

Clinicopathological Study of 117 Body Fluids: Comparison of Conventional Smear and Cell Block Technique

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ABSTRACT: Background. Cell block method (CB) has emerged as an invaluable tool for diagnosis of effusions. It can help overcome the problems faced by conventional smear (CS) by differentiating between reactive, inflammatory and malignant cells. The aim of the study is to compare and correlate the CB diagnosis with the CS findings of various pathological conditions including malignancy. Materials and Methods. Two years prospective cross-sectional study of 117 fluids received for routine examination and/or for cytology was conducted. CS as well as CB was simultaneously prepared from the fluid and the results were correlated and tabulated for statistical analysis. Results. Mean age of presentation was 43±21.1 years and male: female ratio was 1.3:1. Ascitic fluid (46.2%) was the most common followed by pleural (40.2%). Among malignancies, primary ovarian and lung carcinoma were the most common to present with malignant ascites (33.3%) and pleural effusion (66.7%) respectively. Six suspicious for malignancy on CS were provided a definitive diagnosis of malignancy on CB. Overall, CB increased the yield of malignancy by 8.3%. The agreement between CB and CS for malignant effusions and suspicious for malignancy were 41.7% and 14.3% respectively. Sensitivity of CS method when compared to CB, for malignant peritoneal and pleural effusions was 90% and 75% respectively while the specificity was 68% and 79% respectively. Conclusion. CB has a better diagnostic yield of malignancy and helps in providing a definitive diagnosis for cases that are suspicious for malignancy on CS. Hence, CB should be routinely employed along with CS for all effusions.

KEYWORDS: Cell block technique, Conventional smear, body fluids, malignant effusions.

Introduction

Body fluid cytology is a diagnostic procedure worldwide and its history can be traced back to the 19th century.

Lucke and Klebs were believed to be the first investigators who recognized the presence of malignant cells in an ascitic fluid in 1867 [1].

The commonly examined samples include pleural fluid, ascitic fluid, pericardial fluid, synovial fluid and cerebrospinal fluid (CSF) [2].

It provides information about the inflammatory or malignant nature of effusion, cause of effusion, and detection of unknown primary lesion.

It is one of the easiest and best ways to detect malignancy in body fluids.

It has diagnostic, therapeutic and prognostic significance [2].

Cytological examination of body fluids is commonly done by conventional smear (CS) method.

However, the cell block (CB) method is one of the oldest but less commonly used techniques in the evaluation of body fluids even today.

This is due to lack of knowledge about the method of preparation and that all ancillary studies can be done using cellular material obtained from CB such as special stains, immunohistochemistry and flow cytometry.

CS has a lower sensitivity in diagnosis and in typing of malignant tumours. CB technique is a better tool as it provides better cellularity, preserves the morphological details and architectural pattern.

Therefore, CB findings are comparable to the histopathological diagnosis of primary tumours.

The present study was undertaken to establish that the CB technique is a useful adjuvant for establishing a definitive cytopathological diagnosis of effusions.

Materials and Methods

This was a prospective cross-sectional study conducted in the department of pathology over a period of two years.

A total of 117 cases were included in the study.

The fluids were received from medicine and surgery department of our hospital for routine examination and/or fluid for cytology.

Body fluids received only for culture & sensitivity/ADA/LDH/albumin as well as bronchoalveolar lavage and cyst fluids were excluded from the study.

Upon receiving the fluid at the central laboratory of the hospital, a detailed and relevant clinical history, imaging findings and other relevant laboratory investigations were recorded as per the case pro-forma.

Part of the sample was used for routine investigations (wet mount, total count and differential count, sugar and protein estimation). 3-5ml of the fluid was centrifuged (REMI India) at 1500rpm for 5 minutes and the supernatant was discarded.

The sediment at the bottom was then used to prepare CS which was stained by Wright Giemsa stain (WG stain) (Siemens, Germany) and Hematoxylin and Eosin stain (H&E stain) (Siemens, Germany).

Next, 2-3ml of the remaining fluid was taken in a plain tube to which 10% neutral buffered formalin was added as the fixative and mixed.

This was centrifuged at 2500rpm for 15 minutes and the supernatant was discarded.

Two drops of plasma and four drops of thromboplastin (Stago, France) were added to the sediment obtained and kept in water bath overnight at 37 degrees Celsius.

The resultant cell button was then poured onto a filter paper and then placed in a cassette and processed as per the standard histopathological procedure.

After paraffin embedding, 3-5 microns thin sections were cut and Hematoxylin and Eosin (H&E) staining was done.

These slides were then mounted, labelled and studied under light microscopy for details.

The results of CS and CB were then tabulated for comparison.

The data were entered in MS excel and analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA).

In this study, a prior agreement with the ethical committee of our institution and a written informed consent from the patients have been obtained.

Results

A total of 117 fluids were studied which included ascitic fluid, pleural fluid, CSF, synovial fluid and pericardial fluid.

The mean age of patients presenting with effusion was 43 ± 21.1 years.

The most common age group of presentation was less than 30 years (32%).

The percentage of males presenting with serous effusions was higher (57%) as compared to females (43%) with a male: female ratio of 1.3:1.

The most common fluid received was ascitic fluid 54 (46.2%) followed by pleural fluid 47 (40.2%), CSF 8 (6.8%), synovial fluid 6 (5.1%) and pericardial fluid 2 (1.7%) (Table 1).

Table 1. Demographics and distribution of fluid types received (n=117).

| Age (Mean±SD) | 43.5±21.1 years | |
|-----------------|-----------------|------------|
| Age groups | <=30 yrs. | 37 (31.6%) |
| | 31-40 yrs. | 17 (14.5%) |
| | 41-50 yrs. | 16 (13.7%) |
| | 51-60 yrs. | 15 (12.8%) |
| | >60 yrs. | 32 (27.4%) |
| Gender | Male | 67 (57.3%) |
| | Female | 50 (42.7%) |
| Types of fluids | Ascitic | 54 (46.2%) |
| | Pleural | 47 (40.2%) |
| | CSF | 8 (6.8%) |
| | Synovial | 6 (5.1%) |
| | Pericardial | 2 (1.7%) |

Out of 117 fluids, 94 (80.3%) were diagnosed as inflammatory (benign), 7 (6%) as suspicious for malignancy, 5 (4.3%) as malignant and 11 (9.4%) were inadequate for opinion on CS.

On CB, 71 (60.7%) cases were diagnosed as inflammatory (benign), 2 (1.7%) as suspicious for malignancy, 12 (10.3%) as malignant and 32 (27.4%) were inadequate for opinion.

The diagnosis of fluids by CS and CB method were compared based on the three categories, namely inflammatory (benign), suspicious for malignancy and malignant.

Out of the total 117 samples, 33 samples could not be categorized and compared due to inadequate cellularity and therefore, only 84 samples were selected for statistical correlation between CS and CB.

So, out of 84 fluids, 72 (85.7%) were diagnosed as inflammatory (benign), 7 (8.3%) as suspicious for malignancy and 5 (6%) as malignant on CS.

On CB, 70 (83.3%) cases were diagnosed as inflammatory (benign), 2 (2.4%) as suspicious for malignancy and 12 (14.3%) as malignant. (Table 2)

On comparing the CS and CB method we found that out of 72 samples diagnosed as inflammatory on CS, 70 were given as inflammatory on CB; one case was diagnosed as suspicious of malignancy (1.2%) and one as malignancy (1.2%).

Out of the 7 (8.3%) diagnosed as suspicious of malignancy on CS, 6 (7.1%) were diagnosed as malignant on CB and only one (1.2%) was given as suspicious of malignancy.

So, of the 12 (14.3%) malignant effusions on CB, only 5 were diagnosed on CS and rest were missed.

Thus, CS gave a 6% yield of malignancy which was increased to 14.3% on CB.

The additional yield of malignancy was found to be 8.3% by CB method (Table 2).

Table 2. Comparison of diagnosis on Conventional smear and Cell block (n=84).

| Comparison of diagnosis on Conventional smear and Cell block for the three categories of lesions | | | | | | Agreement |
|--|------------------------------|----------------------|---------------------------|---------------------------|--------------|--------------|
| Conventional smear diagnosis | | Cell block diagnosis | | | | |
| | | Inflammatory | Suspicious for malignancy | Malignancy | | |
| Inflammatory | 72 (85.7%) | 70 (83.3%) | 1 (1.2%) | 1 (1.2%) | 97.2% | |
| Suspicious for malignancy | 7 (8.3%) | - | 1 (1.2%) | 6 (7.1%) | 14.3% | |
| Malignancy | 5 (6%) | - | - | 5 (6%) | 41.7% | |
| | Total | 70 (83.3%) | 2 (2.4%) | 12 (14.3%) | 90.5% | |
| Comparison of diagnosis on Conventional smear and Cell block for the three categories of lesions in various fluids | | | | | | Agreement |
| Fluid type | Conventional smear diagnosis | | Cell block diagnosis | | | |
| | | | Inflammatory | Suspicious for malignancy | Malignancy | |
| Ascitic Fluid (39) | Inflammatory | 29 (74.4%) | 29 (74.4%) | - | | 84.6% |
| | Suspicious for malignancy | 7 (17.9%) | - | 1 (2.6%) | 6 (15.4%) | |
| | Malignancy | 3 (7.7%) | - | - | 3 (7.7) | |
| | Total | 29 (74.4%) | 1 (2.6%) | 9 (23.1%) | | |
| Pleural fluid (40) | Inflammatory | 38 (95%) | 36 (90%) | 1 (2.5%) | 1 (2.5%) | 95% |
| | Malignancy | 2 (5%) | - | - | 2 (5) | |
| | Total | 36 (90%) | 1 (2.5%) | 3 (7.5%) | | |
| Synovial Fluid (4) | Inflammatory | 4 (100%) | 4 (100%) | - | - | 100% |
| Pericardial Fluid (1) | Inflammatory | 1 (100%) | 1 (100%) | - | - | 100% |

Additionally, similar comparison was also performed individually for each type of effusion.

Among the 39 ascitic fluid, on CS 29 (74.4%) were inflammatory, 7 (17.9%) were suspicious for malignancy and 3 (7.7%) were malignant whereas, on CB it was 29 (74.4%), 1 (2.6%) and 9 (23.1%) respectively.

Among the 40 pleural fluids, 38 (95%) were inflammatory and 2(5%) were malignant on CS and none were suspicious for malignancy while 36 (90%) were inflammatory, 1 (2.5%) suspicious for malignancy and 3 (7.5%) were malignant on CB.

All 4 synovial fluid samples which were reported as inflammatory on CS were reported as inflammatory on CB too.

Single pericardial fluid, which was reported as inflammatory both on CS and CB. (Figure 1 A,B) (Table 2).

The overall agreement between CS and CB diagnosis was 90.5%.

Amongst the three categories of effusions, the agreement was lowest for effusions suspicious for malignancy (14.3%) followed by malignant effusions 41.7%.

Inflammatory effusions (97.2%) showed the highest agreement.

The agreement between CS and CB diagnosis for the different types of fluid was highest for synovial effusions (4/4, 100%), pericardial effusions (1/1, 100%), followed by pleural fluid (38/40, 95%) and ascitic fluid (33/39, 84.6%).

None of the 8 CSF samples showed diagnostically significant cellularity on CB.

Hence, agreement could not be commented upon (Table 2).

The overall sensitivity and specificity of CS method compared to CB for diagnosis of effusions was 86% and 100% respectively.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for ascitic fluid was 90%, 68%, 39% and 97% respectively whereas for pleural

fluid it was 75%, 79%, 25% and 97% respectively.

The positive likelihood ratio of CS method for peritoneal and pleural effusion diagnosis was

2.8 and 3.6 respectively and the negative likelihood ratio was 0.1 and 0.3 respectively (Table 3).

Table 3. Sensitivity and specificity of CS for diagnosis of malignancy, with CB as the standard.

| For malignancy | All samples | Ascitic | Pleural |
|----------------|---------------------|---------------------|---------------------|
| Prevalence | 0.120 | 0.185 | 0.085 |
| Sensitivity | 0.857 (0.674-1.040) | 0.900 (0.714-1.086) | 0.750 (0.326-1.174) |
| Specificity | 1.000 (1.00-1.00) | 0.682 (0.544-0.819) | 0.791 (0.669-0.912) |
| PPV | 1.000 | 0.391 | 0.250 |
| NPV | 0.981 | 0.968 | 0.971 |
| LR+ | NA | 2.829 | 3.583 |
| LR- | 0.143 | 0.147 | 0.316 |

Discussion

The cytological examination of serous effusions is an important tool in clinical medicine and a positive diagnosis on fluid examination is often considered the definitive diagnosis [3].

Malignant serous effusions are almost always diagnostic of extensive metastasis of primary tumour.

Thus, examination of the serous effusions for malignant cells is routinely done even in case of metastases with unknown primary origin [4].

Microscopy of the fluid is done when infectious or malignant effusion is suspected by the clinician [5].

Distinguishing reactive mesothelial cells from malignant cells is a common diagnostic dilemma encountered during routine CS cytology.

This is because degenerating mesothelial cells appear similar to signet ring cells with an eccentric nucleus and vacuolated cytoplasm [6].

Also, another drawback of CS preparation is that it does not give scope for ancillary studies.

Thus, CB acts as a standard tool for diagnosis of effusions as it increases the cellular yield and also improves the diagnostic accuracy [7,8].

Many CB techniques have been developed over the past century for the diagnostic work-up of patients [9].

Using formalin as a fixative gives superior results as it preserves the morphological details and also improves the sensitivity of the diagnosis [10].

Plasma-thromboplastin method was used in the present study for CB preparation.

It is an easy and convenient method since plasma and thromboplastin reagent is readily available in the haematology laboratory [11].

Advantages of this method are better concentration of cellular material which forms a solid button, better preservation of the cells and the procedure is cost effective.

CB preparations showed better preservation and staining characteristics of the nucleus, nucleoli and cytoplasm and also minimal shrinkage and aberrations when compared to CSs.

In a study by Sujathan et al. [12] out of 85 fluid samples, 53 (62%) were peritoneal fluid followed by 32 (38%) pleural fluids.

In the study by Bhanvadia et al. [13], out of the 150 fluids, 69 (46%) were peritoneal fluid, 79 (53%) were pleural fluids and 2 (1%) were pericardial fluid.

Thus, on comparing both these studies, it was noted that peritoneal fluid was the most common fluid received as was seen in our study too.

The distribution of pleural and peritoneal effusions was similar to Bhanvadia et al. [13] and Sujathan et al. [12].

In our study, the age of patients ranged from less than 30 years to more than 60 years.

Maximum number of patients were aged less than or equal to 30 years.

This was similar to the age range in a study by Shivakumaraswamy et al. [14].

However, Davidson et al. [15] observed that the range was from less than 20 years to more than 60 years.

In a study conducted by Dey et al. [16], the maximum numbers of patients were in the age group of 61-70 years.

In the present study, 55 (65.5%) fluids showed chronic inflammatory cells, 8 (9.5%) showed acute inflammatory cells and 7 (8.3%) showed acute on chronic inflammation on CB. (Figure 1 C,D)

None of the eight CSFs in our study yielded enough cells on CB for a definitive diagnosis.

This was in concordance with a study by Sumitha et al. [17] where no cells were seen on CB.

This could be attributed to the low cell counts of CSF normally seen on smear which is inadequate for tissue processing.

Out of 6 synovial effusions in the present study, 3 showed acute inflammatory cells on both CB and CS.

Out of these three cases, there was a single case of rheumatoid arthritis and a single case of anterior cruciate ligament tear with supra-patellar effusion.

The remaining 3 cases showed chronic inflammatory cells on CS but showed similar features only in 1 case on CB (Figure 1 E,F).

The remaining 2 cases showed only plasmaceous material on CB without any diagnostic cells.

Cytology of all six samples revealed no evidence of malignancy.

A similar study done by Tanu et al. [18] showed non-malignant cells in all samples of synovial fluids.

In a study by Sumitha et al. [17], a single sample of synovial fluid of a case of rheumatoid arthritis was examined which showed only proteinaceous material.

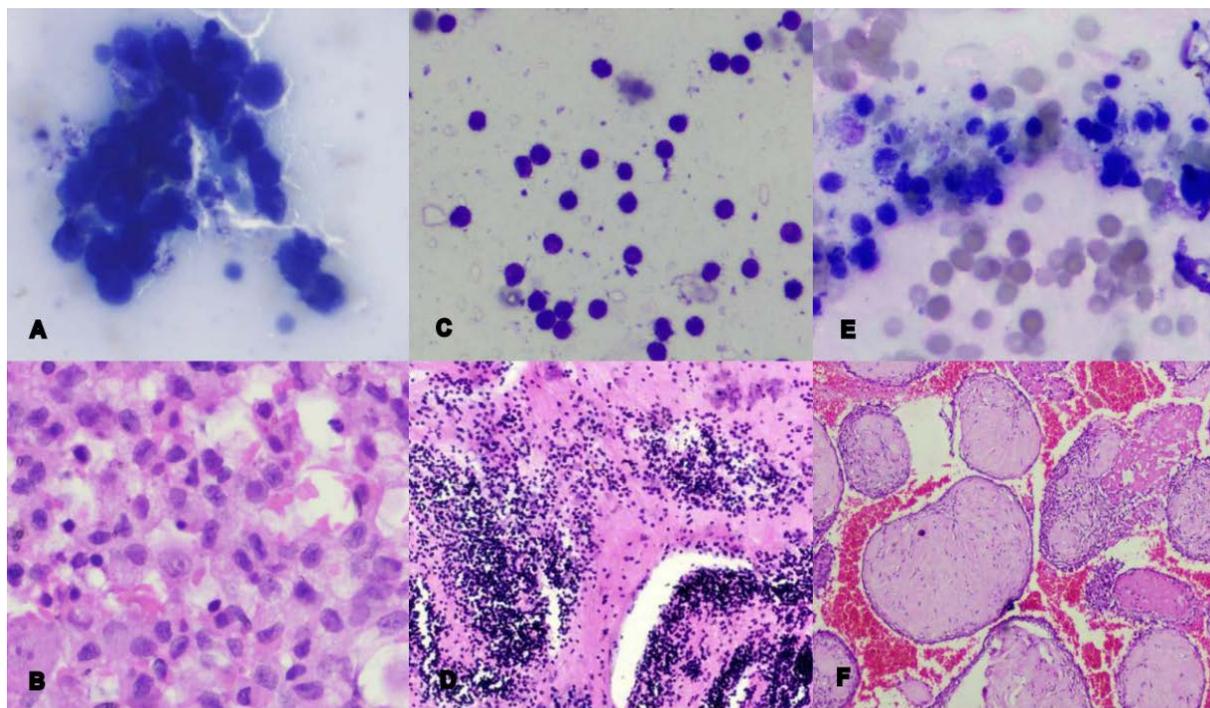


Figure 1. Pericardial fluid-A) Conventional smear showing a small cluster of ill-defined mesothelial cells (WG stain, x400), B) Cell block showing well discernible reactive mesothelial cells and macrophages (H&E, x400). Pleural fluid-C) Conventional smear showing scattered chronic inflammatory cells (WG stain, x400), D) Cell block showing dense chronic inflammatory cell infiltrates (H&E, x100). Synovial fluid-E) conventional smear showing lymphocytes against a hemorrhagic background (WG stain, x400), F) Cell block showing synovial membrane lined by synovial cell, along with fibroblastic proliferation and chronic inflammatory cell infiltrate and hemorrhage (H&E, x100).

Most of the cases were benign with 85.7% on CS and 83.3% on CB.

In the category suspicious for malignancy, 7(8.3%) were suspicious on CS.

All seven samples were ascitic fluids and only one out of these was diagnosed as suspicious for malignancy even on CB.

However, the remaining 6 cases were diagnosed malignant on CB.

Single case of pleural fluid in a clinically suspected lung malignancy showed only chronic

inflammation on CS but, few atypical cells were seen on CB and were given as suspicious for malignancy.

Similar findings were seen in the study by Sujathan et al. [12] where the number of cases suspicious for malignancy on CS were 5 (6%) and 1 (1%) on CB.

Similarly Shivakumaraswamy et al. [14], Dey et al. [16], Bodele et al. [19] and Tanya SP et al. [20] also observed the number of cases

suspicious for malignancy on CS was reduced on CB.

Thus, we can conclude that CB helped in providing a definite diagnosis of malignancy for

effusions which posed a diagnostic dilemma on CS (Table 4).

Table 4: Comparison of diagnosis of effusions on Conventional smear versus Cell block and additional yield of malignancy in present study with other studies.

| Comparison of diagnosis of effusions on Conventional smear and Cell block | | | | | | |
|--|-------------------|-------------------|-----------------|-----------------|---------------|-------------------|
| Study | Benign | | Suspicious | | Malignancy | |
| | CS | CB | CS | CB | CS | CB |
| Bodele et al. (19) | 118 (79%) | 111 (74%) | 3 (2%) | 0 (0%) | 29 (19%) | 39 (26%) |
| Shivakumaraswamy et al. (14) | 54 (90%) | 50 (83%) | 5 (8%) | 0 (0%) | 1 (2%) | 10 (17%) |
| Tanya SP et al. (20) | 0 (0%) | 0 (0%) | 6 (20%) | 4 (13%) | 24 (80%) | 36 (87%) |
| Sujathan et al. (12) | 61 (72%) | 63 (74%) | 5 (6%) | 1 (1%) | 19 (22%) | 21 (25%) |
| Dey et al. (16) | 22 (44%) | 20 (40%) | 15 (30%) | 6 (12%) | 13 (26%) | 24 (48%) |
| Present study | 72 (85.7%) | 70 (83.3%) | 7 (8.3%) | 2 (2.4%) | 5 (6%) | 12 (14.3%) |
| Comparison of additional yield of malignancy by Cell block method compared to Conventional smear | | | | | | |
| Study | % | | | | | |
| Khan et al. (24) | 20% | | | | | |
| Bodele et al. (19) | 7% | | | | | |
| Richardson et al. (29) | 5% | | | | | |
| Bansode et al. (30) | 3% | | | | | |
| Matreja et al. (31) | 2% | | | | | |
| Present study | 8.3% | | | | | |

In our study, out of 12 cases of malignancies diagnosed on CB, nine were detected in ascitic fluid and three in pleural fluid. (Table 2)

The most common cause for malignant ascites was ovarian carcinoma which was seen in 3 cases (33.3%) (Figure 2 A,B), followed by 2 cases (22.2%) of colon carcinoma, 1 case each of hepatocellular carcinoma (HCC), pancreatic carcinoma and renal cell carcinoma.

A single case of malignancy of unknown primary was seen too.

This was similar to a study conducted by Monte SA et al. [21], Karoo et al. [22], Vijay et al. [23], Khan et al. [24] and Mahmmud et al. [25] where the most common cause of malignant primary metastasizing to peritoneal fluid was carcinoma of the ovary.

This is because most women with ovarian carcinoma present with advanced stage of the tumour with ascites being the most common symptom at the time of detection [5].

It has therefore been reported that ascitic fluid cytology is more sensitive for ovarian malignancy than other malignancies with an overall sensitivity of just 60% and specificity of 100% [26].

It is said that peritoneal carcinomatosis due to spread of gastrointestinal and genitourinary malignancies is the most common malignancy related ascites accounting for two-thirds of the cases [27,28].

A noteworthy point is that hepatocellular carcinoma is reported to rarely spread to the peritoneal cavity and is usually seen in less than 10% cases [27].

This was in concordance with our study where we reported a single case of HCC with metastasis to the peritoneal cavity.

Among the three cases of malignant pleural effusion, two cases were of carcinoma lung (66.7%) (Figure 2 C,D), out of which one of the case showed only chronic inflammatory cells on CS.

There was also a case of metastatic mucinous adenocarcinoma with unknown primary.

No case of metastasis of breast malignancy was seen.

This was discordant with a study by Shivakumaraswamy U et al. [14], where the most common cause of malignant neoplasm in pleural effusion was breast carcinoma followed by lung carcinoma and gastrointestinal malignancy.

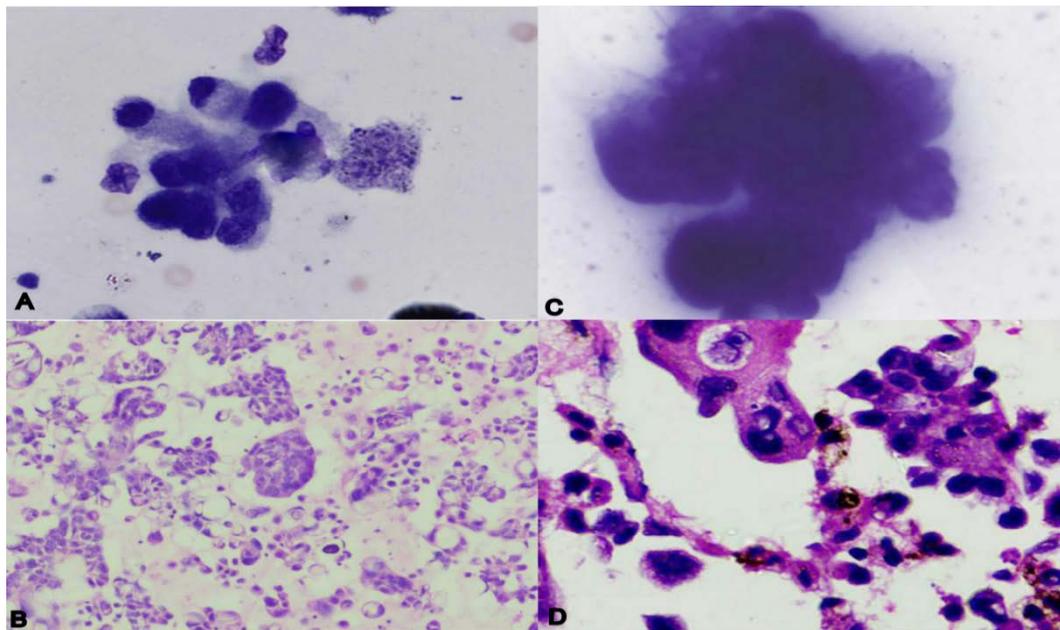


Figure 2. Ascitic fluid in a known case of ovarian mass-A) Conventional smear showing crowding of atypical cells suspicious for malignancy (WG stain, x400), B) Cell block showing malignant epithelial cells arranged in papillary pattern, suggestive of deposits of papillary serous adenocarcinoma of ovary (H&E, x100). Pleural fluid in a known case of carcinoma lung-C) Conventional smear showing atypical cells arranged in vague clusters suggestive of metastases of adenocarcinoma (WG stain, x400), D) Cell block showing features of papillary adenocarcinoma (H&E, x400).

In the present study, two cases of aspergillosis with acute angle branching hyphae were diagnosed on CB of pleural fluid.

One of these cases showed the same morphology on CS as well.

The other case was an incidental finding in a suspected case of hydatid cyst of the lung.

Significant increase was noted in the yield of malignancy when CS method was supplemented by CB method in various studies.

Malignancy was diagnosed in 6% of cases by CS and in 14.3% cases by CB in the present study.

Thus, the CB increased the yield of diagnosis by 8.3%.

Similar findings were seen in many other studies such as those by Khan et al. [24] (20%), Bodele et al. [19] (7%), Richardson et al. [29] (5%), Bansode et al. [30] (3%) and Matreja et al. [31] (2%) (Table 4).

Sensitivity of CS method in the diagnosis of effusions was 86% in our study.

This was in concordance with studies by Tanya et al. [20] where sensitivity was 80%.

The sensitivity was much higher at 91% in the study by Padmavati et al. [32].

Bansode et al. [30], Bhanvadia et al. [13] and Sandeep et al. [31] have reported slightly lower sensitivity of CS method as 79%, 70% and 69% respectively.

However, the study by Geethu et al. [33] reported much lower sensitivity of 32% on CS.

Conclusion

CB provides a higher yield of malignancy than CS.

It is especially helpful in cases with suspicion for malignancy where a definitive diagnosis is difficult on CS. Hence, CB in conjunction with CS method should be routinely done in all effusions.

It has added advantages like identification of primary site of malignancy based on architectural pattern and ancillary techniques.

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Conflicting Interest

The authors declare that they have no conflict of interest.

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