Pleural effusion pathology

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Abstract

Introduction: Cytological examination of pleural fluid is of paramount importance, it reveals information about inflammatory conditions, and malignant and metastatic pleural effusions.

Materials and Methods: This study on pleural fluid cytology, was done over a period of two years and 100 cases of pleural effusion with relevant clinical data were obtained.

Results: Females had predominance of malignant effusions (53.84%) compared to males (46.15%) with M:F ratio of 1:1.2. 84% 0f the samples are exudative and 16% of samples are transudative effusions Among samples received maximum number of samples had a clinical diagnosis of Tuberculosis (52%) Pneumonia (25%), and Malignant effusion (10%).

Conclusion: Pleural fluid cytology is the most useful tests in establishing the diagnosis of pleural effusion. Cytological examination of body fluids is a complete diagnostic modality which aims at pointing out the etiology and prognosis of effusion. The technique is simple, safe, cost-effective and reproducible even in resource limited settings.

Keyword: Pleural fluid, Cytology, Tuberculosis, Pneumonia

Introduction

Pleural cavity is a potential space between the parietal pleura and visceral pleural. It consists of some amount of fluid called pleural fluid which is normally less than 25ml. Pleural fluid is produced by parietal lining and absorbed by visceral lining.(1)

Aspiration of serous cavities is a simple and relatively non-invasive technique to achieve a diagnosis. Cytological examination of pleural fluid obtained by tapping is a simple, inexpensive, diagnostic modality of the cause of pleural effusion and further helps in treatment and follow up of the patients. Not only the infective causes, it also helps in cancer patients either primary or metastatic effusions both in diagnosis and follow up. The good number of cells can be obtained in cytology because the cells lining the cavity will be shed in the effusions which gives cellularity from wider area as compared to pleural biopsies where we get cell material from a single focus. However doing cell block in pleural fluid is more advantageous since it gives better architectural patterns and material can be taken for immunohistochemistry and other aniciallary techniques.

Materials and Methods

This study on pleural fluid cytology was done for two years .Clinical details were taken. The fluid received was immediately processed. Gross Examination of Pleural fluid was done for –volume, colour, clarity and cytological analysis was done for cell count, cell type. And centrifuged smears were stained with H&E, Pap, Giemsa were scanned for malignant cells.

After studying all the available clinical data, based on morphology the smears were divided as inflammatory, benign, suspicious, and malignant lesions.

Discussion

The pleural cavity is a potential space that is present between the visceral which covers the entire surface of the lung, including the interlobar fissure and the parietal pleura which covers the inner surface of thoracic cage, mediastinum, and diaphragm. Grossly the normal pleural surface is smooth, glistening, and semitransparent. Microscopically it lined by layers like mesothelial cells layer, elastic, and deep fibroelastic layer. The size of human mesothelial cell ranges from 16.4+/-6.8 to 41.9+/-9.5 µm .It's surface is covered with microvilli, measuring approximately 0.1 microns in diameter and up to 3 µ in length. The nucleolus is ovoid with a prominent nucleolus. The cytoplasm has moderate to abundant organelles like mitochondria, rough endoplasmic reticulum, golgi apparatus and glycogen granules. The mesothelial cells have typical tight junctions.(2) Appearances of Mesothelial cells in Reactive Effusions;

There is increase in the number of mesothelial cells in effusions with mild nuclear variability, some prominence of the nucleoli, and maintenance of N:C ratio. Nuclear pleomorphism and macronucleoli are absent. Reactive changes in mesothelial cells can be seen in Pulmonary infarction, Cirrhosis, radiation, chemotherapy, systemic diseases, traumatic irritation, underlying neoplasm's, chronic inflammation, foreign substance and infection.(3) Cytoplasm of most mesothelial cells has PAS positive granules concentrated at the periphery and representing neutral mucopolysaccharides.

Cell counts

1. **Red blood cell count:** Analysis of fluid for the presence of red blood cells is routinely performed. Light and co-workers reported that RBC counts of >100,000cells/mm3 are seen only with malignancy, trauma or pulmonary infarction. RBC count of >10,000cells/mm3 have been commonly seen in malignancy and infection (including tuberculosis) but are also frequently noted in cirrhosis and congenital heart failure

White Blood Cell count: A value of 1000cells/mm3 separates transudates from exudates, Transudates are most often lymphocytic, but they may show a predominance of polymorphonuclear leucocytes up to 13% of time. Exudates may have high number of neutrophils and are suggestive of an acute inflammatory process such as infection or vasculitis. However, as the infection or the inflammation become more chronic, differential count shifts to a higher percentage of lymphocytes. Lymphocytic exudates are consistent with tuberculosis or malignancy, particularly lymphoma. Monocytosis is most consistent with malignancy, where as a low number of mesothelial cells is suggestive of tuberculosis.[4]

Cell Population in benign Effusions[3]

- Mesothelial cells
- Macrophages (Histiocytes)
- Blood cells
- Miscellaneous other cells
- **Mesothelial cells:** Appears as sheets of polygonal cells, about 20µm in diameter, that are usually separated from each other by clear gaps or windows. Single cells are usually spherical or oval. The cells have a delicate, yet sharply demarcated, cyanophilic or eosinophilic cytoplasm and round to oval nuclei. Free floating mesothelial cells in effusions may show a narrow brush border. Freely growing mesothelial cells in effusions may also form clusters of various configurations. Some clusters may be circular, linear or form rosette like configuration
- **Macrophages (Histiocytes):** Typically, macrophage measures 15-20µm have a round cell shape with variable cell borders that can be well or ill defined. They may appear singly or in loose clusters. When in clusters, the cytoplasmic borders may not be well maintained and the peripheral contours of the group may appear smooth or knobby. Nuclei are kidney shaped, peripheral in location. Nucleoli are indistinct. Multinucleation may occur, the cytoplasm is highly variable and may appear from pale homogenously cyanophilic to extensively vacuolated. These cells are CD14 positive.[5]

Blood cells

Erythrocytes: Presence of intact red blood cells in body fluids is usually caused by traumatic tap. In haemorrhagic effusion, fresh and degraded erythrocytes are seen against a background of fibrin.

Erythrophagocytosis: Ingestion of the patients own erythrocytes by macrophages. Also seen in Chediak-Higashi syndrome and malignant lymphomas.

Lymphocytes: In chronic effusions, lymphocytes may be the dominant population of leukocytes. Also seen in chylous effusion caused by rupture of thoracic duct, tuberculosis, chronic lymphocytic leukemia and malignant lymphoma.

Granulocytes: Neutrophilic leukocytes indicate an inflammatory process, which may be secondary to infection, cancer or other disease. Eosinophilic leukocytes are seen in eosinophilic effusions.

Plasma cells: May be noted in multiple myeloma and in Hodgkin's disease.

Megakaryocytes: Abnormal megakaryocytes signal a serious haematopoietic disorder

Classification of Pleural effusion[6]

Transudates: Increased hydrostatic Pressure or decreased plasma oncotic pressure.

Common causes

1. CHF
2. Hepatic cirrhosis
3. Hypoproteinemia (e.g. Nephrotic syndrome)

Less common causes

4. Pulmonary infarction
5. Hypothyroidism
6. Mitral stenosis
7. Pulmonary embolism
8. Rare causes
9. Superior vana caval obstruction usually by lung carcinoma
10. Constrictive pericarditis
11. Ovarian hyperstimulation
12. Meig's syndrome.

Exudates: Increased capillary permeability decreased lymphatic resorption

Infections

1. Bacterial pneumonia
2. Tuberculosis
3. Viral or Mycoplasma pneumonia

Neoplasm:

4. Bronchogcnic Carcinoma
5. Metastatic Carcinoma
6. Lymphoma
7. Mesothelioma

Non-infectious inflammatory disease of pleura

8. Rheumatoid disease
9. SLE
10. Pancreatitis
11. Ruptured esophagus
12. Urinothorax

Pleural fluid analysis:[7] The normal volume of liquid in pleural spaces averages 0.1-0.2 ml/Kg body weight. The rate of turn over of pleural fluid is rapid and may exceed 1 lt/day. The rate of fluid entry and efflux is almost equal so the volume of pleural fluid remains virtually constant.

Normal composition of pleural fluid is as follows

Volume	0.1-0.2 ml/Kg
Cells/mm3 % Mesothelial cells % Monocytes % Lymphocytes % Granulocytes	1000-5000 3-70% 30-75% 2-30% 10%
Protein % Albumin	1-2 g/dl 50-70%
Glucose	=Plasma level
LDH	< 50 % Plasma level
PH	>Plasma

The first diagnostic step in the evaluation of a pleural effusion is to determine if it is a transudate or exudates.

Gross characteristics of the Fluid[8]

Characteristics	Significance
Clear and straw-colored	Most transudates Some exudates
Reddish tinge to bloody	If not traumatic tap, suggests tumor, pulmonary infarction or trauma
Turbid, Yellow	Suggests infection, including tuberculosis
Turbid, green	Suggests rheumatoid pleuritis
Cloudy, Milky white	Chylothorax (Chylous effusion) indicates disruption of thoracic duct from trauma and tumor
Thick, Yellow, Metallic sheen	Pseudochylothorax chyliform effusion, usually long standing effusions, e.g. Tuberculous and Rheumatoid pleuritis, trapped lung
Pus(with or without) putrid odour	Empyema
Viscous, haemmorhagic	Suggests malignant mesotheliomas
Anchovy colour	Suggests amoebic liver abscess ruptured in to pleural space.

Microscopic examination: In conventional smears, the accurate identification of cells as either malignant or benign reactive mesothelial cells is a diagnostic problem. The reactive mesothelial cells which are common in hepatic cirrhosis, allergic pleurisy, polyarteritis nodosa, pulmonary infarcts and in long standing effusions due to cardiovascular diseases may show reactive changes such as cytomegaly, nucleomegaly, multinucleation, mitotic figures and high N:C ratio.[9]

Diagnostic problem may arise in diagnosis of malignancy by the morphological study of serous effusions whenever there is little or no morphological distinctions as for example between reactive mesothelial cells and poorly differentiated malignant cells. In such situation to avoid grave clinical implications guarded or ambiguous reports little clinical values are common.[10] Most of the fluid received in the cytology laboratory contains blood clots or small bits of tissue from the lesion while preparing the slide. These bits remain in bottle and not available for microscopy.[11]

Cell block prepared from residual fluid and tissue can be particularly useful for identification of tumors that cause diagnostic difficulties in smears. This technique is simple, reproducible, and safe. Further the effectiveness of cellblock lies in the availability of diagnostic material for further histological examination, histochemistry and IHC studies for better classification of the tumor and identification of infectious causes with microbiological stains.[12]

The disadvantage of the cell block technique is delay in the diagnosis when compared to conventional smears and sometime risk of loosing material during processing. Some mesothelial cells because of centrifugaration artifacts may form rosettes or pseudoacini that can be the source of misdiagnosis.[13]

Drug induced pleural effusion: Pleural effusion as a reaction to drug have been described with only small number of agents like nitrofurantoin, dantrolene, methysergide, bromocriptine, procarbazine, practolol and methotextrate. Nitrofurontoin and dantrolene cause eosinophilic pleural effusion.[14]

Malignant Pleural Effusion: Neoplasms are responsible for higher percentage of pleural effusion. There is an exponential increase in incidence w**.**

Malignant Mesotheliomas: It is most commonly due to occupational exposure to asbestos and carries a worst prognosis with increasing age.[15]

Metastatic Tumours: Lung tumors in males and Breast tumors in females are the malignant diseases most commonly responsible for malignant pleural effusion. Besides the lung and pleura, the primary common sites of malignancy in males were the gastrointestinal tract, Liver and Pancreas. In females, the Breast, Lung, Ovary, Pancreas, Gastrointestinal tract and uterus were in descending order of frequency.[16]

General characteristic of tumor cells in effusions that may help in identifying nature and site of primary lesions.[5]

Results

Maximum number of samples was in the age group of 51-60 Years. Least number of samples was in age group 1-10 Years.

Table 1: Age wise distribution of pleural effusions

Age(Years)	No of Samples	Percentage
1-10	2	2.0
11-20	11	11.0
21-30	7	7.0
31-40	19	19.0
41-50	18	18.0
51-60	23	23.0
61-70	13	13.0
71-80	6	6.0
81-90	1	1.0
Total	100	100.0

Mean ± SD: 46.17±18.52

Table 2: Sex wise distributions of pleural effusions

Sex	No of Samples	Percentage
Male	62	62.0
Female	38	38.0
Total	100	100.0

Table 3: Clinical diagnosis of Pleural effusion samples received

Clinical diagnosis	No of Samples	Percentage	95%CI
Tuberculosis	52	52	42.32-61.54
Pneumonia	22	22	15.00-31.07
CCF	5	5	2.15-11.18
Anaemia/ Hypoproteinemia	6	6	2.78-12.48
Pulmonary infarction	2	2	0.5-7.00
Malignant effusion	13	13	7.76-20.98
Total	100	100	-

Table 4: Nature of Pleural fluid

Nature of fluid	No of Samples	Percentage	95%CI
Exudative effusions	84	84.0	75.58-89.90
Transudative effusions	16	16.0	10.10-24.42
Total	100	100.0	-

84% 0f the samples are exudative and 16% of samples are transudative effusions.

Table 9: Sex wise distribution of Primary site of malignant effusion

Primary site	Male (n=62)	Female (n=38)	Total (n=100)
Ovary	-	2(5.3%)	2(2.0%)
Breast	-	2(5.3%)	2(2.0%)
Lung	1(1.6%)	-	1(1.0%)
GIT	4(6.5%)	2(5.3%)	6(6.0%)
Unknown	1(1.6%)	1(2.6%)	2(2.0%)
Total	6(9.7%)	7(18.4%)	13(13.0%)

Table 10: Role of Cytology to establish definite diagnosis

Initial clinical diagnosis	No of Samples	Cytological diagnosis	No of Samples	Concordance co-efficient
Tuberculosis	52	Tuberculosis Malignant effusion	49 3	88.46%
Pneumonia	22	Pneumonia	22	100.0%
Malignant effusion	10	Malignant effusion	10	100.0%

So 3 cases which were diagnosed as Tuberculosis clinically was diagnosed as Malignant effusions by Cytology.

100 samples of pleural fluid were received. A 8 year old boy was affected, and common were the middle aged to elder people affected. Males were affected more than females. Tuberculosis was the

common condition seen, Effusion was more of exudative than transudates. Diagnosis of malignant effusions was made in 10 cases and 3 cases which were diagnosed as tuberculous was malignant in our study by cytology. So by cytology these 3 cases which turned out as malignant was useful for the patient and the clinician as the mode of treatment was entirely different for both the conditions.

Conclusion

Pleural fluid cytology is one of the easy, inexpensive, mode of diagnosis for the cause of pleural effusion which also helps in the treatment and management of patients. It can be done in any rural set up with basic facilities where sophisticated techniques are not available. Pleural effusion cytology not only finds the infective cause or the local cause of the effusion, but it also helps in diagnosing the metastatic pleural effusion by cellular details and pattern of arrangement of cells where primary is unknown.

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