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The Role of Cell Block in Diagnosing Metastatic Adenocarcinoma in Pleural Fluid: A Case Series

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Abstract

Background: Cytological examination of pleural fluid is an important, inexpensive, and simple test for detecting malignancy in patients with clinical pleural effusion who undergo thoracentesis. Adenocarcinoma is the most common tumor type. However, diagnosis using the conventional smear method can be challenging when the typical glandular-like growth patterns are not visible. Cell block preparation from pleural fluid samples preserves tissue architecture and tumor cell genetic material, enabling further tests such as immunohistochemistry (IHC) and PCR.
Case presentation: We report a series of four patients with pleural effusion who underwent both conventional smear cytology and cell block examination. Tumor cell growth patterns were identified and descriptively analyzed for each sample. In two of these cases, vague glandular-like growth patterns were observed only in the cell block preparations and were absent in the conventional smears, which directly helped establish the diagnosis of metastatic adenocarcinoma.
Conclusion: Differences in tumor cell growth patterns between the conventional smears and the cell block preparations were observed in two cases. The vague glandular-like growth pattern that was present in the cell block but was not identified in the conventional smear aided pathologists in identifying metastatic adenocarcinoma in pleural fluid specimens.

Keywords: *cell block, cytology, pleural fluid, adenocarcinoma, case series*

Introduction

Malignant pleural effusion (MPE) is defined as the presence of neoplastic cells in pleural fluid and accounts for approximately 15–35% of all pleural effusions.[1] The majority of cases are caused by metastatic adenocarcinoma, with the lung and the breast being the most common primary sites in men and women, respectively.[2-4] Pleural fluid cytology is essential in diagnosing malignant lesions, and thoracentesis is the first examination performed in cases of pleural effusion.[3,5] This case series compares the cytological findings of conventional pleural fluid smears with those of the cell block method for diagnosing pleural effusion-related lung disease.

Cytological analysis of pleural fluid is a simple, inexpensive, and effective method for malignancy detection, whereas cell block preparations, which retain tissue architecture, allow histopathological diagnosis and additional immunohistochemical or even molecular studies to subtype various malignancies.[3] As targeted therapy advances, particularly in lung cancer, tumor cell samples that retain architecture and genetic material and are compatible with molecular testing are needed.[6] Cell blocks serve as a practical and economical solution to support diagnosis and treatment.[3]

Despite the widespread use of conventional smear cytology in pleural fluid evaluation, the diagnostic interpretation of metastatic adenocarcinoma may become difficult when the characteristic glandular architecture is poorly preserved or absent.[7] The role of cell block preparations in modern cytopathology is crucial

because they provide more comprehensive diagnostic information.[8] These preparations resemble histological sections stained with hematoxylin-eosin (HE), allowing them to display tissue architecture that is often difficult to discern in conventional cytology preparations. Cell blocks therefore help identify clearer morphological features and support the establishment of a diagnosis. Cell block preparations also allow multiple serial sections to be made, which can be used for further examinations such as special stains, immunohistochemistry, and molecular testing. MPE cell blocks can be used successfully to detect ALK rearrangement when tumor tissue is not available.[9] Cell blocks should also be considered a valuable resource for PD-L1 testing in advanced NSCLC.[10,11] The use of cell blocks for EGFR mutation detection also has a high success rate and yields reliable results.[12,13] Another advantage of this method is that the material can be archived and stored long term, ensuring that specimens can be reused in the future for both diagnostic and research purposes.

Microscopically, adenocarcinoma tumor cells in both conventional smears and cell blocks show large cells with a high nucleus-to-cytoplasm ratio, pleomorphic hyperchromatic nuclei, intranuclear cytoplasmic inclusions, macronucleoli, and atypical mitoses. Growth patterns may be clustered or dispersed (single cells).[3] Previous studies demonstrated that cell block preparation preserved tissue architecture better than conventional smears and increased the opportunity for ancillary testing, including immunohistochemistry and molecular analysis. However, only a limited number of reports have specifically described the differences in tumor cell growth patterns between conventional smears and cell block preparations and how these differences contribute to the recognition of metastatic adenocarcinoma in daily diagnostic practice. Therefore, this case series aimed to compare the tumor cell patterns identified in conventional pleural fluid smears and in cell block preparations in cases of metastatic adenocarcinoma and to evaluate the diagnostic contribution of cell block examination.

The common growth patterns in adenocarcinoma are clusters, glandular-like spheres (clear hollow gland-like structures), vague glandular-like spheres (indistinct hollow gland-like structures), papillary, sheet, and single-cell patterns.[3] Identifying these typical patterns in cell blocks helps distinguish adenocarcinoma from other cancer types. Cell block techniques are valuable for the evaluation of cellular morphology and for IHC staining to identify specific markers.[3]

Case Presentation

Specimen collection and preparation

This case series included four cases of pleural effusion diagnosed as metastatic adenocarcinoma at the Anatomical Pathology Laboratory, Dr. H.A. Rotinsulu Pulmonary Hospital, during the data collection period in May 2025. The inclusion criteria comprised all pleural effusion cases examined using both the conventional smear and the cell block (CB) methods during that period.

Pleural fluid specimens were collected in tubes. For routine cytological examination, 5 mL of homogenized pleural fluid was centrifuged at 2000 rpm for 10 minutes. The supernatant was then discarded, and the cell sediment was used to prepare smears, which were subsequently stained with Papanicolaou and Giemsa stains. For the preparation of CB slides, 10 mL of pleural fluid was processed using the same centrifugation method. After the supernatant was discarded, the resulting cell clumps were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin (HE).

Both the conventional smear and the CB preparations were evaluated independently by two anatomical pathologists, with a consensus review performed to resolve discrepancies, to identify the presence of atypical malignant cells as well as the patterns of atypical cell arrangement.

To ensure consistency, the morphological patterns evaluated were operationally defined as follows: cluster (a solid conglomeration of more than three atypical cells), glandular-like (clear hollow gland-like structures), vague glandular-like spheres (indistinct hollow gland-like structures), papillary (a finger-like arrangement with a fibrovascular core), and single-cell pattern (dispersed individual atypical cells).

This study evaluated four cases that showed more than one pattern of cell growth in the conventional smear preparations and/or the cell blocks upon re-examination. Clinical, radiological, and cytological data from the

conventional smears and the cell blocks were collected. Tumor cell growth patterns were microscopically identified and descriptively analyzed.

Case descriptions

Case 1

An 81-year-old man presented with shortness of breath and cough. He had been receiving anti-tuberculosis treatment for one month prior to admission. Chest X-ray showed active pulmonary tuberculosis with right pleural effusion, and ultrasonography (USG) confirmed right pleural effusion with atelectasis. Pleural fluid aspiration revealed metastatic adenocarcinoma in both the conventional smear and the cell block. The growth patterns identified in both preparations were glandular-like, cluster, and single-cell (Table 1, Figure 1).

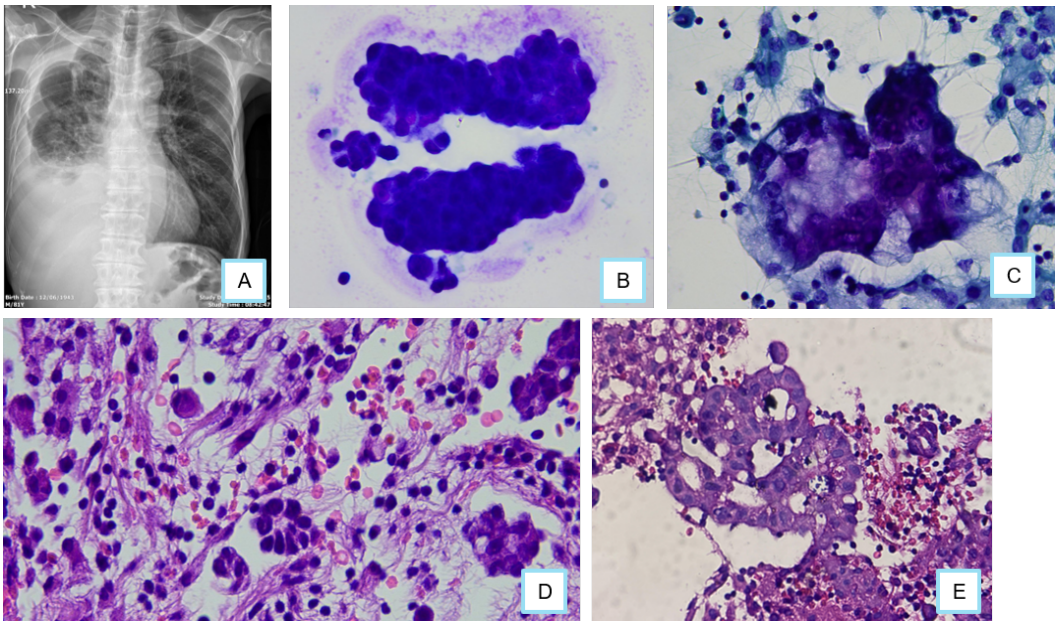

Figure 1. (A) Thoracic X-ray showing coarse hila with an increased bronchovascular pattern and a homogeneous opacity in the right lower lobe. (B) Glandular-like pattern on the conventional smear (400x, Giemsa). (C) Cluster pattern on the conventional smear (400x, Papanicolaou). (D-E) Glandular-like and single-cell patterns on the cell block of pleural fluid.

Case 2

A 58-year-old woman with a clinical pleural effusion suspected of being malignant underwent a thoracic X-ray, which showed left-sided pneumonia, with a working differential diagnosis of lung carcinoma with left pleural effusion. The cytopathological results of both the pleural fluid smear and the cell block were concluded as metastatic adenocarcinoma in the pleural fluid. A cluster growth pattern was found in the conventional smear preparation, whereas vague glandular-like and cluster growth patterns were found in the pleural fluid cell block (Table 1, Figure 2).

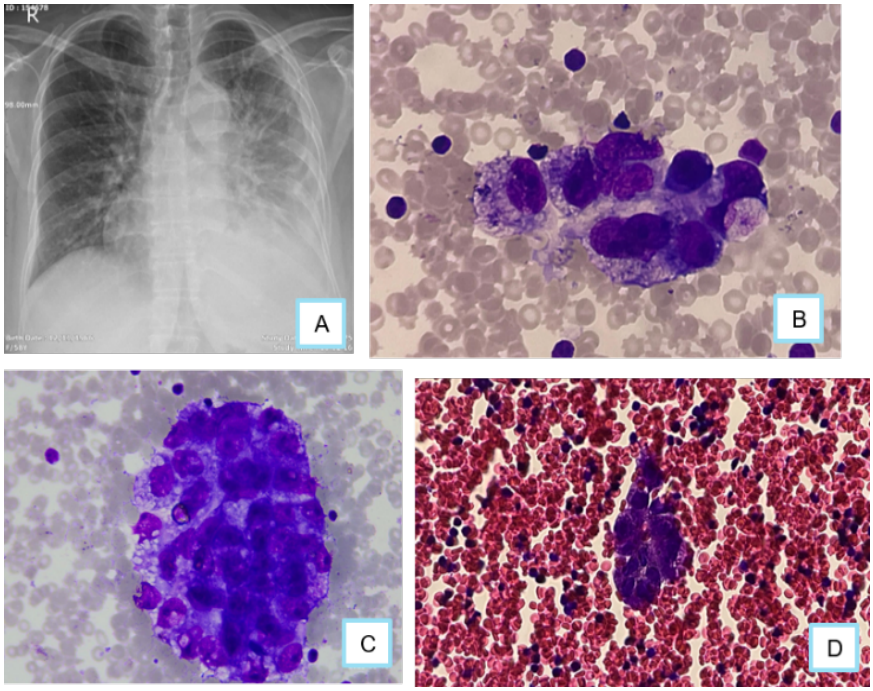

Figure 2. (A) Thoracic X-ray showing coarse hila with an increased bronchovascular pattern and a homogeneous opacity in the left lower lobe. (B-C) Cluster pattern on the conventional smear (400x, Giemsa). (D) Vague glandular-like pattern on the cell block of pleural fluid.

Case 3

A 56-year-old man with a suspected left lung tumor complained of shortness of breath. Chest X-ray examination was performed and showed extensive bilateral pneumonia with right pleural effusion. The results of the pleural fluid smear cytology and the cell block revealed metastatic adenocarcinoma. Microscopically, the tumor cells were arranged in glandular-like, cluster, and single-cell patterns (Table 1, Figure 3).

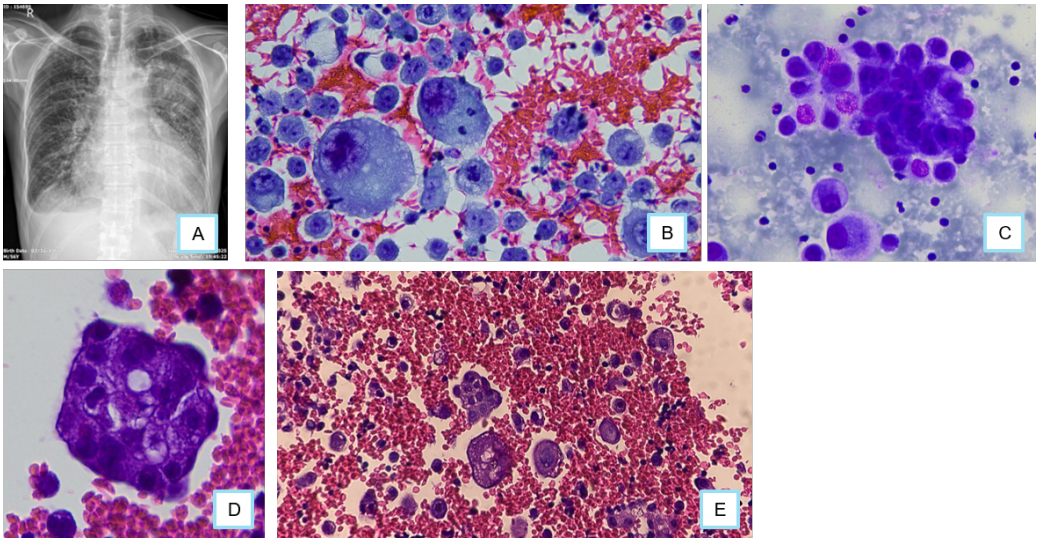

Figure 3. (A) Thoracic X-ray showing coarse hila with an increased bronchovascular pattern and bilateral upper and lower infiltrates. (B) Single-cell pattern on the conventional smear (400x, Papanicolaou). (C) Glandular-like pattern on the conventional smear (400x, Papanicolaou). (D-E) Glandular-like, cluster, and single-cell patterns on the cell block of pleural fluid.

Case 4

A 49-year-old woman with shortness of breath and a history of hypertension underwent chest X-ray examination, which suggested a massive right pleural effusion with suspected malignancy on imaging. Cytology and the cell block confirmed metastatic adenocarcinoma. The conventional smear showed tumor cells with cluster and single-cell growth patterns, whereas the cell block showed cluster, vague glandular-like, and single-cell growth patterns (Table 1, Figure 4).

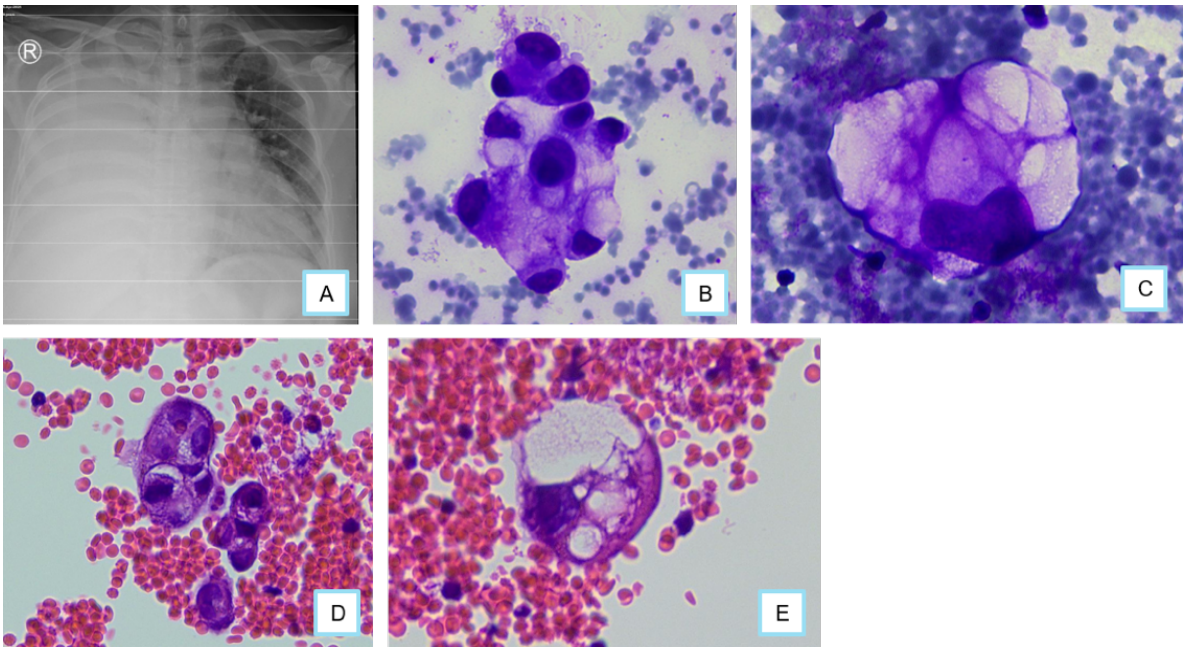

Figure 4. (A) Thoracic X-ray showing coarse hila with an increased bronchovascular pattern and homogeneous right upper and lower infiltrates. (B) Cluster pattern on the conventional smear (400x, Giemsa). (C) Predominant single-cell pattern on the conventional smear (400x, Giemsa). (D-E) Single-cell and vague glandular-like patterns on the cell block of pleural fluid.

Table 1. Distribution of malignant cell patterns in conventional pleural fluid smear preparations and cell blocks

Cases	Conventional pleural fluid smear					Cell block of pleural fluid				
	Cluster	Glandular-like	Vague glandular-like	Papillary	Single-cell	Cluster	Glandular-like	Vague glandular-like	Papillary	Single-cell
Case 1	Present	Present	None	None	Present	Present	Present	None	None	Present
Case 2	Present	None	None	None	None	Present	None	Present	None	None
Case 3	Present	Present	None	None	Present	Present	Present	None	None	Present
Case 4	Present	None	None	None	Present	Present	None	Present	None	Present

The patterns evaluated were cluster (a solid conglomeration of more than three atypical cells), glandular-like (clear hollow gland-like structures), vague glandular-like spheres (indistinct hollow gland-like structures), papillary (a finger-like arrangement with a fibrous core), and single-cell patterns, in both the conventional smears and the cell block preparations.

The comparison between the conventional smears and the cell block preparations across all four cases demonstrated that cell block examination provided valuable supplementary morphological information. Cluster

patterns were consistently identified in all cases, and single-cell patterns appeared in the same three cases (Cases 1, 3, and 4) with both methods, while clear glandular-like patterns were observed in Cases 1 and 3. In contrast, the cell blocks uniquely revealed vague glandular-like patterns in Cases 2 and 4, in which these patterns were entirely absent on the conventional smears. Papillary patterns were not observed in any of the cases with either preparation technique.

Discussion

Differences in tumor cell growth patterns between the conventional cytology and the cell block methods were found in two cases, namely Case 2 and Case 4. In these two cases, the conventional cytology smears showed only a cluster growth pattern, without any glandular-like or vague glandular-like patterns. In the cell block examinations, however, a vague glandular-like growth pattern was identified. The appearance of the vague glandular-like pattern in the cell block preparations, which had not been seen in the conventional smears, served as an aid for pathologists in identifying metastatic adenocarcinoma in pleural fluid specimens and in avoiding suspicious results in pleural fluid.

The findings of this study were consistent with those of Mathew et al. and Ranieri et al., who highlighted the utility of cell block preparation in cytopathology.[3,14] According to Mathew et al.,[3] the presence of characteristic growth patterns such as cluster, glandular-like, and vague glandular-like patterns in cell blocks can assist in the diagnosis of adenocarcinoma and help differentiate it from other tumor types. The cell block is a useful method for evaluating cellular morphology. In addition, it enables pathologists to perform IHC testing to determine specific cellular markers for histopathological subtyping and for identifying the tumor origin, particularly in cases with uncertain morphology.

Similarly, Ranieri et al. reported that cell block techniques can recover valuable architectural details that are often obscured or lost in conventional smears, and that the resulting improvement in morphological assessment can increase the diagnostic yield for malignancy in pleural fluid.[14]

A study by Rani et al. also showed that cell blocks were complementary to the cell smear technique in the overall diagnosis and categorization of both benign and malignant cells. The cell blocks were more useful in the diagnosis of malignancy because the architectural patterns were better preserved, as seen in the corresponding histopathology sections. It therefore appears that cell blocks are a perfect fit to bridge cytology and histopathology.[15] In the study by Shivakumarswamy et al., the cellularity and the additional yield for malignancy were 15% higher with the CB method, which was also found in previous comparative studies evaluating serous fluid cytology.[16] The study by Kumar et al. also showed that, in addition to improving diagnostic confidence, the cell block technique serves as a simple, cost-effective, and indispensable tool that preserves essential tissue for ancillary immunohistochemical and molecular testing.[17]

The conventional smear still effectively highlights malignant cellular changes on standard smears, but cell blocks are uniquely beneficial for clarifying misleading cytological abnormalities, such as reactive mesothelial cells, and for uncovering subtle features in well-differentiated adenocarcinomas. The cell block technique not only increased the number of positive results but also helped to demonstrate better architectural patterns, which could be of great help in making a correct diagnosis of the primary site, as was also found in previous comparative studies evaluating serous fluid cytology. To ensure accurate assessment, it is recommended that both methods will be used jointly for all fluid specimens processed in the laboratory.[18,19] The cell block combined with the conventional smear produced better results in detecting malignant lesions and in reducing suspicious results.[20]

This study has several limitations. First, the number of cases was limited because this was a descriptive case series from a single institution. Second, no immunohistochemical confirmation or molecular analysis was performed. Third, a quantitative assessment of diagnostic sensitivity was not carried out. Nevertheless, this study highlights the practical diagnostic contribution of cell block preparations in the routine evaluation of pleural fluid cytology.

In the current era of personalized therapy, especially in the management of lung carcinoma, pathologists are required to optimize the use of tumor cell samples to produce the most accurate diagnosis possible. This diagnosis can then be used for molecular testing that supports appropriate therapeutic choices, such as EGFR mutation testing, ALK gene rearrangement, and PD-1/PD-L1 expression.[4] The use of cell blocks can be a simple and cost-effective solution that is applicable in daily clinical practice. Therefore, we recommend that conventional smears and cell blocks will be used in combination, and that cell blocks will be routinely employed together with conventional smears for all effusions.

Conclusion

The combination of cell block examination and conventional smear cytology provided benefits in the diagnosis of metastatic adenocarcinoma in pleural fluid by facilitating the evaluation of cellular morphology through the identification of tumor cell growth patterns. In cases with uncertain morphology, cell blocks can be used for IHC examination. In addition, cell blocks can be used for follow-up examinations related to the administration of appropriate targeted therapy.

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Declaration concerning generative AI and AI-augmented technologies in the compositional process

In the course of preparing this paper, the authors utilized ChatGPT to enhance readability and linguistic quality. Subsequent to utilizing this tool/service, the writers assessed and amended the information as necessary and assume complete accountability for the publication's content.

Declarations of competing interest

No potential competing interest was reported by the authors.

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