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Diagnostic Accuracy of Pleural Fluid Cytology and The Predictive Value of Visceral Pleural Involvement: Correlation with Pleural Biopsy Histopathology

Running title: Pleural disease diagnostic correlation

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Abstract

Background: Pleural effusion is a frequent presentation of infectious/inflammatory and neoplastic diseases. Despite its noninvasive nature, pleural-fluid cytology has a variable sensitivity for malignancy and can be negative or indeterminate, necessitating a definitive diagnosis by pleuroscopic biopsy. This study analyzed the diagnostic performance of pleural-fluid cytology and its associations with pleural biopsy results in relation to visceral pleural involvement and lymphocytic predominance.

Methods: An analytical cross-sectional study with retrospective data retrieval and prospective case accrual was conducted among 65 patients with pleural effusion who had underwent medical pleuroscopy with pleural biopsy. The study retrospectively reviewed clinical, pleuroscopic, cytological and histopathological data. Cytology of pleural fluid was available for 58 patients, and it was classified according to the International System for Reporting Serous Fluid Cytopathology. The reference standard was histopathology of pleural biopsy specimens.

Sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy were computed.

Results: Of the 65 patients, histopathological examination revealed benign pleural lesions in 39 (60.0%) and malignant lesions in 26 (40.0%). Visceral pleural involvement was seen in 31 patients (47.7%) and correlated significantly with neoplastic nature. Biopsy results came back as malignant in 54·8% of patients with visceral involvement versus 26·5% without (P=0.020). The cytological classifications of the pleural fluid were strongly correlated with the histopathological diagnosis (P < 0.001). All 5 cases designated as atypia of undetermined significance and all 11 cases marked as suspicious for malignancy were malignant on biopsy. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the overall accuracy of cytology was 65.4%, 96.9%, 94.4%, 77.5% and 82.8% respectively. The ratio of lymphocytic predominance was not significantly correlated with the biopsy (P = 0.072).

Conclusions: Pleural-fluid cytology is both a highly specific and clinically useful first-line investigation for malignant pleural disease, but its moderate sensitivity limits the reliability of negative tests. Malignancy is more common with visceral pleural involvement and could help try to guide site of biopsy. While cytology analysis is the first-line test in a suspected malignancy, pleural biopsy continues to be indicated when cytology is negative, atypical or inconsistent with clinical or pleuroscopic suspicion.

Keywords: Herpes Zoster Ophthalmicus, Yoga Prana Vidya System ®, YPV ®

1. Introduction

The pleura is a thin sero elastic layer made up of visceral and parietal components that covers the lungs and lines the thoracic cavity. In physiologic states, a potential space between these layers contains only a very minimal quantity of lubricating fluid allowing for painless movement in the lungs during respiration. An imbalance between pleural fluid formation and absorption, disturbed homeostasis leads to an effusion, which in clinical terms is the pathological accumulation of fluid in the pleura space. This condition is an expression of a wide array of local and systemic diseases, such as infection, inflammatory disorders, cardiovascular disease and neoplasia [1].

Pleural effusion is one of the commonest pleural abnormalities encountered in clinical practice, which carries a considerable diagnostic and therapeuticim-load. In the United States, around 1.5 million new cases are diagnosed every year; a considerable proportion of these occurs in congestive heart failure and infection or malignancy. In the majority of cases, there is an underlying cause which can be established based on clinical history and findings from physical examination, radiological evaluation and initial pleural fluid analysis, but a significant number of patients remain undiagnosed after standard work-up and subsequently require invasive procedures [2].

The etiological pattern of pleural effusion differs widely by geography, population, socioeconomic status, and the endemic nature of infectious and malignant diseases. Tuberculosis continues to be a significant cause of exudative pleural effusion in developing countries, whilst malignant pleural involvement of lung cancer, breast cancer metastatic disease and malignant pleural mesothelioma have increasingly become important related factors [3].

A systematic, multidisciplinary analysis is necessary to evaluate pleural effusion clinically. The most frequent clinical presentations are progressive dyspnoea, pleuritic chest pain, a non-productive cough, fever and weight loss (constitutional symptoms). Radiological investigations (mainly chest x ray, ultrasonography and computed tomography) are important in confirming the actual presence of pleural fluid as well as other associated athological changes such as pleural thickening, pulmonary lesions, lymphadenopathy, pleural nodularity and unilateral or bilateral involvement. Despite this, the radiological features are not sufficient to distinguish malignant from benign pleural disease due to significant morphological overlap between infectious, inflammatory and neoplastic diseases [4].

In patients with an unexplained pleural effusion, diagnostic thoracentesis is usually the first invasive procedure. Biochemically, analysis helps determine whether the effusion is transudative or exudative while microbiological and cytological investigations can provide evidence of infection or neoplasia.

While imaging techniques can provide useful information, mostly in detecting mass lesions, pleural fluid cytology is of major importance especially when the presence of malignant pleural effusion is suspected as it is a minimally invasive procedure that is easily accessible and can detect malignant cells spilling into thoracic cavity. A positive cytologic result can represent a diagnosis of malignancy, assist with tumor staging and sometimes reveal the primary source through evaluation of morphology and ancillary studies [4,5].

Given its clinical utility, however, the diagnostic sensitivity of pleural fluid cytology is imperfect and dependent on tumor type, tumor load, specimen volume, cellularity, sampling method and laboratory processing. The sensitivity of an initial malignant pleural effusion specimen is reported to be about 60%, whereas the cumulative diagnostic yield increases with further specimens.

Therefore, a negative result in cytology cannot rule out pleural malignancy if clinically or radiologically suspected. Cytological diagnosis can be further complicated because of reactive mesothelial proliferation, degenerative cellular changes, low tumor-cell shedding and morphological overlap between reactive and malignant cells [5].

Pleural tissue is crucial to absolutely diagnosis when pleural fluid examination is non-diagnostic. Medical thoracoscopy (MT), also referred to as pleuroscopy, is a near-minimal-invasive procedure that is most often completed in a conscious, Local Anesthesia. It allows for direct visual examination of the parietal and visceral pleural surfaces, evaluation of pleural fluid and gross lesions as well as directed biopsies from abnormal areas. Thoracoscopic biopsy offers larger and more representative tissue samples than blind pleural biopsy, with diagnostic yield in malignant pleural mesothelioma, metastatic carcinoma, tuberculosis and other causes of unexplained exudative pleural effusion being very high [2,6].

Pleuroscopic findings which can be helpful include nodules, masses, inflammatory changes, diffuse or localized lesions (sealing of the pleural cavity), abnormal vascularity, adhesions and visceral pleural involvement. Nonetheless, such macroscopic characteristics are often not disease specific as benign inflammatory diseases can mimic malignancy and malignant pleural disease may sometimes appear non-specific. Thus, examination of pleural biopsy by histopathology remains the gold standard for a differential diagnosis of benign inflammatory or reactive processes versus primary and secondary malignant lesions.

Moreover, biopsy specimens facilitate the use of histochemical, immunohistochemical and molecular techniques when analysis by morphology is non-diagnostic [2,6]. Therefore, the correct diagnosis of pleural disease relies on the combination of clinical presentation, radiological findings, pleuroscopic appearance, pleural fluid cytology and histopathology from a pleural biopsy.

Each one provides separate but complementary information. Radiological and pleuroscopic examinations help in detecting the lesions and sampling, cytology is a quicker minimally invasive investigation, and histopathology provides definitive tissue confirmation. Assessment of agreement between any two diagnostic modalities would be important in recognizing the strengths and weaknesses of each technique as well guide clinicians to formulate an effective diagnostic algorithm for patients with pleural effusion. Although pleural effusion is a common clinical problem in Iraq, there are only a few local studies of the correlation between pleural fluid cytology and thoracoscopic appearances or radiological features with final histopathological diagnosis. Such a complete pathological evaluation of pleural disease in Babylon Province may thus inform clinically relevant questions about the accuracy of pleural fluid cytology and radiological and pleuroscopic features as predictive markers. Such evidence may help clinicians and pathologists to guide appropriate diagnosis procedures, minimize diagnostic delay and enhance the identification of malignant and non-malignant pleural disorders. This study aimed to assess the diagnostic efficacy of cytology in pleural fluid to diagnose malignant pleural disease and compare histopathological results of pleural fluid cytology and pleural biopsy with clinical, radiological and pleuroscopic features among patients with addition.

2. Materials and methods

2.1 Study design and selection

This is an analytical study with retrospective data collection followed by prospective continuation.

The objective of this study was to correlate pleural biopsy histopathology with pleural-fluid cytology, imaging findings, and pleuroscopic findings. Histopathology of pleural biopsy was established as the gold standard diagnostic tool to classify pleural lesions as malignant or benign.

A total of 65 patients with pleural collection were included. Pleural biopsy through medical pleuroscopy had been performed and sufficient clinical, radiological, pleuroscopic and histopathologic data were available for all patients. Patients were eligible if there was confirmation of a pleural effusion, pulmonary and pleuroscopic examination, definitive pleural biopsy diagnosis, and complete clinically relevant data. Excluded were patients without corresponding pleural biopsy reports or having incomplete records of cytology report.

2.2 Eligibility criteria

Table 1: Eligibility criteria applied during the selection of patients for the study

Category	Criterion
Inclusion	Clinically and radiologically confirmed pleural effusion
Inclusion	Medical pleuroscopy with pleural biopsy performed
Inclusion	Definitive pleural biopsy histopathological diagnosis available
Inclusion	Sufficient clinical, radiological, pleuroscopic, and histopathological data available
Exclusion	Pleural-fluid cytology result without a corresponding pleural biopsy diagnosis
Exclusion	Missing or incomplete records that prevented comparison of the required study variables

2.3 Data collection

Clinical and pathological data were acquainted from the digital archives of our department of respiratory medicine and pathology. Study variables recorded included age, sex, presenting symptoms, findings on CT scan and pleuroscopy features of pleura cytological diagnosis lymphocytic predominance and pleural biopsy. Tomographic findings were pleural thickening, lung lesions associated, lymph-node involvement and laterality of pleural disease. Pleural thickening was defined as normal or mildly when it measured ≤1 cm but increased if it measured >1 cm. Sonographic appearances of pleural fluid, type of lesion on CT, distribution of lesions and visceral pleural involvement on pleuroscopy were examined. Pleural-fluid characteristics were classified as clear, turbid, bloody or purulent. Pleural lesions were further subdivided into nodular, mass-forming or inflammatory, and classified as localized or diffuse. Visceral pleural involvement was reported as absent or present.

2.4 Cytological evaluation

Pleural-fluid cytology was categorized according to the International System for Reporting Serous Fluid Cytopathology, as for the analysis of diagnostic-performance, cytological results classified as negative for malignancy or atypia ofundetermined significance were categorized as non-malignant. Lymphocyte-predominant pleural effusion was defined as an effusion in which lymphocytes made up greater than 50 % of the nucleated inflammatory cells.

2.5 Histopathological evaluation

Pleural biopsy specimens were procured by medical pleuroscopy visual inspection. Archived tissue blocks and haematoxylin-and-eosin-stained slides were retrieved for microscopic re-examination by an expert pathologist. The initial classification of the histopathological findings was benign or malignant. Benign lesions were further divided into acute inflammation, chronic inflammation, reactive mesothelial hyperplasia and benign tumor. When histopathological evidence supported it, tuberculous pleuritis was classified as chronic inflammatory. These were based on whether the malignant lesions were classified as a primary pleural malignancy such as malignant mesothelioma or secondary metastatic malignancies involving the pleura.

2.6 Diagnostic evaluation

Using pleural biopsy histopathology as the reference standard, we evaluated the diagnostic performance of pleural-fluid cytology. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were computed.

2.7 Ethical considerations

The study protocol was approved by the research ethics committee of the IRB of the Scientific Council of Pathology, the Iraqi Board for Medical Specializations according to the code number (Path-94) on (11/12/2024). Participants were identified only via coded study numbers to ensure patient anonymity and confidentiality.

2.8 Statistical analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Effect sizes for categorical associations were reported using the phi coefficient (φ) for 2 × 2 contingency tables and Cramér's V for larger contingency tables. A two-sided P-value < 0.05 was considered statistically significant. Continuous

variables were presented as mean ± SD. Student's t-test was used to compare two groups. Pearson Chi-square test and Fisher's exact test were used to assess the association between categorical variables. A p-value <0.05 was considered statistically significant.

3. Results

3.1 Demographic and clinical characteristics

A total of 65 patients with pleural effusion were included in the present study. Their ages ranged from 15 to 80 years with a median age of 63 years and mean age was 57.1 ± 17.3 years. Of the whole sample, males were represented in a larger proportion with 36 cases (55.4%) compared to females who had 29 cases (44.6%). The mean age of male patients was 60.0 ± 16.4 years and for female patients was 53.6 ± 17.9 years old. Males were older than females but this difference was non-significant (P = 0.142). In terms of clinical presentation, 80% presented with a predominance of pleural or respiratory symptoms such as dyspnoea and pleuritic chest pain. The other 20% presented frequently with only systemic manifestations including fever and weight loss.

3.2 Visceral plural involvement and histological findings

Visceral pleural involvement was significantly associated with histopathological biopsy diagnosis, $\chi^2(1, N = 65) = 5.44$, P = 0.020, $\varphi = 0.289$. Malignancy was identified in 17 of 31 patients (54.8%) with visceral pleural involvement compared with 9 of 34 patients (26.5%) without visceral involvement. As seen in Table 2, visceral pleural involvement was statistically associated with the histopathological biopsy result. Patients with visceral pleural involvement had a 3.4-fold greater odds of receiving a malignant biopsy diagnosis compared to those without visceral involvement (odds ratio = 3.378; 95% confidence interval: 1.193-9.524).

Table 2. Association between visceral involvement and biopsy result

Visceral Involvement	Biopsy Results		Total	P-value
	Benign	Malignant		
Negative	25 (73.5%)	9 (26.5%)	34 (100%)	
Positive	14 (45.2%)	17 (54.8%)	31 (100%)	
Total	39 (60.0%)	26 (40.0%)	65 (100%)	0.020*
OR: 3.378 (95% C.I. 1.193 – 9.524)				

Data are presented as number and row percentage, n (%). The odds ratio indicates the odds of a malignant biopsy result among patients with positive visceral pleural involvement compared with those without visceral involvement. *Statistically significant at P < 0.05., Pearson's chi-square test: $\chi^2(1) = 5.44$, P = 0.020, $\varphi = 0.289$., CI, confidence interval; OR, odds ratio.

3.3 Cytological findings and concordance with pleural biopsy

Cytological classification was strongly associated with the final histopathological diagnosis, $\chi^2(3, N = 58) = 40.21$, P < 0.001, Cramér's V = 0.833. Atypia of undetermined significance was present in five cases, all having malignant biopsy results. Likewise, all 11 suspected malignancies were confirmed malignant by pleural biopsy. Of the seven cases diagnosed as malignant by cytological examination, 6 (85.7%) were required as malignant histopathologically and one case (14.3%) ended with a benign biopsy result. A total of 32 (55.2%) patients showed benign biopsy and 26 (44.8%) malignancy results. As shown in Table 3, there was a highly statistically significant correlation between the cytological classification and the final

histopathological biopsy diagnosis (P < 0.001). Among the 35 cases classified as negative for malignancy, 31 (88.6%) had benign biopsy findings and four (11.4%) were malignant. All five cases classified as atypia of undetermined significance and all 11 cases classified as suspicious for malignancy were malignant on biopsy. Of the seven cytologically confirmed malignant cases, six (85.7%) were malignant on histopathology and one (14.3%) was benign.

Table 3. Comparison of cytological results with biopsy results

Cytology Result	Biopsy Results		Total	P-value
	Benign	Malignant		
Not diagnostic	-	-	-	< 0.001*
Negative for malignancy	31 (88.6%)	4 (11.4%)	35 (100%)	
Atypia of undetermined significance	-	5 (100%)	5 (100%)	
Suspicious for malignancy	-	11 (100%)	11 (100%)	
Confirmed malignancy	1 (14.3%)	6 (85.7%)	7 (100%)	
Total	32 (55.2%)	26 (44.8%)	58 (100%)	

Data are presented as number and row percentage, n (%). A highly significant association was observed between pleural-fluid cytological classification and pleural biopsy histopathology (P < 0.001). * P < 0.05 was considered statistically significant. Pearson's chi-square test: $\chi^2(3) = 40.21$, Cramér's V = 0.833 also indicates a very strong association.

3.4 Lymphocytic effusion and biopsy findings

Lymphocytic predominance was not significantly associated with histopathological biopsy diagnosis, $\chi^2(1, N = 58) = 3.24$, P = 0.072, $\varphi = 0.236$. As shown in Table 4, out of the 33 patients who did not have lymphocytic predominance, 16 (48.5%) showed benign lesions and 17 (51.5%) had malignant lesions. Patients without lymphocytic predominance had a higher proportion of malignant disease, but the relationship between lymphocytic effusion and biopsy diagnosis was not statistically significant (Table 4).

Table 4. Association between lymphocytic effusion and biopsy result

Lymphocytic effusion	Biopsy Results		Total	P-value
	Benign	Malignant		
Present	18 (72.0%)	7 (28.0%)	25 (100%)	0.072
Not present	16 (48.5%)	17 (51.5%)	33 (100%)	
Total	34 (58.6%)	24 (41.4%)	58 (100%)	

Diagnostic performance of pleural-fluid cytology for detecting malignant pleural disease, using pleural biopsy histopathology as the reference standard. Values are presented as percentages. Pearson's chi-square test: $\chi^2(1) = 3.24$, $P = 0.072$, $\varphi = 0.236$.

3.5 Diagnostic performance of pleural fluid cytology

Using pleural biopsy histopathology as the reference standard, pleural-fluid cytology demonstrated a sensitivity of 65.4%, specificity of 96.9%, positive predictive value of 94.4%, negative predictive value of 77.5%, and overall diagnostic accuracy of 82.8%. These diagnostic-performance measures are summarized in Table 5.

Table 5. Accuracy of cytology in the diagnosis of malignancy

Parameter	Value (%)
Sensitivity	65.4%
Specificity	96.9%
Positive Predictive Value (PPV)	94.4%
Negative Predictive Value (NPV)	77.5%
Overall Accuracy	82.8%

Compared with pleural biopsy histopathology as the reference standard, pleural-fluid cytology showed a sensitivity of 65.4% and specificity of 96.9% in malignant pleural disease diagnoses (adjustment for gold standard). The positive predictive value was 94.4%, and the negative predictive value was 77.5%. Pleural-fluid cytology characterisation Diagnostic accuracy — summary table The overall diagnostic accuracy of pleural-fluid cytology was 82.8%. The results suggest cytology correctly identified a large number of non-neoplastic patients but had a lower sensitivity for detecting all histopathologically confirmed malignant cases.

3.6 Cytological and histopathological findings

The pleural biopsy and pleural-fluid specimens each reveal characteristic features as shown in Figure 1.

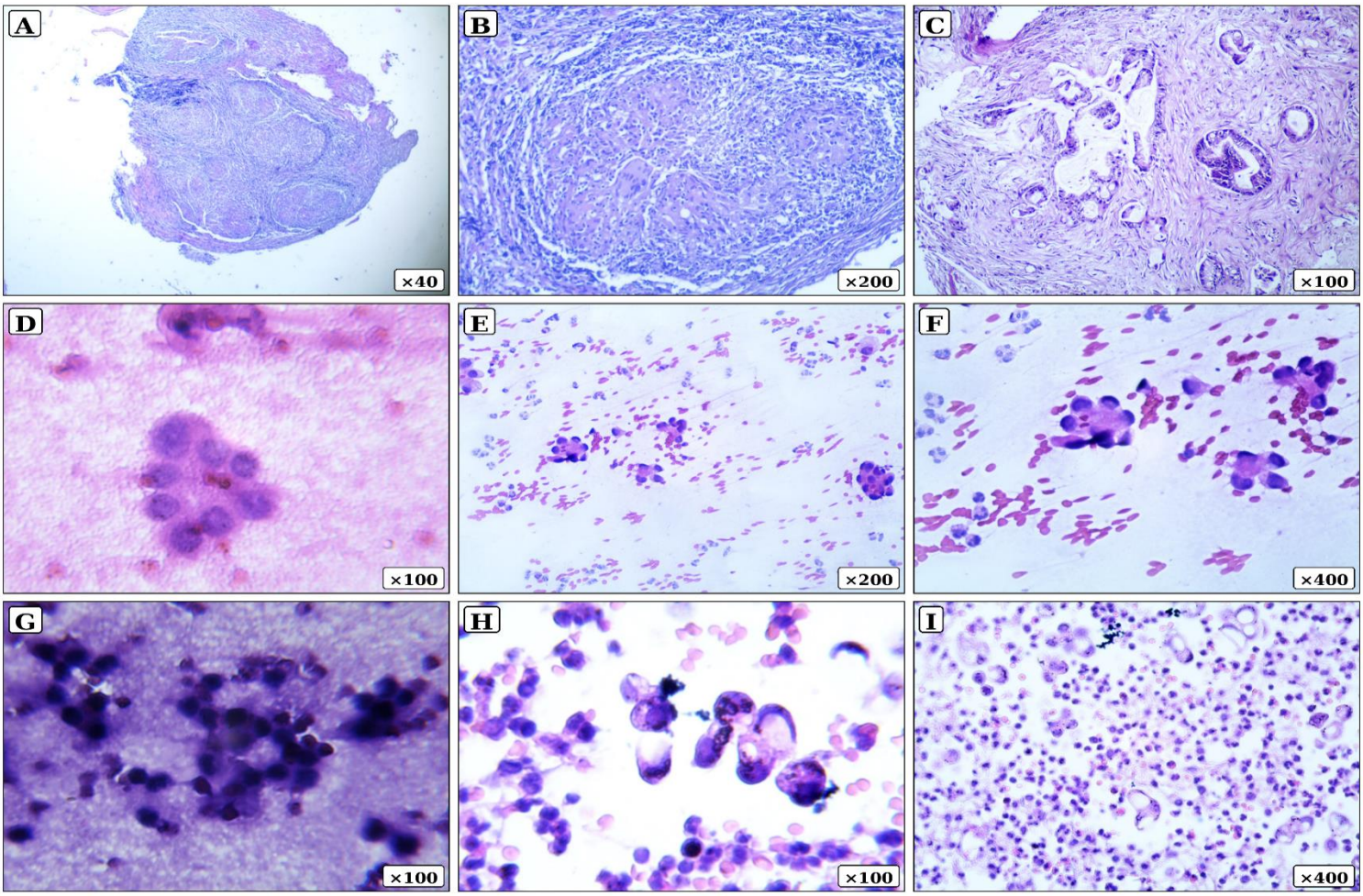

Figure 1. Representative histopathological and cytological findings in pleural diseases

(A , B) Pleural tuberculosis showing caseating granulomatous inflammation and multinucleated giant cells on haematoxylin-and-eosin staining at ×40 and ×200 magnification, respectively. (C) Pleural biopsy showing secondary metastatic well-differentiated adenocarcinoma at ×100 magnification. (D) Pleural-fluid cytology showing metastatic non-small-cell carcinoma characterized by three-dimensional cellular clusters, vesicular nuclei, and gland-like architecture at ×100 magnification.
(E , F) Pulmonary adenocarcinoma metastatic to the pleura at ×200 and ×400 magnification, respectively. (G) Pleural-fluid cytology showing atypical lymphoid cells at ×100 magnification.
(H , I) Pleural-fluid cell-block preparation showing metastatic adenocarcinoma of gastric origin at ×100 and ×400 magnification, respectively. All sections were stained with haematoxylin and eosin.

Histopathological examination showed a range of pleural pathology from isolated benign granulomatous infection to malignant secondary involvement. In pleuritis due to tuberculosis, the analysis revealed well-formed caseating granulomas containing epithelioid histiocytes and multinucleated giant cells. Pleural biopsy in malignant cases showed infiltrating well differentiated adenocarcinoma with typical irregular glandular pattern in desmoplastic stromal background, further supporting secondary pleura metastasis.

Some malignant and atypical cell subtypes were also found in pleural-fluid cytology. Macrometastasis of nonsmall cell carcinoma tumor was detected as intact 3D cohesive clusters of atypical epithelial cells with enlarged vesicular nuclei, nuclear pleomorphism and formation of gland-like architecture. The metastatic malignancies in the pleural cavity were characterized by scattered and clustered malignant epithelial cells with prominent nuclear atypia and nucleoli that had gone to represent pulmonary adenocarcinoma. Furthermore, atypical lymphoid

cells demonstrated large hyperchromatic nuclei with irregular nuclear borders and increased nuclear/cytoplasmic ratios.

Better cell architecture preservation via cell-block preparations allows for more detailed evaluation of neoplastic epithelial patterns. For example, in the case of metastatic gastric adenocarcinoma, such atypical gland-forming cells with cytoplasmic vacuolation were observed within an inflammatory background. Together, these results show the morphologic variation of pleural disease and illustrate the complementarity of pleural-fluid cytology and cell-block examination with histopathology from excised specimens to distinguish inflammatory diseases versus primary or metastatic malignant processes.

4. Discussion

The current study assessed the correlation of pleuroscopic, cytological and histopathological findings in patients investigated for pleural effusion. Three principal findings emerged. Malignant pleural biopsy findings were also significantly associated with visceral pleural involvement first. Second, there was a strong association between the final histopathological diagnosis and the classified pleural fluid cytology. The second major observation is that the pleural-fluid cytology was largely specific and predictive positive but of moderate sensitivity. Therefore, a positive cytology was reliable in diagnosing malignant pleural disease but there was only a low confidence that negative cytology would exclude malignancy. Conversely, lymphocytic predominance was not significantly associated with the biopsy diagnosis. Visceral pleural involvement was identified in 31 patients, of whom 17 (54.8%) had malignant biopsy findings. By comparison, malignancy was diagnosed in nine of the 34 patients (26.5%) without visceral pleural involvement. Patients with visceral involvement had approximately 3.4-fold higher odds of having malignant pleural disease than those without such involvement. This finding suggests that extension of the pathological process to the visceral pleural surface may serve as a useful macroscopic indicator of malignant pleural dissemination. This association is biologically plausible and related to the distribution pattern of malignancy in a pleural environment. After pleural implantation, neoplastic cells can spread over the parietal and visceral pleurae followed by formation of nodules, plaques, irregular thickening or diffuse infiltration in tumor. Thus, involvement of these visceral sites may reflect increased pleural disease burden or even greater dissemination. Expectedly, previous thoracoscopic studies have shown the potential for direct visualization of pleural surface abnormalities to help guide identification of suspicious malignant patterns and determine representative biopsy sites [7,8]. However, visceral pleural involvement should not be considered diagnostic of malignancy on its own. 45.2% of patients with visceral involvement in the current study had benign histopathological findings. Parasitic infections and inflammatory diseases, particularly tuberculous pleuritis and chronic nonspecific pleuritis, can also lead to pleural thickening, adhesions, nodularity, and changes in the visceral surface. Thus, the pleuroscopic appearance should only be viewed as a surrogate of increased suspicion for malignant disease and an indication of where to sample during biopsy, rather than replacement for biopsies with histopathological examination. This interpretation is in line with the recognized role of thoracoscopically guided pleura in direct pleural visualization and tissue sampling [2,6-8]. The pleural biopsy diagnosis was also strongly associated with the cytological classification of pleural-fluid. Of the 35 cases classified as negative for malignancy, 31 showed benign biopsy results and four were subsequently proven malignant. Histological diagnoses confirmed malignancy in all five atypia of undetermined significance cases and all 11 suspicious for malignancy cases. Also, six of the seven cytologically diagnosed malignant cases on the pleural biopsy samples were confirmed as malignant. These results demonstrate that the presence of increasing cytological atypia is highly correlated with a higher probability of malignancy on tissue biopsy. This finding is consistent with larger comparative studies of pleural-fluid cytology and corresponding pleural biopsy specimens. Poon et al. showed that pleural-fluid cytology is highly diagnostic, but only moderately sensitive to specific tumor types and patterns of pleural involvement [9].

Pairman et al. likewise indicated that pleural-fluid cytology is clinically useful for malignant pleural effusion diagnosis, but highlights that sensitivity varies considerably by malignancy type [10]. These findings together provide evidence for cytology as an adequate preliminary diagnostic investigation whilst confirming that tissue sampling is required when the diagnosis remains uncertain. When pleural biopsy histopathology was used as the reference standard, pleural fluid cytology demonstrated a sensitivity of 65.4%, specificity of 96.9%, positive predictive value of 94.4%, negative predictive value of 77.5%, and overall diagnostic accuracy of 82.8%. This pattern of moderate sensitivity and high specificity is important for clinical practice. The presence of a malignant cellular examination is consistent with the diagnosis of malignant pleural disease; in contrast, the absence of malignancy on cytology is far less helpful for ruling out malignancy. The reasons for the high specificity and positive predictive value are likely to be due to the recognizable cytomorphological characteristics of malignant cells in sufficiently cellular samples. In general, they are characterized by cohesive three-dimensional epithelial clusters associated with loss of cytoplasmic differentiation and increased nuclear-

cytoplasmic ratios in the absence of significant stroma; enlargement and pleomorphism of nuclei, irregularity of chromatin distribution, prominent nucleoli, and architecture that is glandular or papillary. False-positive diagnoses are uncommon when these findings are unequivocally recognized. Only one cytologically diagnosed malignant case in the current study had a benign biopsy. This discordant result may have been due to overinterpretation of markedly reactive mesothelial cells, which can occasionally exhibit nuclear enlargement, prominent nucleoli, multinucleation and complex cellular clustering. Or it could represent sampling heterogeneity in that cytology detected malignant cells that were shed from a pleural focus not seen on biopsy. These repetitive conflicting results should be followed by the integrated evaluation of cytological slides, cell-block preparations, biopsy sections, imaging findings and pleuroscopic observations. Cytochemistry and Immuno-histochemistry studied cytochemical properties in low volume on small sample from needle aspirates. The moderate sensitivity indicates that nine of the 26 histopathologically malignant cases (34.6%) were classified as non-malignant in the binary cytological analysis. False-negative cytology may result from low tumor-cell shedding, limited specimen cellularity, cellular degeneration, uneven pleural involvement, or sampling before extensive dissemination across the pleural surface. Diagnostic sensitivity is also influenced by tumor type. Adenocarcinomas commonly exfoliate into pleural fluid, whereas malignant mesothelioma, squamous carcinoma, lymphoma, and certain mesenchymal malignancies may be more difficult to identify cytologically [9,10].The diagnostic pattern observed in the present study is consistent with the recent findings of Maleki et al. [11], who evaluated 223 paired pleural-fluid cytology and pleural biopsy specimens using the International System for Reporting Serous Fluid Cytopathology. They reported an overall accuracy of 79.4%, sensitivity of 45.0%, specificity of 97.7%, positive predictive value of 91.2%, and negative predictive value of 77.0%. Although their sensitivity was lower than that observed in the present study, both studies demonstrated high specificity and positive predictive value with a comparatively modest negative predictive value. These findings indicate that pleural-fluid cytology is more reliable for confirming malignancy when malignant cells are identified than for excluding malignancy when cytology is negative.

These findings are clinically relevant. Positive pleural-fluid cytology is a definitive marker for malignant pleural disease, and cell-block preparations can yield material for tumor typing, immunocytochemistry, and molecular biomarkers. Nonetheless, there should not be a halt in diagnostic assessment when cytology is negative but clinical (such as the use of if there remains doubt regarding malignancy), radiological, or pleuroscopic suspicion remains. Under these circumstances, however, thoracoscopic pleural biopsy is still needed because it provides larger specimens, retains tissue architecture and allows evaluation of stroma and tissue invasion [2,6,9,10]. The indeterminate cytological categories warrant particular attention. All five cases categorized as atypia of undetermined significance and all 11 cases categorized as suspicious for malignancy were malignant on pleural biopsy. While the number of cases was small, this suggests that neither category may be reassuring in a clinically suspicious pleural effusion. Atypia of undetermined significance and suspicious for malignancy are classified by the International System for Reporting Serous Fluid Cytopathology into intermediate diagnostic categories that require clinical correlation, repeat sampling, ancillary investigations or tissue biopsy according to clinical suspicion [12]. Second, the reported high sensitivity and negative predictive value must be interpreted in light of the classification by binary diagnostic analysis which classifies atypia of undetermined significance as nonmalignant. As five of the atypical cases turned out to be malignant on biopsy, they would have contributed additional false-negatives when included with negative cytology and lowered sensitivity. This does not disprove the analysis; rather, it highlights the problems of collapsing a five-tier diagnostic system down into two. In the future, additional analyses may include reframing atypical cases as either negative, positive or excluded from binary calculation. Cell-block preparation could be especially useful in cases with indeterminate or inconclusive result. Preserves cellular architecture, allows for identification of glandular and papillary arrangements as well as immunocytochemical testing. Rani et al. came to the conclusion that examination of pleural-fluid cell-block and pleural biopsy provide complementary diagnostic information, supporting their combined use as an improved method for diagnosing malignant pleural effusions [13]. The case of metastatic gastric adenocarcinoma in the present study also shows that cell-block preparations are helpful in making a diagnosis by revealing malignant, gland-forming epithelial cells and cytoplasmic vacuolation. In a 2025 prospective study of patients with histopathologically confirmed malignant pleural effusion, Vu-Hoai et al. compared conventional smears, cell-block preparations, and liquid-based cytology [14]. The individual techniques demonstrated comparable sensitivity, whereas combining two cytological methods improved sensitivity in most comparisons; however, combining cell block with liquid-based cytology did not significantly outperform liquid-based cytology alone. These findings support a multimodal cytological approach rather than reliance on a single preparation method. The metastatic gastric adenocarcinoma illustrated in the present study similarly demonstrates the value of cell-block preparation in preserving glandular architecture and cytoplasmic vacuolation. Lymphocytic predominance was not significantly

related to pleural biopsy outcome. In patients with lymphocyte-predominant effusions, we found 72.0% benign lesions and 28.0% malignant lesions. By contrast, malignancy was detected in 51.5% of patients not classified as lymphocytic predominance.

Malignancy was diagnosed more frequently in patients without lymphocytic predominance, but the association did not achieve statistical significance. This lack of specificity is expected since polyclonal lymphocyte-predominant pleural effusions may develop in a wide range of chronic pleural disorders. Lymphocyte predominance may also occur in tuberculous pleuritis, malignancy, lymphoma and chronic inflammatory disease or longstanding effusions. Pleural biopsy has previously been shown to be helpful in distinguishing between tuberculosis, malignancy and other causes of lymphocytic exudative effusions [15]. Therefore, lymphocytic predominance should not be interpreted as a marker of disease but rather as a marker of chronic pleural process. The morphological results also confirmed the diagnostic overlap seen in pleural pathology. Caseating granulomatous inflammation with epithelioid histiocytes and multinucleated giant cells characterized tuberculous pleuritis. Biopsy specimens of malignant lesions showed infiltrative glandular structures, and pleural-fluid preparations revealed cohesive or dispersed atypical epithelial cells. These findings highlight the adjunctive roles that cytology and histopathology play. Cytology finds atypical exfoliated cells, while biopsy shows tissue architecture, stromal response and invasion and is often required for definitive diagnosis. Several limitations should be considered when interpreting the study. The single center nature and smaller sample size of this study limit statistical precision and generalizability. In seven patients, pleural-fluid cytology was unavailable, and the confidence interval for malignancy with visceral involvement had wide limits. Additionally, cytological data impacted the calculated sensitivity and negative predictive value if atypia of undetermined significance was grouped with non-malignant. Larger multicenter studies, assessing diagnostic performance stratified by tumor type and cytological category are thus warranted. Overall, the findings support a complementary diagnostic strategy. Pleural-fluid cytology is a highly specific and clinically valuable first-line investigation for malignant pleural disease; however, its moderate sensitivity limits its ability to exclude malignancy. Visceral pleural involvement is associated with an increased likelihood of malignant histopathology and may guide targeted biopsy, but it cannot replace tissue examination. Pleural biopsy remains essential when cytology is negative, atypical, or discordant with persistent clinical or pleuroscopic suspicion.

Conclusions

Pleural-fluid cytology is a highly specific and clinically valuable initial investigation for malignant pleural disease. However, its moderate sensitivity limits its ability to exclude malignancy when results are negative or indeterminate. Visceral pleural involvement was significantly associated with malignant histopathology and may help guide targeted pleural biopsy, but it is not sufficiently specific to replace tissue examination. Pleural biopsy therefore remains essential when clinical or pleuroscopic suspicion persists despite negative or atypical cytology.

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List of Abbreviations

Abbreviation	Full term
AUS	Atypia of Undetermined Significance
CI	Confidence Interval
CT	Computed Tomography
H&E	Haematoxylin and Eosin
MPE	Malignant Pleural Effusion
MT	Medical Thoracoscopy
NPV	Negative Predictive Value
NSCLC	Non-Small-Cell Lung Carcinoma
OR	Odds Ratio
PE	Pleural Effusion
PPV	Positive Predictive Value
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences

Abbreviation	Full term
TIS	The International System for Reporting Serous Fluid Cytopathology

This list contains the principal abbreviations used in the manuscript.

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