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Original Research Article

Spectrum of uncommon malignancies in pleural fluid cytology: A study from a tertiary care center in South India

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ABSTRACT

Background: Pleural fluid cytology is a useful diagnostic test to detect metastasis to pleura. Among the metastatic neoplasms to pleural cavity adenocarcinoma is the most common. However there are other neoplasms which rarely infiltrate pleura and produce effusion. The aim of this study is to analyse the spectrum of these unusual malignancies involving pleural fluid with cytomorphology and ancillary studies.
Materials and Methods: This is a retrospective study which includes the pleural fluid samples submitted to the cytology section of our institute between 2015 to 2018. A total of 1510 samples are reviewed. Cases with diagnosis other than adenocarcinoma are selected and their cytomorphological details are analysed with ancillary tests wherever available.
Results: Out of 1510 samples analysed, 468 are positive for malignancy. Out of 468, 42 cases are uncommon malignancies. These are classified into hematolymphoid (33/42 cases) which includes Nonhodgkin lyphoma, acute lymphoblastic leukemia, chronic myeloid leukemia, multiple myeloma and nonhematolymphoid neoplasms (9 /42) which includes small round cell tumours, squamous cell carcinoma, small cell carcinoma, germ cell tumor and granulosa cell tumour.
Conclusion: There are certain uncommonly encountered malignancies in pleural fluid. Cytomorphology plays a key role in diagnosing them with certain cases requiring ancillary studies to confirm the diagnosis.

1. Introduction

Pleural effusion cytology is one of the first lines of investigation when a neoplastic pleural effusion is suspected. It is a minimally invasive and cost-effective modality. Among the etiologies for exudative pleural effusion, malignancy is the second most common followed by parapneumonic effusions.[1] Malignant cells when observed in pleural fluid impart poor prognostic significance to an oncologic patient by defining a higher clinical stage. The most common type of cancer metastasising to pleura and producing effusion is adenocarcinoma with the primary in lung, breast, ovary and gastrointestinal tract. Adenocarcinoma in fluids is relatively easier for a cytopathologist to diagnose. However, there some unusual malignancies in the fluids which can be diagnosed with careful screening and with an insight into the cytomorphological details. Also in certain cases ancillary tests are needed to confirm the diagnosis.

2. Materials and Methods

This study is a retrospective one. The pleural effusion samples submitted to cytology section of department of pathology, in our institute between January 2015 to December 2018 for analysis were retrieved from the register. A total of 1510 samples were reviewed. Cases with diagnosis other than adenocarcinoma were selected and their cytomorphological details were analysed. Three smears for each case were available for analysis, two of

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which were wet fixed and stained by Papanicolaou stain and the other one was dry fixed and stained with MayGrunwald Giemsa stain. Cell block slides and immunohistochemistry (IHC) slides were also reviewed. Cell block was processed using clot method and agar method. IHC was done on cell block using avid in biotin peroxidase method.

3. Results

The total number of pleural fluid samples received during the study period was 1510. Out of them, 468 samples were positive for malignancy. Among 468 malignant samples, 426 were positive for metastatic adenocarcinoma and 42 cases were positive for uncommon malignancies. The age of these patients ranged from 2 to 63 years with 24 male and 18 female cases. The infiltrations were classified into hematolymphoid (33/42 cases) and non hematolymphoid neoplasms (9/42).

Among the hematolymphoid neoplasms, 21 cases of Nonhodgkin lymphoma, 9 cases of acute lymphoblastic leukemia (Figure 1 A), 2 cases of chronic myeloid leukemia (Figure 1 B) and 1 case of multiple myeloma infiltration (Figure 1 C) were noted. Among the Non Hodgkin lymphoma 3 cases of Burkitt lymphoma and 1 case of Anaplastic large cell lymphoma(ALCL) infiltration were noted. (Table 1). The smears of Burkitt lymphoma and lymphoblastic lymphoma had monomorphic population of lymphoid cells with deep basophilic cytoplasm and fine vacuolations observed in Burkitt lymphoma cells. Increased mitosis, and karyorrhexis was also noted. The case of ALCL showed scattered large sized atypical cells with lobulated nuclei, irregular nuclear membrane and moderate amount of cytoplasm with background of lymphocytes, eosinophils and plasma cells (Figure 1D). Occasional cells exhibited hall mark cell like morphology. Immunohistochemistry on cell block showed tumour cells positive for CD3, CD 30 and negative for ALK, EMA, CD 20, CK confirming the infiltration in case of ALK negative ALCL proven on lymphnode biopsy.

Table 1: Spectrum of malignancies in pleural fluid cytology

Unusual malignancies in pleural fluid	Number of cases
Hematolymphoid neoplasms	33/42
1. Nonhodgkin lymphoma	21
2. Acute lymphoblastic leukemia	9
3. Chronic myeloid leukemia	2
4. Multiple myeloma	1
Non hematolymphoid neoplasms	9/42
1. Squamous cell carcinoma	2
2. Small cell carcinoma	1
3. Small round cell tumours	4
4. Germ cell tumour	1
5. Juvenile granulosa cell tumour	1

The nonhematolymphoid neoplasms consisted of 2 cases of squamous cell carcinoma (Figure 2B), 1 case of small

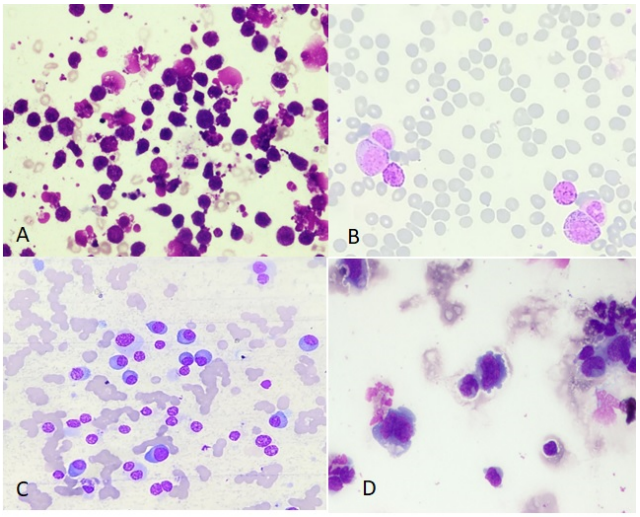

Fig. 1: A: Pleural fluid smear shows, blasts some of them with hand mirror morphology and karyorrhexis in case of acute lymphoblastic leukemia. MGG X400; **B:** Pleural fluid smear shows few myeloid precursors and basophils in case of CML infiltration. MGGX400; **C:** pleural fluid smear shows infitration by plasma cells in a case of multiple myeloma. MGG X400; **D:** Pleural fluid smear shows large atypical lymphoid cells with lobated nuclei and basophilic cytoplasm in a case of ALCL infiltration. MGG X400

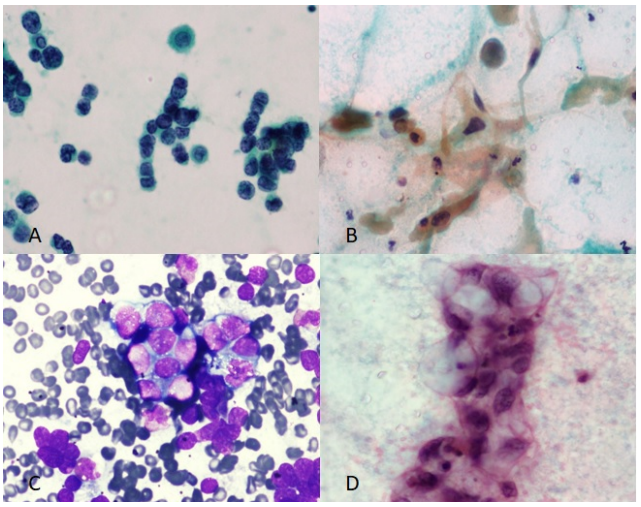

Fig. 2: A: Pleural fluid smear shows small cells with scant cytoplasm, speckled nuclear chromatin and nuclear moulding in case of small cell carcinoma. PAP X400; **B:** Pleural fluid smear shows keratinised squamous cells, anucleate squames of odd shapes in a case of squamous cell carcinoma. PAP X400; **C:** Pleural fluid smear shows small round blue tumour cells with vacuolations in cytoplasm in a case of ewing sarcoma. MGG X400; **D:** Pleural fluid smear shows a cluster of tumour cells withvesicular nuclei and vacuolated cytoplasm in a case of germ cell tumour. PAPX400

cell neuroendocrine carcinoma (Figure 2A), 1 case of germ cell tumour (Figure 2D), 4 cases of small round cell tumour and 1 case of granulosa cell tumour of ovary. Of the 4 cases of malignant small round cell tumour, there were 2 cases of rhabdomyosarcoma, 1 case of wilm's tumour and Ewing sarcoma (Figure 2C). The case of ewing sarcoma had classic biphasic population of tumour cells, the larger ones with cytoplasmic vacuolations and the smaller darker cells in the fluid smear. However rosette formation was not observed. In the case of Wilms tumour, the small round cells were of blastemal nature without epithelial component. Loosely aggregated population of small round blue cells were observed in smears of rhabdomyosarcoma. Both the cases of squamous cell carcinoma had keratinising squamous cells and atypical squames in the smears. In the smear showing infiltration by small cell carcinoma the tumour cells were arranged in small clusters and as individual cells. Tumour cells were 2-3 times the size of small lymphocytes and had fine granular chromatin with nuclear moulding. We had a two year old girl who presented with a ovarian mass and pleural effusion with elevated AFP levels. The pleural fluid smears showed infiltration by tumour cells which are arranged in loose clusters having vesicular nuclei and abundant vacuolated cytoplasm. Histopathology of ovarian mass was diagnosed as germ cell tumour – Yolk sac type. Correlating cytomorphology with elevated serum AFP levels the pleural fluid cytology was reported as positive with germ cell tumour infiltration.

We also had a rare case of granulosa cell tumour (Juvenile type) of ovary in 25 years old female infiltrating the pleural cavity where tumour cells were exhibiting focal follicular pattern of arrangement with moderate amount of cytoplasm and round hyperchromatic nuclei. IHC on cell block was done and tumour cells were immunoreactive for inhibin, calretinin, CD56, CD 99 and immunonegative for CK, EMA confirming the diagnosis.

4. Discussion

Pleural effusions are a frequently encountered manifestation of metastatic disease and can occur in 15% of the patients with cancer.[2] Malignant pleural effusions are often the initial manifestation of cancer.[3] The most common histologic type of cancer to produce metastasis is adenocarcinoma and the primary is in lung, breast, gastrointestinal tract and ovary.[4–7] A variety of other cancers also can cause pleural effusion but their occurrence is unusual. In this study the most common unusual cause of pleural effusion is Nonhodgkin lymphoma which constitutes (22/468) 4.7% of total malignant samples whereas in the study by Aswathi et al NHL contributed to 12.2% of MPE.[8] Pleural effusion is a relatively common finding in patients with Non-Hodgkin lymphoma with a frequency of up to 20%.[9] The various mechanisms for the formation of pleural effusion includes lymphomatous infiltration of pleura which is the most common followed by lymphatic obstruction due to infiltration of pulmonary and mediastinal lymphnodes and obstruction of thoracic ducts.[10,11] As described by Gupta et al. in their audit the most important aspects of cytology of NHL and leukemia was that the neoplastic cells did not exhibit genuine attachment to each other and there is massive necrosis/karyorrhexis which is never seen in carcinomas.[12] Also we observed the presence of lymphoglandular bodies in the background in such cases in our study.

The neoplastic lymphocytes of low grade lymphoma are difficult to distinguish from benign lymphocytes of chronic inflammation or tuberculosis. However the monomorphic nature of the cell population with immunohistochemistry and flow cytometry can help in diagnosis of the lymphoma. In our study there were 9 cases of acute lymphoid leukemic infiltration of the pleura. According to the literature, cases with lymphoid leukemic infiltration are commoner than myeloid leukemic infiltration.[11] Leukemic infiltration of the lungs/pleura may occur as a part of systemic relapse or rarely as an isolated leukemic infiltrate. The other causes for pleural effusion in leukemic patients such as bacterial, viral infections and complications of chemotherapy should be excluded.

Cakir et al. in their study had observed that some large cell lymphomas may have more abundant cytoplasm and needs to be distinguished from poorly differentiated carcinoma and melanoma.[13] This diagnostic dilemma is encountered when ALCL infiltrates the serous cavities as the lymphoma cells are large having lobated nucleus and abundant cytoplasm resembling carcinoma or melanoma cells. We had a case of ALK negative ALCL in pleural fluid cytology where the diagnosis was confirmed with the support of IHC on cell block of the fluid.

In our study we have two cases of positive pleural fluid cytology with chronic myeloid leukemia infiltration. One of the cases had blast crisis and the other showed all stages of myeloid precursors with increased blasts. Pleural effusion in CML patients is a rare occurrence and is poorly understood.[14] The possible mechanisms of exudative pleural effusion in CML patients include leukemic infiltration into the pleura, extra-medullary hematopoiesis, non malignant causes and drugs.[2]

Malignant myelomatous pleural effusions are very rare and occur in less than 1% of the cases of multiple myeloma.[15] In multiple myeloma cases pleural effusion usually occurs due to concurrent disease process or coexisting illness such as heart failure, amyloidosis, pulmonary embolism etc and rarely due to myeloma cells infiltration. Our case was an elderly female who presented with pleural effusion and paravertebral mass. Pleural fluid smears revealed plasma cells with mature and immature morphology. IHC was done on cell block of pleural fluid which revealed immunoreactivity to CD138 and kappa

restriction and confirmed as myelomatous infiltration.[16] This case highlights the significance of ancillary studies like immunohistochemistry which can be done on the cell block of the fluid sample to diagnose the uncommon infiltrations.

Exudative pleural effusion due to malignant small round cell tumour infiltration is another unusual event. We have four cases of pleural fluid positive for small round cell tumour infiltration. One of the cases is Wilms tumour of kidney, other case is Ewing sarcoma of bone and the other two cases are rhabdomyosarcoma of soft tissue and uterus. These are some common pediatric tumours which can have pleural effusion. In a study by Wong et al. where they analysed serous effusion cytology in a large pediatric cohort they reported eight cases of neuroblastoma, five cases of wilms tumour and two cases of Ewing sarcoma.[17]

Though the most common histologic type of epithelial neoplasm to metastasise to pleural cavity is adenocarcinoma, there are a small proportion of other types like squamous cell carcinoma and neuroendocrine carcinoma. In this study there are two cases of pleural fluid cytology with squamous cell carcinoma infiltration and one case with neuroendocrine carcinoma (small cell type) infiltration. The squamous cell carcinoma cases had their primaries in tongue and esophagus. Gupta et al. in their study has observed that 32% of squamous cell carcinoma presented with pleural effusion and the most common primary was lung followed by head and neck region.[12] The presence of keratinising squamous cells with abnormal anucleate squames and squamous keratin pearls in the fluid smear are the characteristic morphological features for diagnosis. However cells of nonkeratinizing squamous cell carcinoma can be mistaken for adenocarcinoma or mesothelial cells and can be overlooked.

The single case of pleural fluid cytology with neuroendocrine carcinoma (small cell type) infiltration observed in this study had classic cytomorphological features which includes small cells with scant cytoplasm, hyperchromatic nuclei and absence of nucleoli. There are also short chains of flattened tumour cells resembling pile of coins. The small cells in fluid can at times be mistaken for inflammatory cells or can be confused with other small round cell tumour.[18] Ancillary tests like IHC can be done to confirm the diagnosis in such cases.

Pleural fluid infiltration with germ cell tumour is a rare occurrence. In this study we had a case with germ cell tumour infiltration, where the cytomorphology was correlated with clinical history and elevated serum tumour marker (AFP). In the study by Gupta et al. there were two cases of pleural fluid cytology with germ cell tumour infiltration where the neoplasm was typed on cytology with the background of primary site and clinical diagnosis.[12]

In this series we had a very rare and uncommon case of juvenile granulosa cell tumour of ovary in a 25 years old female patient infiltrating pleural cavity. This was not been previously described in literature.[19]

5. Conclusion

There are malignancies other than adenocarcinoma which can infiltrate pleural cavity and present with effusions but their occurrence is unusual. Cytomorphological features play a significant role in detecting these uncommon malignancies in pleural fluid. However in certain rare cases, clinical history and ancillary studies help in confirming the diagnosis.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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