

Cytology with cell block evaluation of non-adenocarcinomatous exfoliated malignancies in pleural and peritoneal fluids- A series of five rare cases

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Abstract

Malignant effusions have been known to affect humans since ancient times and are most commonly linked with adenocarcinomas originating from organs such as the lung, ovary, colon, and breast. However, in certain cases, non-adenocarcinomatous malignant cells, such as those from squamous cell carcinoma, mesothelioma, and sarcoma, may also be found in the effusion fluid. This retrospective case series includes five instances of non-adenocarcinomatous malignancies identified in pleural and peritoneal fluids at a tertiary care hospital over one year (January to December 2024). Cytomorphological analysis of the neoplastic effusions was conducted using MGG and PAP stains. Additionally, H&E-stained tissue sections from cell blocks were examined, and immunohistochemical tests (EMA, Calretinin, and CD20) were used as supplementary tools for diagnosis. Among the five cases studied, one case each of squamous cell carcinoma, transitional cell carcinoma, mesothelioma, lymphoma, and dysgerminoma was identified. Histopathological examination of cell blocks, supported by immunohistochemistry, is crucial in identifying the type of malignancy present in effusions. This approach is particularly important for distinguishing between metastatic epithelial cells and reactive mesothelial cells in cases where the diagnosis is complex.

Keywords: Cytology; Non-adenocarcinomatous malignancies; Pleural and peritoneal fluids.

Introduction

Malignant effusions are most commonly the result of metastatic adenocarcinomas. In contrast, serous effusions caused by metastatic squamous cell carcinoma (SCC) are quite uncommon, making up only about 0.5-2.7% of all malignant effusions. Poorly differentiated SCC can be particularly

challenging to identify in effusion cytology due to its rarity and limited distinct cytomorphological features, often leading to potential misdiagnosis as poorly differentiated adenocarcinoma (1). It is important to note that not all cases of malignant effusion show detectable malignant cells on cytological examination. This is because some

effusions occur due to a paramalignant process, where pleural effusion is present in cancer patients without direct tumor involvement of the pleura and no malignant cells in the fluid. Paramalignant effusions account for roughly 50% of pleural effusions associated with cancer. The most frequent underlying cause is lymphatic blockage due to mediastinal lymph node enlargement (2). Various non-adenocarcinomatous malignancies can occasionally be identified in pleural or peritoneal fluid, including lymphoma, multiple myeloma, mesothelioma, SCC, small cell lung carcinoma, melanoma, malignant germ cell tumors, and neuroblastoma. However, the presence of such malignancies in body cavity fluids is extremely rare, with only a limited number of cases reported in the literature (3).

Methods

This retrospective study was conducted over one year, from January to December 2024, at a tertiary care hospital located in the northeastern region of India. Five cases of non-adenocarcinomatous malignancies were identified in pleural and peritoneal fluid samples from patients admitted to the oncology and oncosurgery departments. The research protocol received approval from the Institutional Ethics Committee. Comprehensive clinical histories were taken, and thorough physical examinations were performed. Approximately 20-30 ml of fluid was collected via thoracentesis, using a 21G-22G wide-bore needle inserted through the posterior chest wall. The fluid samples were placed in clean, dry containers and subjected to physical, chemical, and cytological analysis. For cytological assessment, the samples were stained using May-Grünwald-Giemsa (MGG) and Papanicolaou (PAP) stains. In cases where diagnosis was challenging, particularly to distinguish between reactive mesothelial cells and malignant epithelial cells, cell blocks were prepared. These cell block sections were then stained with Hematoxylin and Eosin (H&E), and immunohistochemical (IHC) markers, including

epithelial membrane antigen (EMA), calretinin, CD20, and CD3, were employed to confirm the diagnosis.

Case 01

A 54-year-old male presented with pleural effusion and a known history of lung carcinoma. Cytological examination of the pleural fluid revealed atypical squamous epithelial cells characterized by nuclear pleomorphism, a high nuclear-to-cytoplasmic ratio, and prominent nucleoli. The diagnosis of metastatic SCC was confirmed through H&E-stained cell block sections. Immunohistochemistry showed positivity for EMA, while calretinin, CD20, and CD3 were negative. [Figure: 1a and 1b]

Case 02

A 63-year-old male with a known history of urinary bladder carcinoma presented with ascites. Cytological analysis of the peritoneal fluid indicated the presence of malignant cells. The diagnosis of metastatic transitional cell carcinoma (TCC) was confirmed through examination of cell block sections. Immunohistochemical staining showed positivity for EMA, while calretinin, CD20, and CD3 were negative. [Figure: 1c and 1d]

Case 03

A 52-year-old male presented with pleural effusion accompanied by multiple plaque-like, nodular thickenings of the parietal pleura. Cytological examination of the pleural fluid showed three-dimensional cohesive clusters of atypical cells, indicating the presence of malignancy. While H&E-stained cell block sections confirmed the presence of malignant cells, the specific type of malignancy could not be determined initially. Immunohistochemistry revealed positivity for both EMA and calretinin, while CD20 and CD3 were negative. Based on the cytological findings and immunohistochemical profile, a diagnosis of malignant mesothelioma was established. [Figure: 2a, 2b, 2c and 2d]

Case 04

A 46-year-old male presented with both pleural and peritoneal effusions, along with generalized lymphadenopathy. Cytological examination of the effusion fluids revealed numerous atypical lymphoid cells, dispersed singly, with enlarged, hyperchromatic, and convoluted nuclei. H&E stained sections from the cell block showed sheets of large lymphoid cells, but a definitive diagnosis could not be reached based on morphology alone. Immunohistochemical analysis demonstrated positivity for CD20, while CD3, EMA, and calretinin were negative. Taking into account the clinical presentation, imaging findings, and cytological features, a diagnosis of Non-Hodgkin lymphoma was suggested. [Figure: 3a and 3b]

Case 05

A 28-year-old female presented with ascites and a known history of an ovarian tumor. Cytological analysis of the effusion revealed large, round to polygonal cells with abundant clear cytoplasm, coarse chromatin, and prominent nucleoli, set against a background rich in lymphocytes. These features raised suspicion of malignancy. Initial immunohistochemistry was negative for common markers. However, based on clinical and radiological suspicion of a metastatic ovarian germ cell tumor, CD117 immunostaining was performed and found to be positive. Taking into account the clinical, radiological, cytological, and immunohistochemical findings, a diagnosis of metastatic dysgerminoma was considered. [Figure: 3c and 3d]

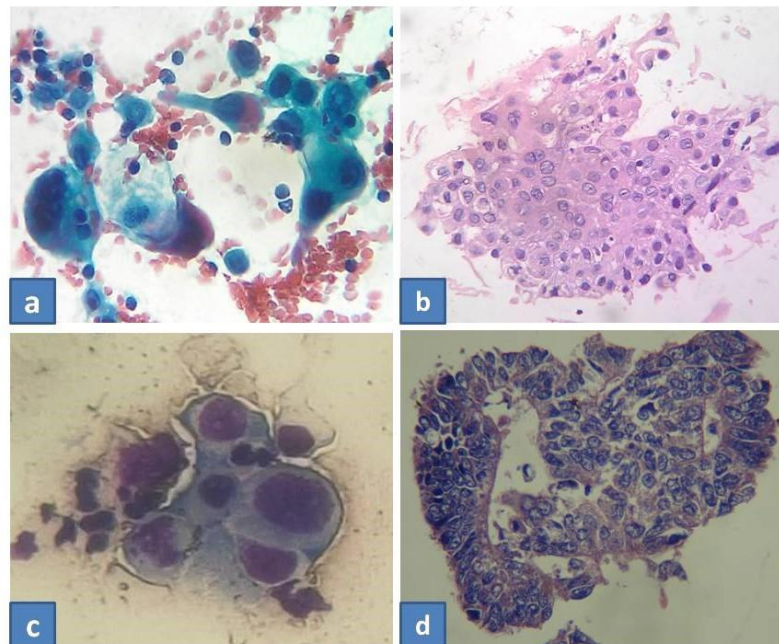


Figure 1: a) Cytomorphology of SCC (PAP stained, 400X), b) Tissue section from cell block of SCC (H&E stained, 100X), c) Cytomorphology of TCC (PAP stained, 400X), d) Tissue section from cell block of TCC (H&E stained, 100X)

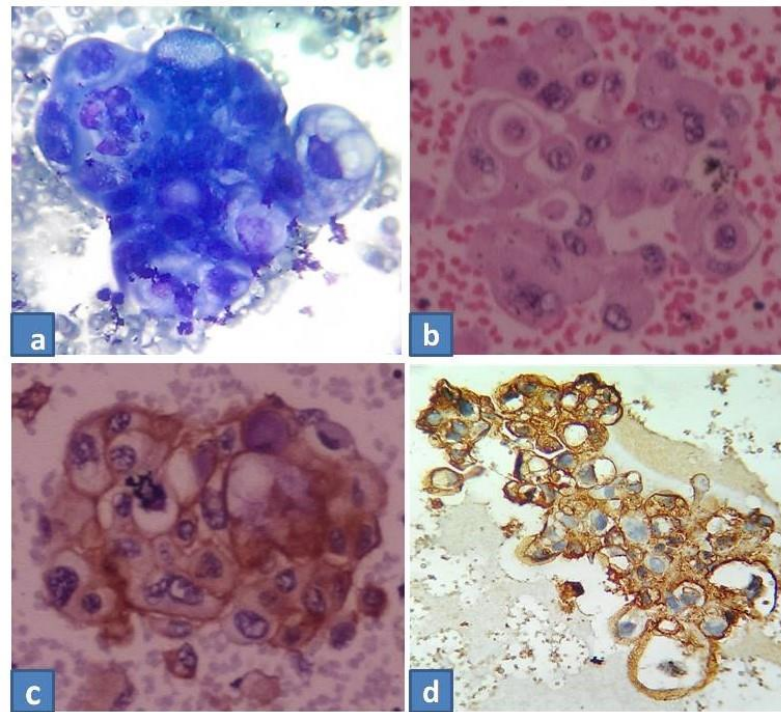


Figure 2: Malignant mesothelioma a) Cytomorphology (MGG stained, 400X), b) Tissue section from cell block (H&E stained, 400X), c) IHC shows Calretinin: Positive and d) EMA: Positive [ScyTek Lab, Logan, UTAH, USA]. All IHCs were compared with controls.

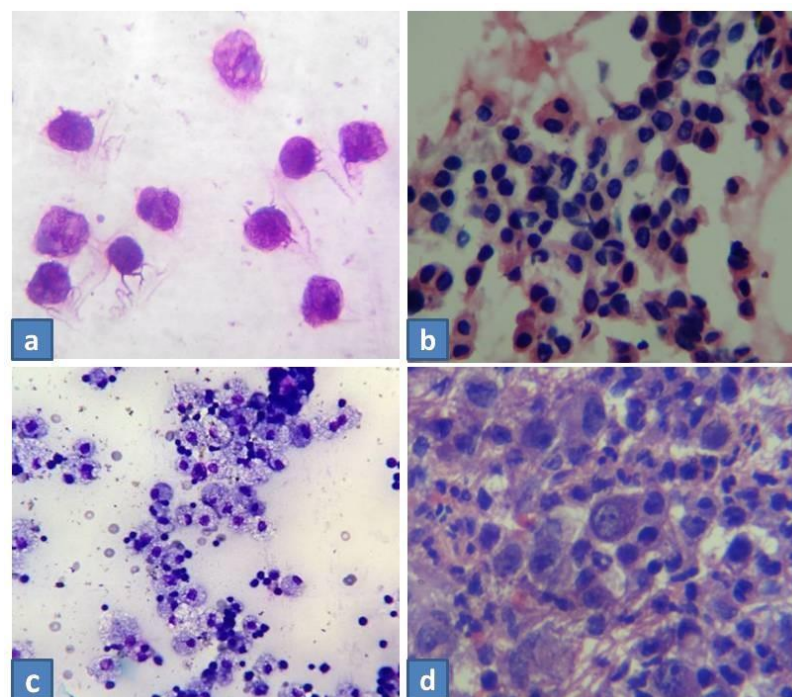


Figure 3: a) Cytomorphology of NHL (MGG stained, 400X), b) Tissue section from cell block of NHL (H&E stained, 100X), c) Cytomorphology of dysgerminoma (MGG stained, 100X), d) Tissue section from cell block of dysgerminoma (H&E stained, 400X)

Table 1: Summary of five different types of malignancies after confirmation by cell block with immunohistochemistry.

Case no.	Cytology cum cell block findings	IHC interpretations				Final diagnosis
		EMA	Calretinin	CD20	CD3	
Case 01 54 yrs/M	Metastatic squamous cell carcinoma	+++	—	—	—	Metastatic squamous cell carcinoma
Case 02 63 yrs/M	Metastatic transitional cell carcinoma	+++	—	—	—	Metastatic transitional cell carcinoma
Case 03 52 yrs/M	Positive for malignant cells	++	+++	—	—	Malignant mesothelioma
Case 04 46 yrs/M	Suspicious for malignant cells	—	—	+++	—	Non-Hodgkin lymphoma spillover
Case 05 28 yrs/F	Suspicious for malignant cells	—	—	—	—	Metastatic dysgerminoma

Discussion

It has been consistently observed that over 80% of malignant pleural effusions are due to metastatic adenocarcinomas, most commonly originating from primary tumors in the lung or breast. Similarly, in cases of malignant peritoneal effusions, ovarian carcinoma is the most frequent primary source.

Although squamous cell carcinoma (SCC) is a prevalent form of lung cancer, its presence in pleural fluid is relatively rare when compared to adenocarcinoma. This is largely because SCC

typically arises in the central airways, making direct spread to the pleural cavity less likely than in lung adenocarcinoma, which tends to have a peripheral origin and a higher tendency to involve the pleura (4).

In a study by Dorry M et al., only 10.46% of malignant pleural effusion cytology cases were identified as SCC, whereas the majority (89.54%) were metastatic adenocarcinoma (4). Other literature reports the incidence of SCC metastasis in serous body fluids as less than 1%, though older large-scale

population studies have shown rates ranging from 4% to 7% (5).

Chrysikopoulos H et al. described three patients with peritoneal metastases originating from transitional cell carcinoma (TCC) of the urinary tract. One patient's CT scan revealed significant ascites along with subtle peritoneal thickening and omental fat infiltration (6). Similarly, Khosla M et al. reported a rare case involving a 48-year-old man with peritoneal carcinomatosis and ascites due to metastatic TCC. Cytology and biopsy confirmed high-grade TCC with papillary features, a presentation associated with a poor prognosis due to its advanced stage and limited treatment options (7).

Shaker N et al. documented a case of malignant mesothelioma presenting as a right-sided pleural effusion in a 63-year-old man. The patient had a long occupational history of asbestos exposure, having worked in a shipyard for three decades (8).

In a study by Kim CH et al., thirty cases of lymphoma with associated pleural effusions were recorded over a five-year period (2011-2016). However, malignant cells were detected in the pleural fluid cytology in only four patients, all of whom had B-cell non-Hodgkin lymphoma (9).

Balakrishnan M et al. reported on a 15-year-old girl who presented to the emergency department with painful ascites and respiratory distress. Initially suspected to have an undifferentiated round cell tumor, further immunohistochemical analysis of cell block preparations, guided by clinical suspicion of an ovarian mass, revealed tumor cells positive for CD117 and PLAP. A final diagnosis of metastatic dysgerminoma was made (10).

Conclusion

Although metastatic adenocarcinoma is the most frequently encountered malignancy in pleural and peritoneal effusions, there are occasional cases where non-adenocarcinomatous tumors shed into

these fluids. In such cases, the cytological characteristics can be difficult to interpret, sometimes resulting in diagnostic errors. The five cases presented in this study represent exceptionally rare occurrences, with only a limited number of similar cases reported in the literature. In these uncommon scenarios, additional analysis using H&E-stained cell block sections, along with supplementary immunohistochemical markers, proves highly valuable in identifying both the origin and type of malignancy present in the effusion.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study. Written consent was obtained from the patient/kin of the patient.

Institutional Ethics Committee approval was obtained for this study.

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Contributions by each author:

- 1. Dr. Bidhan Chandra Das-** Interpretation of cytology, cell block, and Immunohistochemistry slides, writing the manuscript, conceptualization, and designing of the study.
- 2. Dr. Basob Jyoti Hazarika-** Clinical guidance and providing samples.
- 3. Dr. Mayuri Saikia-** Preparation of slides, data collection, and typing of manuscript.

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