Original Article

Challenges of Pleural Aspirate Cytology: A 5-year Review

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Abstract

Introduction: Pleural effusion is a common medical condition, and the aspiration of the pleural cavity is a minimally invasive, cheap, and simple technique with the potential to achieve a clinically useful diagnosis. Challenges in the optimization of this investigative modality, however, occur in our everyday practice. **Aim:** The purpose of this review was to highlight the challenges in the cytopathological evaluation of pleural aspirates in our environment. **Materials and Methods:** The data regarding pleural fluid (PF) aspirates received for cytopathological evaluation between January 1, 2010, and December 31, 2014, were retrieved from departmental records and analyzed. **Results:** PF aspirates from 69 patients, with a male–female ratio of 1:1.03, were studied. The modal age group was 30–39 years, and the mean age was 45 ± 21.40 years. Of 69 smears, 40.6% were categorized as unsatisfactory/nondiagnostic, 44.9% were in the "negative for malignancy/normal/benign" category, 1.4% were in the "atypical-favor reactive" category, 4.3% were "atypical-suspicious for malignancy," and 8.7% were "positive for malignancy." The male–female ratio of patients with malignant pleural effusions was 1:5, and 66.7% of malignant smears were from persons above 50 years. Thirty-nine percent of total smears wear "inflammatory." The large number of unsatisfactory smears is a major challenge. **Conclusion:** Pleural aspirate cytology can be a useful investigative tool with the potential for definitive diagnosis or other useful information for clinical decision-making. To maximize its diagnostic potential in our environment, however, the current challenges must be overcome.

Keywords: Cytology, cytopathology, pleural aspirate, pleural effusion

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Introduction

Pleural effusion is the accumulation of fluid in the pleural cavity. It can be a result of pleural, lung parenchymal, and systemic disease.[1] The pleural cavity is a potential space normally containing about 0.1–0.3 ml/kg of pleural fluid (PF) which is being exchanged constantly.[2] The PF is produced by the parietal pleural vasculature and gets absorbed by the lymphatics in the mediastinal and diaphragmatic parietal pleura. The aspiration of the pleural cavity is a minimally invasive, cheap, and simple technique with the potential to achieve clinically useful diagnoses. The cytological examination of serous effusions has increasingly gained acceptance in clinical medicine, and the examination of PF aspirates provides information about various inflammatory and noninflammatory lesions and is useful in staging, prognostication, and management of the patients with various malignancies.[3]

Pleural effusions may be transudative or exudative. Transudative pleural effusions are due to systemic illnesses that result in altered hydrostatic or oncotic pressures in the pleural space, such as congestive heart failure, hypoalbuminemia, nephrotic syndrome, and hepatic disorders (cirrhosis). Exudative pleural effusion occurs due to the local pleural or lung parenchymal pathology associated with increased mesothelial and capillary permeability. The common causes of exudative pleural effusion include pleural or pulmonary tuberculosis, pneumonia, malignancy, and inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, chylothorax (thoracic duct injury or lymphatic obstruction), postcardiac injury syndrome, hemothorax, and asbestosis. Some causes of pleural effusion may result in transudative or exudative effusions. The classification of pleural effusions into transudates or exudates is commonly done based on the modified Light's criteria.[4,5] Exudative

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PF has at least one of the following criteria identified by Light: (a) PF protein/serum protein ratio more than 0.5, (b) PF lactate dehydrogenase (LDH)/serum LDH ratio more than 0.6. (c) Pleural LDH is more than two-thirds of the upper limits of normal laboratory value for serum LDH. If none of these criteria is met, then the fluid is considered a transudate.

Pleural effusions may also be broadly classified as benign or malignant. This is based on the finding, or not, of malignant cells or benign cells on cytologic examination of PF. A positive diagnosis of malignancy is considered definitive and obviates explorative surgery, whereas a negative diagnosis does not rule out the possibility of a malignancy and may warrant a repeat or further investigation, especially if malignancy is considered likely. The finding of atypical cells should always prompt further investigations.

Diagnostic challenges arise in everyday practice of cytopathology, especially with regard to differentiating reactive mesothelial cells from malignant cells in conventional cytologic smear method. Modified epithelial cells (mesothelial cells) line body cavities and are often shed in serous effusions as an almost ubiquitous component. They respond readily to irritation or inflammation and may undergo reactive hyperplastic, metaplastic, or degenerative changes and show multinucleation and other atypical features, resulting in diagnostic problems.[3,6] Difficulties may also arise due to the subtle cytomorphological features of some malignant neoplasms, particularly well-differentiated adenocarcinomas. This may become compounded by technical problems. In addition, the cytological examination of effusions, using the conventional smear method, has only a sensitivity of only 40%–70% for the detection of malignancy.[6] Reasons for this include overcrowding of cells, abundance of inflammatory cells, paucity of representative cells, cell loss, and other technical problems.[6,7] Some of these problems can be overcome using the cellblock method. This tends to improve the yield of cells and preserve better architectural patterns such as glands, sheets, three-dimensional cell clusters, and cell balls, resulting in up to 15% increase in the detection of malignant cells compared to the conventional smear method.[6] Special and immunohistochemical stains can also be easily added.

Other challenges in diagnostic cytopathology of pleural effusions arise as a result of the dilemma faced in deciding what to do with transudative effusions. A lot has been published on the optimal clinical management of patients with pleural exudates, particularly those caused by malignant tumors, whereas little information is available on the diagnosis and treatment of pleural transudates.[8] As pleural transudates can be caused by rare diseases, analysis of transudative PF can be useful for establishing diagnosis. The dilemma lies in knowing when to request PF cytology to rule out malignancy.[8] The traditional teaching is that malignant effusions are rarely transudative and performing cytology to diagnose malignancy on a transudative pleural effusion has a low yield and might not be cost-effective.[9] It is important to note, however, that up to 10% of malignant pleural effusions behave biochemically as transudates, and several mechanisms may be involved.[8,10-12] Cytologically proven cases of transudative malignant pleural effusions are well documented.[9] Kushwaha *et al*. reported 28 malignant pleural effusions, 10.71% of which were transudative.[13] It has been suggested that cytology to rule out malignancy should be requested if pulmonary embolism is not bilateral,[4] if nodules/lung masses, pulmonary atelectasis, or mediastinal lymphadenopathies are observed on the chest X-ray or computed tomography, if the patient does not have dyspnea, if the PF is of serous bloody appearance, or if PF carcinoembryonic antigen levels are high.[8,10]

Even as international recommendations are taken into consideration, the practice of pathology must address region-specific questions and be based on local guidelines tailored toward serving locoregional needs and overcoming identified locoregional challenges. This study highlights the challenges encountered in the cytopathological evaluation of PF aspirates in our environment, with the aim to identify possible targets for quality improvement efforts.

Materials and Methods

All PF samples aspirated by surgical teams were routinely processed immediately upon receival, using the double centrifugation method. The volume received varied greatly between a few milliliters and hundreds of milliliters. Aliquots were centrifuged in a bucket centrifuge at 10,000 rpm for 10 min, to produce a supernatant and a sediment. The supernatants were discarded and the sediments were resuspended and respun in the cytocentrifuge at 10,000 rpm for another 10 min to produce supernatants and sediments. The (second stage) supernatants were pipetted off and stored (these were sometimes reconcentrated and used for repeat smears in cases with poor yield). A minimum of three thin smears are prepared from the (second stage) sediments. Two smears were immediately fixed in 96% ethanol and stained with the Papanicolaou and hematoxylin–eosin stains, whereas one smear was air-dried and stained with the May–Grünwald–Giemsa stain. Smears were interpreted in accordance with the College of American Pathologists guidelines for the reporting of nongynecologic cytopathology specimens.[14] Specimens were categorized as negative for malignancy/normal/benign, atypical (favor reactive or suspicious for malignancy), positive for malignancy, or unsatisfactory/nondiagnostic. More specific diagnoses were made where possible.

A retrospective database study of all PF aspirates cytologically examined at the Histopathology Department of the University of Benin Teaching Hospital between January 2010 and December 2014 was done. Where records were incomplete, attempts were made to retrieve the original slides; but cases of unavailable slides were excluded from the study. Data retrieved included age, gender, clinical information, and diagnoses. The

data obtained were analyzed using the Statistical Program for the Social Sciences, version 20 (SPSS Inc., IL, USA). Confidentiality of the identity of the patients and personal health information was maintained.

Results

A total of 69 pleural aspirate specimens were received for cytopathological evaluation during this 5-year period. Of these, 35 were male, whereas 34 were female, with a male–female ratio of 1:1.03. Patients' ages ranged from 1 to 89 years, with a mean age of 45 ± 21.40 years, and the modal age group being the 30–39-year age bracket. The age distribution of patients is displayed in Figure 1.

Of a total of 69 smears, 31 (44.9%) were in the "negative for malignancy/normal/benign" category, only 1 (1.4%) case was in the "atypical-favor reactive" category, 3 (4.3%) cases were "atypical-suspicious for malignancy," whereas 6 (8.7%) cases were "positive for malignancy." Twenty-eight cases (40.6%) were categorized as unsatisfactory/non diagnostic [Table 1]. Twenty-seven of thirty-one "negative" smears, constituting 39% of total smears, wear inflammatory. The malignant smear category was made up of 1 adenocarcinoma, 1 lymphoma, and 4 malignant smears not otherwise specified. Four of six (66.7%) cases were above the 50-year mark.

Of 28 smears that were considered unsatisfactory/nondiagnostic, 6 smears (8.7%) were considered nondiagnostic due to acellularity or pauci-cellularity. Four smears (5.7%) were due to obscuring hemorrhage, and one of these was a repeat cytologic examination in a patient who had had a previous unsatisfactory smear. Three had follow-up histologic examination of pleural biopsies which showed adenocarcinoma in all three. Eighteen smears (26.1%) were considered unsatisfactory for various other reasons including obscuring inflammation, debris, and poor preservation of cell due to delays in processing, sometimes as a result of failure to send samples to the laboratory immediately. Of these, two were repeated with equally unsatisfactory results and seven had follow-up pleural biopsies which were normal in two cases, revealed pleuritis in three cases, mesothelial hyperplasia in one case, and mesothelioma in another.

Overall, there was repeat pleural aspirate cytology in three cases, two for unsatisfactory smears which still came out as unsatisfactory and one for a malignant smear where a repeat cytologic examination leads to a more specific diagnosis of adenocarcinoma. Correlation of pleural cytology results was done in 18 cases which had histologic examination of pleural biopsies. Ten of whom had previous unsatisfactory pleural aspirate cytology. Pleural biopsy confirmed malignancy in five cases (27.8%) who had previous "unsatisfactory" or "negative" pleural aspirate cytology results [Table 2].

Table 1: Cytopathologic diagnoses of pleural aspirates

Diagnostic categories	Frequencies (%)
Negative for malignant cells/normal/benign	31 (44.9)
Atypical favor reactive	1 (1.4)
Atypical suspicious for malignancy	3 (4.3)
Positive for malignant cells	6 (8.7)
Unsatisfactory/nondiagnostic	28 (40.6)
Total	69 (100)

Discussion

Sixty-nine patients between the ages of 1 and 89 years were examined, with a mean age of 45 ± 21.40 years, and the modal age group being the 30–39-year age bracket. Majority of the smears within this age group were, however, either nondiagnostic or negative for malignancy. Forty-five percent of smears were in the "negative for malignancy/normal/benign" category, majority being inflammatory, 1.4% were atypical favor reactive, 4.3% of cases were "atypical suspicious for malignancy," and 8.7% cases were frankly malignant.

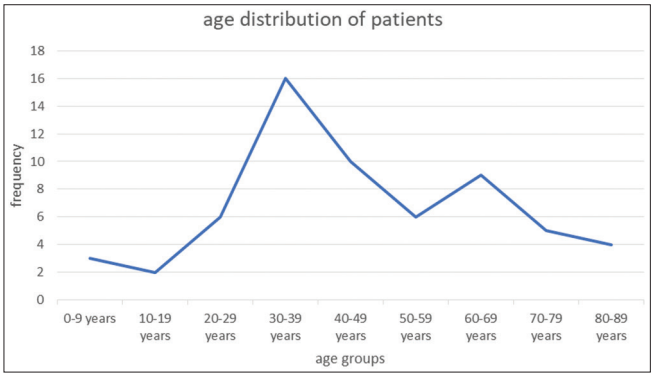

Figure 1: Age distribution of patients who had pleural aspirate cytologic examination

Table 2: Correlation of pleural aspirate cytology and pleural biopsy in 18 cases

Pleural aspirate cytology	Pleural biopsy histology				
	Malignant	Mesothelial hyperplasia	Pleuritis	Normal pleura	Total (%)
Negative for malignant cells/normal/benign	1	0	4	2	7 (38.9)
Atypical favor reactive	0	0	0	0	0 (0)
Atypical suspicious for malignancy	0	0	0	0	0 (0)
Positive for malignant cells	0	0	0	1	1 (5.6)
Unsatisfactory/nondiagnostic	4	1	3	2	10 (55.6)
Total (%)	5 (27.8)	1 (5.6)	7 (38.9)	5 (27.8)	18 (100)

A high percentage (40.6%) of smears were considered unsatisfactory or nondiagnostic for various reasons. A report of "unsatisfactory for cytological diagnosis" is disappointing to the pathologist, clinician, and the patients and their relatives, considering the potential of the procedure to yield a reliable diagnosis. Cytology is important not only in the diagnosis of pleural effusions but also helps in staging and prognostication of malignant lesions. Although PF aspiration is minimally invasive and cheap, hence easily repeated, valuable time is lost when the pleural aspirate cytology report is noncontributory to clinical decision-making, especially in patients who are very ill as is likely in malignant effusions.

The diagnostic yield of pleural aspirate cytology can be enhanced if both cellblocks and smears of the PF samples are examined.[9] Moreover, aspirates should be sent in for processing immediately after they are obtained to prevent degeneration of the cells since no fixatives or preservatives are employed in specimen transportation.[15] These measures will help reduce the rate of inadequacy of smears. Cellblock technique is presently not employed in our center but hopefully in the near future will be. This in addition to other measures targeting delays in specimen transportation to the laboratory should reduce the rates of unsatisfactory smears.

A proportion of smears (8.7%) were considered nondiagnostic due to acellularity or pauci-cellularity. This category usually as a routine has extra smears made from any leftover specimen including stored supernatants before a diagnosis was made. The likelihood of a transudative effusion is always a consideration in this group, and a repeat PF aspirate with repeat cytologic examination is done as guided by biochemical PF analysis, using the Light criteria,[5] as well as clinical assessment of the managing clinician. Pleural effusion could be due to hemodynamic, inflammatory, or neoplastic causes, where the basis is hemodynamic as occurs with cardiac failure or liver cirrhosis, for example, the effusion is transudative and is thus cell and protein poor. An aspirate would, therefore, be of no cytopathological interest. However, not all transudative pleural effusions are benign, and the importance of integrating clinical judgment into decision-making cannot be overemphasized. When malignancy is suspected as a cause, transudative effusions should be sent for cytologic analysis.[9] The British Thoracic Society (BTS) pleural disease 2010 updated guidelines, however, recommend that, except there is a failure of response to treatment or presence of unusual features, PF cytology should not be done in any clinical setting of bilateral pleural effusion where the cause is likely hemodynamic or the effusion is transudative.[16] None of the six acellular smears in this study have a record of a repeat aspirate sent for cytologic examination or a follow-up biopsy and were likely managed as transudative effusions.

A sizeable proportion (39%) of the aspirates in this study were adjudged to be "inflammatory smears." Both pleural effusions due to chronic inflammation, and those due to neoplasia are associated with the presence of inflammatory cells in the pleural aspirate, and unless neoplastic epithelial or mesenchymal cells are seen among the inflammatory cells, both patients with inflammatory and neoplastic clinical conditions will have their smears diagnosed as "inflammatory smears." The cytological diagnosis of inflammatory smear, therefore, does not satisfactorily exclude a malignancy. The same applies to pleural aspirates reported to be "negative for malignant cells."[15] In such cases, a cytological diagnosis cannot be definitive. Its findings must then be interpreted in the light of other investigative procedures. Moreover, a biopsy and histopathological examination of any mass lesion detected will prove to be a superior investigation. In this study, correlation of pleural cytology results was done in 18 cases who had histologic examination of pleural biopsies, Seven of whom had " inflammatory smears," and ten of whom had previous "unsatisfactory pleural aspirate cytology."

Of seven "inflammatory smears" subjected to pleural biopsy, four had pleuritis on histology and one was diagnosed as malignant. Overall, pleural biopsy confirmed malignancy in 27.8% of 18 cases in which PF cytology was correlated with pleural biopsy histology. Pleural biopsies appeared to yield more clinically useful results as a follow-up to PF cytology, when compared to repeat PF aspirate cytology, except in one patient whose repeat PF cytologic examination leads to a more specific diagnosis of adenocarcinoma as compared to a diagnostic categorization of "positive for malignancy."

When the smears have cells that show features of malignancy, and reactive or metaplastic mesothelial cells can be excluded, they are reported as malignant smears. If possible, the cell type and tissue of origin should be determined. In this study, malignant cells were detected in 8.7% (6) of PFs. Two of these six cases were diagnosed as adenocarcinoma and lymphoma based on cytologic features. An additional 4.3% (3) of cases were "atypical suspicious for malignancy" without any determination of the cell type. According to the BTS pleural disease guidelines,[16] immunocytochemistry is required for the typing of unequivocally malignant cells. None of our malignant smears were further typed to determine the primary tumour site, due to inconsistency of immunocytochemistry services. The male–female ratio of patients with malignant pleural effusions was 1: 5. Over 60% of patients with malignant smears, and those detected through pleural biopsy were above 50 years. Malignant pleural effusions have also been found to be more common in females in other studies.[6] Studies have reported carcinoma of the breast as the most common primary neoplasms causing pleural effusions (24%–30%), followed by lung (19%–20%), and other common primary sources are gastrointestinal system and lymphoreticular system.[6] Adenocarcinoma is the most likely malignancy to be demonstrated by PF aspirate cytology,[15] and lymphoid neoplasms represent a major cause in children.[6]

While cytopathology has its peculiar challenges, the contribution of any pathologist to patients' care is the interpretive report. Pathology reports represent a pivotal point

in clinical care and should be a primary target for quality improvement efforts.[14] All pathology consultations require a comprehensive evaluation of the circumstances surrounding the patient's complaint, including review of clinical laboratory test results, imaging studies, clinical symptoms, and personal or family medical history. When adequate clinical information is not provided, the pathologists' task becomes even more challenging. Pathologists are not obliged to review patient records to find data because they may not have easy access to those records.[14] However, easy accessibility of patient record in electronic format, as is the growing trend, can optimize the outcome for the patient because a pathologist can review all pertinent medical findings and significantly narrow the differential diagnosis for a particular case.[14]

Conclusion

Pleural aspirate cytology can be a useful investigative tool with the potential for definitive diagnosis or other useful information for clinical decision-making. Findings should always be considered in the light of other investigative modalities. Concerted efforts focused on ensuring immediate transport of specimens for cytologic evaluation to the laboratory, provision of adequate clinical information to pathologists, the preparation and examination of cellblocks in addition to smears, and use of immunocytochemical stains and will improve diagnostic yield and specificity.

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Conflicts of interest

There are no conflicts of interest.

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