.

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