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Outcome of patients diagnosed with fibrinous pleuritis after medical thoracoscopy

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Summary
Background: In patients with post- medical thoracoscopy histopathological diagnoses of fibrinous pleuritis, confusion can occur concerning subsequent procedures. This issue is particularly important in regions where mesothelioma is prevalent. We aimed to identify false negatives among patients where mesothelioma was common due to asbestos exposure whose histopathological diagnosis following thoracoscopy was fibrinous pleuritis. We also determined risk factors associated with patients that required additional advanced invasive procedures for diagnosis.
Methods: Overall, 287 patients who underwent thoracoscopy were included in the study. Patients diagnosed with fibrinous pleuritis as a result of thoracoscopy were followed for 2 years regarding this condition. More invasive procedures were performed on patients who showed no recuperation or developed pleural disease again during the follow-up period.
Results: Fibrinous pleuritis was observed in 101 (35.2%) patients. Follow-up of these patients revealed that the false negative rate was 18% for malignant pleural diseases. The thoracoscopist's opinion regarding the pleural space, computed tomography scan findings indicating malignancy, pain and female gender were determined to be risk factors for malignant pleural diseases.
Conclusions: In regions where mesothelioma is prevalent and one of the above-stated risk factors is present, patients whose post-thoracoscopy histopathological diagnosis is fibrinous pleuritis should be treated with a more advanced invasive diagnosis procedure.

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Introduction

Medical thoracoscopy (MT) is increasingly being utilized in the diagnosis of pleural diseases following undiagnosed pleural effusion cytology and/or needle biopsy because MT procedures have a 90% success rate for the diagnosis of malignant pleural diseases and pleural tuberculosis.[1–5] However, in the patients except malignant pleural diseases or tuberculosis, histopathological changes on pleural biopsy samples are always reported as fibrinous pleuritis.[6–8] While the diagnosis of fibrinous pleuritis may be preserved in some of these cases through other clinical, radiological or effusion findings, in the remaining cases, problems can occur in clinics because concerns exist whether this histopathological diagnosis points to a benign disease, or if MT observation and sampling failed to properly identify a malignancy.

This study aimed to evaluate the proportion of false-negative results for malignant pleural diseases among patients in a region with a high incidence rate of malignant mesothelioma with a post-MT histopathological diagnosis of fibrinous pleuritis; and determine the epidemiological, clinical, radiological and laboratory characteristics of patients initially diagnosed with fibrinous pleuritis concerning the prediction of malignant pleural disease.

Methods and materials

This study was conducted in the Chest Diseases Department of the Medical Faculty of Eskisehir Osmangazi University from January 2002 to January 2009. The study was approved by the Ethical Committee of Eskisehir Osmangazi University (2010/245, PR-10-09-23-10). A trial registration was also performed (Clinicaltrials.gov Identifier: NCT01196585).

In 2002, a database for pleural diseases was created and prospectively filled in the department. All pleural disease cases and their associated data with the indications for thoracoscopy or other invasive procedures have been added into this database.

Patients

Consecutive patients who underwent MT for diagnostic purposes were invited to participate in this study. They were those in whom the cause of the pleural fluid was not identified by the clinical examinations or the laboratory and imaging findings and who had negative pleural fluid cytology.[3,4] These patients were thoroughly informed before undergoing MT, and all of the patients provided informed written consent.

The patients whose histopathological diagnoses were reported to be fibrinous pleuritis were monitored at reasonable intervals for at least 24 months following MT by clinical examination and by imaging modalities, including computerized tomography scans. During follow-up, VATS or open surgical biopsy were performed for final diagnosis in the patients whose pleural pathology did not recuperate or stabilize or whose pleural pathology recurred. The patients whose final diagnosis could not be obtained were excluded from the study.

Thoracoscopy

Medical thoracoscopy procedures were performed by a team that consisted of M. M. plus G. A. or M. M. plus H. Y. In each case, a rigid thoracoscope (Karl Storz, Tuttlingen, Germany) was utilized under mild sedation and local anesthesia. Biopsy samples were taken for histopathological investigation and, if necessary, for microbiological investigation as previously defined.[1,9] During the MT procedure, at least 8 biopsy samples, 7 from different sites and one from the diaphragmatic parietal pleura, were obtained from all of the patients. Occasionally, the number of biopsy samples increased according to the distribution pattern of the lesions and the appearance of the pleura. We also obtained a biopsy sample from the visceral pleura if there was a pathological appearance. Otherwise, a biopsy sample was not obtained routinely from the visceral pleura. We did not obtain biopsy samples from the fissure or the pericardium. If there was a lesion at any location on the pleura or a large lesion on the lung that could be defined as a large nodule or a mass, at least 3 additional biopsy samples were obtained from these lesions. In each case of normal-appearing pleura, we obtained one biopsy specimen from this tissue exactly over the rib. Because obtaining the biopsy specimen from the intact pleura in conscious, sedated patients would be very painful, we sprayed local anesthetic on the biopsy area. However, due to widespread pathological changes to the pleura, we could not locate any intact pleural area in some patients. In contrast, in patients with an entirely normal-appearing pleural space, we also sprayed local anesthetic on the biopsy area and obtained at least 6 biopsy specimens: one from the superior costal pleura, two from the mid-costal pleura, two from the inferior costal pleura and one over the diaphragm.

After MT, the impression of the thoracoscopists and the thoracoscopic findings regarding pleural appearance, nodularity, irregular or smooth thickening, hyperemia, plaques, inflammation and normal conditions were documented. Histopathological results, microbiological results, early and late complications of MT, other diagnostic or therapeutic procedures and treatment outcomes were also recorded.

Histopathological evaluation of samples

Biopsy samples were evaluated by the Department of Pathology of the Medical Faculty of Eskisehir Osmangazi University. The cases were primarily categorized as benign and malignant; malignant patients were also categorized according to cellular properties. Positive and negative mesothelial immunomarkers were used to differentiate tumors of mesothelial origin from those of epithelial origin. Negative mesothelial immunomarkers included carcinoembryonic antigen (CEA), Ber Ep4, B 72.3, MOC-31 and CD 15 (Leu-M1), while positive mesothelial immunomarkers included calretinin, Wilm's tumor 1 (WT-1), cytokeratin 5/6, mesothelin, mesothelioma (HBME-1), and N-cadherin. Additionally, epithelial membrane antigen (EMA), desmin, vimentin, p53, pan-cytokeratin, TTF-1, cytokeratin 7, and cytokeratin 20 were used when required. In the granulomatous lesions, periodic acid- Schiff (PAS) and

Ziehl—Neelsen histochemical stains were performed to investigate the presence of fungi and acid-resistant bacilli (*Mycobacterium tuberculosis*), respectively.

Histological diagnosis of fibrinous pleuritis was defined according to previous reports.[1,6] Briefly, if the histology report of the pleural tissue revealed any of the following, we identified these cases as fibrinous pleuritis: reactive fibrous pleural thickening, fibrinous pleurisy, fibrosis, fibrous connective tissue, chronic inflammation, benign changes in the absence of malignant pleural infiltration, granulomata, pleural vasculitis or evidence of bacterial infection.[1,6]

Risk factors

A two-phase study was performed to determine predictive risk factors for false-negative results in relation to malignant pleural involvement among the patients with MT-diagnosed fibrinous pleuritis. In the first phase, the impression of the thoracoscopist concerning the pleural space during the MT was accepted as a possible risk factor. It was evaluated separately from patient variables because it was the opinion of the doctor rather than a patient characteristic. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the thoracoscopist's impression were calculated in regards to malignant pleural involvement.

In the second phase, risk factors including gender; smoking status; asbestos exposure; computed tomography findings indicating malignant pleural involvement; pain; hemorrhagic pleural effusion; the presence of elevated (above 30%) mesothelial cells and/or the presence of clustered, atypical mesothelial cells (cell balls) in the pleural fluid were evaluated by uni- and multivariate analysis for false-negative results in relation to malignant pleural involvement.

Thoracoscopic impression

The thoracoscopic impression was classified as malignant, benign or indeterminate.[1,5]

Malignant pleural impression

Nodules on pleura; nodular invasion; mass on pleura; pleural thickening, including hyperemia with varying levels of invasion and irregular manifestation characteristics; and typical lymphangitic involvement. While one of the above-stated cases was present, observation of non-calcified or calcified pleural plaques did not change the impression of malignant pleural involvement.

Benign pleural impression

A typical case makes the structures under the pleura visible and shows no other changes. Grey-beige-iridescent fibrous plaque formation in the pleura, normal pleural appearance, calcified plaques, diffuse but smooth thickening of the parietal and visceral pleura, diffuse typical granuloma appearance in the pleura, typical small nodular appearance in relation to rheumatoid arthritis in the pleura with fibrous protrusions, and typical infection findings in the pleura were considered benign.

Indeterminate impression

If no certain opinion was provided with regard to either of the categories, an impression of "pleural pathology with no certain division between benign and malignant" was considered to be acceptable.

CT scan findings suggesting pleural malignancy

One or more of the following CT findings were accepted as factors that suggested malignant pleural diseases: "rind-like pleural involvement"; "mediastinal pleural involvement"; "pleural nodularity"; "pleural thickness greater than 1 cm" and invasion of thoracic structures such as pericardium, chest wall, diaphragm, and mediastinum.[10,11]

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences v 13.5 (SPSS Inc, Chicago, IL, USA; www.qrsinternational.com). Predictive factors of false negative biopsy results were first compared according to background characteristic categories using the X^2 test and an unadjusted logistic regression model. Multiple regression models were applied in the second step to identify independent risk factors for predictive factors of false negative biopsy results. For multivariate analysis, we included outcome predictors as assessed in univariate analysis. Hosmer and Lemeshow statistics was used to determine sensitivity and specificity of the model and to assess suitability. The efficiency of MT for achieving the final diagnosis and the validity of observation made by thoracoscopist during the procedure were calculated; additionally, their sensitivity, specificity, PPV, NPV and 95% confidence interval (CI) values were calculated.

Results

During the study period, MT procedures were performed on 355 patients. MT was performed for the purposes of diagnosis in 320 of the 355 patients. Of the 320 patients, 13 patients could not be followed for the specified period following the procedure. In seven patients, the presence of pleural fluid resolved without treatment during the follow-up period. These patients were considered to have idiopathic plural effusions. Thirteen patients remain in follow-up. As a result, the MT procedures of 287 patients were included in the study. The overall study group was comprised of 160 (55.7%) men and 127 (44.3%) women. The mean age for men was 60.9 $\pm$ 12.2 years; for women, the mean age was 61.1 $\pm$ 12.3 years. The overall mean age of the patient population was 61.0 $\pm$ 12.2 years. The final diagnostic distribution of cases is shown in Table 1.

The diagnostic methods and the results for the 287 patients who underwent diagnostic MT procedures are shown in Fig. 1.

While histopathological examinations provided a specific diagnosis in 186 (64.8%) of 287 patients, the histopathological result was recorded as fibrinous pleuritis in 101 (35.2%) patients. The distribution of diagnoses obtained as a result of histopathological examination of tissue samples

Table 1 Diagnoses of 287 patients, whose data were taken into account.

Diagnosis	Female	Male	Number (%)
Mesothelioma	58	50	108 (37.6)
Metastatic malignant pleural effusion	32	36	68 (23.7)
Lymphoma	4	5	9 (3.1)
Tuberculous pleurisy	7	13	20 (7.0)
Meigs syndrome	2	—	2 (0.7)
Chilothorax	1	—	1 (0.4)
Paramalignant pleural effusion	4	8	12 (4.2)
Benign asbestos pleurisy	6	33	39 (13.6)
Parapneumonic pleural effusion	1	2	3 (1.0)
Rheumatoid pleural effusion	—	7	7 (2.4)
Cardiac pleural effusion	5	5	10 (3.4)
Renal failure	2	—	2 (0.7)
Hepatic pleural effusion	2	—	2 (0.7)
Pulmonary thromboembolism	2	—	2 (0.7)
Radiotherapy related pleural effusion	1	—	1 (0.4)
Viral pleuritis	—	1	1 (0.4)
All	127	160	287 (100)

taken during MT and the final diagnosis achieved during or after follow-up of the patients is presented in Table 2.

In 3 of 9 patients who were diagnosed with lymphoma and subjected to MT, a final diagnosis was determined for lymphoma. However, in the remaining 6 patients, the histopathological assessment of biopsy tissues indicated lymphohematogenous malignant pleural involvement, and a certain diagnosis of lymphoma was not made. For this reason, it was suggested that lymph node sampling procedures should be performed. Therefore, all 6 of the remaining patients were diagnosed with lymphoma as a result of additional invasive procedures.

The number of patients with a final diagnosis of malignant mesothelioma, metastatic malignant pleural effusion,

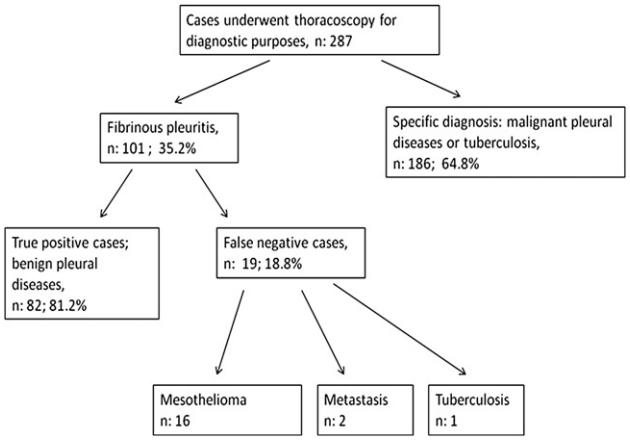

Figure 1 Diagnostic distribution of patients undergoing medical thoracoscopy.

Table 2 Distribution of patients subjected to a histopathological diagnosis following MT and the final diagnosis at follow-up.

Diagnosis	Working diagnosis (%)	Final diagnosis (%)
Mesothelioma	92 (85.2)	108
Metastatic malignant pleural effusion	66 (97.1)	68
Lymphoma	9 (100)	9
Tuberculous pleurisy	19 (95.0)	20
Fibrinous pleuritis	101 (18.8[a])	82
Total	287	287

[a] False negativity rate for malignant pleural disease and pleurisy tuberculosis.

lymphoma or pleurisy tuberculosis as a result of post-MT histopathological examination was 205. In these patients, the rate of achieving a final diagnosis through MT was determined to be 90.7% (186/205). MT diagnostic sensitivity was the lowest for malignant mesothelioma, with a diagnostic sensitivity of 85.2% (95% CI, 81.09—89.31). For this group, MT diagnosis had a specificity of 100, with PPV and NPV of 100 and 91.8, respectively (95% CI, 88.63—94.97).

Among 287 patients available for the evaluation, 18 out of 101 patients whose histopathological diagnosis was initially reported as fibrinous pleuritis were identified as having malignant pleural pathology during the follow-up period. Thus, the false negativity for malignancy in 287 patients was 6.3% (18/287). When the case of pleurisy tuberculosis, which was diagnosed as false negative following MT, was excluded, the false negative rate of MT biopsy-diagnosed fibrinous pleuritis for malignant pleural disease was 18% (18/100). Of these 18 cases, 16 patients were diagnosed with malignant mesothelioma and 2 with metastatic malignant pleural involvement.

To reduce the occurrence of false negatives for malignant pleural involvement in relation to post-MT histopathological diagnosis, an analysis was made of the possible risk factors. In the first phase, the relationship between the thoracoscopist's observation of the pleural space and the post-MT histopathological diagnosis was examined. The distribution of the thoracoscopist's impression according to the final diagnosis in 101 patients initially diagnosed with fibrinous pleuritis is given in Table 3.

According to the data presented in Table 3, in the event that the thoracoscopist's impression of the appearance of the pleural space was malignant, the sensitivity was 76.9% (95% CI, 67.9—85.9), and the specificity was 93.1% (95% CI, 87.7—98.5); additionally, the PPV was 66.7% (95% CI, 56.7—76.7), and the NPV was 95.7% (95% CI, 91.4—100.0). In the event that the thoracoscopist's impression of the appearance of the pleural space was malignant or indeterminate for malignant involvement, the sensitivity for malignant pleural involvement was 83.3% (95% CI, 76.0—90.6) and the specificity was 80.7% (95% CI, 73.0—88.4); the PPV and NPV were 48.4% (95% CI, 38.7—58.2) and 95.7% (95% CI, 91.7—99.7), respectively.

For the patients with MT-diagnosed fibrinous pleuritis, other predictive factors for false-negative biopsy results for malignant pleural disease were evaluated by uni- and

Table 3 Distribution of the final diagnosis according to the thoracoscopist's impression in patients initially diagnosed with fibrinous pleuritis.

Thoracoscopic impression	Final diagnosis malign (%)	Final diagnosis benign (%)	Total
Malign	10 (66.7)	5 (33.3)	15
Benign	3 (04.3)	67 (95.7)	70
Indeterminate	5 (31.3)	11 (68.7)	16
Total	18	83	101

multivariate analyses. The results of these analyses are presented in Table 4.

While the variables of female gender, asbestos exposure, CT scan findings indicating malignant pleural involvement and complaints regarding pain were found to be significant according to univariate analysis, the variables of female gender, CT scan findings and complaints regarding pain were considered independent variables according to multivariate analysis.

Discussion

Although the ability of MT to provide specific histopathological diagnosis for cancer and tuberculous pleurisy is quite high, a considerable amount of patients who undergo MT are diagnosed with fibrinous pleuritis because all benign pleural pathologies, excluding pleural tuberculosis, provide a diagnosis of fibrinous pleuritis.[6,7] Therefore, when clinical, radiological and laboratory findings are not definitive, it becomes difficult for clinicians to delineate between benign diseases and malignant diseases utilizing only diagnostic MT procedures; further, confusion can occur with regard to the steps taken following diagnosis.

The rate of MT samples histopathologically determined to be "fibrinous pleuritis" varies between 9% and 50%.[1,6] Among these patients, false negatives range between 5% and 25.5% for malignant pleural disease.[12–14] In a recent study, the rate for fibrinous pleuritis diagnosis was 31%, with a false-negative rate of 12%.[1] In our study, 35% (101/287) of 287 cases were diagnosed as fibrinous pleuritis. Of these 101 cases, 18 patients did present with malignant pleural disease, and 1 patient had tuberculosis pleurisy. Given these rates of false-negative results, the question remains whether a clinician should "wait and see", as proposed by certain authors as described below, or request a more advanced invasive procedure because of the chance of malignant disease in patients whose post-MT histopathological diagnosis was fibrinous pleuritis. Additionally, the length and follow-up regime for these patients have yet to be defined.[1,6,14,15] The responses to these questions are becoming increasingly important due to the distinctive rise in the incidence of malignant pleural diseases and malignant mesothelioma.[1,14–16]

According to the literature, two methods can be applied in relation to this issue. First, a "wait and see" approach can be utilized for the majority of these patients because

Table 4 Results of factors predictive for false negative biopsy result among patients with a diagnosis of fibrinous pleuritis.

Variable	%	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Gender					
Male	11.1	1	**0.014**	1	
Female	31.6	3.69 (1.30–10.46)		4.36 (1.27–14.89)	**0.019**
Smoking					
No	23.7	1	0.155		
Yes	12.2	0.45 (0.15–1.36)			
Asbestos exposure					
No	3.6	1	**0.037**		
Yes	25.0	9.00 (1.14–71.04)			
CT scan findings					
No	11.6	1	**0.005**	1	**0.033**
Yes	38.5	4.77 (1.62–14.04)		3.86 (1.11–13.43)	
Pain					
No	8.2	1	**0.007**	1	
Yes	31.3	5.11 (1.55–16.82)		3.81 (1.03–14.12)	**0.045**
Hemorrhagic pleural effusion					
No	14.6	1			
Yes	30.8	2.59 (0.69–9.78)	0.096		
Increased mesothelial cells/cell balls					
No	14.9	1	0.052		
Yes	33.3	2.86 (0.99–8.29)			

OR: Odds ratio value.

the rate of false negatives is not high. However, if there are adhesions in the pleural space that prohibit the MT procedure, then VATS or open surgical biopsy should be proposed, especially if there is a clinical suspicion of mesothelioma.[13,14] Otherwise, the patients should be monitored through chest X-rays, and MT should be repeated if the pleural effusion persists or increases with lymphocytosis or an increased level of LDH.[13] According to the other view, because no clinical or radiological predictors for pleural malignancy have been assessed in the studies, each patient should be considered on a case-by-case basis, with the approach depending on the clinical suspicion and whether the patient is fit and willing to tolerate general anesthesia. In a recent study, asbestos exposure, smoking, pleural effusion size, presence of previous malignant diseases and the thoracoscopist's impression of the macroscopic appearance of the pleural space were analyzed as risk factors. However, the authors concluded that there was no correlation between the diagnosis of malignant pleural diseases and any of these factors.[1] Future studies are needed in which appropriate patients should be selected based on risk factors after negative or nonspecific pleural biopsies from MT to undergo more invasive surgical procedures.[1,14]

To this end, we used a two-step method in our study. First, we analyzed the efficiency of the thoracoscopist's impression of malignancy during the MT procedure. As this property was an impression rather than a patient characteristic, it was evaluated independently from the patient variables as a risk factor indicating malignant pleural involvement (Table 3).

In the event that the thoracoscopist's impression of the appearance of the pleural space was malignant or indeterminate for malignant involvement, the sensitivity and specificity for malignant pleural involvement were high (83.3% and 80.7%, respectively). However, if the thoracoscopist's impression of the pleural space was not malignant or indeterminate, the chance of a benign pleural pathology was very high (95.7%). Thus, we believe that if a thoracoscopist's impression of a patient is indeterminate or suggestive of malignant pleural involvement, the recommendation for VATS or open surgical biopsy should occur. In contrast, if a thoracoscopist's observation is benign, then the "wait and see" method may be preferred, assuming that the patient does not exhibit any other risk factor discussed below.

When risk factors indicating malignant pleural involvement were analyzed for the patients diagnosed with fibrinous pleuritis (Table 4), CT scan findings indicating malignant involvement, complaints concerning pain and female gender were found to be significant variables in multivariate analysis.

CT scan findings indicating malignant involvement are important, as was shown in previous studies.[10,11] Pain should be considered to be a highly suggestive finding for malignant mesothelioma in patients with pleural effusion and asbestos exposure.[11,15] In our study, the observation that pain was a significant risk factor may be attributed to the fact that the majority of the undiagnosed cases (16/18; 88.9%) were malignant mesothelioma. Similarly, female gender was a significant risk factor in our study. In our study area, which was rural, asbestos exposure is common, and the malignant mesothelioma incidence for the exposed population was 114.8/100,000 for men and 159.8/100,000 for women. These figures indicate that the risk of malignant mesothelioma is 88.3 and 799 times greater in men and women, respectively, than for similar groups in the rest of the world.[17] Malignant mesothelioma development is more prevalent in women exposed to asbestos in our region. Women have a higher cumulative exposure to asbestos than men because of lifestyle and the division of labor in rural areas. The mean cumulative exposures to asbestos were 4.0 fiber-years/ml for women with a median exposure duration of 52 years and 2.7 fiber-years/ml for men with a median exposure duration of 55 years ($p < 0.001$). As for comparison among women living in rural areas, it may be suggested that a highly elevated risk for mesothelioma in asbestos-exposed women is associated with a higher level of asbestos exposure.[17,18] In a study from Wittenoom, the authors concluded that, after residential exposure to asbestos, women exhibited a dose—response curve that was significantly steeper than that observed in men.[19]

False negativities through post-MT histopathological analysis for malignant pleural involvement appear to be locally affected by the frequency of malignant mesothelioma. In a study by Davies, cases of malignant mesothelioma accounted for all of the false negative results.[1] In our study, false negatives predominantly resulted from cases of malignant mesothelioma. When patients diagnosed with tuberculosis pleurisy and metastatic pleural involvement were excluded from the 101 cases, the false negative rate for patients diagnosed with fibrinous pleuritis through post-MT histopathological analysis for malignant mesothelioma was 16.3% (16/98) for 98 fibrinous pleuritis cases; this ratio becomes only 2.3% (2/84) for metastatic malignant pleural involvement. Then, the diagnostic problem for MT, even if the ratio is low, becomes striking for malignant mesothelioma, as specified previously.[20] MT false negative results for malignant mesothelioma have generally been attributed to pleural adhesions that limit inspection, very early malignant mesothelioma in which the pleura appears predominantly normal with only focal abnormalities, and the thoracoscopist's inexperience.[4,21] In addition, because neoplastic invasion in malignant mesothelioma occurs submesothelially,[22] it may be difficult for a thoracoscopist to detect these areas on grossly normal appearing pleura.

Consequently, in regions where malignant mesothelioma is endemic, patients diagnosed with fibrinous pleuritis as a result of post-MT histopathological analysis should be recommended for VATS or open surgical biopsy as soon as possible if the thoracoscopist's impression is not benign pleural inflammation, if the CT findings indicate malignant pleural changes or if the patient has a pain on the effusion side. In regions where environmental asbestos exposure occurs, "female gender" should be accepted as a risk factor for malignant pleural disease.

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M.Metintas and G.Ak. Histopathological studies on the biopsy samples of the patients were performed by E.Dundar. The management of the patients in clinic were performed by M.Metintas, G.Ak, H.Yildirim, and O.Cadirci.

Conflict of interest

All authors in this paper have no financial or personal conflicts of interest to disclose.

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