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 epithelioid 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.

Keywords:
- malignant mesothelioma
- medical thoracoscopy
- pleural fluid cytology

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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 thoracentesis 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 $\chi^2$-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 epithelioid 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 epithelioid 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 (%)] | $\chi^2$ | $P$ |
|------------------------|----------------------------------------|------------------------------------------|------------------------------------------|--------|-----|
| 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 | | | | 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).

**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].

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

| Pleural fluid cytology | Biphasic ($n=20$) | Epithelioid ($n=55$) | Sarcomatoid ($n=10$) | $\chi^2$ | $P$ |
|------------------------|-------------------|----------------------|----------------------|--------|-----|
| Positive cytolgy       |                   |                      |                      |        |     |
| Positive               | 8 (40)            | 13 (23.6)            | 3 (30)               | 1.96   | 0.3 |
| Negative               | 0 (20)            | 42 (76.4)            | 7 (70)               |        |     |

**Table 3 Relation between thoracoscopic findings and pleural fluid cytology**

| Thoracoscopic findings | Pleural fluid cytology | $\chi^2$ | $P$ |
|------------------------|------------------------|--------|-----|
|                        | 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. *$P<0.05$. 

**Figure 1**

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

**Figure 2**

Relations between thoracoscopic findings and cytological results.
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.

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 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.

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

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### 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 | χ² | P |
|------------------------------------|------------------------|----|---|
| Masses                             | Positive               | 2  | 1 | 1.76 | 0.4 |
| Nodules                            | Negative               | 1  |   |      |     |
| Thickening                         | Positive               | 8  | 1 |      |     |
|                                    | Negative               | 9  | 5 |      |     |

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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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