Diagnostic and Prognostic Implications of Pleural Adhesions in Malignant Effusions

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Background and objective: We aimed to examine the frequency of pleural adhesions and to determine their relationship with pleural tumor burden, pleural fluid (PF) biochemistries, PF cytologic yield, and survival in patients with malignant pleural effusion (MPE).
Methods: We performed retrospective analysis of 540 consecutive patients with MPE who underwent medical thoracoscopy. Pleural lesion rating and grade of pleural adhesions based on a thoracoscopic score model were recorded.
Results: Sixty percent of patients with MPE were found to have adhesions in the pleural space. The sensitivity of PF cytology was 71% if there were no pleural adhesions, and 20% if the maximum adhesion score was reached ($p < 0.01$). The extent of pleural adhesions correlated positively with the pleural tumor burden, and inversely with PF pH. The median survival of patients with minimal or no adhesions in the pleural space was 9 months as compared with patients with the highest grade of adhesions, whose median survival was 5 months ($p < 0.01$).
Conclusion: MPE are often loculated. The higher the grade of pleural adhesions, the greater the tumor burden exists, and paradoxically the lower the PF cytologic yield. The presence of pleural adhesions in MPE implies a poor prognosis.

Key Words: Thoracoscopy, Pleural effusion, Pleural tumors.

Thoracoscopy is the recommended procedure for patients with an undiagnosed exudative effusion and negative pleural fluid (PF) cytology who are suspected of having a malignancy.[1] In a prospective study by Loddenkemper and coworkers, 208 patients with malignant pleural effusion (MPE) underwent simultaneous closed pleural biopsy (using a tru-cut needle), PF cytology, and thoracoscopic pleural biopsy. They found that thoracoscopy had a sensitivity of 95% for diagnosing malignancy as compared with 44% for closed pleural biopsy and 62% for PF cytology.[2] Similar results have been reported by other investigators.[3]

The presence of pleural adhesions may prevent full examination of the pleural cavity and thus reduce the success of a thoracoscopic procedure.[4] In addition, it could increase the risk of lung injury during trocar placement if ultrasound is not used.[5] PF may become encapsulated by adhesions between the parietal and the visceral pleura in conditions that cause pleural inflammation, such as empyema, tuberculosis, or hemothorax.[6] However, reports documenting the frequency of adhesions in different types of pleural tumors and their influence on PF cytologic yield or prognosis of the MPE are lacking. Additionally, no study has evaluated the relationship that pleural adhesions might have with the tumor burden found in the pleural cavity.

The present study analyzes a large thoracoscopic series of patients with MPE to determine the frequency of pleural adhesions and their relationship with the type of tumor, the tumor burden, the PF biochemistry, the diagnostic yield of PF cytology, and the patient's survival.

METHODS

Patients

Information gathered on all patients who undergo diagnostic or therapeutic thoracoscopic examination at the University Hospital Virgen del Rocío (Sevilla, Spain) is stored in a prospectively maintained database. A retrospective analysis was performed only on those patients with a confirmed pleural malignancy from January 1982 to April 2007. An MPE was defined by the presence of malignant cells either in the PF examination or in the pleural tissue obtained at thoracoscopy, thoracotomy, or autopsy. The local ethics committee approved this study.

Data Collection

The evaluation of patients included age, gender, symptom chronology, size of the pleural effusion in a postero-anterior chest radiograph, appearance of PF (bloody versus nonbloody), PF biochemistry (cell count, total protein, glucose, lactate dehydrogenase [LDH], and pH), PF cultures on bacterial and mycobacterial media, PF cytology, thoracoscopic findings (i.e., pleural lesion rating, presence and extent of adhesions, pleural histology), final diagnosis, and primary tumor.

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The PF total protein, LDH and glucose concentrations were determined by standard methodologies. The PF sample for pH measurement was taken under anaerobic conditions with a syringe rinsed with heparin and measured in a blood gas analyzer. A cytologic examination was done using the Papanicolau smear.

Massive pleural effusions were defined as those effusions occupying the entire hemithorax in a postero-anterior chest radiography.

Tumor Burden and Pleural Adhesion Rating

Medical thoracoscopy was performed under local anesthesia using a 10-mm thoracoscope with a single entry. Pleural tumor burden was rated at the time of thoracoscopy, using a locally developed scoring system that was published a decade after the study began.[7] That system ranges from a minimum of 0 to a maximum of 9 and consists of an incremental scale from 0 to 3 that reflects the morphologic extent of diaphragmatic, costoparietal, and visceral pleural involvement. For each pleural surface, a score of 0 represents no visible disease; a score of 1 represents focal disease (thickening or tumor nodules) covering a small, distinct part of the pleural surface; a score of 2 represents extensive disease covering most of the pleural surface; and a score of 3 represents diffuse disease covering the entire pleural surface. The sum of individual scores for each of these surfaces provides a maximum score of 9.

The presence of adhesions in the pleural cavity was also rated during the thoracoscopic procedure, using a locally developed scoring system, but later published score,[8] ranging from a minimal of 0 to a maximum of 4. One point was assigned to isolated adhesions that permitted thoracoscopy without problems, 2 points to adhesions that obstructed about one third of the vision, 3 points to adhesions that obstructed about two thirds of the vision and 4 points to adhesions of sufficient density to preclude entry into the pleural space. In this case, biopsies were taken from the thickened pleura at the site of planned entry. All thoracoscopic examinations were fully video-recorded and, therefore, both pleural tumor burden and adhesion rating could be rechecked at any time, if necessary.

Statistical Analysis

Continuous variables were expressed as the mean (SD) or median (interquartile range) as appropriate. Analysis of variance evaluated differences in PF biochemistries according to the grade of pleural adhesions, and also in the grade of adhesions at thoracoscopy in relation to the type of tumor and lesion rating. Cytologic sensitivity values and their 95% confidence intervals (CI) were calculated from a standard 2 × 2 table. Logistic regression analyses were used to assess the relationship between sensitivity of PF cytology and grade of pleural adhesions. Spearman correlation analysis measured relationships between: (1) grade of adhesions and PF biochemistries; (2) grade of adhesions and the duration of the patient's symptoms; (3) tumor burden and PF biochemistries; and (4) tumor burden and the duration of the patient's symptoms (measured in months). An ordinal logistic regression analysis was performed for independent predictors of the

pleural grade of adhesions. We used the Kaplan-Meier method to test the relationship between survival and grade of pleural adhesions, calculating the 95% CI and using the log-rank test for comparison. Of note, patients with the 4th grade of adhesions were excluded from some of these analyses (e.g., correlation with tumor burden) because of the impossibility of calculating a correct lesion rating when the pleural space is full of adhesions that prevent complete inspection. Survival from the time of MPE diagnosis was analyzed as a function of the grade of adhesions, in addition to other factors known to be associated with a poor prognosis (i.e., tumor burden, PF pH, and tumor type),[9] using Cox regression. Results were considered statistically significant at $p < 0.05$. Statistical software (SPSS version 14.0, Chicago, IL) was used for the analysis.

RESULTS

Tumor Types

A total of 647 consecutive thoracoscopic examinations were performed during the study period. Five hundred forty patients had MPE (mean age 60 ± 13 years, 50.2% males) as demonstrated by thoracoscopic pleural biopsy. The primary tumors are shown in Table 1. Analysis of histologic types indicated that the great majority of these malignancies were adenocarcinomas, (326) followed by mesotheliomas, (79) lymphomas,(47) epidermoid carcinomas,(33) small-cell carcinomas, (14) undifferentiated carcinomas (13), and sarcomas, (28) among others.

Frequency of Pleural Adhesions and Relationship with PF Biochemical Parameters

At thoracoscopy, 208 of 540 (39%) patients were found to have no adhesions in the pleural space, 109 (20%) had

TABLE 1. Tumor Type in Patients with Malignant Pleural Effusion

Tumor type	n (%)
Lung	132 (24)
Adenocarcinoma	82 (15)
Squamous	23 (4)
Small-cell	14 (3)
Undifferentiated	9 (2)
Breast	100 (19)
Mesothelioma	79 (15)
Unknown primary	62 (12)
Lymphoma	46 (9)
Ovary	27 (5)
Kidney	24 (4)
Colorectal	18 (3)
Stomach	12 (2)
Sarcoma	12 (2)
Others[a]	28 (5)
Total	540

[a] Eight gynecological, 4 head and neck, 3 thymoma, 3 cholangiocarcinoma, 2 thyroid, 2 urinary bladder, and 1 each melanoma, pancreas, ependymoma, esophagus, myeloma, and myelodysplastic syndrome.

isolated adhesions (grade 1), 139 (26%) had grade 2 adhesions, 72 (13%) had grade 3 adhesions, and 12 (2%) had grade 4 adhesions.

Both the grade of adhesions (Table 2) and the pleural tumor burden (data not shown) correlated positively with the mean LDH PF values and inversely with the mean PF levels of glucose and pH (all $p < 0.01$).

Pleural Adhesions and Sensitivity of Pleural Fluid Cytology

We found an inverse correlation between the extent of pleural adhesions and the sensitivity of PF cytology. Cytologic sensitivity in patients without pleural adhesions (grade 0) was 71% (95% CI, 65–77%), whereas sensitivity in those with the maximum adhesion-score (grade 4) was 20% (95% CI, 0–50%, $p = 0.002$) (Table 2).

Pleural Adhesions, Tumor Types and Tumor Burden

Mean pleural adhesion grade differed among tumor types ($p < 0.01$). A lower grade of pleural adhesions was observed in lymphoma, breast cancer, and mesothelioma as compared with sarcoma, colorectal, stomach or kidney tumors (Figure 1). After excluding patients with grade 4 adhesions for the reasons mentioned above, the adhesion score also increased with the extent of tumor on the pleural surfaces -tumor burden- ($p < 0.01$) (Figure 2).

There was no significant correlation between the duration of symptoms (measured in months) and tumor burden ($p = 0.87$) or the extent of pleural adhesions ($p = 0.54$). Patients had pleural-related symptoms for a median (interquartile range) of 2 (1–4) months before the performance of the thoracoscopic procedure.

**TABLE 2.** Pleural Fluid Biochemistries and Cytological Yield at Different Grades of Pleural Adhesion

Grade of Adhesions	*n* (%)	PF Glucose, mg/dl[a]	PF pH[a]	PF LDH, IU/liter[a]	Sensitivity of Cytology (95% CI)[b]
Grade 0	208 (38.5)	92 ± 52	7.35 ± 0.08	638 ± 539	71 (65–77)
Grade 1	109 (20.2)	85 ± 47	7.34 ± 0.08	892 ± 1145	62 (52–71)
Grade 2	139 (25.7)	79 ± 46	7.31 ± 0.11	1141 ± 1558	61 (53–70)
Grade 3	72 (13.3)	59 ± 45	7.24 ± 0.14	1568 ± 2065	56 (45–68)
Grade 4	12 (2.2)	87 ± 12	7.37 ± 0.01	677 ± 763	20 (0–50)
Total	540	82 ± 49	7.32 ± 0.11	951 ± 1301	63 (59–68)

Values are given as mean ± SD.
[a] Differences are significant by the analysis of variance method ($p < 0.01$).
[b] Differences are significant by logistic regression analyses ($p < 0.01$).
PF, pleural fluid; LDH, lactate dehydrogenase; CI, confidence intervals.
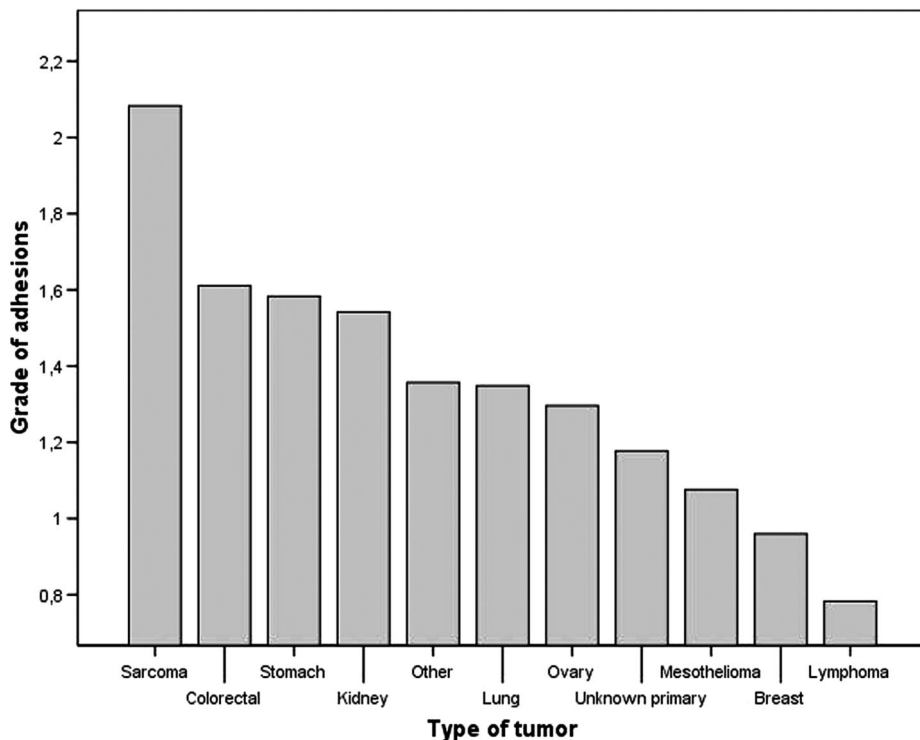
FIGURE 1. Relationship between mean grade of adhesions found at thoracoscopy and tumor type. Pleural adhesions grade is presented as a continuous variable. Mean differences are significant by the analysis of variance method ($p < 0.01$).

Predictors of Higher Grade of Pleural Adhesions in the Multivariate Analysis

An ordinal logistic regression analysis showed the following variables as predictors of a higher grade of pleural adhesions (considering up to a grade 3 adhesion score): PF pH $\leq$ 7.21, negative cytology and high lesion rating (Table 3).

Pleural Adhesions and Survival

The median survival of patients without pleural adhesions or with isolated adhesions was 9 months, whereas that of patients with adhesions of grades 2 and 3 was around 5 months ($p < 0.01$) (Table 4). The grade 4 adhesion group was not deemed suitable for calculations due to the scarce number of patients ($n = 12$) with a known date of death among this
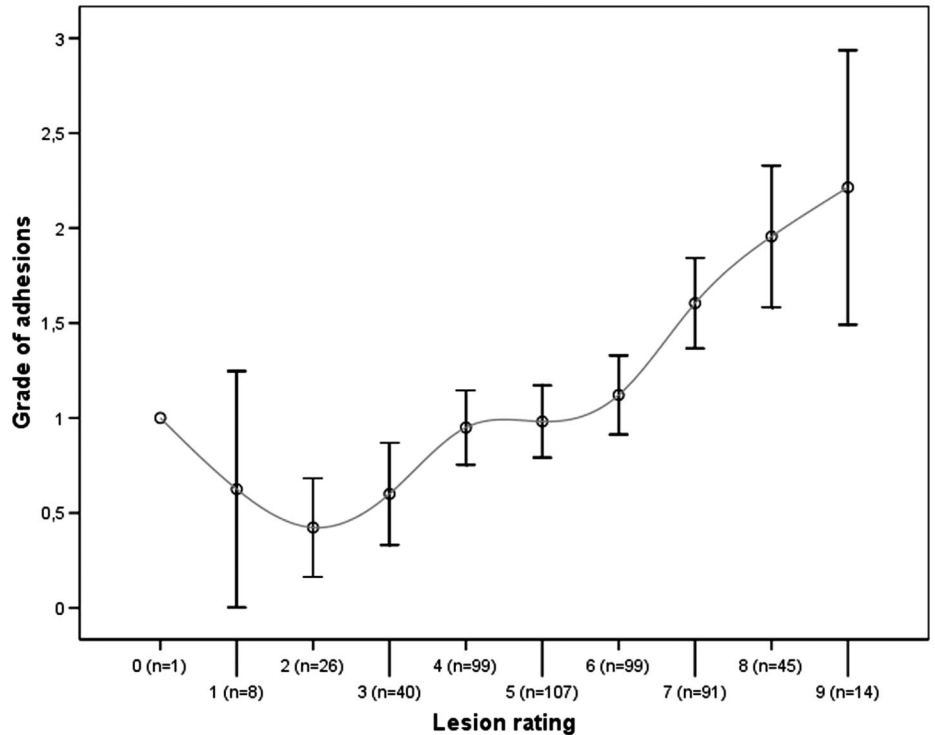
FIGURE 2. Relationship between mean grade of adhesions and lesion rating found at thoracoscopy. Pleural adhesions grade is presented as a continuous variable. Circles show mean value and "I" bars represent standard deviation value. Mean differences are significant ($p < 0.001$) by the analysis of variance method.

TABLE 3. Variables that Predict the Grade of Pleural Adhesions at Thoracoscopy

Variable	Value	*n* (%)	Grade of Adhesions, Mean (95% CI)	p^a	p^b
PF appearance	Bloody	186 (37)	1.49 (1.32–1.67)	<0.01	0.45
	Nonbloody	311 (63)	1.04 (0.92–1.15)		
Effusion's size	Massive	86 (16)	1.44 (1.20–1.68)	0.04	0.32
	Nonmassive	441 (84)	1.18 (1.07–1.29)		
PF pH	$\leq$7.21	64 (19)	1.92 (1.64–2.20)	<0.01	0.02
	>7.21	278 (81)	1.12 (0.99–1.24)		
PF glucose, mg/dl	$\leq$60	111 (28)	1.61 (1.40–1.82)	<0.01	0.74
	>60	287 (72)	1.04 (0.92–1.17)		
PF LDH, UI/liter	<1000	289 (76)	1.07 (0.94–1.20)	<0.01	0.95
	$\geq$1000	92 (24)	1.57 (1.34–1.81)		
PF cytology	Negative	189 (36)	1.41 (1.23–1.58)	<0.01	<0.01
	Positive	341 (64)	1.09 (0.97–1.20)		
Pleural tumor burden			See Figure 2	<0.01	<0.01
Primary tumor			See Figure 1	<0.01	0.1

Pleural adhesions grade is presented as a continuous variable to perform the statistic analysis.
[a] Analysis of variance or Spearman correlation analysis when appropriate.
[b] Ordinal logistic regression analysis.
PF, pleural fluid; CI, confidence intervals; LDH, lactate dehydrogenase.

TABLE 4. Survival Depending on the Grade of Pleural Adhesions

Grade of Adhesions	n	Median Survival, mo (95% CI)[a]
0	208	9 (5–13)
1	109	9 (6–12)
2	139	5.4 (3.8–7.1)
3	72	4.8 (2.7–6.8)

[a] Differences are significant by the Kaplan-Meier method with the log rank test ($p < 0.01$).

group, which resulted in wide CI. The influence of adhesion grade on survival did not change over three consecutive time periods studied (data not shown).

When PF pH, pleural lesion rating and type of tumor, in addition to the grade of pleural adhesions, were included in a multivariate analysis of survival, only the first 2 variables remained as independent predictors of survival (respective *p* values 0.04 and <0.01).

DISCUSSION

Fluid loculations are common in inflammatory pleural exudates, including parapneumonic effusions, tuberculosis, and hemothoraces.[10] Also, the frequency of significant adhesions in MPE seems to be high (40% in this study). Ernst et al.[11] found adhesions in 12 (33%) and loculations in 8 (22%) of 36 pleuroscopic procedures, 22 of them in patients with MPE. In one series of 26 patients with symptomatic MPE who underwent thoracentesis with drainage of 500 ml of PF per day for 3 consecutive days, pleural fibrin strands were detected by ultrasonography in 11 patients (42%) on day 6, suggesting an association between the number of thoracentesis and pleural adhesion formation.[12] However, Wolff et al.[13] were unable to find such a relationship in 74 patients with MPE submitted to medical thoracoscopy. Half of these patients had some degree of pleural adhesions, duration of the effusion more than 5 months being the only significant predictor of the presence and extent of pleural adhesions. Contrary to these findings, we failed to find an association between duration of the effusion and pleural adhesion formation or grade. Although the exact number of previous thoracenteses was not recorded in the present study, the majority of our patients had been subjected to more than one diagnostic and/or therapeutic thoracentesis before medical thoracoscopy.

There is not an accepted grading system for the extent of pleural adhesions.[14] Chest sonography and computed tomography have only moderate utility in predicting adhesions seen during thoracoscopy.[5,14,15] For example, Sasaki et al.[5] found a sensitivity of 81.5% and a specificity of 81% in detecting pleural adhesions with ultrasonography in a series of 42 patients who underwent thoracotomy or video-assisted thoracic surgery. Mason et al.[14] correctly identified pleural adhesions by computed tomography in 28 of 39 cases (sensitivity 71%) and ruled out adhesions in 18 of 25 cases (specificity 72%); the surgeon confirmed or excluded each suspected adhesion during video-assisted thoracoscopic surgery.

For uncertain reasons, we found an inverse correlation between the extent of adhesions and cytologic sensitivity, despite the correlation between a higher grade of pleural adhesions and a greater tumor burden. Whether this is the result of patients with pleural adhesions having a compartmentalized cell distribution affecting areas not sampled during thoracentesis or because they do not exfoliate a sufficient number of cells into the pleural cavity because of a fibrin layer is a matter of speculation.

Pleural inflammation results in fibrin deposition, which may additionally initiate a sequence of events that lead to tissue remodeling and ultimate fibrosis.[16,17] The grade of adhesions in a pleural effusion may vary according to the underlying cause of pleural inflammation and the balance between coagulation and fibrinolysis.[18,19] Compared with free-flowing pleural effusions, pleural inflammation is increased in loculated pleural effusions.[10] A study that compared the differences between loculated and free-flowing effusions of different etiologies (29 malignancies, of which 11 were loculated, 19 tuberculosis and 30 pneumonias) showed a higher intensity of pleural inflammation in the former via release of various mediators and proteins.[10] We found that the pleural adhesion grade paralleled tumor burden; therefore there may be a link between pleural inflammation and tumor burden. Likewise, PF acidosis, low PF glucose, and high LDH concentrations, well known markers of intense pleural inflammation,[20] were associated with a high tumor burden and grade of adhesions. We also observed that the prolonged duration of the patient's symptoms was not necessarily indicative of the higher extent of pleural cancer or the higher grade of pleural adhesions during thoracoscopic visualization. This seems to be an apparent paradox, but an intrinsically different aggressive tumor could produce variable amounts of procoagulant-fibrinolytic mediators into the pleural space,[7] therefore leading to a different grade of adhesion.

The prognosis of patients with MPE is poor. In a meta-analysis, the median survival of 417 patients with MPE was only 4 months.[21] It is generally thought that the most important factor influencing life expectancy in patients with MPE is the primary tumor.[9] However, no study has specifically evaluated the tumor burden as a factor of poor prognosis. Instead, a low PF pH or glucose or a high PF LDH concentration are well recognized predictors of poor survival, yet they reflect, as the grade of pleural adhesions, a greater tumor burden in the pleural space.[9] This may explain why in our multivariate survival analysis the grade of pleural adhesions lost significance.

This study has limitations. The scores used for tumor burden and pleural adhesions need to be validated in further studies. In addition, we only studied patients who were suitable for undergoing thoracoscopy. Therefore, our findings probably could not be generalized to all patients with MPE.

In conclusion, this study demonstrates that significant pleural adhesions (grades 2–4) occur in more than one third of patients with MPE, and that pleural adhesions, which parallel tumor burden, correlate with a lower PF cytologic sensitivity and survival expectancy.

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