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ORIGINAL ARTICLE

EVALUATING THE RELIABILITY OF CYTOLOGICAL ANALYSIS IN DIAGNOSING MALIGNANT PLEURAL EFFUSIONS: CHALLENGES AND IMPLICATIONS

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Abstract. *Malignant pleural effusions (MPE) have huge implications for clinical practice and healthcare systems, affecting roughly one million patients annually. They are commonly associated with metastatic malignancies, leading to severe dyspnea and reduced quality of life. This study aimed to evaluate the reliability of cytological analysis for detecting neoplastic pleural involvement. Over a one-year period, a case-control study was conducted involving 151 patients, 79 of whom had confirmed malignant pleural pathology. Among the cases with positive cytology, 95.7% were diagnosed with pleural carcinomatosis, demonstrating the high specificity of the method. However, false-positive results and a high rate of false negatives were noted, reflecting challenges in sample collection, interpretation, and cellularity. Results indicate that cytological analysis is a valuable diagnostic tool, particularly for adenocarcinoma, with sensitivity rates as high as 89.9%. Nonetheless, the method is less effective for mesothelioma and other malignancies. Morphological features of pleural punctates, including turbidity and coloration, were shown to enhance diagnostic accuracy, while CT evidence of pleural thickening reduced sensitivity. The study highlights the critical need for improved sampling techniques and the integration of complementary diagnostic methods to mitigate false-negative rates and enhance reliability.*

Key words: *malignant pleural effusion, pleural carcinomatosis, hydrothorax, cytology, diagnosis*

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INTRODUCTION

Malignant pleural effusions (MPE) pose a significant challenge in clinical practice and carry substantial socioeconomic implications, exerting a considerable burden on healthcare systems. Affecting approximately one million individuals annually, MPEs are a leading cause of debilitating dyspnea and reduced quality of life for many patients. With distant metastases to pleural layers being

one of the most frequent complications in various malignancies, approximately 20% of cancer patients develop pleural effusions during their treatment [1].

The median survival following an MPE diagnosis ranges from 4 to 9 months, depending on the type and stage of the underlying malignancy [2]. This underscores the critical need for timely recognition of this condition and the development of an effective diagnostic and therapeutic algorithm to mitigate its impact.

In the differential cytological analysis of normal pleural fluid, the highest percentage of observed cells belongs to the white blood cell lineage, with 1.716×10^3 cells/mL. Of these, cells from the monocyte-macrophage system constitute approximately 70–75%. Lymphocytes account for about 23%, while mesothelial cells are marginally represented at only 1–2%. Differential counts also reveal populations of polymorphonuclear leukocytes (neutrophils), eosinophils, and undifferentiated cells [3].

Various pathologies of the pleural space lead to diverse changes in the composition and proportions of the presented cells. Inflammatory diseases associated with pleural effusions result in increased white blood cell counts, with bacterial infections further stimulating the expression of polymorphonuclear leukocytes. Some malignant conditions, such as lymphomas and leukemias associated with pleural infiltration, are characterized by an increased percentage of the affected cellular line in pleural punctates [3].

Pleural lymphocytosis is highly suggestive of a tuberculous pleural effusion (TPE), but chronic pleural effusions also show high lymphocyte differentiation, often exceeding 50%. Nevertheless, the most common causes of pleural lymphocytosis include: tuberculosis, pleural carcinomatosis, chronic congestive heart failure, lymphoma, liver failure, rheumatoid arthritis, and recent coronary interventions [4].

An increased percentage of eosinophils is described in malignant diseases affecting the pleura, parapneumonic pleural effusions, and in 25% of cases, the etiology is idiopathic [4].

Of particular importance in malignant pleural effusions is the presence of tumor cells in pleural punctates, confirmed through cytopathological laboratory testing. The volume of fluid obtained is of debatable significance. Some authors suggest that the material should be taken from the mid-portion of the punctate, and the quantity of fluid should be maximized, as larger volume sent for cytopathological analysis is associated with a higher likelihood of detecting atypical cells [5]. A threshold of 75 mL is considered significant, as volumes above this show minimal statistical deviations [5].

OBJECTIVES AND STUDY DESIGN

To elucidate the biochemical analysis of malignant pleural effusions, we conducted a one-year observational case-control study. Our aim was to better understand the characteristics of this pathology, identify key risk factors, and improve recognition and management strategies for affected patients.

The study encompassed 151 patients representing various age groups, clinical presentations, and primary etiologies. For comparison, there was a control group consisting of 72 patients, all diagnosed with benign conditions through biopsy. Biochemical analysis of pleural effusions in the control group were performed. This group was further divided into two subgroups: 38 cases confirmed as inflammatory and 34 cases classified as pleural effusions of non-inflammatory origin.

Out of the total sample, malignant pleural involvement was confirmed via biopsy in 79 patients. These two cohorts – benign and malignant – provide a representative comparison of the main types of pleural pathology.

MATERIALS AND METHODS

Each of the studied patients with radiographically proven pleural effusion underwent pleural puncture with the aim of completely draining the pleural cavity before performing a pleural biopsy and pleurodesis via VATS. After the initial drainage, they underwent computed tomography, followed by surgical intervention.

From each patient, a pleural fluid sample of at least 30 mL was collected through evacuation of a middle portion of the punctate, which was then separated for cytopathological examination in a sterile container. This container was also used for taking a microbiological sample, while three monovials of Firatmed Coagulation/Sandwich tubes/9NC Sodium Citrate 3.8% were used for clinical-biochemical analysis. The biological samples were promptly transported to the relevant clinical unit, as any delay increased the risk of cellular hemolysis, which alters the biological composition of the pleural fluid.

Statistical analysis

The choice of statistical methods was made in accordance with the objectives of the study, the type of variables, and established practices in scientific research

in the field of thoracic surgery. The systematization, processing, and analysis of primary data were carried out using the IBM SPSS Statistics software package. The analysis and conclusions from the study were derived after a summarized presentation of the empirical results in tabular form and were illustrated with corresponding graphs. The graphical analysis was conducted using MS Office 365. To clarify the results of the conducted analyses, Pearson's Chi-Square Test, a non-parametric statistical analysis used to measure the differences between observed and expected frequencies in categorical data was used.

RESULTS

We calculated the distribution of patients based on the results of cytopathological examinations for the presence of tumor cells. The findings reveal that 84.8% (n=128) of the total patients had negative cytology, while only 15.2% (n=23) showed tumor cells in the pleural punctate. The preliminary results are displayed in Figure 1.

Applying Pearson's Chi-Square Test yielded statistically significant results ($p<0.001$; $\chi^2=20.42$), as shown in Figure 2.

Among patients with negative cytology, 55.47% (n=77) had non-malignant histology upon biopsy, accounting for 98.6% of all non-malignant cases. Conversely, 44.53% (n=57) of patients with negative cytology had malignant histology, representing 72.2% of all cases with malignancy.

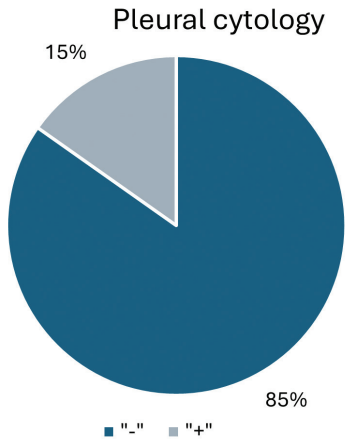

Fig. 1. Overall cytology distribution in both groups

For patients with positive cytology, 4.3% (n=1) were found to have non-malignant histology upon biopsy, constituting 1.4% of the non-malignant group. In contrast, 95.7% (n=22) were confirmed to have pleural carcinomatosis, representing 27.8% of all malignant histology cases. All results are shown together in Figure 3.

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	20.425	1	0.000		
Continuity Correction	18.427	1	0.000		
Likelihood Ratio	24.868	1	0.000		
Fisher's Exact Test				0.000	0.000
Linear-by-Linear Association	20.289	1	0.000		
N of Valid Cases	151				

Fig. 2. The Pearson Chi-Square test carried out for pleural cytology

The relationship between malignancy and cytology					
			Malignancy		Total
			No	Yes	
Cytology	"-"	Count	71	57	128
		% within cytology	55.5%	44.5%	100.0%
		% within malignancy	98.6%	72.2%	84.8%
	"+"	Count	1	22	23
		% within cytology	4.3%	95.7%	100.0%
		% within malignancy	1.4%	27.8%	15.2%
Total		Count	72	79	151
		% within cytology	47.7%	52.3%	100.0%
		% within malignancy	100.0%	100.0%	100.0%

Fig. 3. Cytology distribution by study groups

In summary, 95.7% of the patients with positive cytology were diagnosed with pleural carcinomatosis. This high percentage confirms the diagnostic specificity of the method. However, the high false-negative rate of 72.2%, highlights a crucial limitation, emphasizing the need for complementary diagnostic approaches.

DISCUSSION

Among all data collected the most controversial findings relate to the cytopathological examination of pleural fluid. Despite the statistically significant advantage of the method in confirming malignancy in the presence of tumor cells, inconsistencies were observed. In 4.3% (n=1) of cases, there was a false-positive result, while 72.2% (n=57) were false negatives. False-positive results may stem from inflammatory pleural conditions causing mesothelial proliferation or nonspecific pleural thickening, which can be mistaken for atypia. Conversely, false-negative results may occur when the pleural fluid sample is too small or errors are made in interpreting cellular atypia [6].

A study by Shidham [7] highlights that 0.5% of patients produce false-negative samples, and 30% of punctates are false negatives. In another retrospective cohort study of patients with pleural effusions over two years, including 117 patients with malignant pleural effusions, nearly 95% had positive cytology on initial pleural puncture. The method's sensitivity was highest for adenocarcinoma (89.9%) and lowest for pleural mesothelioma (33.3%), aligning with global data. Breast cancer-associated carcinomatosis was the most commonly diagnosed (91.3%).

Further analysis of our results shows that most patients with negative cytology are found to have non-malignant histology upon biopsy (98.6%). Meanwhile, patients with positive cytology are confirmed to have malignant histology in 95.7% of cases. Thus, a positive cytological result strongly correlates with pleural carcinomatosis.

An intriguing finding is that the morphological characteristics of pleural punctates during thoracentesis, such as turbidity indicating cellularity and a yellow-golden coloration, enhance the sensitivity of the cytopathological test [8]. Conversely, pleural thickening observed on CT scans appears to reduce the test's sensitivity, corroborating existing hypotheses [8].

The reliability of cytopathological testing varies widely across studies. It is also believed that cellular atypia is more likely to be observed in long-standing pleural effusions, even if a malignant process is absent [9]. Therefore, several authors discuss the reliability of pleural cytology [9].

An interesting study by Gurung [10], involving 419 patients – 162 of whom had confirmed neoplasia – found that pleural cytology has a sensitivity of 48.8% for detecting malignant pleural effusions. Sensitivity also depends on the histological subtype of the metastases. The highest sensitivity was observed for gynecological neoplasms (78%), followed by pulmonary adenocarcinoma (72%), breast carcinoma (68%), mesothelioma (26%), and hematologic malignancies (20%).

Thus, our results emphasize the limitations of cytology in isolation. Clinicians should consider integrating advanced imaging techniques or biomarkers to address the high false-negative rates and improve diagnostic accuracy.

CONCLUSIONS

Positive cytology results in pleural fluid are strongly indicative of pleural carcinomatosis, demonstrating high specificity for confirming malignant involvement. A small percentage of false-positive cases do occur – often due to reactive changes in mesothelial cells associated with inflammatory processes or benign conditions resulting in morphological alterations with tumor atypia features on cytological level. This small proportion of false-positive samples is acceptable, considering the overall specificity of the method.

On the other hand, the high rate of false-negative results is a notable limitation, reducing the method's sensitivity. Technical errors during sample collection, transport, and processing affect accuracy. The low cellularity samples and poor sample handling can lead to rapid cell degradation, therefore complicating identification and interpretation of the method.

Future studies should explore the combination of cytological analysis with molecular or imaging biomarkers that could reduce false negative results. Clinicians are encouraged to adopt a multidisciplinary approach when evaluating suspected malignant pleural effusions.

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Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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