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RESEARCH ARTICLE

CATEGORIZATION OF PLEURAL EFFUSION SPECIMEN ON THE BASIS OF THE INTERNATIONAL SYSTEM FOR REPORTING SEROUS FLUID CYTOPATHOLOGY: AN INSTITUTIONAL EXPERIENCE

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Abstract

Background: The International System for Reporting Serous Fluid Cytology (ISRSFC) has been proposed to systemize serous fluid cytopathology reporting and to guide for further clinical management. The present study focused on assessing the feasibility of utilizing ISRSFC reporting categories for pleural fluids, estimating the risk of malignancy (ROM) of each category.

Methods: Samples of Pleural effusion sent to cytopathology lab in our institution were evaluated. Cases were categorized into one of the five categories proposed by ISRSFC: Non-diagnostic (ND), Negative for malignancy (NFM), Atypia of undetermined significance (AUS), Suspicious for malignancy (SFM), and Malignant (MAL) respectively. ROM was calculated for each category.

Result: The present study examined 200 Pleural effusion samples. The Pleural effusion samples were categorized as ND 10 (5%), NFM 160 (80%), AUS 12 (6%), SFM 06 (3%) and MAL 12 (6%), and ROM for each above category were 12.5%, 3.3%, 25%, 75% and 100%, respectively.

Conclusion: The ISRSFC for categorizing pleural effusion cytology sample is easy to use and reduces reporting diversity. ROM assessment for each category improves the quality of clinical care.

Introduction:-

Accumulation of fluid in the body cavities like pleural, pericardium and peritoneum can occur in various pathological conditions, both neoplastic and non – neoplastic.[1]

Cytologic evaluation of serous fluid is often the first line of investigation and provides valuable information for the patient's clinical management.Cell morphology can be quite diverse and can be really deceptive. The absence of a universal and more uniform reporting system of body fluid cytopathology forced cytopathologists to use anonymous terminologies like atypical, suspicious, suggestive, favors reactive etc.Thus, developing discrepancies in the diagnosis and eventually causing the hurdles in reaching a definitive management plan.[2]In attempt to provide a standardized system for reporting serous fluid cytopathology across the countries, The International Academy of Cytology and the American society of cytopathology (ASC) recently proposed The International System for Reporting Serous Fluid Cytopathology (ISRSFC) in 2020.[3]

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The International System for Reporting Serous Fluid Cytopathology targets the improvement of communication among the clinicians and cytopathologists by providing a unique category to each effusion fluid, as a result directing them to better patient management and therapeutic strategies.[4]

The purpose of this study is to evaluate the effectiveness, utility and categorization of body fluids as per The International System for Reporting Serous Fluid cytopathology (TIS).

The ISRSFC have recommended five categories **(I- V)** along with the risk of malignancy (**ROM**)

1. **Nondiagnostic (ND),** Specimens with insufficient cellular elements for a cytologic interpretation.ROM- 17 % (± 8.9%)
2. **Negative for malignancy (NFM),** Specimens with cellular changes completely lacking evidence of mesothelial or non-mesothelial malignancy.ROM-21 % (± 0.3%)
3. **Atypia of undetermined significance (AUS),** Specimens showing limited cellular (nuclear) and/or architectural atypia (e.g., papillary clusters or pseudo-glandular formations).ROM-66 % (± 10.6 %)
4. **Suspicious for malignancy (SFM), Specimens** showing features suspicious but not definitively diagnostic for malignancy.ROM- 82 % (± 4.8 %)
5. **Malignant (MAL),** Specimens include those with definitive findings and/or supportive studies indicating mesothelial or non-mesothelial malignancies.ROM- 99% (± 0.1%)

Materials and Methods:-

The present study was a prospective observational cross-sectional study done after the ethical clearance from Institutional Ethical committee (MMC/IEC/2022124); After applying inclusion and exclusion criteria we evaluated200 cases of Pleural fluid sent for cytology in the department of Pathology, with in the duration of 12 months. Inclusion criteria involving all pleural fluids received in cytology unit of Pathology. Exclusion criteria were fluids with quantity less than 50 ml, frankly hemorrhagic,synovial, ascitic, Pericardial, cerebrospinal fluids.

Preparation of smear

Processing was done within one hour of specimen collection. Fluids were centrifuged for 10 to 15 min at 3000 rpm. Supernatant was decanted, and smears were prepared from each sample by placing one to two drops of the sediment on slide, allowing them to spread evenly by placing another slide over it. Minimum **six slide** were prepared. Two smears from each sample were stained with Leishman/Giemsa stain, one each with Papanicolaou and Hematoxylin & Eosin and two were kept spared, one fixed and other unfixed. Smears were studied under microscope.

Statistical Analysis

The data were entered in Microsoft excel 2019 (Microsoft, WA, USA).SPSS17/20 statcal2 software used for calculation of mean, SD etc.

Results:-

The present study was conducted over a period of 12 months, with total 200 samples of pleuraleffusion being collected and analyzed. We have categorized the cytological findings according to International System for Reporting Serous Fluid Cytopathology (ISRSFC).Risk of malignancy (ROM) was ascertained by comparing final diagnosis with histopathological, radiological or clinical diagnosis wherever possible.

The gold standard for correct diagnosis was based on histological diagnoses or clinico-radiological diagnoses. The histological diagnoses were made on the basis of the biopsy; cell block or postoperative pathological results of the pleura, peritoneum, pericardium corresponding to the effusion.

All cytological and histological diagnosis were performed blindly by two pathologists (AM, KG).The clinical diagnoses were made in combination with clinical manifestation; laboratory result & medical imaging examination results.(Figure 1)

In the present study the mean age was 42.2 years (ranging from 10to 87 years)Majority of the cases were falling in the third decade.Male predominance was seen with Male: Female ratio of 1.8:1 (Male - 65% and females -35%). Majority of the cases were observed under category NFM (80%) and least number of cases were observed under category SFM (3%) (Table 1)

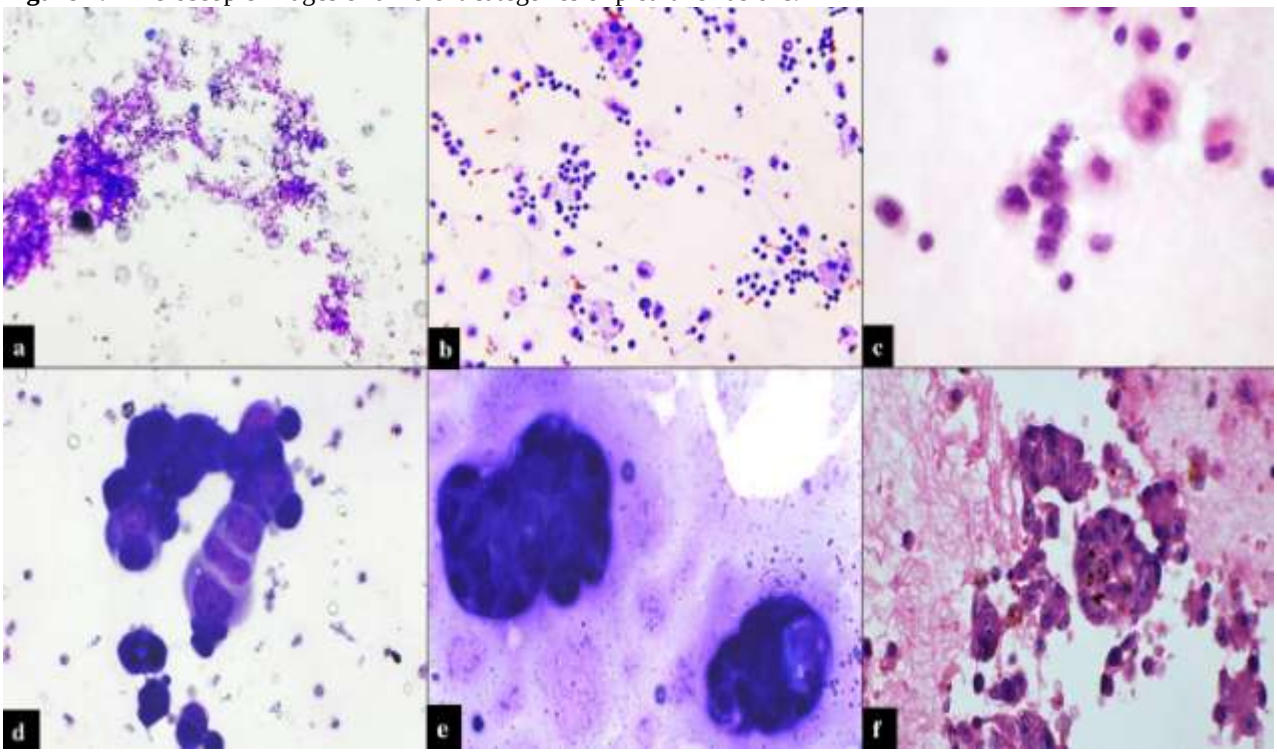
Risk of malignancy (ROM)

The Follow-up was available for 148 cases (74%) by either biopsy, imaging studies or clinical evaluation, due to loss of follow up as few of the cases were referred to higher centres for further treatment. Out of these 148 cases, it was found that 16 cases were malignant and 132 were benign conditions. (Table-1) The follow-up data was used for the calculation of the ROM for each category. The follow up was done every third month for a period of one year.

Table 1:- Total no. of cases with follow-up and estimated ROM in the ISRSFC category.

ISRSFC Category	Cases (n)	Follow -up available	Benign outcome on confirmatory tests/ clinico-radiological findings	Malignant outcome on confirmatory tests/ clinico-radiological findings	Estimated ROM (%)
I (ND)	10	08	07	01	12.5 %
II (NFM)	160	120	118	02	1.67 %
III (AUS)	12	08	06	02	25 %
IV (SFM)	06	04	01	03	75 %
V (MAL)	12	08	00	08	100 %
TOTAL	**200**	**148**	**132**	**16**	-

Figure 1:- Microscopic images of different categories of pleural effusions.



(a) **Cat I Non-Diagnostic:** Cytomorphology showing smear with over-stained degenerated cells, MGG, 400x
(b) **Cat II Negative for malignancy:** Cytomorphology showing reactive mesothelial cells against background of inflammatory infiltrates, MGG 400x
(c) **Cat III Atypia of undetermined significance:** Cytomorphology showing clustered small atypical cells with scant cytoplasm and nuclei with coarse chromatin, MGG, 400x
(d) **Cat IV Suspicious of malignancy:** Cytomorphology showing aggregates of atypical cells with high nucleocytoplasmic ratio, vesicular chromatin and prominent nucleoli, MGG, 400x
(e) **Cat V Malignant:** Cytomorphology showing acinar formation, 3Dcluster pattern consistent with pleomorphic cells having high nuclear to cytoplasmic ratio, MGG, 400x
(f) **Cell block:** malignant fluid showing multiple clusters of atypical cells arranged in papillary fashion, H&E, 400x

Discussion:-

This study analyzed and categorized 200 pleural effusion cases according to the categories given by TIS. In this study patient age ranging from 10 to 87 years old with mean age of 42.2 years.There were 130 males (65%) and 70 females (35%) in this study. Similar demographic observation seen in study of **Pergaris et al**[6] i.e.286 male and 242 female, age ranging from 11- 95 yr with mean age of 68.9 yr.

The volume of samples in this study varied from as 50 ml to as high as 1000ml. The minimum volume threshold of adequacy forfluid interpretation is controversial and has not been described in TIS clearly. A study done by **Gokozan et al**[7] suggested that 50ml and below were considered low volume samples, while studies like **Swiderek J et al**[8], **Thomas SC et al** [9] **and Rooper LM et al**[10]suggested a minimum of 50 – 75 ml to ensure good diagnostic material.

In the present study 200 pleural effusion samples were grouped according to TIS categories as 10(5%), 160(80%), 12(6%), 6(3%) and 12(6%) under Non-Diagnostic (ND), Negative for Malignancy (NFM), Atypia of Undetermined Significance (AUS), Suspicious for Malignancy (SFM) and Malignant (MAL) categories respectively. This was similar to the results derived by **Jha et al**.[11] i.e., 4.3%, 74.3%, 4.59%, 2.9%, 13.8% for ND, NFM, AUS, SFM and MAL respectively. Various other researcherslike **Farhani (2019) and Baloch** [12],**Lobo et al (2020)** [14],**Pergaris et al (2021)** [6], **Xu et al (2021)** [15], **Pinto et al (2021)** [16], **Zhu et al (2022)** [13]**and Kala et al (2023)** [17]have also done similar studies (Table no. 2)

Table 2:- Comparison of case distribution according to ISRSFC with other studies on pleural fluids.

Study Total cases n	ND%	NFM%	AUS%	SFM%	MAL%
Farhani (2019) and Baloch[12]	0.3	69.2	0.6	3.5	26.4
Lobo et al (2020) [14]	0.8	63.1	0.6	3.6	31.9
Pergaris et al (2021) [6]	0.6	81.4	2.8	2.8	12.3
Jha et al (2021) [11]	4.3	74.3	4.69	2.9	13.8
Xu et al (2021) [15]	1.2	68.1	6.2	2.2	22.4
Pinto et al (2021) [16]	1.43	72.3	2	4	20.6
Zhu et al (2022) [13]	0.4	29.7	3	19	47.7
Kala et al (2023) [17]	0.1	79.3	0.4	1.8	18.3
Present study	**5**	**80**	**6**	**3**	**6**

Risk of malignancy in each Category (ROM)

The ROM in this study for ND, NFM, AUS, SFM and MAL was 12.5%, 3.33%, 25%, 75%, 100% respectively. The ROM was in concordant with the study done by **Pergaris et al**[6]which was 0%, 5.3%, 33.3%, 93.33% and 100% for ND, NFM, AUS, SFM and MAL respectively. The ROM was comparable with the other published studies and ISRSFC except for categories NFM and AUS.

The ROM for NFM category was 3.33% in the present study, whereas it ranged between 12% and 51.61% in other studies done by **Farhani and Baloch et al** [12], **Lobo et al** [14], **Jha et al** [11], **Pinto et al** [16], **Xu et al** [15], **Zhu et al** [13] **and Kala et al** [17]. **(**Table 3)

Table 3:- Comparison of estimated ROM with other studies on pleural fluid.

STUDY	ND%	NFM%	AUS%	SFM%	MAL%
Farhani (2019) and Baloch [12]	25.7	22.3	71.8	75.9	99.2
Lobo et al (2020) [14]	57.1	23.9	50	76.2	100
Pergaris et al (2021) [6]	0	5.3	33.33	93.33	100
Jha et al (2021) [11]	87.5	51.61	88.23	87.5	100
Xu et al (2021) [15]	26.7	12	62.3	77.8	100
Pinto et al (2021) [16]	40	20.16	42.8	78.57	100
Zhu et al (2022) [16]	40	29.8	49.3	99.3	100
Kala et al (2023) [17]	33.3	19.6	85.7	75.86	98.64
Present study	**12.5**	**3.33**	**25**	**75**	**100**

The ROM of the AUS was 25% in the present study, whereas it ranged between 39% to 88.23 % in other studies done**(**Table 3). The ROM in the present study came out to be low possibly due to less follow up of cases.

Conclusion:-

International system for reporting serous fluid cytopathology highlights the need for universal criteria and introduces essential diagnostic categories, thereby, assuring standardised global fluid cytology reporting in adjunct to aiding quality assurance and research. The system facilitates improved diagnostic precision, which helps enhance communication between pathologists and attending clinicians.The results from the present study showed the efficacy of TIS in view of cytological evaluation in confirming the diagnosis.We further recommend more studies on this area of cytopathology on a bigger sample size so that more representative results can be perceived and analysed.

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Competing Interests:
NA.

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