International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(2): 73-76
Received: 08-02-2021
Accepted: 12-03-2021

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Exfoliative cytology of different body fluids: An important aid to diagnose cancer

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DOI: https://doi.org/10.33545/pathol.2021.v4.i2b.360

Abstract
Background: The cytological examination of exfoliated cells in various effusion fluids is very challenging and is of paramount importance for early diagnosis and management of various pathological processes. It is of utmost significance in identification of malignant cells and hence throws light on the cause, staging and prognosis of various cancers.
Materials and Methods: Retrospective, analytical, observational study done over a period of one year from January 2020 to December 2020. A total of 228 cases including peritoneal and pleural and cerebrospinal fluid and urine were analyzed. Samples were centrifuged for five minutes at 2000 rpm and smears prepared from deposit were stained by Papanicolaou (PAP) and May-Grunwald- Giemsa (MGG) stains.
Results: Out of 221, 116 were peritoneal effusions, 87 were pleural, 15 cerebrospinal fluids and 3 urine. Out of 116 cases of peritoneal effusions, 60 were non neoplastic and 31 were malignant effusion. Out of total 87pleural effusions 51 were non neoplastic and 19 neoplastic. Commonest malignancy in peritoneal and pleural fluid was adenocarcinoma from ovary and lung respectively.
Conclusions: Cytological evaluation of different body fluids is a simple, rapid, inexpensive and less invasive tool with high accuracy and thereby reducing the need for invasive investigations. It is especially helpful in evaluating and staging malignancies thereby guiding the clinician in further management of the patient.

Keywords: Cerebrospinal fluid [CSF], cytology, peritoneal fluid, pleural fluid, urine

Introduction
There are three major cavities present in our body: pleural, pericardial, and peritoneal. These cavities have parietal and visceral layers, bothof which are lined by mesothelial cells overlying the submesothelial stromal matrix tissue [1]. The parietal and visceral layers are separated by thin layer of lubricating fluid which facilitates the movement of both membranes against each other in the absence of disease [2]. However in pathologic states, these cavities develop spontaneous effusions attributable to various patho-physiological processes. This fluid acts as a clinically useful specimen for cytological evaluation to diagnose the underlying pathologic process, such as infections, inflammation, neoplasia, etc [3]. Tapping and analyzing these fluids in terms of biochemical parameters and cytology not only serves in diagnosis and therapeutic intervention but also aids in staging, treatment outcome, disease monitoring and prognosis [4, 5]. The diagnostic yield of effusion fluid is higher than needle biopsy since the cell population present in the sediment is representative of a much larger surface area [6, 7]. Almost 20% of the effusions examined are directly or indirectly related to the presence of malignant disease [5, 8]. Many studies were performed previously on different fluids, few focusing on single fluid.

Materials and Methods
Our study is a descriptive, analytical and retrospective observational study, undertaken in the department of pathology in a tertiary care cancer centre. The duration of the study was one year; from January 2020 to December 2020. Inclusion criteria were samples from pleural effusion, peritoneal effusion, cerebrospinal fluid (CSF) and urine. Cases from either sex of any age group were included in the study. Exclusion criteria were body fluids other than those in the inclusion criteria were excluded. Complete clinical history including clinical examination along with all relevant blood, serum and radiological investigations of the

patients were noted from the medical records of the patients. All the samples received were immediately processed. Sample volume ranged from 2 ml to 2000 ml. The gross appearance of the fluid was assessed. For hemorrhagic fluids, glacial acetic acid was used as a hemolysing agent and then it was processed routinely. The fluids were centrifuged at 2000 revolution per minute (rpm) for five minutes to produce uniform suspension of cells. Both wet fixed (methyl alcohol) and air dried smears were made and stained with Papanicolaou (PAP) and May-Grunwald Giemsa (MGG) stains respectively. PAP stain helped in the better interpretation of nuclear features and MGG stain for cytoplasmic features. The stained smears were studied on light microscopy and evaluated for cellularity, predominant cell type, size, architecture (acini / sheets/ 3-dimensional balls/ papillae/ rosette, singly scattered), nuclear and cytoplasmic features, chromatin, degree of inflammation, reactive changes and other background features. All the data was analyzed and summarized.

Results

The cytologic examination of 221fluids was done which included pleural fluid, peritoneal fluid, cerebrospinal fluid and urine. The age ranged from 3 years to 85 years. Male preponderance was observed with M: F ratio of 1:0.9. The most common fluid was peritoneal fluid, 116 (52.4%) cases, followed by pleural fluid 87 (39.3%) cases, CSF 15 (6.7%) and least common was urine 3 (1.3%) cases (Table 1). The most common age group affected was 4th decade followed by 5th decade. (Table 2) All individual cases were categorized into 3 major categories; benign/negative for malignancy, suspicious for malignancy and positive for malignancy (Table-3). Out of 221 cases of cytological specimens, 123 (55.6%) were negative for malignancy. In peritoneal fluid 51.7% (60/116), pleural fluid 58.6% (51/87), CSF 66.6% (10/15) and in urine 66.6 (2/3) were present in this category. These cases included smears which were predominantly inflammatory (acute, chronic as well as mixed) or reactive, having mesothelial cells and macrophages in abundance. 45 out of 221 cases (20.3%) were kept in the category of suspicious of malignancy. These cases did not show definitive features of malignancy. However showed presence of atypical looking cells, either obscured by too much of hemorrhage, inflammation, necrosis, etc. or had low cellularity with changes depicting only a doubt of malignancy. Presence of reactive mesothelial cells, close mimickers of malignancy also raised suspicion of malignancy in few cases. Few of these cases lost follow-up and few underwent repeat cytological or histopathological test rendering a definite diagnosis. Malignant cells were detected definitely in 53 (23.9%) cases. Maximum number of malignant effusions were peritoneal (26.7%) followed by pleural (21.8%) and cerebrospinal fluid (13.3%). 33.3% (1/3) cases of urine specimen show malignancy.

Table 1: Distribution of cases according to the type of specimen and their gender wise incidence.

Type of Specimen	Number of Cases	Male	Female
Peritoneal	116	51	65
Pleural	87	52	35
CSF	15	6	9
Urine	03	03	00
Total	221	112	109

Table 2: Age wise distribution of cases in peritoneal and pleural effusion, CSF and urine

Age in years	Peritoneal fluid	Pleural fluid	CSF	Urine	Total
0-10	1	-	7	-	8
11-20	2	3	3	-	8
21-30	7	4	2	-	13
31-40	18	8	-	-	26
41-50	36	24	-	-	60
51-60	27	21	-	-	48
61-70	11	15	-	-	26
71-80	8	5	1	2	16
>80	5	7	2	1	15
Total	116	87	15	3	221

Table 3: Distribution of cases on the basis of diagnosis

Site	Benign/negative for malignancy		Suspicious for malignancy		Malignant		Total
	(No.)	%	(No.)	%	(No.)	%	
Peritoneal fluid	60	51.7	25	21.5	31	26.7	116
Pleural fluid	51	58.6	17	19.5	19	21.8	87
CSF	10	66.6	3	20	2	13.3	15
Urine	2	66.6	-	-	1	33.3	3
Total	123	55.6	45	20.3	53	23.9	221

Discussion

The history of serous effusion cytology can be traced back to the 19th century. Lucke and Klebs were apparently the first investigators who recognized the presence of malignant cells in an ascitic fluid in 1867. In 1882 Quincke was credited for detailed descriptions of ovarian and lung cancer cells in serous effusions. Since that time reports on effusion cytology have started to appear in the medical literature, and serous effusion cytology is now a routine diagnostic procedure worldwide Further with the advent of lumbar puncture in the year 1891, in Germany CSF cytological examination was introduced in the field of cytopathology [7]. In the current scenario the cytological examination of effusion has become a complete diagnostic modality which aims at pointing out the etiology of effusions [9] 'Starlings Law governs the mechanism of formation of abnormal fluid in the body cavity. It states that fluid is accumulated when there is decrease in the plasma colloidal pressure and increased capillary hydrostatic pressure [9-11]. However; it is not always possible to characterize a fluid into an exudate or transudate. This provides only a general guideline for possible underlying etiology. Hence, fluid protein is used as a basis to distinguish between exudates and transudates [9].

In the present study of 221cases of fluids, the age ranged from 3- 85 years. The age range in most of the other studies were from first to ninth decade which was in concordance to our study [4-7, 9, 10, 12-15]. Male preponderance was found in most of the studies [4, 5, 7-10, 12-14] which is similar to the present study. The most common fluid received was peritoneal fluid (52.4%), followed by pleural fluid (39.3%), CSF (6.7%) and least common was urine (1.3%). The

present study correlated with the findings of Chakrabarti *et al*. [8] Shulbha *et al*. [10] Bhagat *et al*. [13] Bhade *et al*. [14] and Gupta *et al*. [15]. Other authors found pleural fluid as the commonest fluid [4-7, 9, 12]. This could be attributed to the various epidemiological factors. In our study the difference may be due to more number of cases of abdominal malignancies.

In 116 cases of peritoneal fluid, most common age group involved was 41-50 years with a female preponderance. These findings were in concordance with Ayyagari *et al.* and Chakrabarti *et al*. Who also observed female preponderance. However age group affected was different in their studies [6, 8].

Pleural fluid was found as the second most common effusion fluid having 87cases (39.3%) similar to the observation by various authors. 8, 10, 13-15 Most common age group involved was 41-50 years. There was a slight male preponderance having M: F ratio of 1.48: 1, this was in concordance with Hathila *et al*. and Chakrbarti *et al*. [5, 8].

CSF remained the third most common fluid in many of the studies [4, 7, 12-15]. This corroborates with our finding; CSF being the third most common fluid (4.8%). Most of the patients in our study were in the age group of 0-10 years which is similar to the findings of Saba *et al*. and Bhagat *et al*. [12, 13]. Identifying blast cells and their percentage in the CSF is an important prognostic factor in pediatric ALL and determines the incidence of relapse and need for the change in treatment protocol. 20 It is important to identify infectious causes of exudative CSF effusion for early diagnosis, improvement in prognosis and reduce spread of disease and complication [10, 14].

Urine cytology for screening of transitional cell carcinoma (TCC) has been used for long time. Despite the advent of several newer techniques for screening and diagnosis of urothelial malignancies, cytomorphology still remains an important tool. "Atypical cells" in urine have been recognized and studied time and again. The accurate interpretation of the character of "Atypical cell" in urine is a major challenge for cytopathologists [16]. Three urine specimens with suspected cases of carcinoma urinary bladder presenting as intermittent hematuria in elderly patients were included in our study. The reason for less number of urine specimens may be due epidemiological factors. Two of these cases showed cytological features of urinary tract infection. Only one of the case showed presence of malignant cells.

Almost all the studies came across difficulty in interpretation of malignancy due to the presence of reactive mesothelial cells which are a very close mimicker of malignancy as they also have the tendency of rosette formation, pseudoacini or acini, with or without prominent nucleoli [4-6]. In our study, we also found 45 out of 221 cases (20.3%) of various fluids being reported as suspicious of malignancy. There is an increased role of cytocentrifuge and cell block study which not only increases the cellularity, but cellular morphology, nuclear and cytoplasmic details, are better appreciated. We can reduce false negative results and increase diagnostic sensitivity and specificity. Also, cell block carries advantage of performing immunohistochemistry which helps in the diagnosis and can be used for typing of tumor without invasive tissue biopsy [4, 17, 18].

Conclusion

Preliminary cytological analysis of various fluids remains the simple, relatively painless, convenient, less time consuming, cost effective, first line method in arriving at the diagnosis and to understand the disease progression. This thereby reduces the need for invasive investigations and their related complications. Cytological analysis of serous effusions have a better diagnostic performance visa-vis needle biopsy as the population of cells acquired in a sediment is representative of a larger surface area than the latter. It is especially helpful in evaluating and staging malignancies thereby guiding the clinician in further management. This results in the upstaging or down staging of tumor and thereby affects treatment plan and prognosis for the patient. Some cases may present major interpretative challenges to the pathologist like presence of reactive mesothelial cells which at times poses difficulty in diagnosis, being close mimicker of malignancy. These limitations can be overcome by cell block, histopathology and immunohistochemistry that are usually diagnostic.

Source of Funding: None

Conflict of Interest: There is no conflict of interest.

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