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ORIGINAL ARTICLE – OPEN ACCESS

Role of Cytology in Pleural Effusion: A Single-Center Experience

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ABSTRACT

Objective: As a fast and effective method, cytopathological examination of the pleural fluid is the diagnostic tool of choice in determining the etiology of a spectrum of inflammatory to neoplastic conditions. The aim of the present study was to investigate the role of pleural cytology samples examined within a certain time period in determining the presence of malignant cells.

Materials and Methods: Cytological materials of 433 patients with pleural effusion (PE) were retrospectively analyzed. Clinical parameters and cytological diagnosis were recorded in consecutive patients with PE.

Results: Of the 433 cases enrolled in the study, 264 (61%) were male, and 169 (39%) were female. 15.6% (67/433) of the cases were reported as malignant, and 85% were aged >50 years. It was found that the contribution of repeated cytological examination of a material to diagnosis was approximately 3%. The sensitivity and specificity of the cytological method were calculated as 34% and 99%, respectively. Immunocytochemistry was performed in 50 patients who received cell-block techniques, and 42.4% of those were diagnosed as malignant. Molecular tests were also performed in 5 patients.

Conclusion: Although the sensitivity is low, cytological examination of the pleura can be considered a diagnostic tool of vital importance, especially in patients with an advanced-stage disease and poor performance, who can benefit from rapidly evolving and changing treatment options.

Keywords: Immunocytochemistry, molecular targeted therapy, malignant pleural effusion

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INTRODUCTION

Pleural effusions (PEs) occur as a result of increased fluid formation and/or decreased fluid resorption. The effusion develops for many reasons, such as systemic diseases, trauma, organ dysfunction, and cancer (1). In some cases, it may even be the first sign of a primary malignant tumor. Although the classification of PEs as transudates and exudates by clinical data makes a significant contribution to narrowing the differential diagnosis and organizing of subsequent examinations and treatments, the presence of malignant cells on cytology material is also important because of its association with cancer staging, prognosis, and survival (2–4). The main purpose of this method is to detect the presence of malignant cells. When malignant cells are detected cytologically, the next step is to determine the tumor subtype and primary organ, if possible (5).

Almost all cancers can spread to the pleura, and the local and systemic effects of tumors, as well as the effects of radiotherapy and chemotherapy used during the treatment, may cause the formation of PEs (6). The cytological examination of the pleural fluid is a very fast and effective method, particularly for diagnosing malignancy, although cytological samples of all cancer patients may not include malignant cells (4, 6). The diagnosis of malignant PE is performed by cytopathological examination of pleural fluid and by pleural biopsy. Since it is a minimally invasive and effective method for both diagnosis and treatment, the cytological examination is frequently used in daily practice. The sensitivity of PEs in detecting the presence of malignant cells was reported to be 40%–87% (4, 7–9).

Although the recent development of targeted treatment options has increased the interest in cytological materials obtained by minimally invasive methods, the potential for cytological evaluation of serous effusions has been examined in a limited number of studies (5, 7, 10). The aim of this study was to determine the diagnosis efficacy of the cytological method of evaluation in determining the presence of malignant cells in all PEs examined cytopathologically within a certain period of time.

MATERIALS and METHODS

Patient Selection

Between January 2016 and June 2018, a total of 663 cytological samples from 462 patients diagnosed with PE in the Department of Chest Diseases in Antalya Training and Research Hospital were sent to the pathology lab-

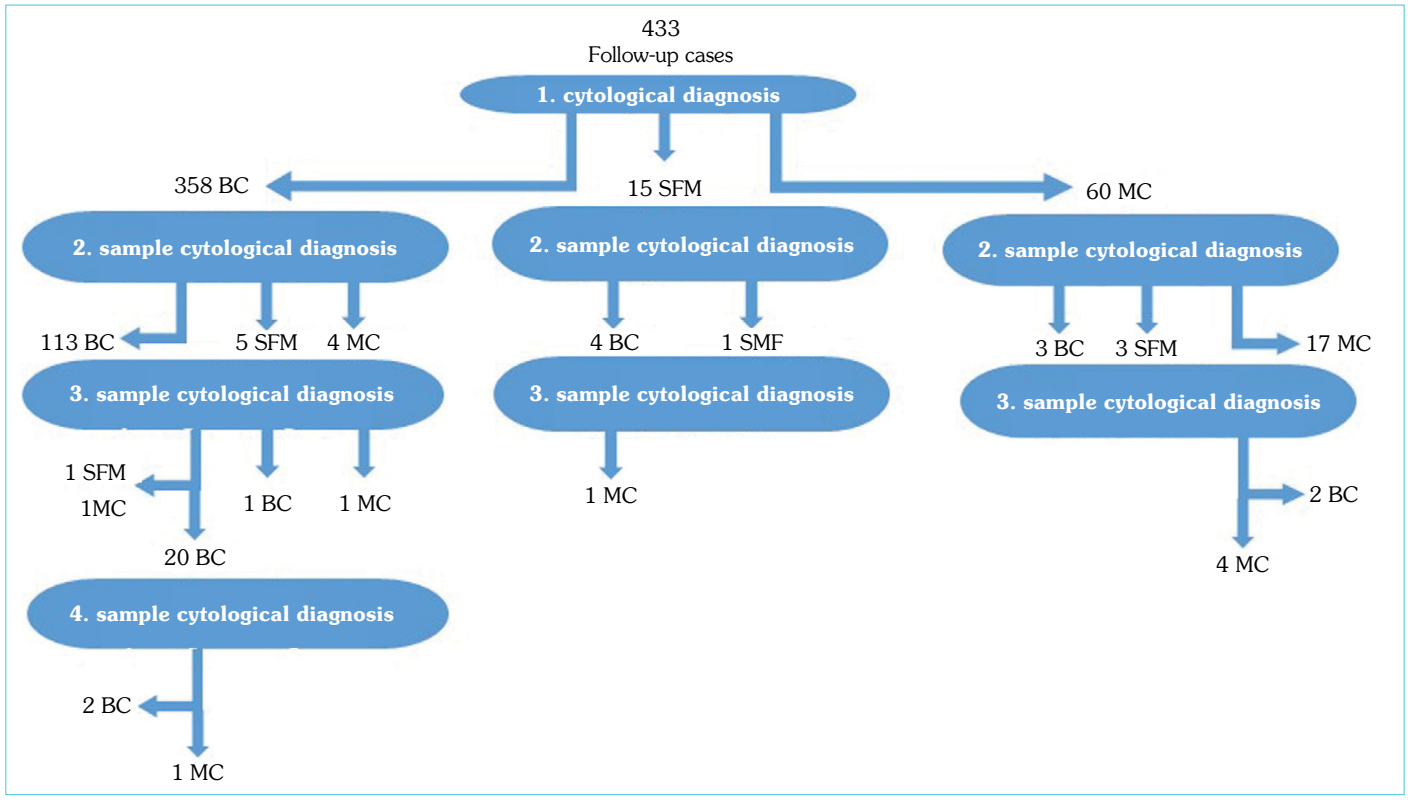

Figure 1. Scale of study

BC: Benign cytology; SFM: Suspicious for malignancy; MC: Malignant cytology

oratory. These cytological samples were retrospectively reviewed. Forty-six cytological samples of 29 patients without follow-up were excluded from the study. Four hundred and thirty-three patients with a total of 617 specimens were identified. Approval for the study was granted by the Ethics Committee of Antalya Training and Research Hospital (approval no: 025-2019). Demographic data, including age and gender, and clinical, radiological, and histopathological data of 433 patients with follow¬-up were obtained from the hospital information system, and definitive diagnoses of patients and the number of cytological samples taken from each patient and their cytological diagnoses were recorded (Fig. 1). The final diagnosis of the patients was classified into two groups as non-neoplastic or neoplastic disease, and the patients were classified according to their age as Group 1: <30 years; Group 2: 30–49 years; Group 3: 50–70 years; and Group 4: >70 years.

Cytological Process

All cytological samples were obtained from patients with previously diagnosed or undiagnosed pleural effusion (PE). PEs were collected via diagnostic thoracentesis. Cytological samples were placed into containers with a special protective solution and were sent to the pathology laboratory for cytological examination. All cytological samples were subjected to a liquid-based cytology method (SurePath) in accordance with the manufacturer's instructions and were stained with the Papanicolaou stain. The cytological samples were assessed by a cytopathologist experienced in the process of blanking. They were classified into three groups according to the cytologic diagnosis, as benign, suspicious for malignancy, malignant: 1) benign cytology, no malignant cells; 2) suspicious for malignancy, present suspicious cells and these cells were no identified by various immunocytochemistry stains; 3) malignant cytology, present malignant cells.

In addition, a cell block was prepared to perform reactive mesothelial and malignant cell differentiation, to determine primary cancer, or to perform molecular tests in patients with adequate cytological materials using samples, if needed. For these cell blocks, two mesothelial markers (HMBE-1, calretinin) and two epithelial markers (MOC-31, Ber-EP4) were applied to distinguish reactive mesothelial cells and malignant cells, while additional immunohistochemical stains (TTF-1, Napsin A for lung adenocarcinoma and lymphoid marker panel for cases diagnosed with lymphoma) were applied to confirm diagnosis with known or unknown primary cancer. Molecular tests (EGFR and FISH) were performed on the cell blocks obtained from the cytological materials if patients had inadequate tissue.

Statistical Analysis

Data obtained in the study were analyzed statistically using the SPSS software version 22.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were stated as frequency and percentage values. The chi-squared test was used to examine the variations in measurements, changes, definitive diagnoses, and cytology results based on patient age and gender. For the statistical analyses, the study group was designed as follows: 1) 66 malignant cytologies were defined as true positive; 2) 217 cytologies were defined as true-negative; 3) 128 cases of benign cytology but with histopathologically malignant findings were defined as false-negative; and 4) 1 case of malignant cytology but histopathologically defined as

Table 1. Gender and age distribution according to the cytological diagnoses of 433 patients

	Benign Cytology		Suspicious for Malignancy		Malignant Cytology		
	n	%	n	%	n	%	
Gender							
M (n=264)	216	81.8	12	4.6	36	13.6	P=0.36
F (n=169)	129	76.3	9	5.3	31	18.4	
Age (years)							
<30	25	96.1	0	0	1	3.9	
31–50	58	85.3	1	1.4	9	13.3	
51–70	167	77	13	6	37	17	P=0.24
>71	95	78	7	5.7	20	16.3	
Total n=433	345	79.6	21	4.8	67	15.6	

false-positive. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A p-value <0.05 was considered to be statistically significant.

RESULTS

Of the 433 cases enrolled in the study, 264 (61%) were male, and 169 (39%) were female, with a mean age of 60.7±12 years (range, 3–94 years). Of the total cases, 77.6% were reported as benign cytology and 15.6% as malignant cytology. On the basis of the cytology results, a benign diagnosis was made in 81.8% of 264 male patients and in 76.3% of 169 female patients. The cytology results of the patients did not differ based on gender (p=0.36). In 3.9% of 26 patients aged <30 years, 13.3% (9/68) in the 31–50 years age group, 17% (37/217) in the 51–70 years age group, and 16.3% (20/122) aged >71 years, malignant cytology was reported (Table 1). No statistically significant difference was determined between the age groups based on the cytology results, but 85% of 67 patients diagnosed with malignant cytology were aged >50 years (p=0.24).

The distribution of primary cancer in patients with cancer and the diagnoses of patients without cancer are shown in Table 2. The causes of PE were determined as parapneumonia in 25% (109/433) and lung cancer in 26.7% of the cases. Of the 221 non-neoplastic patients with clinical follow-up, 98.1% were diagnosed with benign cytology. Of the 212 patients with cancer diagnosis or with cancer detected during the follow-up, 31.1% were reported as malignant cytology (Table 2). In the first cytological samples, 60 patients were diagnosed as malignant cytology, while in the second, third, and fourth cytological samples, 4, 2, and 1 patients were diagnosed as malignant cytology, respectively (Fig. 1). In addition, immunocytochemical staining was conducted on 11.5% (50/433) of the cases to perform reactive mesothelial and malignant cell differentiation or to identify the primary cancer (Fig. 2). As a result of staining, 56% of the patients (28/50) were diagnosed with malignant cytology, 36% (18/50) benign cytology, and 8% (4/50) suspected malignancy. Of 212 patients with a final diagnosis of cancer, 66 were reported as malignant cytology. In 42.4% (28/66) of the patients reported as malignant cytology, a definitive cytological diagnosis was reached as a result of immunocytochemical examination. Of the 5 patients with a diagnosis of lung adenocarcinoma, 2 had EGFR, 1 had ALK, and 2 had both EGFR and ALK tests performed on the cell blocks obtained from residual cytological materials of the patients, and although they had adequate tissue, no mutation, deletion, or rearrangements were detected.

Table 2. Final diagnosis of all patients with pleural effusion according to the diagnosis during the follow-up and surgery

		Cytology diagnosis		
Non-neoplastic	**n**	**BC**	**SFM**	**MC**
Parapneumonia	109	106	2	1
Empyema	22	21	1	–
CHF	18	18	–	–
Tuberculosis	18	18	–	–
CRF	15	15	–	–
Other intra-abdominal causes (abscess and dialysis)	11	11	–	–
Post-traumatic	9	9	–	–
Connective tissue disease	6	6	–	–
Cirrhosis	5	5	–	–
Hemopneumothorax	5	5	–	–
PTE	2	2	–	–
Asbestosis	1	1	–	–
Total	221	217 (98.1%)	3 (1.3%)	1 (0.6%)
Neoplastic				
Lung cancer	116	69	10	37
Lymphomatoid diseases	23	18	1	4
Breast cancer	22	17	2	5
Gastric cancer	10	6	2	2
Ovarian cancer	9	4	–	5
Colon cancer	8	5	2	1
Cancer with unknown primary	6	1		5
Mesothelioma	4	2	1	1
Liver cancer	3	3	–	–
Endometrial cancer	3	3	–	–
Prostate cancer	2	–	–	2
Pancreatic cancer	2	–	–	2
Bladder cancer	1	–	–	1
Thyroid cancer	1	1	–	–
Vulva cancer	1			1
Total	212	128 (60.3%)	18 (8.6%)	66 (31.1%)

CHF: Congestive heart failure; CRT: Chronic renal failure; PTE: Pulmonary thromboembolism; BC: Benign cytology; SFM: Suspicious for malignancy; MC: Malignant cytology

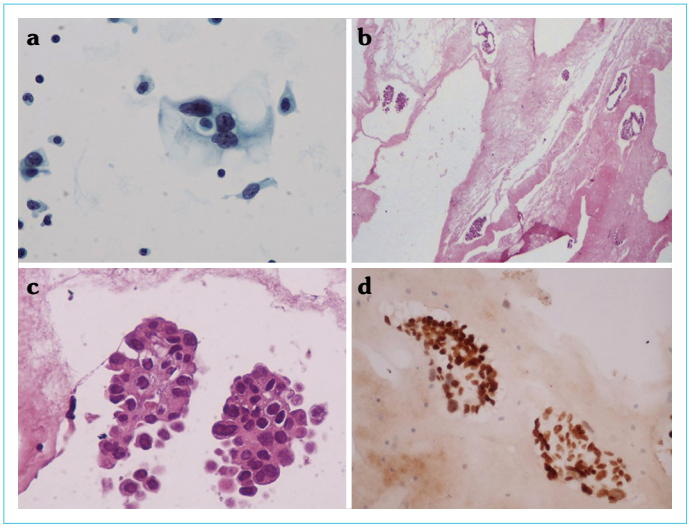

Figure 2. a–d. (a) Lung adenocarcinoma; tumor cells with nuclear contour irregularities are shown in the liquid-based preparation (PAP, ×400). (b, c) In these cells, adenoid structures are shown in the cell block (H&E, ×40, and ×400) and (d) nuclear positivity for TTF-1 (DAB, ×200)

PAP: Papanicolaou stain; H&E: Hematoxylin&Eosin staining

The sensitivity, specificity, positive predictive value, and negative predictive value of the cytology method were calculated as 34%, 99%, 98.5%, and 62.8.%, respectively.

DISCUSSION

The sole evaluation of PE using cytological examination may not be sufficient for diagnosis. However, this method is a critical and widely used diagnostic tool as it is simple, safe, and cost effective in determining the presence of malignant cells in patients with suspected cancer, albeit with low sensitivity (11). In a study that examined cytological materials from 3,811 patients, Hsu et al. reported 20.5% of the patients as showing malignant cytology whereas in the present study, this percentage was 15.6% (8). The most common causes of PE in the current study were found to be parapneumonia and lung cancer, in accordance with the literature (1).

In a study examining the demographic data of 474 patients with malignant PE, approximately 85% of the patients diagnosed with malignant cytology were over 50 years of age, which was similar to our findings (12).

While PE develops in approximately 60% of patients with pleural metastasis, in addition to metastasis, in patients with cancer, it may develop due to the effects of the mass or medications used for the treatment, such as chemotherapy drugs (13, 14). Of the 212 patients with a cancer diagnosis or with cancer detected during the follow-up in the current study, 31.1% (66/212) were found to have malignant cells as a result of cytological examination. In the first cytological samples, 60 patients were diagnosed with malignant cytology, while in the second, third, and fourth cytologic samples, 4, 2, and 1 patients, respectively, were diagnosed with malignant cytology. In the literature, it has been reported that in cases with suspected cancer, if the malignant cell was not identified in the first cytological sample, repeated examination of the cytological material increases the likelihood of malignant neoplasm (1). However, since the contribution of repeated cytological samples to diagnosis is low, pleural biopsy is recommended in addition to the second cytological sampling (4). In another study, 44% of the first cytological samples of 414 patients were diagnosed with malignant cells, while 3 and more cytological samples obtained from all patients were found to contribute 6% to the diagnosis (15). In the current study, this rate was approximately 3%.

The cytomorphological appearance of reactive mesothelial cells may be similar to that of malignant cells. In such cases, auxiliary techniques are critical in obtaining an accurate diagnosis (2, 3). In a study by Woo et al., which investigated the efficacy of the cytological method and immunocytochemical applications in malignant PE, it was reported that immunocytochemical applications increased the malignant diagnosis rate compared to cytological evaluation alone (16). In the current study, 66 of 212 patients with a final diagnosis of cancer were reported as malignant cytology. In 42.4% (28/66) of these patients reported as malignant cytology, a definitive cytological diagnosis was obtained as a result of immunocytochemical examination.

Most of the lung non-small-cell carcinomas where targeted therapy is frequently used are at an advanced stage at the time of initial diagnosis, and it is difficult to obtain sufficient tumor tissue from this group of patients because they cannot tolerate the diagnostic methods (10, 17). Therefore, pleural cytological materials are invaluable for molecular tests due to the advances in targeted treatment options (10). In a study comparing PE and primary tissue samples from 192 patients with non-small cell carcinoma, it was reported that PE samples may be effective in the EGFR mutation analysis, especially in the advanced-stage patients because of high compatibility detected between the EGFR mutations (18). In the current study, only a limited number of patients underwent the mutation analysis, as enough tissue could not be obtained in 2 years. Of the 5 patients diagnosed with lung adenocarcinoma, 2 had EGFR, 1 had ALK, and 2 had both EGFR and ALK tests performed on the cell blocks, and although they had adequate cells in their cell blocks, no mutation, deletion, or rearrangements were detected.

Although the sensitivity of the pleural cytological examination method is low, its specificity is high. In the literature, the sensitivity has been to range between 40% and 87% (4, 19), and in the current study, the sensitivity and specificity rates of the cytology method were calculated as 34% and 99%, respectively.

CONCLUSIONS

The importance of cytological specimens obtained with a minimally invasive procedure is currently increasing due to new developments in molecular tests and treatment options. Although cytopathological examination of PE has a low sensitivity for the detection of the presence of malignant cells, it can be considered that in the near future, this will be the method primarily selected due to its contribution to the diagnosis, treatment, and prognosis of the patients.

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Antalya Training and Research Hospital (approval no: 025-2019).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – CS, RU; Design – CS, RU; Supervision – CS, RU; Resource – CS, RU; Materials – CS, RU; Data Collection and/or Processing – CS, RU; Analysis and/or Interpretation – CS, RU; Literature Search – CS, RU; Writing – CS, RU; Critical Reviews – CS, RU.

Conflict of Interest: The authors have no conflict of interest to declare.

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