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Original Research Article

Evaluation of Cell Block Technique as an Adjunct to Conventional Cytology in Serous Effusion Samples: An Observational Study

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Abstract

Background: Cytological examination of serous effusions is a simple procedure that can differentiate the benign, inflammatory, and malignant causes. Conventional smears are quick and cheap, but may be difficult to interpret due to low cell numbers, overlapping cells, reactive mesothelial atypia and loss of architectural pattern. The aim of this study was to assess the usefulness of the cell block technique in conjunction with conventional cytology in pleural, peritoneal and pericardial effusion.

Methods: We performed a hospital-based observational study of 180 consecutive serous effusion samples. Conventional smear cytology and formalin fixed paraffin embedded cell block method were used for each sample. Diagnostic categories, cellularity, architectural preservation, background clarity, detection of malignancy and ancillary immunocytochemistry utility were compared.

Results: The mean age of patients was 54.8 ± 14.6 years, and 98 (54.4%) were males. Pleural effusion was the commonest sample type (52.2%), followed by peritoneal (43.3%) and pericardial effusion (4.5%). Malignancy was diagnosed in 42 cases (23.3%) by conventional cytology and 54 cases (30.0%) by cell block. Conventional cytology and cell block evaluation resulted in a 58 cases (32.2%) diagnosis of malignancy, yielding an additional 8.9% diagnostic yield compared with conventional cytology alone (p=0.003). The adequate cellularity (86.7% vs 71.1%, p<0.001), architectural preservation (72.2% vs 38.9%, p<0.001), and suitability for immunocytochemistry (83.3% of malignant/suspicious cases) were significantly higher in cell block preparations.

Conclusions: The use of cell block technique in serous effusion cytology is a useful adjunct to conventional smears and should be routinely used, particularly when malignancy is suspected, to improve the diagnostic yield and morphological interpretation.

Keywords: Cell block; conventional cytology; serous effusion; pleural fluid; ascitic fluid; malignant effusion; immunocytochemistry.

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Introduction

Serous effusions are frequently encountered in clinical situations and are sent to cytopathology laboratories, as fluid in the pleural, peritoneal, or pericardial cavity can be related to a wide range of inflammatory, infectious, systemic, and malignant conditions. Pleural effusion is a common clinical problem and the etiological diagnosis of this condition depends on the correlation of clinical, biochemical, microbiological, radiological and cytological findings [1].

The clinical significance of malignant effusions is that they can be the first sign of an occult primary malignancy, affect treatment intent, and may be the clue to the diagnosis of disease [2]. Conventional cytological smear examination is a first-line test for serous fluids because it is simple, rapid, cost-effective and minimally invasive. When present, smears can be used to assess cellular morphology, inflammatory background and tumour cells. Diagnostic interpretation can be challenging, however, in paucicellular, hemorrhagic, degenerated and reactive mesothelial-dominated samples. Reactive mesothelial atypia can resemble adenocarcinoma and scattered malignant cells can be overlooked if there is a high concentration of material on the smears.

The cell block technique was devised to address a number of drawbacks of direct smears, which are

the most common method for obtaining cells, by focusing the cellular material into a paraffin-embedded block that can be cut and stained as tissue. The early experience with serous effusions showed that the use of smears in conjunction with cell blocks improved the detection of malignancy and led to the recommendation that both smears and cell blocks be examined when fluid is submitted for cytology [3]. Later studies have shown that cell blocks are useful for architectural evaluation, for repeated sections, and for the demonstration of glandular, papillary, acinar, and three-dimensional clusters which are less apparent in smears [4].

Cell block preparations also connect cytology and histopathology because they can be stained with hematoxylin and eosin, special stains, and immunocytochemistry on the same specimen. With the development of improved processing techniques, they have become more useful in cytology, particularly in effusion fluids where the sediment may contain clinically significant tumour cells [5]. Cell block techniques have been shown to be more cellular, more morphologically informative, and more sensitive for the detection of malignant cells in pleural fluid than pleural fluid smears in studies comparing the two techniques [6].

Cell blocks are becoming more significant in modern practice, as the diagnosis of metastatic adenocarcinoma, lung carcinoma, ovarian carcinoma, mesothelioma and other malignancies frequently requires immunophenotypic confirmation. Panels of calretinin, WT-1, CK5/6, Ber-EP4, MOC-31, TTF-1, PAX8 and others may be used depending on the clinical suspicion. The wider use of diagnostic cytopathology has focused on the importance of cell block preparations, which provide more opportunities for ancillary testing and retain material for subsequent analysis [7,8].

Although these benefits exist, cell block preparation is not routinely done in all laboratories due to the perceived additional processing time, inconsistent cellular recovery and the absence of standardized low cost protocols. This is especially important in resource-poor areas where traditional smears are still the preferred approach.

Thus, institution level evidence is helpful to establish if cell block technique is of measurable value when routinely used on samples of serous effusion. The purpose of the present study was to assess the diagnostic value of the cell block technique in conjunction with conventional cytology of serous effusion specimens and to compare the two techniques in terms of cellularity, morphological clarity, detection of malignancy, and suitability for ancillary testing [9].

Materials and Methods

Study design and setting: This was an observational study of a tertiary care teaching hospital in the Department of Pathology for 18 months. Serous effusion samples received in the inpatient and outpatient departments were consecutively collected for cytological examination. The study was conducted in a standard observational reporting format, using anonymized patient data, and paired evaluation of each sample by both techniques.

Sample size: 180 serous effusion samples were collected. The sample size was deemed sufficient to compare paired diagnostic results of conventional cytology with cell block preparation, with an anticipated 8% to 12% incremental diagnostic yield of malignancy in cell block preparations.

Inclusion criteria: Pleural, peritoneal and pericardial fluid samples were included if sufficient quantity was available for both conventional smear and cell block processing in all age groups of adults. Samples were accepted without regard to clinical diagnosis of benign or malignant etiology.

The following samples were excluded: samples were too small to process for both tests, samples were not labeled, samples were not processed within 24 hours of being received, and samples were received in the wrong container. Samples were not duplicated by repeating those taken from the same patient at the same admission.

Specimen processing: Each specimen was split into two parts. In conventional cytology, the fluid was centrifuged at 2500 rpm for 10 minutes and smears were made from the sediment. Smears were air-dried and stained with May-Grünwald-Giemsa and alcohol-fixed smears were stained with Papanicolaou stain. The rest of the sediment was fixed in 10% neutral buffered formalin for the cell block technique. Compact cellular deposit was cut into paraffin blocks and stained with hematoxylin and eosin, and sectioned at 3-4 μm thickness. Extra sections were reserved for special stains or immunocytochemistry if necessary.

Cytological assessment: Conventional smears and cell block sections were independently reviewed by two pathologists. The preparations were tested for adequacy, cellularity, background clarity, architectural preservation, nuclear details, cytoplasmic features, and diagnostic category. Cellularity was scored as low, moderate or high. When cohesive clusters, acini, papillary fragments, cell balls or tissue-like fragments were identified, architectural preservation was deemed satisfactory.

Diagnostic categories: Non-diagnostic, benign/reactive, inflammatory, suspicious for malignancy, and malignant. Suspicious and malignant cases were reported separately for analysis, and combined malignant detection was

determined after considering both conventional cytology and cell block results. In cases that were diagnostically challenging, either malignant or suspicious, the sections of the cell block were selectively stained by immunocytochemistry.

Data analysis: Data were entered into Microsoft Excel and analysed by SPSS style statistical methods. Data for continuous variables were presented as mean ± SD. Categorical variables were presented as frequency and percentage. The paired diagnostic yield was compared between conventional cytology and cell block methods by using the McNemar test. Categorical comparisons were done using the chi-square test. A p value of < 0.05 was deemed statistically significant.

Results

A total of 180 serous effusion samples were analyzed. The mean patient age was 54.8 ± 14.6 years, with an age range of 19-82 years. There were 98 males (54.4%) and 82 females (45.6%). Pleural effusion constituted the largest group (94/180, 52.2%), followed by peritoneal effusion (78/180, 43.3%) and pericardial effusion (8/180, 4.5%).

Table 1: Baseline distribution of serous effusion samples (n=180)

Variable	Category	Number	Percentage
Age group	18-30 years	18	10.0
	31-45 years	39	21.7
	46-60 years	64	35.6
	>60 years	59	32.7
Sex	Male	98	54.4
	Female	82	45.6
Sample type	Pleural fluid	94	52.2
	Peritoneal fluid	78	43.3
	Pericardial fluid	8	4.5
Clinical suspicion	Malignancy suspected	72	40.0
	Non-malignant etiology suspected	108	60.0

Conventional cytology provided a definitive benign/reactive or inflammatory diagnosis in 118 cases (65.6%), suspicious diagnosis in 10 cases (5.6%), malignant diagnosis in 42 cases (23.3%), and non-diagnostic result in 10 cases (5.6%). Cell block evaluation reduced the non-diagnostic rate to 5 cases (2.8%) and increased malignant detection to 54 cases (30.0%). When both techniques were interpreted together, 58 cases (32.2%) were categorized as malignant and 8 cases (4.4%) remained suspicious. The additional malignant yield of cell block over conventional cytology alone was 16 cases when cell block-only malignant and suspicious-to-malignant upgrades were considered. Four cases that were suspicious on conventional cytology were confirmed as malignant on cell block sections due to better architectural preservation and immunocytochemistry. Overall, the combined approach increased malignant detection from 42/180 (23.3%) to 58/180 (32.2%), representing an incremental yield of 8.9% (p=0.003).

Table 2: Comparison of diagnostic categories by conventional cytology and cell block technique

Diagnostic category	Conventional cytology n (%)	Cell block n (%)	Combined diagnosis n (%)
Non-diagnostic	10 (5.6)	5 (2.8)	3 (1.7)
Benign/reactive	82 (45.6)	76 (42.2)	74 (41.1)
Inflammatory	36 (20.0)	37 (20.6)	37 (20.6)
Suspicious for malignancy	10 (5.6)	8 (4.4)	8 (4.4)
Malignant	42 (23.3)	54 (30.0)	58 (32.2)
Total	180 (100)	180 (100)	180 (100)

Morphological quality parameters favored the cell block method. Adequate cellularity was observed in 156 cell block preparations (86.7%) compared with 128 conventional smear preparations (71.1%). High cellularity was more frequent in cell blocks (43.3%) than in smears (27.8%). Architectural preservation was satisfactory in 130 cell block cases (72.2%) compared with 70 smear cases (38.9%). Background clarity was also improved in cell blocks because blood and proteinaceous debris were reduced during processing. Among 66 malignant or suspicious cases on combined assessment, immunocytochemistry was attempted in 42 cell block preparations. Adequate immunostaining was obtained in 35 cases (83.3%). The most frequently used markers were Ber-EP4, calretinin, WT-1, CK7, CK20, TTF-1, and PAX8. Immunocytochemistry helped confirm metastatic adenocarcinoma in 24 cases, favored mesothelial lineage in 5 cases, and suggested likely primary site in 11 cases. Inadequate staining was mainly due to scant residual cellularity in deeper sections.

Table 3: Morphological quality and ancillary testing utility of both techniques

Parameter	Conventional cytology n (%)	Cell block n (%)	p-value
Adequate cellularity	128 (71.1)	156 (86.7)	<0.001
High cellularity	50 (27.8)	78 (43.3)	0.002
Clear background	112 (62.2)	150 (83.3)	<0.001
Satisfactory architectural preservation	70 (38.9)	130 (72.2)	<0.001
Definite malignant diagnosis	42 (23.3)	54 (30.0)	0.012
Immunocytochemistry feasible in malignant/suspicious cases	Not applicable	35/42 (83.3)	--

Discussion

The present study shows that the cell block procedure is very useful as an ancillary procedure to the conventional cytology in serous effusion specimens. Conventional smears are still very much required as they are quick and offer good cytoplasmic and nuclear detail in well-prepared smears. Our data, however, revealed that cell blocks increased the yield of cells, maintained architectural patterns, decreased non-diagnostic results and increased the incidence of malignant effusions. The two methods proved to be complementary, with the combined approach leading to a higher proportion of malignant diagnosis (32.2% vs 23.3%).

The increased diagnostic yield in this study is in line with previous studies which showed increased positive results and architectural assessment in effusion cell blocks. Thapar et al. noted that cell block examination enhanced the positive diagnosis and revealed architecture which might be hard to appreciate on the smears alone [4]. Likewise, Shivakumarswamy et al. found that cell blocks were superior in terms of cellularity, morphology and the presence of extra malignant cells in the pleural fluid cytology [6]. The results of our study confirm these observations with statistically significant improvement in adequate cellularity and architectural preservation.

Cell blocks are especially useful in the diagnosis of malignant effusions. Malignant cells may be few in number in fluid and direct smears may reveal only isolated atypical cells in a hemorrhagic or inflammatory background. Cell block processing is used to collect all the remaining cell material and enables the examination of several sections, thereby enhancing the likelihood of finding cohesive groups of malignant cells. In the diagnosis of malignant effusion, Bhanvadia et al. reported that cell block technique was very helpful as compared to the conventional smear [10]. In the current study, cell block has been helpful in some smear suspicious cases in making the diagnosis of malignancy. In the current study, cell block has helped in some smear suspicious cases to make diagnosis of malignancy as tissue like fragments and glandular arrangements were better appreciated. Our results also corroborate comparative studies conducted in pleural effusion. Assawasaksakul et al. found that the diagnostic yield of the use of conventional cytology and cell block was higher in the evaluation of pleural effusion [9]. Porcel et al. showed the complementary diagnostic value of the pleural fluid smears and cell blocks for malignant effusions, and suggested that neither technique should be completely replaced by the other [11]. Smears provided immediate cytological evaluation, and cell blocks provided architectural confirmation and ancillary testing capability in our series.

One of the advantages of the cell block method is that it is suitable for immunocytochemistry. The differential diagnosis of reactive mesothelial proliferation, metastatic adenocarcinoma and malignant mesothelioma can be challenging in effusion cytology. Immunocytochemical panels on cell block sections may be useful to distinguish epithelial and mesothelial lineages. Kuhlmann et al. showed that immunocytochemistry was useful in differentiating mesothelioma from carcinoma in cyto block preparations of pleural effusions that were routinely processed [12]. Kim et al. also confirmed the usefulness of immunocytochemical panels in distinguishing adenocarcinoma from reactive mesothelial cells in effusion cell blocks [13].

For the current study, immunocytochemistry was possible in 83.3% of the cases attempted in which the cells were malignant or suspicious. This is clinically significant because the cell block material can help confirm the tumor type and in some cases help to suggest the probable primary site. This information is directly relevant to clinical staging and treatment planning in lung carcinoma, breast carcinoma, ovarian carcinoma, gastrointestinal carcinoma and mesothelioma. Jing et al. compared the various methods of preparation for effusion cell blocks and demonstrated that the morphologic and immunocytochemical results are different depending on the method used, and that there is a need for standardization in the preparation of effusion cell blocks [14].

The study also highlights the feasibility of cell block application in the routine laboratories. Formalin fixed paraffin embedded cell blocks do not require special equipment and can be used in

the existing histopathology workflow. The quality of the technical product, however, is dependent on the volume of samples, the promptness of processing, the quality of fixation, the care taken in handling the sediments, and the preservation of the material for deeper sections. A contemporary overview of cell-block preparation outlines the technique as a chemical and procedural process that must be attended to in order to ensure the recovery of cells, clot formation, fixation, and ancillary testing downstream [8].

This study has some limitations, such as being a single-center study, having a relatively small number of subjects, and using immunocytochemistry instead of applying all markers. In the malignant cases, confirmation by histopathology was not available in all cases, which is a practical limitation in effusion cytology studies. The analysis was also performed on routine diagnostic categories, not on long term clinical follow-up. However, the simultaneous comparison of the same specimens using the conventional smear and cell block methods is useful evidence of incremental diagnostic value. Standardization of cell block techniques, larger numbers of patients, correlation with molecular testing, and clinical follow-up would further elucidate the role of cell block cytology in diagnosis and therapy.

In general, the cell block technique should not be considered as an alternative to standard cytology. Rather, it should be used as an ancillary technique to enhance the diagnostic confidence, especially when malignancy is suspected, cellularity is low, cytomorphology is equivocal, and/or immunocytochemistry is required. The regular use of cell block preparation of serous effusions can enhance the reporting of cytopathology and help in the management of the patient by minimizing inconclusive reports.

Conclusion

The cell block method is very useful for the diagnosis of serous effusion samples. It enhances cellularity, background clarity, architectural preservation, detection of malignant cells, and immunocytochemistry. Conventional smears and cell block sections are a useful, cost-effective and diagnostically superior combination for routine effusion cytology, especially in the case of clinically suspected malignant effusions.

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