Original paper

Towards standardized categorization of serous effusions: application of the International System for Reporting Serous Fluid Cytopathology diagnostic framework with a special emphasis on borderline ovarian tumors

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Borderline ovarian tumors (BOT) in effusion cytology are rare, and to date only limited literature has existed.

The current study used the International System for Reporting Fluid Cytopathology (ISRSFC) criteria to reclassify 321 effusion cytology cases from 302 patients, analyzed diagnostic performance among different positive groups and evaluated the risk of malignancy (ROM). A total of 14 BOTs were included, majority of them were mucinous borderline and these tumors were reclassified into atypia of uncertain significance (AUS) and suspicious for malignancy (SFM) intermediate categories. According to ISRSFC criteria, effusion cases were categorized into five different groups: non-diagnostic (ND), negative for malignancy, AUS, SFM and malignant. The corresponding overall ROMs were 23.3%, 19.4%, 44%, 87.8% and 100%. Morphologically, mucinous BOTs in effusions presented mostly as acellular mucin, while serous BOTs exhibited mesothelial cells with few atypical cells showing mild to moderate nuclear atypia.

These findings highlight the diagnostic difficulty of BOTs in effusion cytology and the need to apply ISRSFC criteria especially for AUS and SFM grey zone categories for standard reporting and clinical guidance.

Key words: ISRSFC, effusion cytology, borderline ovarian tumors.

Introduction

Effusions occur in serous cavities due to both non neoplastic and neoplastic etiologies. Effusion cytology is a more affordable and simpler method to distinguish between non neoplastic and neoplastic causes [1]. There is diagnostic uncertainty in describing serous effusion cytology regarding quantity, adequacy of the provided sample and uniformity in reporting the borderline tumor cases. A consistent reporting system for effusion cytology does not exist. In 2020, the International System for Reporting Serous Fluid Cytopathology (ISRSFC) was published as the initial effort to standardize the reporting terminology and to enhance the professional communications [2, 3]. This system suggests five diagnostic groups: non-diagnostic (ND), negative for malignancy (NFM), atypia of uncertain significance (AUS), suspicious for malignancy (SFM), and malignant (MAL) [2, 3]. Similar to the ISRSFC system, the Indian Academy of Cytologists (IAC) in the year 2020 also recommended guidelines for reporting serous effusion fluids consisting of almost similar five diagnostic groups [4, 5]. The International System for Reporting Serous Fluid Cytopathology and IAC published definite criteria for ambiguous AUS and SFM categories.

These reporting systems improve uniform reporting and facilitate effective communication between clinicians and cytopathologists. With a focus on borderline ovarian tumors (BOT), our study aimed to evaluate the performance analysis among different groups and to estimate the risk of malignancy (ROM) using ISRSFC reporting system in effusion cytology. The current study focuses on BOT because of their subtle nuclear features and intermediate biological behavior. To the best of our knowledge, there have only been few case reports, but this is the first study to use ISRSFC criteria to evaluate peritoneal fluid cytology with a special emphasis on BOTs.

Material and methods

Data collection

This cross-sectional study was done in the department of pathology from January 2021 to December 2021, after obtaining approval from the institutional ethical committee. All the demographic, clinical, radiological and histopathological data were extracted from the medical records. The study omitted the cases with incomplete clinical and imaging data.

Sample preparation

All the fresh samples were collected from the anticoagulant-free containers and processed within 4 hours. Following 10 minutes of centrifugation at 2000 revolutions per minute, the fluid supernatant was discarded. From every effusion sample, three conventional smears were prepared, two were fixed in alcohol for Papanicolaou, hematoxylin and eosin staining while the third was allowed to air dry for Giemsa staining. In cases where the malignancy was suspected, cell block processing was done using thrombin method.

Previous reporting system followed

Before introduction of the ISRSFC system, our institute's cytomorphology-based reporting system had the following categories: malignant, atypical cells present, NFM and descriptive format. Descriptive cases included samples with scant cellularity, abundant blood elements, only mucinous background where definitive categorization was not possible. Atypical cases category showed very scant atypical cells with insufficient cytologic features to classify them as malignant. But after applying ISRSFC criteria, the category with atypical cells was moved to AUS and SFM categories.

Reclassification using ISRSFC criteria

Following a blind and independent review by two experienced pathologists, all the cases were categorized into five groups based on ISRSFC criteria.

Statistical analysis

Data were compiled into office excel spreadsheet. Risk of malignancy and performance analysis was calculated and performed taking biopsy or postoperative histopathological findings as gold standard. When histopathology was not available, complete clinical, radiological and follow up data were considered as gold standard for those cases. Patients who do not have any malignancy on one-year follow-up were considered to be NFM.

Performance analysis included calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy for effusion samples. Overall diagnostic accuracy was calculated using the standard formula: true positives + true negatives/total number of cases. Performance analysis was prepared taking MAL as a positive group, MAL and SFM as positive groups, and MAL, SFM and AUS as other positive group [6]. Non-diagnostic cases were excluded from the performance analysis.

Results

Cases before reclassification

In the present study, a total of 321 effusions from 302 patients were analyzed. Of these, 42 cases were reported in a descriptive format as they showed low cellularity and only blood elements. A total of 202 cases were considered as NFM when the smears showed only benign mesothelial cells and inflammatory cells. Another 23 cases were reported as presence of atypical cells whenever the cellularity was lower and not possible to differentiate between reactive and neoplastic process. The remaining 35 cases were diagnosed as malignant when the smears showed obvious malignant cytomorphology with high density of cells. The initial diagnostic categories are summarized in Table I.

Demographic data

The present study comprised 302 effusion samples with age range of 11–85 years. The male to female ratio is 0.6 : 1 with a female predominance. After reclassification, 30 (9.93%) cases were classified as ND, 175 (57.95%) cases as NFM, 25 (8.28%) cases as AUS, 33 (10.93%) cases as SFM and remaining 39 (12.91%) as MAL categories. The study showed predominance of peritoneal fluids 149 (49.34%) followed by pleural effusions142 (47.02%) and pericardial effusions 11 (3.64%). Redistribution of cases and patient demographic data are shown in Tables I, II, respectively

Peritoneal effusions

A total of 149 cases of peritoneal effusions were reclassified according to ISRSFC criteria as follows: 12 (8.05%) ND, 80 (53.69%) NFM, 16 (10.74%)

Table I. Distribution of cases according to initial diagnostic categories and after reclassification according to the International System for Reporting Serous Fluid Cytopathology category

Initial diagnostic category	Number of cases, *n* (%)	ISRSFC categories	Number of cases, *n* (%)
Descriptive format	42 (13.91)	Inadequate	30 (9.93)
Negative for malignancy	202 (66.89)	NFM	175 (57.95)
Atypical cells present	23 (7.61)	AUS SFM	25 (8.28) 33 (10.93)
Malignancy	35 (11.59)	MAL	39 (12.91)
Total	302 (100)		302 (100)

AUS – atypia of undetermined significance, ISRSFC – the International System for Reporting Serous Fluid Cytopathology, MAL – malignancy, NFM – negative for malignancy, SFM – suspicious for malignancy

Table II. Distribution of effusion cases based on age, sex and according to each International System for Reporting Serous Fluid Cytopathology category

Parameters	Peritoneal fluid	Pleural fluid	Pericardial fluid	Total cases
Males	32	78	4	114
Females	117	64	7	188
Male : female	0.27 : 1	1.2 : 1	0.5 : 1	0.6 : 1
ND, *n* (%)	12	16	2	30 (9.93)
NFM, *n* (%)	80	91	4	175 (57.95)
AUS, *n* (%)	16	08	1	25 (8.28)
SFM, *n* (%)	22	11	0	33 (10.93)
MAL, *n* (%)	19	16	4	39 (12.91)
Total, *n* (%)	149 (49.3)	142 (47)	11 (3.7)	302 (100)

AUS – atypia of undetermined significance, cat – category, ISRSFC – the International System for Reporting Serous Fluid Cytopathology, MAL – malignancy, ND – non-diagnostic, NFM – negative for malignancy, SFM – suspicious for malignancy

AUS, 22 (14.77%) SFM and 19 (12.75%) MAL. The risk of malignancy was 41.66% for ND, 26.25% for NFM, 50% for AUS, 95.45% for SFM and 100% for MAL categories. When only MAL were taken as a positive group, there were 50 false negative cases and no false positives. When MAL and SFM were taken as a positive group, there was one false positive case and 29 false negative cases. When MAL, SFM and AUS categories were taken as a positive group, there were 9 false positives and 21 false negative cases. Ovarian high grade serous carcinoma was the most common malignancy involving peritoneal fluids followed by gastrointestinal carcinomas and lung adenocarcinoma.

Pleural effusions

In this study a total 142 cases of pleural effusions were analyzed and categorized as ND 16 (11.27%), NFM 91 (64.08%), AUS 8 (5.63%), SFM 11 (7.75%) and MAL 16 (11.27%) according to ISRSFC criteria. The risk of malignancy was 12.5% for ND, 13.2% for NFM, 25% for AUS, 72.72% for SFM and 100% for MAL categories. When only MAL were taken as a positive group, there were 22 false negatives and no false positive cases. When MAL and SFM groups were considered as positive, there were 3 false positives and 14 false negative cases. When MAL, SFM and AUS categories were considered as a positive group, there were 9 false positives and 12 false negative cases. The most common malignancy involving pleural effusion was lung adenocarcinoma followed by invasive breast carcinoma.

Pericardial effusions

According to ISRSFC standards, 11 pericardial effusions were reclassified as follows: 2 (18.18%) as ND, 4 (36.36%) as NFM, 1 (9.1%) as AUS, 0% as SFM and 4 (36.36%) as MAL categories. The risk of malignancy was 0% for ND, 25% for NFM 100% for AUS and 100% for MAL categories. When only MAL category was considered as a positive group, there were only 2 false negatives without any false positives. When MAL and SFM were taken as a positive group, there were only 2 false negatives and no false positives. When MAL, SFM and AUS groups were considered as positive, there was only one false negative case. Lung adenocarcinoma was the most common malignancy involving pericardial cavity, followed by invasive breast carcinoma.

Table III. Risk of malignancy based on the International System for Reporting Serous Fluid Cytopathology category

Type of effusion	ND	NFM	AUS	SFM	MAL	Total cases
Peritoneal fluid, *n*/*N* (%)	5/12 (41.66)	21/80 (26.25)	8/16 (50)	21/22 (95.45)	19/19	149 (100)
Pleural fluid, *n*/*N* (%)	2/16 (12.5)	12/91 (13.18)	2/8 (25)	8/11 72.72)	16/16	142 (100)
Pericardial fluid, *n*/*N* (%)	0/2 (0)	1/4 (25)	1/1 (100)	–	4/4	11 (100)
Total cases, *n*/*N* (%)	7/30 (23.34)	34/175 (19.42)	11/25 (44)	29/33 (87.8)	39/39	302 (100)

AUS – atypia of undetermined significance, ISRSFC – the International System for Reporting Serous Fluid Cytopathology, MAL – malignancy, ND – non-diagnostic, NFM – negative for malignancy, SFM – suspicious for malignancy

Table IV. Detailed performance analysis among different positive groups

Type of effusion	Performance analysis	MAL (%)	MAL + SFM (%)	MAL + SFM + AUS (%)
Peritoneal fluid, $n = 137$ cases (excluding ND cases)	Sensitivity	27.5	58	69.6
	Specificity	100	98.5	86.8
	PPV	100	97.6	84.2
	NPV	57.63	69.8	73.7
	Diagnostic accuracy	63.5	78.1	78.1
Pleural fluid, $n = 126$ cases (excluding ND cases)	Sensitivity	42.1	63.2	68.4
	Specificity	100	96.6	89.8
	PPV	100	88.9	74.3
	NPV	80	85.7	86.8
	Diagnostic accuracy	82.54	86.5	83.3
Pericardial fluid, $n = 9$ cases (excluding ND cases)	Sensitivity	66.7	66.7	83.3
	Specificity	100	100	100
	PPV	100	100	100
	NPV	60	60	75
	Diagnostic accuracy	77.8	77.8	88.9

AUS – atypia of undetermined significance, MAL – malignancy, n – number of cases, NPV – negative predictive value, PPV – positive predictive value, SFM – suspicious for malignancy

The overall ROMs for each group ND, NFM, AUS, SFM and MAL were 23.3%, 19.4%, 44%, 87.8% and 100%, respectively as shown in Table III. The detailed performance analysis of peritoneal, pleural and pericardial fluids is summarized in Table IV.

Total BOTs were 14 in number, among them 9 cases were diagnosed as borderline mucinous tumors (BMT) and 5 cases as serous borderline tumors (SBT) on histopathology. After reclassification, peritoneal washings and effusion cytology from these patients were reported as SFM in 6 cases, of which 4 were mucinous borderline tumors (MBT) and 2 were serous borderline tumors. Two cases were reclassified under AUS category and on follow up, one case was confirmed as SBT and other case as MBT. Remaining 6 cases were reclassified under NFM category. Effusion cases reported as NFM were confirmed as MBT in four cases and as SBT in two cases. Complete cytomorphological details after reclassification of BOTs are summarized in Table V. Examples for each NFM, AUS, SFM and MAL category are shown in Figures 1–4, respectively.

Cell blocks were done for 94 (31.1%) cases, of them 24 cases (28.6%) were reported as metastatic adenocarcinoma on cell block, effusion cytology among these malignant cases were reported as SFM in 3 cases, one case as AUS and the remaining 20 cases as NFM.

Table V. Complete cytomorphological details of borderline ovarian tumors reclassified into different International System for Reporting Serous Fluid Cytopathology categories

Case number	Category	Cytological features	Final histopathology
1	SFM	Mucinous background, few tiny groups of atypical cells with moderate nuclear atypia and mesothelial cells	MBT with microinvasion
2, 3	SFM	Only mucin without epithelial cells	MBT
4	SFM	Abundant mucin with bland looking epithelial cells	MBT with pseudomyxoma peritonei
5, 6	SFM	Few groups and individual atypical cells with moderate nuclear atypia and sheets of mesothelial cells	SBT
7	AUS	Predominantly mesothelial cells with an occasional atypical cell with mild nuclear atypia	SBT
8	AUS	Predominantly mesothelial cells admixed with an occasional cluster showing intracytoplasmic mucin and mild nuclear atypia	MBT
9–14	NFM	Mesothelial and inflammatory cells	Cases 9, 10, 11, 12 – MBT Cases 13, 14 – SBT

AUS – atypia of undetermined significance, MBT – mucinous borderline tumor, n – number of cases, SBT –serous borderline tumor, SFM – suspicious for malignancy

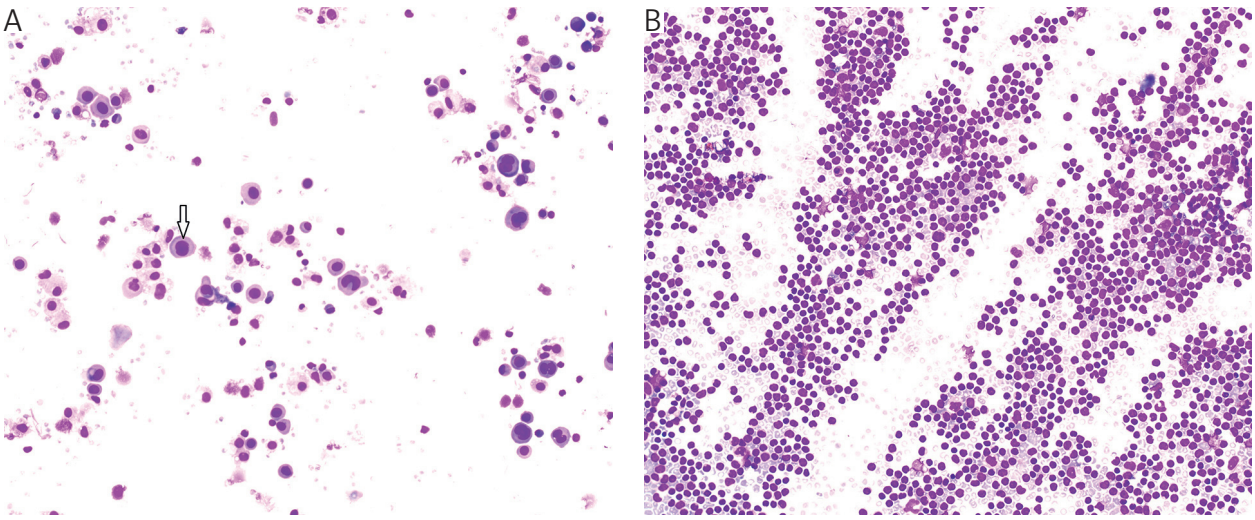

Figure 1. Negative for malignancy. **A**) Showing reactive mesothelial cells, arrow highlighting the dual toned cytoplasm of mesothelial cells (MGG stain, 200× magnification). **B**) A case of pulmonary tuberculosis, pleural effusion showing mature and activated lymphocytes (MGG stain, 200× magnification)

MGG – May-Grunwald Giemsa

Discussion

Effusion cytology represents a significant proportion of cytopathology material in laboratory workload. Cytology from effusion samples plays an important role to exclude malignancy and to obtain additional information for etiological classification and management. In the current study we applied ISRSFC for reclassification of serous effusion cytology and to determine ROM and performance analysis among different effusions. A special focus was placed on borderline ovarian tumors, as they represent a diagnostically challenging group where cytological interpretation often falls into indeterminate categories.

The age ranged 11– 85 years, which is similar to the age group of Pergaris *et al.* [7], whose study observed ages ranging 11– 95 years. In our study peritoneal fluids constituted 49.3% and pleural fluids constituted 47% of cases. This difference could be due to local disease pattern and the addition of peritoneal washings obtained during staging together with ascitic fluids. A similar observation was made by Straccia *et al*. [8] who also reported higher proportion of peritoneal fluids in their cohort.

After reclassification, the number of cases in undiagnosable and NFM reduced to 42–30 and 202–175 cases respectively and the remaining 39 cases were reassigned to AUS, SFM and MAL categories. Malignant

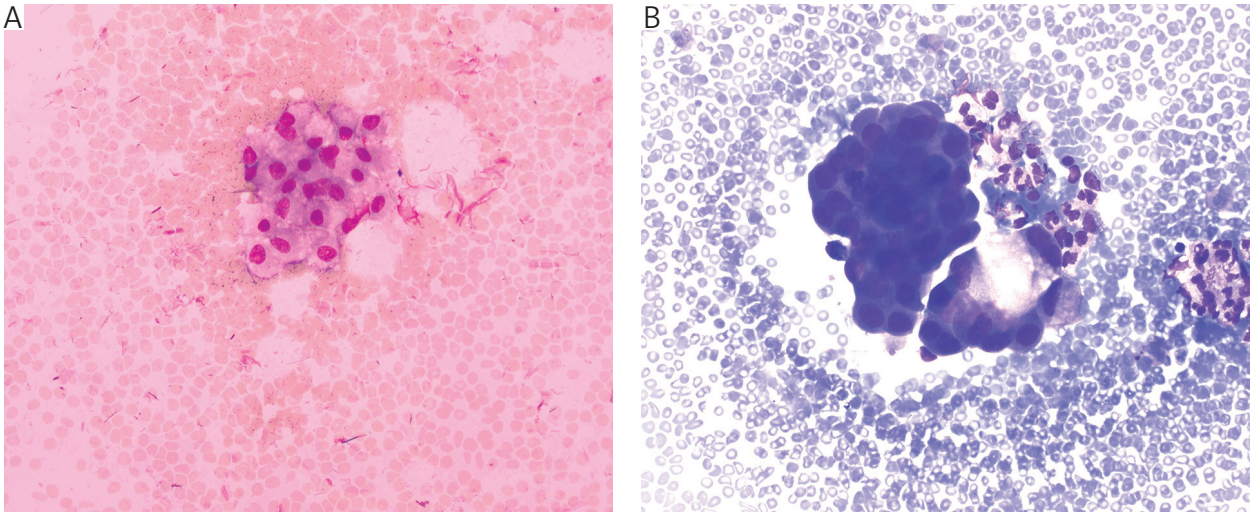

Figure 2. Atypia of undetermined significance. **A**) A case of mucinous borderline tumor, peritoneal effusion showing an occasional cluster of cells with bland looking nuclei and mucinous cytoplasm (MGG stain, 400× magnification). **B**) Ascitic fluid showing predominantly mesothelial cells, with few tiny clusters of atypical cells with knobby contours and mild nuclear atypia, on follow up the patient is a case of cirrhosis (MGG stain, 200× magnification)

MGG – May-Grunwald Giemsa

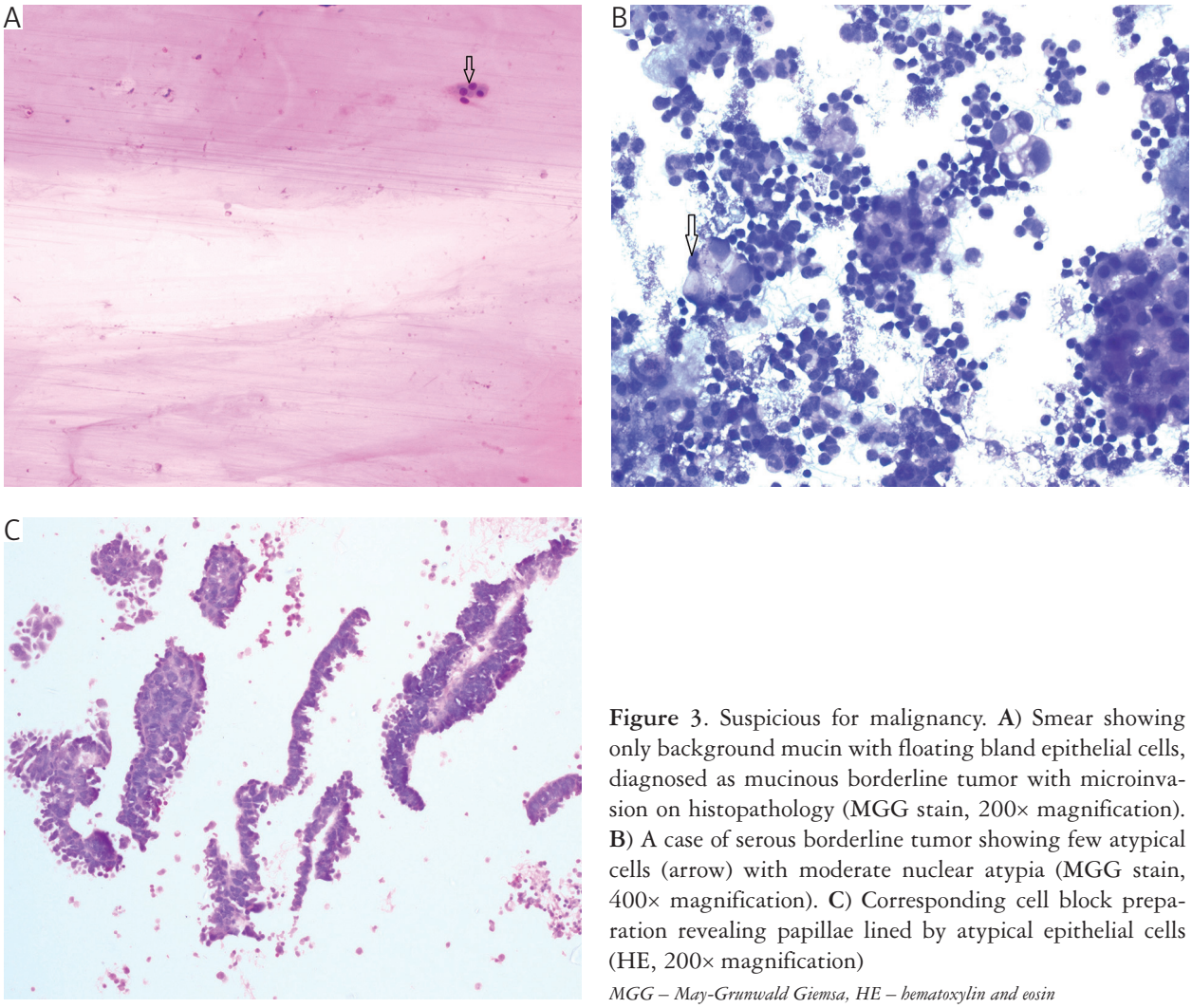

Figure 3. Suspicious for malignancy. **A**) Smear showing only background mucin with floating bland epithelial cells, diagnosed as mucinous borderline tumor with microinvasion on histopathology (MGG stain, 200× magnification). **B**) A case of serous borderline tumor showing few atypical cells (arrow) with moderate nuclear atypia (MGG stain, 400× magnification). **C**) Corresponding cell block preparation revealing papillae lined by atypical epithelial cells (HE, 200× magnification)

MGG – May-Grunwald Giemsa, HE – hematoxylin and eosin

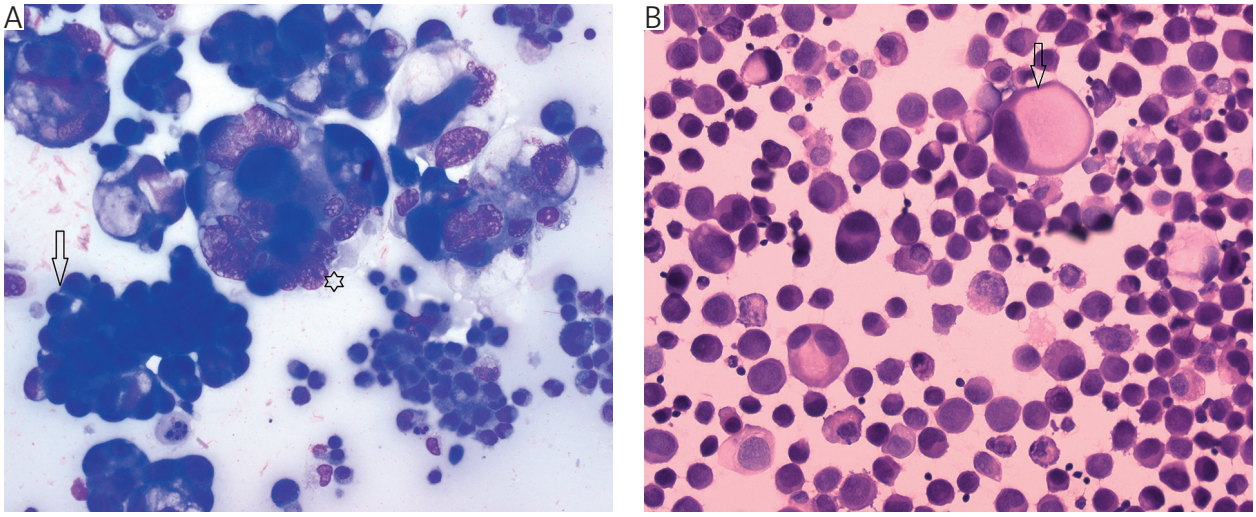

Figure 4. Malignancy. **A**) A case of high grade serous carcinoma, peritoneal wash showing many papillaroid clusters of atypical cells with irregular borders, marked nuclear pleomorphism, prominent nucleoli (MGG stain, 200× magnification). **B**) A diagnosed case of poorly differentiated adenocarcinoma rectum, ascitic fluid showing many individual atypical cells with marked nuclear atypia and signet ring cell morphology (PAP stain, 400× magnification)
MGG – May-Grunwald Giemsa, PAP – Papanicolaou

cases increased to 35–39 cases. Cases within initial atypical cells category were redistributed to AUS and SFM categories highlighting one of the key strengths of ISRSFC criteria. A similar redistribution of cases was reported in a study done by Yang *et al*. [6]. In our study sample volume ranged from as low as 1–250 ml. The existing literature recommends at least 50–75 ml [3, 9] for definitive diagnosis.

Lung adenocarcinoma was the most common cause of malignancy in pleural effusions followed by invasive breast carcinoma. Our findings are in agreement with other studies that solely included pleural effusions [10] as well as other studies that included different effusion types [5–7, 11]. The most frequent cause for malignant ascites in women was ovarian cancer consistent with similar studies [5–7, 11–13]. In the current study, the most common cause for malignant pericardial effusion was spread of lung cancer which was also noted in a study with a significant number of pericardial effusions [14, 15].

The overall ROMs for ND, NFM, AUS, SFM and MAL categories were 23.3%, 19.4%, 44%, 87.8% and 100%, respectively. Regardless of the sample type, ROM for the ND category in our study was higher than that of NFM and AUS categories. This might be the result of low cellularity samples particularly in early stages of illness. Because of well-preserved morphology, adequate cellularity, and obvious absence of malignant cells, ROM values in the NFM group were lower than those in the AUS category. Risk of malignancy values of the present study align with the results reported by Kundu *et al*. [5] and Pergaris *et al*. [7]. For each diagnostic category, they reported overall ROMs of 20% and 11.1% for ND, 12% and 7% for NFM, 50% and 35.7% for AUS, 77.8% and 88.9% for SFM and 100% for MAL categories. A recent systemic review by da Silva *et al*. [16] reported overall ROM values of 23.55% for ND, 16.46% for NFM, 50.78% for AUS, 91.34% for SFM, and 98.21% for MAL, which are comparable to our study. Following reclassification, the ND category accounted for 9.9% of cases in the current study, which is slightly higher than the percentage found in the published literature [6, 7]. The suspicious for malignancy samples percentages are slightly higher than in previous studies [5, 7]. This may be because previous equivocal cases were reclassified into the SFM category, thereby reducing underdiagnosis.

In the present study, the highest diagnostic accuracy for pleural effusions was observed when MAL and SFM categories were considered as positive. In contrast, for peritoneal fluids, diagnostic accuracy was similar when MAL, SFM and AUS and MAL and SFM were taken as positive groups. This implies that reactive changes in peritoneal effusions often overlap with neoplastic features particularly in peritoneal washings where mesothelial cells exhibit mild architectural complexity by forming papillaroid structures but with minimal nuclear atypia. As a result, adding AUS under the positive group does not substantially change the diagnostic accuracy. The highest specificity and PPV were observed when only MAL category was considered as a positive group. These results are compatible with these of Yang *et al*. [6] and Zhu *et al*. [17]. Highest values for sensitivity and NPV were obtained when MAL, SFM and AUS were considered as a positive group. The current study showed low sensitivity of 27.5% for peritoneal fluids when only MAL was considered as a positive group, which may be due to the reason of few malignant cases fall-

ing under AUS and SFM categories leading to underestimation of real positive cases.

There were 7 and 34 false negative cases within ND and NFM categories, respectively. Possible reasons for false negatives in the ND category include low cellularity, poor preservation of specimen and obscured morphology. False negatives in the NFM category may result from lack of spillage of tumor cells into the body cavities particularly in borderline ovarian tumors. False positive cases in AUS and SFM categories were 14 and 4 cases, respectively. In the AUS category, false positivity was due to over-interpretation of reactive atypia within the mesothelial cells. In the SFM category, three false positive cases had nuclear hyperchromasia and distinct dispersed atypical cells with nuclear hyperchromasia but were subsequently lost to follow up.

Among 14 cases of BOT in our study, peritoneal effusion cytology was reported as SFM in 6 cases, two cases as AUS and the remaining 6 cases as NFM. Among 6 SFM cases, 4 cases were diagnosed as BMT on histopathology and two cases as SBT. The relative increase in MBT can be explained by regional variations in tumor distribution. Peritoneal fluid smears from both SBT cases under the SFM category, showed increased cellularity with predominance of mesothelial cells admixed with few groups and individual cells of atypical cells showing moderate nuclear atypia. One of the SBT showed only papillaroid structures lined by atypical epithelial cells on cell block. Sharma *et al*. [18] performed a detailed cytomorphological study of 8 peritoneal effusions in borderline serous tumors and compared them with cytological features of the ovaries. They described cytomorphological features such as papillary fragments with regular borders, mild to moderate nuclear atypia, fine chromatin, and psammoma bodies in borderline serous tumors. In our study, four MBTs were placed in the SFM category. Cytology smears in these cases were characterized by low cellularity, presence of background acellular mucin admixed with mesothelial cells. Such findings were previously reported in a descriptive format and now after reclassification, these cases were categorized as SFM, demonstrating one of the ISRSFC advantage. One case of MBT showed acellular mucin with floating bland epithelial cells and presented as pseudomyxoma peritonei. None of the BOTs demonstrated peritoneal or omental implants. Even in cases where gross examination did not reveal implants, the appearance of atypical cells in effusion cytology could be explained by small capsular breaches or microscopic implants that were undetected during grossing. This emphasizes the importance of peritoneal fluid cytology in detecting extra ovarian spread in borderline ovarian tumors.

In the AUS category, one case was diagnosed as SBT and the other as MBT. Both were peritoneal washings obtained intraoperatively. The serous borderline tumors in the AUS category showed papillaroid clusters of cells and minimal atypia and the BMT showed only a single cluster with cytoplasmic mucin and subtle nuclear atypia highlighted on MGG stain. Among the NFM category, four were diagnosed as MBTs and two as serous borderline tumors. This false negativity in this category resulted due to lack of spillage tumor cells into the body cavities. However, in three cases radiology showed peritoneal thickening and this may represent benign conditions such as fibrosis, endometriosis or prior inflammatory changes. Because BOTs lack definite malignant characteristics, they pose diagnostic challenge in effusion cytology. However, certain findings may raise suspicion for low grade malignancy in BOTs, these include presence of dual cell population, clusters with architectural complexity, mild to moderate nuclear atypia and background acellular mucin. Presence of ovarian surface nodularity, capsular breach and omental deposits on radiology supports a diagnosis towards malignancy.

Although cell blocks were performed in a subset of our cases, absence of ancillary tests and immunohistochemistry (IHC) is a limitation, especially for borderline ovarian cases where cytomorphology alone might not be sufficient. Ancillary IHC markers such as PAX8, WT1, CK7 and P53, can aid in distinguishing ovarian or mullerian origin tumors from other primaries or reactive mesothelial proliferations. According to ISRSFC validation studies by Lu *et al*. [19] and Lim *et al*. [20], combining ancillary tests with cell block evaluation increases diagnosis accuracy and decreases indeterminate diagnoses. We recognize the limitations of routine cytology in interpreting serous effusions and emphasize that ancillary testing including IHC on cell blocks could strengthen the diagnosis.

Limitation

Limitations of the study include:

- in most of the cases, tissue biopsies from primary tumor were used,
- retrospective analysis,
- lack of cell block availability for all cases,
- lack of inter-observer agreement analysis or κ-statistics.

Conclusions

The present study demonstrates that the ISRSFC system provides uniform and well-defined categories for reporting serous effusions. Importantly, cases that fell into the grey zone are now clearly classified as either AUS or SFM, which reduces ambiguity and strengthens communication with clinicians for appropriate patient management.

Disclosures

1. Institutional review board statement: The study was approved by the Ethics Committee, approval number: IEC No. 1832.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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