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KEY WORDS: .

EVALUATION OF HEMORRHAGIC PLEURAL EFFUSION WITH SPECIAL REFERENCE TO MALIGNANCY

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ABSTRACT

INTRODUCTION: Pleural effusion is a common clinical condition with various etiologies. Though malignancy is the most common cause of hemorrhagic pleural effusion, it also encompasses a diverse set of various other clinical entities, e.g trauma to chest, tuberculosis, parapneumonic effusion, pulmonary embolism etc. we studied the clinical features of hemorrhagic pleural effusion as well as diagnostic procedures.

OBJECTIVE: The main objective of this study is to find out the various causes of hemorrhagic pleural effusion, their mode of clinical presentation and laboratory analysis of pleural fluid to aid in diagnosis of patients with hemorrhagic pleural effusion.

MATERIALS & METHODS: prospective study conducted on 58 patients with hemorrhagic pleural effusion coming to Dept. of pulmonary medicine, SCB Medical College & hospital, Cuttack from Sept'2013 to Aug'2015. All patients underwent pleural fluid aspiration and samples were sent for biochemical (sugar, protein, ADA, LDH), Microbiological (gram stain, culture & sensitivity), and cytological studies. CT Thorax with/without fine needle aspiration cytology/biopsy and bronchoscopy were done in appropriate cases.

RESULTS: 31 males and 27 females presenting with hemorrhagic pleural effusion were included in this study. The commonest age group was of above 60 years. Prevalence of hemorrhagic pleural effusion was almost same in both urban & rural population. 27 patients (46.5%) of hemorrhagic pleural effusion were smokers or ex-smokers. Cough with/without expectoration (67.2%)Chest pain (56.9%), breathlessness (48.3%), fever(25.86%), haemoptysis (12%) were common symptoms. 19 patients (32.7%) were having lymphadenopathy. Majority of the effusions were right sided (65.5%), followed by left sided (31%), and bilateral (3.5%). 36 cases (62%) presented with massive effusion and 25 cases (43%) were having lung mass on CT-Thorax. Most of the cases(96.5%) were exudative. 41 patients were diagnosed as malignancy associated , the most common primary site being lung and the commonest cell type was Adenocarcinoma (27 cases), followed by squamous cell carcinoma(5 cases), large cell carcinoma(3 cases), Non-Hodgkin's Lymphoma(2 cases), and broncho-alveolar carcinoma, round cell carcinoma, anaplastic carcinoma, CML each of 1 case. 10 cases were diagnosed as tubercular and 2 cases having parapneumonic effusion. No diagnosis could be made in 5 patients.

CONCLUSION: pleural fluid analysis can have an important contribution for investigation of patients with hemorrhagicpleurakl effusion. Multiple diagnostic modalities are required, with a multi-disciplinary approach can yield diagnosis in most cases with relative short time.

INTRODUCTION:

A pleural effusion is a condition, where abnormal fluid builds up in the pleural space. Pleural effusion is either a manifestation or a complication of respiratory or non-respiratory disease which may herald a serious prognosis, if not diagnosed or treated properly. Thoracocentesis is confirmative and is the only way of differentiating the nature of effusion, e.g. pus, bloody, chyle, serosanguinous etc. Hemorrhagic pleural effusion (uniformly blood stained fluid i.e hematocrit > 1%) can be caused by malignancy, trauma to chest, tuberculosis, parapneumonic effusion, SLE, pulmonary embolism, fungal infection, anti-coagulant therapy, hemophilia, acute aortic dissection/thoracic aortic aneurysm, pleural endometriosis, dialysis, sarcoidosis, pleuritis associated with amoebic liver abscess, hemorrhagic pancreatitis, microfilaria, post-operative cases of cardic surgery etc. Hence etiology of bloody pleural effusion not only encompasses malignancy, but also a diverse set of other clinical entities. Pleural fluid analysis is the most common way of establishing the etiology of pleural effusion. FNAC of superficial lymphnodes, USG/CT guided FNAC of focal pleural involvement or lung mass has substantially increases the diagnostic yield. In case of undiagnosed hemorrhagic pleural effusion, more invasive diagnostic techniques such as pleural biopsy, bronchoscopy, thoracoscopy should be performed. In spite of all efforts, etiology remains undetermined in as many as 15% cases of exudative pleural effusion.

So, the main purpose of this prospective study is to evaluate the common causes of hemorrhagic pleural effusion. Though malignancy is the most common causes of hemorrhagic effusion, we have taken every effort to find out the exact etiology.

MATERIALS & METHODS:

This is a prospective study conducted among the patients admitted to Dept. Of Pulmonary Medicine, SCB Medical college, Cuttack, who were having hemorrhagic pleural effusion, the study period spanned from Sept' 2013 to Aug' 2015. This study included 58 patients of hemorrhagic pleural effusion after taking written informed consent and were subjected to pleural fluid biochemical, cytological and Gram stain & culture study. FNAC of superficial lymphnodes, pleural nodules or lung nasses performed in appropriate cases. To ascertain further etiological diagnosis, Bronchoscopy was done and bronchial wash, bronchoalveolar lavage collected for cytological examination and whenever possible, bronchial biopsy was taken for histopathologiacal study.

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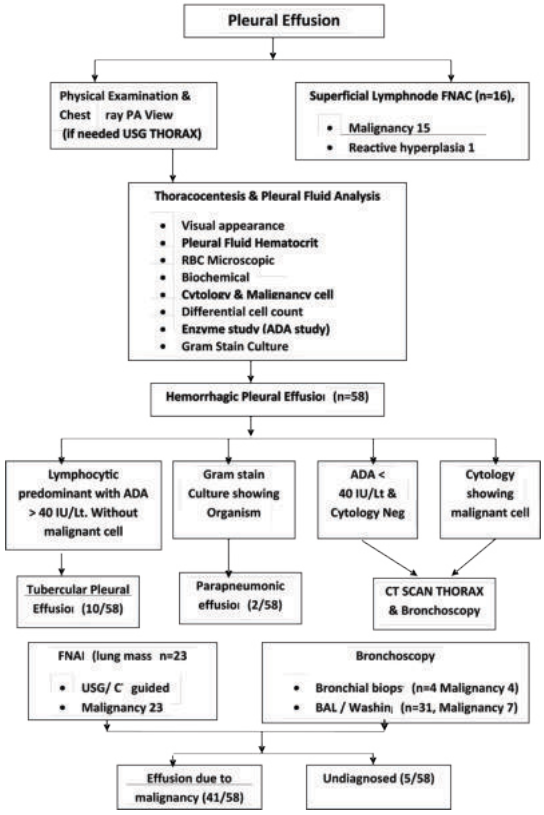

METHODS, APPARATUS & PROCEDURES:

- **THORACOCENTESIS & PLEURAL FLUID ANALYSIS:** After a brief explanation regarding the procedure and proper positioning of the patients, thoracocentesis were carried out, one intercostals space below the upper border of area of diminished vocal fremitus in the mid-axillary or posterior-axillary line, under all aseptic condition and local anaesthesia with 2% xylocaine. The appearance of the pleural fluid was assessed and the fluid was sent for hematocrit, biochemical (sugar, protein, LDH, ADA), cytological (total cell count, differential count, malignant cells), microbiological (gram stain, culture & sensitivity) examination.

- **FNAC OF SUPERFICIAL LYMPHNODES:** Lymphnodes are the part of the peripheral immune system located along the course of the lymphatics, which acts as a mirror of the underlying disease process e.g. malignancy, tuberculosis. It should be the first investigation to be performed when patients complaining of lymphnode enlargement wherever in the body. FNAC of the superficial lymphnodes were done in the Dept. Of Pathology, SCB Medical College, Cuttack.

- **FNAC OF FOCAL PLEURAL NODULES/ LUNG MASS:** Percutaneous transthoracic fine needle aspiration cytology is a well established diagnostic method in the cytological evaluation of pleural based or thoracic mass lesion, which is a relatively safe and accurate means of diagnosing benign and malignant lesions of the chest. In the appropriate cases, USG/CT guided FNAC were performed in the Dept. Of Radiology, SCB Medical College, Cuttack with the assistance of Pathologist.

- **BRONCHOSCOPY & BRONCHOSCOPIC COLLECTIONS:** Fibre-optic bronchoscopy was carried out in our Dept., in suitable cases, after written informed consent and under local anaesthesia. Bronchial wash were taken by instilling around 20ml of normal saline and collecting it in a trap to obtain superficial airway cells. Bronchoalveolar lavage(BAL) was obtained by instilling 100ml of sterile saline through the bronchoscope channel after wedging the scope into a segmental bronchus in the radiological abnormal lobe. Both the collected fluid were sent for cytological examination. Bronchial biopsies (5-7 samples) were taken with the biopsy forcep from the visibly abnormal areas and sent for histological and microbiological studies.

ETHICS: The study was approved by the institutional ethical committee on dt and the data collected were used for academic purpose.

STATISTIC METHODS:

RESULTS: In this study, total 58 patients of hemorrhagic pleural effusion were included. Most of the patients (50%) were of the age group > 60years, followed by 20.7% patients of 50-59 years. The male to female ratio was 1.15:1 having 31 male and 27 female patients. There is no significant difference among urban vs rural population. Smoking history (either current or ex-smoker) was present in 46.5% of patients. Most common presentation was cough with/without expectoration in 67.2% patients followed by chest pain in 56.9% . Other symptoms during presentation were breathlessness (48.3%), loss of appetite (44.8%), fever (25.8%) and hemoptysis (12%). Superficial lymphadenopathy were presents in 32.7% cases. On radiology, 62% cases had massive pleural effusion followed by moderate effusion in 32.8% and minimal in 5.2% cases. Majority (65.5%) cases had right sided pleural effusion. Central mediastinum and mediastinum shifted to same side observed in 46.5% cases and rest (53.5%) had mediastinum shifted to opposite side. Computed Tomography scan showed lung masses and nodules in 78.4% cases, pleural thickening and lymphangitis carcinomatosis in 8% and 5.4% cases respectively. According to pleural fluid protein criteria, 89.6% cases were exudative and rest 6 cases (10.4%) had transudative effusion. But as per pleural fluid and serum LDH criteria, 56 cases(96.5%) were exudative. Pleural fluid glucose were less than 20mg/dl in 12(7%) cases, 63.8%(37) cases had more than 70mg/dl. In majority cases i.e 32 cases(55.2%) had pleural fluid ADA level below 40 IU/L, whereas 10 cases(17.2%) had above 70 IU/L. On cytological study of pleural fluid; 39 cases(67.3%) had lymphocytic followed by mesothelial cells found in 12 (20.7%)cases. Among all these; malignant cells were detected in 35 cases(60.4%). Fibre-optic Bronchoscopy was performed on 31 patients; the finding as follows, extrinsic compression in 15(48%) cases, endobronchial growth in 4 (13%) cases, inflammatory lesions in 4 (13%) cases. The bronchial wash cytology yielded malignant cells in 4 cases. Among the 4 patients having endobronchial growth, bronchial biopsy was done and the histopathological study showed adenocarcinoma in 3 cases, squamous cell carcinoma in 1 case. To support the diagnosis, FNAC of superficial lymphnodes were performed in 16 out of 19 patients of hemorrhagic effusion associated with lymphadenopathy. Out of 16 cases; 12 cases found to be adenocarcinoma, 2 cases as squamous cell carcinoma, 1 case as basal cell carcinoma and rest 1 case as reactive hyperplasia. USG/CT guided FNAC of lung masses were performed in 23 cases of hemorrhagic effusion associated with lung mass. All these, 14 cases diagnosed as adenocarcinoma, 3 cases as squamous cell carcinoma, 3 cases as large cell carcinoma, 2 cases as NHL and 1 case as round cell carcinoma. In a suspected case of haematological malignancy, bone marrow study was done in 1 case, which came out to be chronic myeloid leukaemia.

Out of 58 cases, the most common cause was malignant effusion, which included 41 cases(70.7%). Ocana M et al,1983; Valdes L et al,1993; Greco S et al,2003 observed that pleural fluid ADA is 92% sensitive and 89% specific in diagnosing tuberculous pleuritis. Light RW et al suggests that pleural fluid ADA level above 70 IU/L is highly suggestive of tuberculosis and that of below 40IU/L virtually rules out this. In this study; 26 cases out of 58 cases of hemorrhagic effusions had pleural fluid ADA level above 40 IU/L; of which 18 cases had predominant lymphocytic in the cytology. But among 18 cases, in 8 number of cases malignant cells were detected and hence rest 10 cases were considered to be tubercular. In 2 cases, pleural fluid culture revealed bacterial growth and established as

effusion associated with pneumonia; of which, 1 case revealed growth of acinetobacter and another 1 as staphylococcus.

In rest 5 cases(8.6%), diagnosis could not be established in spite of all efforts and remained as undiagnosed effusion.

Among the 41 cases of diagnosed pleural effusion, the most common primary site is the lungs(63.4%), followed by breast(17%), GI malignancy (7.4%), ovary (4.9%), lymphoma(4.9%) and leukaemia(2.4%). The commonest cytological type is adenocarcinoma(66%), followed by squamous cell carcinoma(12%), large cell carcinoma(7.3%) NHL(4.8%) and bronchoalveolar carcinoma, round cell neoplasm, anaplastic carcinoma, CML comprised of 2.4% each.

Pleural fluid ADA value of more than 40IU/L was 100% sensitivity and 66.7% specificity in diagnosing tubercular effusion. Pleural effusion due to malignancy with ADA less than 40IU/L had sensitivity 65.85% and specificity of 70.6%.

The complications found with various procedures were minimal i.e iatrogenic pneumothorax was found in 1.7% cases following FNAC of lung mass and 1.7% cases following transthoracic aspiration. Hemoptysis was found in 1.7% cases during bronchoscopy.

DISCUSSION: Most of the hemorrhagic effusions due to malignancy i.e 41.5% were in the age group above 60 years, which corroborates with the study by Zay Soe et al[1], 2012 and Basavaraj HG et al[2], where the commonest age group of malignant pleural effusion was in the sixth decade. Among 41 cases of effusion due to malignancy, 17 cases were male and 27 cases being female corroborating with the study of Zay Soe et al,2012[1]. But in tubercular and parapneumonic effusion, male predominance was seen, may be due to earlier access to health system by male patients. Considering all the etiologies, there is no obvious difference in males(52.8%) and females(47.2%), with a male to female ratio 1.12:1, which is at par with the study of Dhital KR et al,2009[3] and Bhasavaraj HG et al,2008[2].

Out of 41 cases of hemorrhagic effusion due to malignancy, 15(28.3%) cases had history of smoking. The study by Zay Soe et al, 2012[1] found that smoking history was present in 82.2% cases of malignant pleural effusion. The low percentage of smoking history in our study, may be due to 24 cases of female patients who are non-smokers. Considering all smokers i.e 23 cases, malignant etiology was found in 15 cases i.e 65.2% cases.

Our study is at par with the Maher CG et al, 1972[4], who found massive effusion in 67% cases of malignant effusions. We observed massive effusion in 65.8% cases in effusion due to malignancy.

Rodriguez et al, 1989[5] found that the extent of malignancy was significantly greater in those with low pleural fluid glucose level. But, in our study, though pleural fluid had cytology positive for malignancy, the glucose levels were high. As per Light RW et al, 1971[6] observation, approximately 15-25% cases of malignant pleural effusion had the pleural fluid glucose level below 60mg/dl. Our study tally with this, as 11 cases out of 41 cases i.e 26.8% cases having pleural fluid glucose below 60mg/dl. Again Light RW et al, 1973[7] opined that majority of the patients with tubercular effusion had pleural fluid glucose above 80mg/dl and that of low in some cases of parapneumonic effusion or empyema. Our study more or less corroborates with this study, as we had observed pleura fluid glucose of more than 70mg/dl in 60% cases of tubercular effusions and that of low(<20mg/dl) in 50% cases and in the range of 61-70mg/dl in rest 50% cases of parapneumonic effusions.

In our study, out of 10 cases of tubercular effusion, 5 cases(50%) had pleural fluid ADA level above 70IU/L and rest 5 cases had that of in the range 40-70IU/L; which correlates with the study of Valdes L et al,1993[8], who stated that pleural fluid ADA more than 40IU/L is suggestive for tubercular etiology in 96.8% of cases.

Our study again tallies with the study of Light RW et al,1973[7]; where it was found that 67% of malignant effusion and 93.4% of tubercular effusion had predominantly lymphocytes in pleural fluid cytology. Our study showed that 67.4% of effusion with malignancy cases and 80% of the tubercular effusion cases had predominantly lymphocytes. However in 35 patinets (85.4%) of hemorrhagic pleural effusion, cytology for malignant cells were positive correlating with the study of Ozcakar B et al,2010[9].

CONCLUSION: It is well known that, pleural effusion is a frequent presentation in chest OPD. Pleural effusion is hemorrhagic is to be confirmed only after thoracentesis and macroscopic appearance of the pleural fluid. Though etiology of hemorrhagic pleural effusion is most commonly malignancy, but also a diverse set of disease of other clinical entities can't be ruled out. Multiple diagnostic modalities are required for diagnosis of hemorrhagic pleural effusion and if used judiciously with multidisciplinary approach involving clinicians, radiologists, pathologists and microbiologists; can yield diagnosis in most of the cases with relative short time frame.

Table -1
Aetiology of Hemorrhagic Pleural Effusion (N=58)

Causes	No. of Cases	Percentage
Malignancy	41	70.7%
Tubercular	10	17.2%
Parapneumonic	2	3.4%
Undiagnosed	5	8.6%

Table -2
Different Cytological Types of Effusions of Malignancy (N=46)

Cytological Type	No. of Cases	Percentage
Adenocarcinoma	27	58.7%
Squamous Cell CA	5	10.8%
Large Cell Carcinoma	3	6.5%
Broncho Alveolar CA	1	2.2%
Round Cell CA	1	2.2%
Anaplastic CA	1	2.2%
NHL	2	4.4%
CML	1	2.2%
Undiagnosed	5	10.8%

Table -3
Primary Tumor in Hemorrhagic Effusion due to Malignancy (N=41)

Primary Tumor	No. of Cases	Percentage
Lung	26	63.4%
Breast	7	17%
GI Malignancy	3	7.4%
Ovary	2	4.9%
Lymphoma	2	4.9%
Leukaemia	1	2.4%

Table -4
Results of Various Procedures for Malignancy

Sl No.	Pleural fluid cytology for malignant cells	FNAC Lymphnode S/O Malignancy	FNAC Lung Mass S/O Malignancy	Bronchial wash cytology for malignancy cells	Bronchial Biopsy S/O Malignancy	Bone Marrow Study	No. of Cases
1	4	-	-	-	-	-	4
2	10	10	-	-	-	-	10
3	2	2	2	-	-	-	2
4	12	-	12	-	-	-	12
5	1	-	1	1	-	-	1
6	1	-	-	1	-	-	2
7	1	-	-	1	1	-	1
8	1	-	1	-	1	-	1

9	2	-	2	2	-	-	2
10	1	-	-	-	-	1	1
11	-	2	2	-	-	-	2
12	-	1	-	-	1	-	1
13	-	-	1	-	1	-	1
14	-	-	2	-	-	-	2
15	-	-	-	-	-	-	17
Total	**35**	**15**	**23**	**5**	**4**	**1**	**58**

Table -5
Correlation of Etiology with Age & Sex Distribution (N=53)

Age Group in Yrs	Malignancy	Tubercular	Parapneumonic	Total
15-20	1(2.4%)	0	0	1(1.9%)
21-30	3(7.3%)	1(10%)	0	4(7.5%)
31-40	3(7.3%)	2(20%)	0	5(9.5%)
41-50	6(14.6%)	4(40%)	0	10(18.9%)
51-60	11(26.8%)	1(10%)	0	12(22.6%)
>60	17(41.5%)	2(20%)	2(100%)	21(39.6%)
Total Sex	**41**	**10**	**2**	**53**
Male	17(41.5%)	9(90%)	2(100%)	28(52.8%)
Female	24(58.5%)	1(10%0	0	25(47.2%)
Total	**41**	**10**	**2**	**53**

Table -6
Correction of Smoking with Etiological Diagnosis (N=53)

Diagnosis	Non-Smoker	%	Smoker	%	Ex-Smoker	%	Total	%
Malignancy	26 (female 24)	49.1 %	12	22.6 %	3	5.7 %	41	77.4 %
Tubercular	4 (female 3)	7.5%	4	7.5%	2	3.8 %	10	18.8 %
Parapneumonic	0	0%	1	1.9%	1	1.9 %	2	3.8%
Total	**30(female 27)**	**56.6 %**	**17**	**32%**	**6**	**11.4%**	**53**	**100 %**

Table -7
Correlation of Pleural Fluid ADA Level with Clinical Diagnosis (N=53)

Diagnosis	No. of Cases	ADA <40 U/L	ADA 40-70 U/L	ADA >70 U/L
Malignancy	41	27	9	5
Tubercular	10	0	5	5
Parapneumonic	2	1	1	0

Acknowledgement
the date of the ethical committee clearance i.e 26/2/17

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