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Positive pleural cytology is an indicator for visceral pleural invasion in metastatic pleural effusions

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Abstract

Introduction: In case of undiagnosed pleural effusions, it is necessary to conduct thoracentesis with pleural fluid (PF) cytology. Yet, sensitivity of PF cytology is widely variable as a result of sample size, experience, and preparation method.

Objectives: The aim of this study was to assess whether pleural fluid (PF) cytology is correlated to visceral or parietal pleural invasion as assessed by thoracoscopy in metastatic pleural effusions.

Methods: All records of patients with pleural effusion were reviewed. The inclusion criteria were as follows: PF cytology, reported appearance of macroscopic pleural invasion during thoracoscopy and malignant diagnosis. Patients with mesothelioma were excluded. Finally, 287 patients who met all criteria were selected. According to the thoracoscopy findings, the extent of the disease on the pleura was analyzed in relation to the PF cytology.

Results: In this study, 160 patients (55.7%) had a positive PF cytology (Group A) while 127 (44.3%) recorded negative PF cytology (Group B). From Group A, patients with visceral pleural invasion were 120 (75%) while only 49 patients (38.5%) were found from Group B and the difference was statistically significant ($P < .00001$). In univariate analysis, visceral pleural invasion was strongly associated with positive PF cytology ($P < .001$). Other significant associations with positive PF cytology included PF bloody aspect ($P = .012$), and endoscopic mixed pattern of pleural invasion ($P = .0039$). Only visceral pleural invasion was statistically significant in multivariate analysis ($P < .001$).

Conclusions: In patients with pleural metastatic disease, visceral pleural invasion is the only significant factor associated with positive pleural fluid cytology.

KEYWORDS

malignant pleural effusion, cytology, thoracoscopy

1 | INTRODUCTION

Malignant pleural effusions (MPEs) are common in cancer patients, with an estimated annual incidence of 150,000 cases per year in the United States.¹ MPE may be the first manifes-

tation or the evolution of many different types of cancer. More than 75% of MPEs are caused by metastases originating from the lung carcinoma, breast carcinoma, gynecological neoplasm, or lymphomas. In less than 10% of patients with MPEs, no primary tumor was identified.^{2,3}

It is necessary to confirm diagnosis for patient information, prognosis and therapeutic decisions. Indeed, the survival

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of patients depends on the primary tumor and their performance status, in case of newly diagnosed MPE.^{4,5} Pleural biopsies by thoracoscopy recorded the highest diagnostic yield with a reported sensitivity of more than 95% but it is a minimal invasive procedure available only in specialized centers,⁶ while thoracentesis with cytological analysis of pleural effusion is the first, fast, simple and safe step in the diagnosis strategy.⁷ Yet, the accuracy of pleural cytology analysis is widely variable with reported sensitivity of 33%-72%.⁸⁻¹¹ This important variation, even if not fully explained, is attributed to sample size, experience of the cytologist and sample preparation method.^{12,13} The pleural extension of the disease, in patients with malignant pleural mesothelioma (MPM), has been shown to be a factor of positive pleural cytology.¹⁴ However, little is known in patients with metastatic pleural invasion from other primary tumors.

Therefore, the aim of this study was to determine whether pleural fluid (PF) cytology is correlated to visceral or parietal pleural invasion, as investigated by thoracoscopy in metastatic pleural effusions.

2 | MATERIALS AND METHODS

2.1 | Study design—population

Patients were included if they presented thoracentesis with routine cytological examination of PF before thoracoscopy, if the appearance of visceral and parietal pleural during thoracoscopy was clearly reported and if malignant diagnosis was confirmed on histological analysis of the biopsy material. Patients diagnosed with MPM were excluded. Patients who met all criteria were reviewed from the Division of Thoracic Oncology, Pleural Diseases and Interventional Pulmonology, Hôpital Nord, Marseille France and the Department of Respiratory Medicine, University Hospital of Alexandroupolis, Greece, between January 1st 2011 and December 31st 2013. For this retrospective study, approval was obtained from both local institutional review boards according to local ethical regulations.

2.2 | Thoracoscopy

Thoracoscopy was standardized in accordance with the current European recommendations¹⁵ for both study sites. The patient was placed in lateral decubitus position on the healthy side and maintained in spontaneous breathing and thoracoscopy was performed under local anesthesia with 1% lidocaine and analgesia or mild sedation.

A 7-mm trocar was inserted on the mid-axillary line, in the appropriate intercostal space and a 0° telescope (R. Wolf GmbH, Knittlingen, Germany) was inserted and connected to a video camera. The pleura cavity was then inspected and

their involvement was assessed and described in the thoracoscopy report. The pattern of parietal and visceral pleural invasion was defined as pleural masses, nodules, lymphangitis, diffuse pleural inflammation, and pleural thickening. Biopsies were taken from the parietal pleura membrane for histological diagnosis.

2.3 | Statistical analysis

Descriptive statistics were used to study patient's characteristics. Data are expressed as percentage of the total study population, median or mean (SD) when appropriate. Group comparison (positive vs. negative cytology) was conducted using Fisher's exact test for categorical variables and two-tailed *t*-test for continuous variables. Univariate and multivariate logistic regressions were used to determine the clinical and thoracoscopy factors associated with positive pleural cytology. All analyses were performed using the Statview® 5.1 software (Berkley, CA, USA). Statistical significance was determined at $P < .05$.

3 | RESULTS

A total of 287 patients were included in this study (Marseille 158 and Alexandroupolis 129) and their demographics are shown in Table 1. All had a pleural effusion at the time of the first chest radiography and underwent thoracentesis. One hundred and sixty patients (55.7%) had a positive PF cytology (Group A) while 127 (44.3%) had a negative PF cytology (Group B) (Table 1). The histopathological diagnosis was confirmed by biopsies provided by the thoracoscopy route for all patients. Non-small cell lung cancer and breast cancer were the most frequent causes of MPE, accounting for 53% ($n = 151$) and 21% ($n = 61$) of patients, respectively (Table 1). The side of the pleural effusion was equally distributed with 144 right side and 143 left side effusions.

Overall, Group A ($n = 160$) consisted of 160 patients (55.7%) having positive pleural cytology while Group B was defined by 127 patients (44.3%) who tested negative. During thoracoscopy, parietal pleura invasion was found in 278 patients (97%) while visceral invasion was detected in 169 (58.9%). From Group A, patients with visceral pleural invasion were 120 (75%) while only 49 patients (38.5%) were from Group B. This difference was statistically significant ($P < .00001$, Table 1). On the contrary, no difference was found regarding parietal pleura invasion at thoracoscopy between the two groups ($P = .307$, Table 1). In univariate analysis, visceral pleural invasion was strongly associated with positive PF cytology (OR 10.6, 95% CI 6.06-18.39, $P < .001$). Conversely, the parietal pleural invasion that was found in 97% ($n = 278$) of patients was not statistically associated with positive PF cytology ($P = .195$).

TABLE 1 Patients' characteristics according to pleural fluid cytology

		Total (<i>n</i> = 287)	Group A (<i>n</i> = 160)	Group B (<i>n</i> = 127)	<i>P</i> value
Age	(years $\pm$ SD)	63.9 $\pm$ 12.6	62.4 $\pm$ 11.8	65.7 $\pm$ 13.3	.028
Gender	Males (<i>n</i> , %)	156, 54.3%	74, 46.25%	82, 64.57%	.003
Diagnosis	Genito-urinary tract	16	9	7	.032
	Breast	61	37	24	
	Gastrointestinal tract	8	7	1	
	Head-neck	3		3	
	Lymphoma	7	2	5	
	Melanoma	10	7	3	
	NSCLC	151	87	64	
	Sarcoma	4		4	
	SCLC	12	5	7	
	Thyroid	1		1	
	Unknown	14	6	8	
Fluid aspect	Bloody	153	96	57	.012
	Serous	134	64	70	
Side of thoracoscopy	Right	144	81	63	.906
	Left	143	79	64	
Endoscopic invasion	Any parietal negative	9	7	2	.307
	Any parietal positive	278	153	125	
	Any visceral negative	118	40	78	<.0001
	Any visceral positive	169	120	49	
Endoscopic appearance	Thickening	12	9	3	.012
	Lymphagitis	27	15	12	
	Masses	47	20	27	
	Nodules	138	74	64	
	Diffuse inflammation	15	6	9	
	Mixed pattern	48	36	12	

Group A: cytology positive group, Group B: cytology negative group, SD: standard deviation.

Between both groups, a statistically significant difference was found in age ($P = .028$), gender ($P = .003$) and primary cancer origin ($P = .032$) (Table 1). Female predominance in the positive cytology group was due to the statistically significant invasion of the visceral pleura ($P = .0013$) by breast carcinoma, but this was not the case for parietal pleura invasion ($P = .9$). This significant difference between both groups, regarding the primary cancer was also due to NSCLC, which was found to invade the visceral pleura in a

statistically significant manner, during thoracoscopy in Group A ($P < .0001$).

The pleural fluid was described as bloody in 153 patients (53.3%) and serous in 134 (46.7%). From Group A, 96 patients (60%) demonstrated bloody PF versus 64 serous (40%), while from Group B, 57 (44.8%) presented bloody PF versus 70 serous (5.2%). Bloody PF was associated with positive PF cytology ($P = .012$) as compared with the serous aspect (Table 1). In the same manner, bloody fluid was

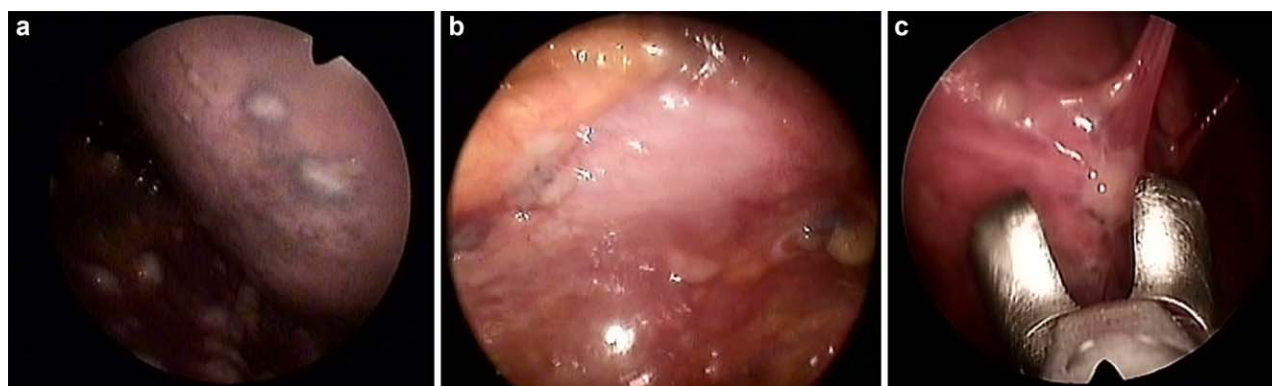


FIGURE 1 (A) Visceral and parietal pleural nodules from a lung adenocarcinoma. (B) Parietal pleural nodules associated to lymphangitis from a lung adenocarcinoma. (C) Metastatic nodules on visceral adhesions from breast adenocarcinoma (Photos provided from cases of Prof. M. Froudarakis)

associated with only visceral pleura invasion ($P = .022$) while serous fluid was not.

The endoscopic appearance of parietal pleural invasion was as follows:

- In Group A: 74 patients (46.2%) had nodules (Figure 1A), 20 (12.5%) had masses, 15 (9.3%) had lymphangitis (Figure 1B), 9 (5.6%) had pleural thickening, 6 (3.7%) had diffuse pleural inflammation, and in 36 (22.5%) patients the pattern was mixed (no predominance) (Table 1).
- In Group B: 64 patients (50.4%) had nodules, 27 (21.2%) had masses, 12 (9.4%) had lymphangitis, 9 (7.1%) had diffuse inflammation of the cavity, 3 (2.3%) had pleural thickening and 12 patients (9.4%) had no predominant endoscopic pattern (Table 1).
- A significant relationship (Table 1) was found between endoscopic appearance and positive cytology (Group A) ($P = .012$), mainly due to the association of endoscopic appearance and visceral pleural invasion ($P = .016$), while there was no association with parietal pleura invasion. More specifically, a significant relationship was found between mixed endoscopic appearance, positive cytology ($P = .0039$) and visceral pleural invasion ($P = .015$).

In multivariate regression analysis, visceral pleural invasion was the only independent factor predicting pleural fluid cytology analysis ($P < .001$) (Table 2).

4 | DISCUSSION

The present study investigated whether the diagnostic yield of PF cytology might be related to pleural involvement. Although this study is retrospective regarding data analysis, these data were extracted from electronic files filled in a prospective way. Our data showed that patients with positive PF cytology had a significantly higher visceral pleural invasion in comparison with those having negative PF cytology. Also,

when visceral pleural invasion was present at thoracoscopy, the yield of PF cytology was found to be significantly higher. Furthermore, multivariate analysis identified visceral pleural invasion, as the only independent factor predicting the possibility of positive cytology. The link between visceral pleural invasion and positive PF cytology has been shown only in patients with mesothelioma¹⁴ and with NSCLC, who underwent perioperative pleural lavage for surgical resection.^{16,17} The highest appearance of tumor cells in the pleural lavage fluid of these NSCLC patients can be explained by tumor desquamation.¹⁸

The gold standard for the diagnosis of MPE is the histological analysis of pleural samples obtained by thoracoscopy.^{6,15} Despite its high diagnostic yield, thoracoscopy is not available in every center, although it is regarded as minimally invasive.⁷ In addition, many patients presenting MPE are symptomatic and require a therapeutic procedure.¹⁵ Therefore, PF cytology is still the first recommended step for the evaluation of pleural effusion in patients suffering from malignancy.^{2,7} The sensitivity of PF cytological analysis for malignant cells identification is highly variable and generally considered to be approximately 60%,^{8–10} as confirmed in our study with an overall sensitivity of 55.7%. Although the wide variation of diagnostic yield depends on several parameters, the most frequently reported causes include the amount of fluid sent for analysis, the preparation method and the cytologist's expertise.¹²

TABLE 2 Predictors of positive cytology in pleural effusion (multivariate regression analysis)

Variables	Odds ratio	<i>P</i> value
Visceral pleural invasion	13.38	<.001
Fluid aspect	0.72	.304
Endoscopic appearance	0.69	.4
Gender	0.92	.78
Age	1	.992

To our knowledge, this is the largest study that describes the pattern of pleural involvement in metastatic pleural disease at thoracoscopy. The main mechanisms of parietal pleural spread are direct invasion, hematogenous or lymphatic spread, especially in breast and chest wall neoplasms.¹⁹ This hypothesis correlates with our results showing a parietal pleural invasion in 97% of patients and a visceral pleural invasion in only 58.9% of patients assessed by thoracoscopy, suggesting that parietal pleural invasion occurs earlier in the pleural metastatic process. However, postmortem studies suggest that pleural metastasis may arise from tumor emboli to the visceral pleural surface with secondary seeding to the parietal pleura.²⁰ It may also be possible to have a parietal pleural invasion through adhesions to the visceral pleura (Figure 1C).²¹

This study recorded a significant predominance of female patients in the group with positive cytology as compared with the negative group. This was due to both NSCLC and breast cancer,⁴ which significantly invaded the visceral pleura. It is already known from post mortem studies²⁰ that lung carcinomas spread through the visceral pleura; however, thus far, this information has not been reported in mammary carcinoma. Yet, confirmatory studies ought to be done in each specific patient population such as breast or lung cancer, as a limitation of our study consists in the heterogeneity of our population. Bloody effusion, in our univariate analysis, was significantly related to positive cytology and to visceral pleural invasion. The diagnostic value of bloody pleural effusion is controversial, as some researchers believe that it is likely related to malignancy,^{22,23} while others do not.²⁴ Also in our study, the appearance of lesions was related to both positive cytology and visceral pleural invasion in univariate analysis, with the mixed pattern being the most important. This information is quite new, as in mesothelioma, thoroscopic appearance did not match with positive cytology.¹⁴ However, no confirmation of findings was found after multivariate analysis.

In conclusion, this study suggests that in patients with metastatic pleural effusion, the diagnostic yield of fluid cytology might be related to invasion of the visceral pleura as assessed by thoracoscopy. This finding may explain, at least in a part, the variations reported in the literature of the yield of diagnostic thoracocentesis in this patient population.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

PA and MEF conceived the study. MEF, SA and GK collected all patients data from Alexandroupolis. JP, EK, SL, ER, HD, DA, HD and PA collected all patients data from Marseille. DA and MEF performed statistical analysis of

data. MEF, JP and PA drafted the manuscript, which was reviewed, and approved by all authors.

ETHICS

For this retrospective study, approval was obtained from both local institutional review boards according to local ethical regulations.

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