IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 01 Ver. IV January. (2018), PP 21-30
www.iosrjournals.org

Study of Etiology and Diagnostic Modalities of Neoplastic Pleural effusion in a Tertiary Care Teaching Hospital

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Abstract

Aims and Objectives:

Pleural effusion is not a disease by itself but a manifestation of various pathological states. The present study focuses on cases of neoplastic pleural effusion requiring hospitalisation in a Medical college with aim to:

1. Pathological classification of malignancy associated with pleural effusion

2. Evaluate role of different diagnostic modalities.

3. Assess the time span of diagnostic methods.

Materials and methods:

This is a prospective observational study over one year (Feb 2014 – Feb 2015) among 84 adult cases hospitalised in I.P.G.M.E & R., Kolkata. Pleural fluid assessment (biochemical, cytological, bacteriological) and common procedures like closed pleural biopsy using Cope needle, image guided CT/ USG FNAC/Biopsy from approachable intrathoracic lesions, flexible bronchoscopy and FNAC/ biopsy from peripheral lymph nodes were performed.

Results: *Total 84 patients was included in the study with mean age: 55.55 years with neoplastic pleural effusion. Metastasis from primary lung malignancy (86.9%), other metastatic malignancy (5.95%, from breast, cervix & thyroid) Lymphoma(4.76%) and malignant mesothelioma (1.19%). Adenocarcinoma was the commonest lung malignancy (39.29%) followed by, squamous cell carcinoma (22.62%) undifferentiated non small cell lung carcinoma (19.05%) and small cell carcinoma (4.76%). Surprisingly, pleural biopsy has given the highest yield (93.62%) and followed by FNAC from peripheral lymph nodes or nodules (83.33%). Median time span of diagnosis is 4 days among cytology based tests, 9 days in biopsy based tests and 16 days if immunohistochemistry is combined. Iatrogenic hydropneumothorax has been seen after pleural biopsy in around 7% cases.*

Conclusion:

Neoplastic pleural effusions require multiple diagnostic modalities to reach the etiology. Closed pleural biopsy is a valuable diagnostic procedure in the absence of thoracoscopy.

Keywords: *Malignant, Pleural effusion, Pleural biopsy, Lung carcinoma*

I. Introduction

The clinical or radiological recognition of a pleural effusion suggests an abnormal pathophysiological state resulting in an imbalance between absorption and production of fluid in the pleural space [1,2]. Pleural effusion is a manifestation of various pathological states involving different systems like lung, heart, kidney and abdominal organs. Pleural effusion even may be the result of a generalised disorder like connective tissue diseases, vasculitis or lymphoma. Therefore, aetiology of this effusion is diverse. Approximately a million patients worldwide develop pleural effusion each year[3]. Several studies have reported that there is large number

of patients admitted in hospital, in whom a definitive diagnosis is not possible in spite of extensive investigations[4,5,6,7].

Neoplastic pleural effusion is often a late presentation of the underlying disease. Moreover, many investigations are required in a subsequent manner to reach the final diagnosis. Therefore, an important amount of time span is consumed before the diagnosis is being reached and the proper treatment could be initiated.

The primary objective of present study is to find out pathological classification of malignancy associated with pleural effusion, the role of various diagnostic modalities and time span to reach the etiological diagnosis.

II. Materials and Methods

This study was conducted for One year and 3 months (Feb 2014- Apr 2015) in the Department of Pulmonary Medicine, I.P.G.M.E. & R., Kolkata.

Inclusion Criteria: Patients admitted with pleural effusion and finally diagnosed malignancy, in the Department of Pulmonary Medicine, I.P.G.M.E. & R., Kolkata with informed consent.

Exclusion criteria:

- Age < 15 years
- Patients with minimal effusion noted on CT scan of the thorax but not on chest radiograph and not amenable to aspiration.
- Coagulopathy (PT greater than 2.0 by international normalized ratio, [INR]) and/or platelet count less than 20000/L.
- Patients not willing to take part in the study

Total 84 patients were included. No sampling technique was adopted. Control was not required.

Study technique:

- Patients with inclusion criteria were enrolled
- Informed consent was taken
- History was taken and clinical examination was performed.
- Following investigations were done:
- Thoracentesis and pleural fluid analysis: for cytology, biochemical study and microbiological analysis
- Pleural biopsy: using Cope needle
- USG Hemithorax and USG Whole abdomen
- CT thorax, and CT guided FNAC in relevant cases
- FNAC, Biopsy from peripheral lymph nodes or metastatic nodules.
- Flexible Bronchoscopy, Bronchial wash and Lavage fluid examination for cytopathology and bacteriological evaluation.
- Other relevant investigations as per the clinical findings of the patients like: pleural fluid and serum lipase, amylase, ADA.

Laboratory Investigations:

Blood for Hb%, Total and Differential count, ESR, Platelet, Fasting & Postprandial blood sugar, lipid profile, Urea, Serum creatinine, Serum LDH, Liver function test, Serum sodium and potassium, urine routine examination.

- Chest x ray
- CT SCAN of thorax
- ECG
- Echocardiography
- Markers for autoantibody in selected cases.

Specific Investigations: as mentioned above.

Case categorization:

- Categorisation of effusion (exudative/transudative using Light's criteria, nutrophilic/ lymphocytic etc)
- Etiological diagnosis of Pleural effusion
- Comparison among different diagnostic modalities in special situations.
- Assessment of time frame of diagnosis.

Schedule of Data Collection:
Data was collected from the patient admitted in the hospital with provisional diagnosis of Pleural effusion during their diagnostic work up.

Statistical analysis:
Data obtained were recorded on excel data sheet & statistical analysis was done by GraphPad prism® version 6.0 as applicable. For statistical analysis tests like Chi-square test, Fischer's exact test and others were done as applicable.

Procedure:
The diagnosis of pleural effusion was made by clinical and radiological examination. Patients who were admitted in the hospital were fully informed about the study procedure and written consent was taken. Demographical data, characteristics of the pleural effusion, clinical presentation, and investigation results were obtained. Following investigations were performed and final diagnosis was reached.
Aspiration of fluid from pleural spaces was done subsequently. A 50 ml syringe, 18G needle and 3 way stop cock were used in the thoracentesis. Subsequently the fluid was sent for a series of physical, biochemical, cytological and microbiological tests for determination of nature of the effusion.
Following tests of pleural fluid had been performed:
1. Physical – Colour, appearance, presence of coagulum
2. Biochemical – Protein, Sugar, LDH, ADA
3. Cytological- Cell count, cell types, Haematocrit, Malignant cell (PAP stain, cell block study)
4. Microbiological – Gram stain, Culture and sensitivity, ZN stain, culture for Micobecterium.
5. Special tests – ADA (Adenosine deaminase), cholesterol, triglyceride, amylase, lipase (in selected cases)

Amount of pleural fluid sent for different investigation included:
1. Biochemical examination: 5 ml
2. Cytological examination – 5ml (Cell type, cell count, haematocrit)
3. Cytology for malignant cells: 50ml (Sodium citrate or Heparin as preservative)
4. Microbiological examination : Gram stain and culture – 10 ml. ZN stain and Culture for MTB complex: 20 ml

Serum sample was obtained within 24 hours of thoracentesis and following tests were done:
1. Serum glucose
2. Total protein
3. LDH
4. LFT
5. Urea
6. Creatinine

When reports are available pleural fluids were classified into transudates or exudates according to Light's critetia[8].

Investigations done in exudative pleural effusion:
Pleural biopsy was performed using Cope's pleural biopsy needle. Other investigations that might contribute to the diagnosis were carried out. These include sputum smear examination for AFB, Contrast enhanced CT scan of the thorax, and bronchoscopic examination for suspected lung carcinoma and pulmonary tuberculosis, image guided (USG or CT guided) Tru-cut biopsy or FNAC from the lung lesion. In patients with peripheral lymph node or lump anywhere in the body with suspected malignant metastasis were undergone FNAC or biopsy from the lesion.

Establishment of etiological diagnosis:

Tubercular pleural effusions were diagnosed when one or more of the following criteria were satisfied:

1. sputum or pleural fluid AFB smear or Mycobacterial culture positivity;
2. presence of epithelioid granulomas with or without caseating necrosis
3. presence of AFB on histological examination of pleural biopsy or lymph node biopsy specimen;
4. cytological evidence of tubercular inflammation
5. AFB staining positivity of fine-needle aspiration sample from lung lesion or lymph nodes.

Parapneumonic effusions were defined as pleural effusions associated with an acute febrile illness and cough, in which the chest radiographs revealed pulmonary infiltrates and the patient responded to antibiotic treatment. Empyema was diagnosed when pus was present or microorganisms were isolated from the pleural aspirate. Empyema cases were excluded from the study.

Effusions associated with rheumatoid arthritis cases were diagnosed by excluding other possible causes, RA or anti-CCP positivity and pleural biopsy report suggestive of rheumatoid aetiology.

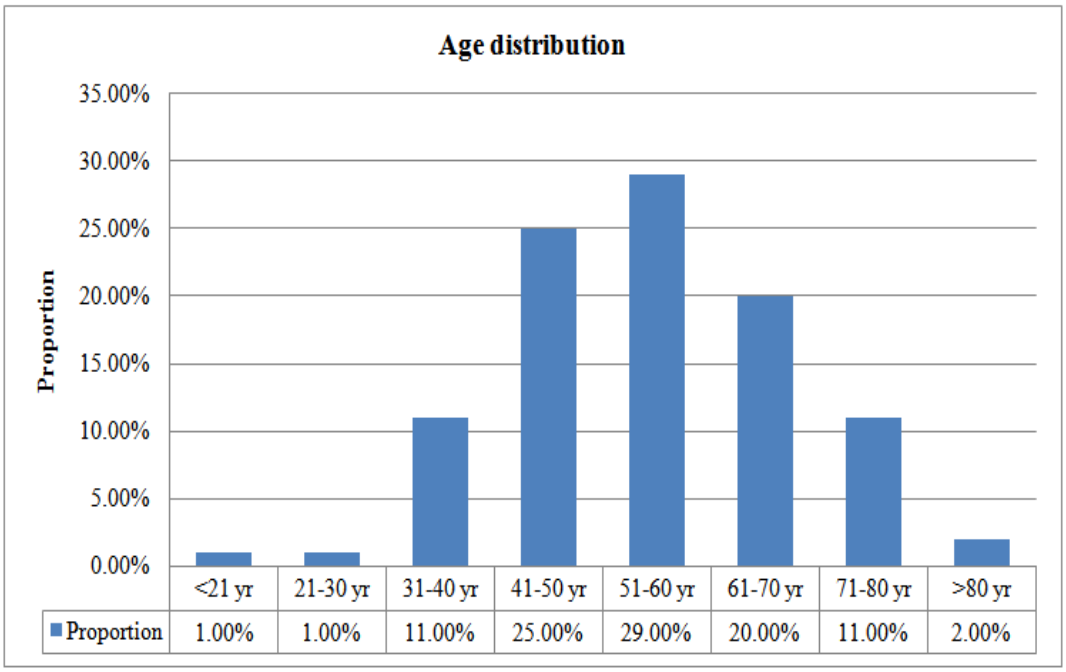
These cases were excluded from the study.

A neoplastic pleural effusion was defined as an effusion due to an underlying malignancy. It can be a malignant or paramalignant effusion. Malignant effusions were diagnosed when pleural biopsy specimens or pleural fluid cytology specimens were conclusively positive for malignancy. Paramalignant effusions were diagnosed when pleural biopsy specimens or pleural fluid cytology specimen were negative and other known causes of the pleural effusions were also excluded in patients with a histology proven malignancy elsewhere, for example, by percutaneous or image (CT) guided lung biopsy or trans-bronchial lung biopsy or percutaneous needle aspiration or biopsy from peripheral lymph nodes or nodular lesion.

Data were analysed as mentioned above.

III. Results

Total 84 patients were divided in their age group in decades. This distribution shows majority was in 5th and 6th decades. Among total 84 malignancy patients, 45 patients (53.57%) were male and 39 patients (46.43%) were female. Twenty five patients were smokers. Among them 24 patients were male and one patient was female. Odds ratio was 3.39.



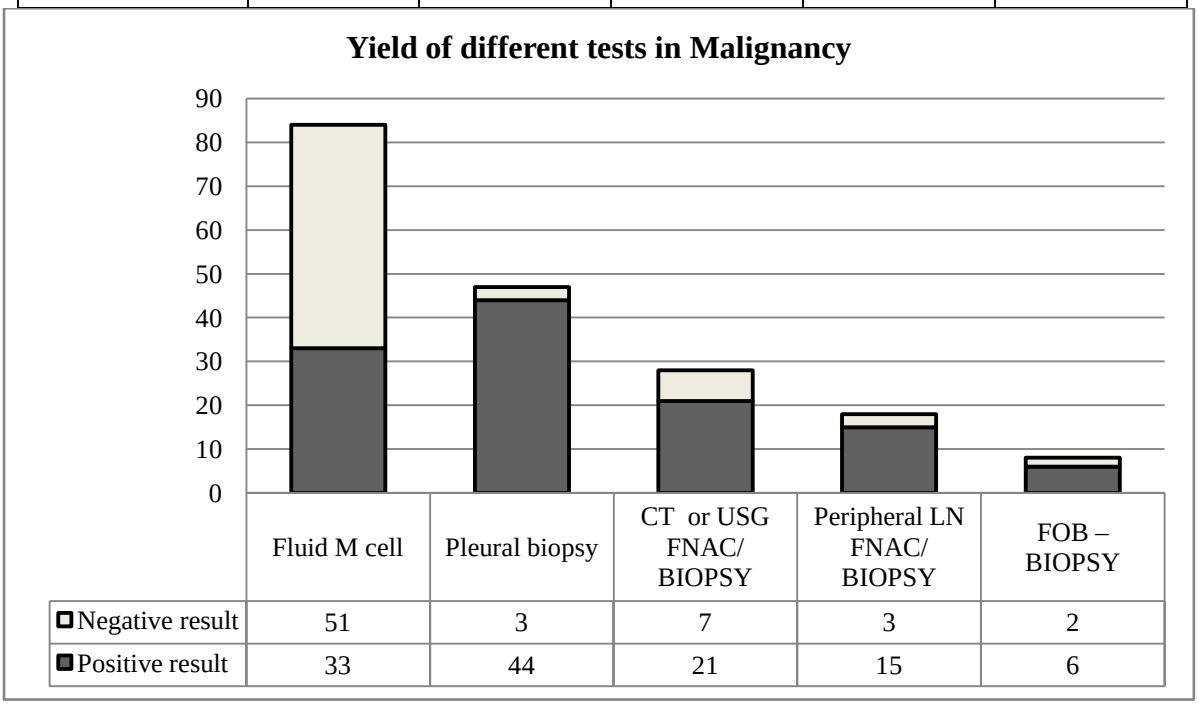
Among the 84 malignancy cases 48 patients (57.14%) had massive pleural effusion, 31 patients (36.90%) had moderate amount and 5 patients (5.95%) had mild pleural effusion. Twenty one patients (25%) had one or more palpable peripheral lymph nodes. Among 84 neoplastic pleural effusion 73 (86.90%) were lymphocytic, 11 (13.10%) were neutrophilic. Among 84 malignancy cases all was evaluated for fluid malignant cell for total 3 occasions. Of them 44 patients were undergone pleural biopsy. From above analysis there were 56 malignant effusions and 28 paramalignant effusions. Proportion of malignant effusion in malignancy is 66.67%. In malignancy, 74 patients (88.10%) patients had ADA < 40, 9 patients (10.71%) had ADA level in between 40 – 70 IU/L, and 1 patient (1.19%) had ADA > 70 IU/L.

Yield of different diagnostic modalities in pleural effusion in malignancy is as follows:

Pleural biopsy has 93.62% yield. Yield in FNAC or Biopsy from peripheral Lymph node or nodule was 83.33%. Yield in both image (CT or USG) guided FNAC of biopsy from lung mass and Flexible bronchoscopic biopsy from endobronchial lesion was 75%. Twenty one patients was undertaken for diagnostic bronchoscopy. Among them, 8 patients revealed endobronchial lesion. Yield in pleural fluid cytology study for malignant cell was 39.29%.

TABLE: Yield of different tests in Malignancy

	Fluid M cell	Pleural biopsy	CT or USG FNAC/ BIOPSY	Peripheral LN FNAC/ BIOPSY	FOB – BIOPSY
Positive cases	31	44	22	15	6
Total cases	84	47	28	18	8
Yield(%)	36.90	93.62	78.57	83.33	75



Various tests were evaluated and it showed, 95% CI mean (range) was for: Fluid M cell: 39.28% (28.80% – 50.54%), Pleural biopsy: 93.61% (82.46% - 98.66%), CT of USG guided FNAC or biopsy: 75% (55.12% - 89.30%), Peripheral Lymph node FNAC or biopsy: 83.33% (58.58% - 96.42%) and Bronchoscopy and biopsy: 75% (34.91% - 96.81%).

TABLE: 95% confidence interval of yields of various tests in malignancy

	Mean(%)	95% confidence interval
Fluid M cell	39.28	50.54 - 28.80
Pleural biopsy	93.61	98.66 - 82.46
CT or USG FNAC/ BIOPSY	75.00	89.30 - 55.12
Peripheral LN FNAC/ BIOPSY	83.33	96.42 - 58.58
FOB – BIOPSY	75.00	96.81 - 34.91

Complications:

Among the tests performed most common complication was Haemoptysis (14.28%) following Bronchoscopy which was managed conservatively. Pleural biopsy had following complications: development of Hydropneumothorax (6.81%), Vasovagal attack during procedure (4.45%) and development of empyema (2.27%). Image guided FNAC or biopsy and FNAC or Biopsy from peripheral lymph node or nodule showed no complication under the study population.

Etiology:

Etiology of malignancy was as follows. Metastasis from primary lung malignancy in 73 (86.9%) patients, other metastatic malignancy in 5 (5.95%) patients. Among primary lung malignancy the number of cases are: 33 Adenocarcinoma (39.29%), 19 squamous cell carcinoma (22.62%), 16 Undifferentiated NSCLC (19.05%), 4 small cell carcinoma (4.476%) and 1 fibrosarcoma (1.19%).

TABLE: Etiological distribution of effusion.

			Total cases:
Primary lung malignancy 86.9% (n= 73)	Adenocarcinoma	33(39.29%)	**84**
	Squamous cell carcinoma	19(22.62%)	
	Undifferentiated NSCLC:	16(19.05%)	
	Small cell carcinoma:	4(4.76%)	
	Fibrosarcoma	1(1.19%)	
Metastasis from other sites, 5.95% (n= 5)	Breast carcinoma	3(3.57%)	
	Thyroid carcinoma	1(1.19%)	
	Cervical carcinoma	1(1.19%)	
Pleural malignancy (Malignant mesothelioma)		1 (1.19%)	
Lymphoma		4 (4.76%)	
Other rare malignancy (Desmoid fibromatosis)		1 (1.19%)	

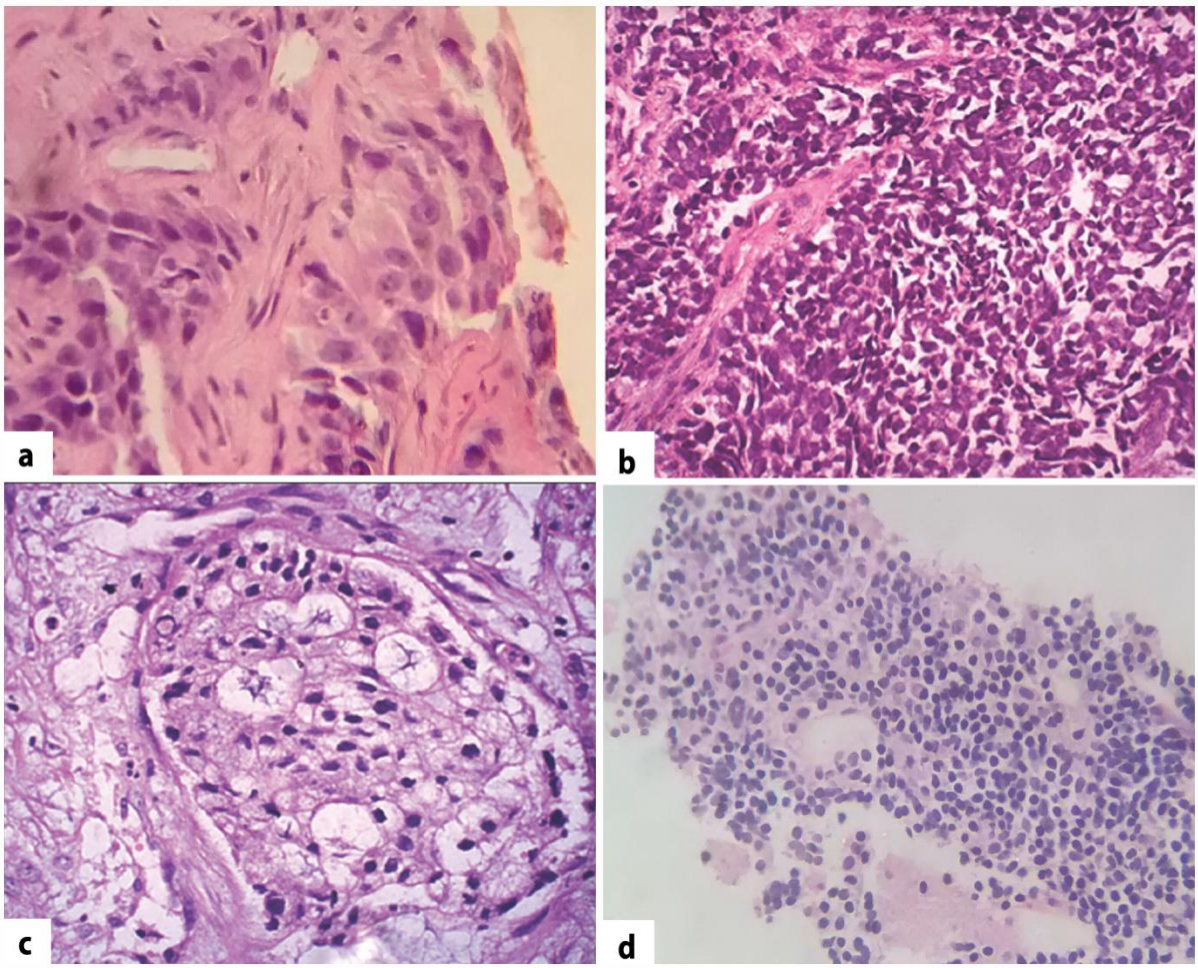
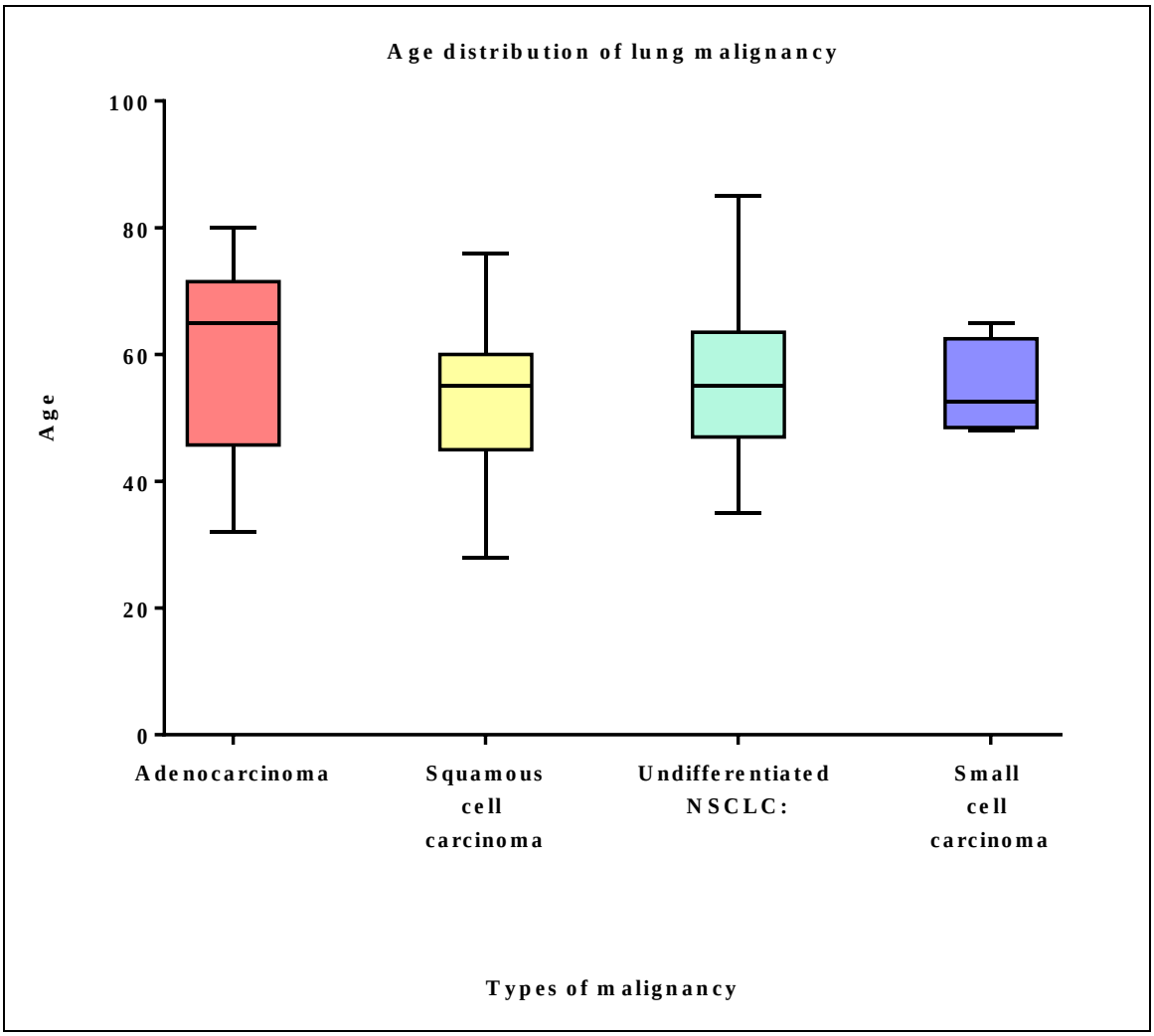


FIGURE: Pleural biopsy slides microscopy in 400x magnification prepared from different aetiology of pleural effusion. a. Undifferentiated NSCLC, b. Small cell carcinoma, c. Adenocarcinoma, d. Lymphoma.

Among primary lung malignancy, Adenocarcinoma had mean age 60.17 (± 14.99) years, squamous cell carcinoma had mean age 54.05 (± 11.90) years, undifferentiated non small cell carcinoma had mean age 55.68 (± 11.81) years and small cell carcinoma had mean age of 54.5 (± 7.59) years.

TABLE : Aetiological classification and age group in Primary lung malignancy

Age	**Adenocarcinoma**	**Squamous cell carcinoma**	**Undifferentiated NSCLC:**	**Small cell carcinoma**
Range(years)	32 – 80	28 – 76	35 – 85	48 - 65
Mean ± SD	60.17 ± 14.99	54.05 ± 11.90	55.68 ± 11.81	54.5 ± 7.59



Median time span of diagnosis was 4 days in cytology based studies, 9 days in biopsy based studies and 16 days if IHC was combined from the day of admission.

IV. Discussion

Neoplastic Pleural effusion is often becomes diagnostic challenge. Hospitalised patients with suspected neoplastic pleural effusion often undergo battery of investigations before reaching the final diagnosis.

Our study included 84 adult cases of neoplastic pleural effusion requiring hospitalisation in a tertiary care hospital. Among them 45 were male (53.57%) and 39 were female (46.43%). Male:female ratio was 1.15:1. Two similar studies, conducted by Mehta AA et al. and Maji et al. in India are worth mentioning here. One of them[9] showed male : female ratio of 410:165 (2.63:1) and the other[10] showed the ratio as 3:1. Both of them showed that in all age groups, male patients are more than female. Our findings are consistent with this finding. Patients were maximally affected in 5th and 6th decade (41 to 60 years of age).

The mean age (± SD) in malignancy, in our study, is 55.55 (± 13.47) years. Previous studies[9,10] showed the age group (± SD) in malignancy is 61.6 - 63 (± 12 -13.48) years. Our study findings are comparative with these studies. Other findings evident from the above table are as follows. Among patients with malignancy 29.76% were smoker. The finding was statistically significant (p= 0.0359) and Odds ratio was 3.39. Peripheral lymph node was present in 25% patients (n=21). Pleural fluid tended to be massive in malignancy (57.14%). Our study is consistent with what Maher GG et al.[11] has stated previously that massive or near massive effusions are most commonly malignant.

Present study revealed, among neoplastic cases majority was metastasis from primary lung malignancy (86.9%). Adenocarcinoma was the most common (39.29%) followed by squamous cell carcinoma (22.62%), undifferentiated NSCLC (19.05%), small cell carcinoma (4.76%) and fibrosarcoma (1.19%). There is also

metastasis from other sites like: breast carcinoma (3.57%), cervical carcinoma (1.19%) and thyroid carcinoma (1.19%). Previous studies[9,10] also demonstrated that the adenocarcinoma of lung was the most common cause of neoplastic pleural effusion followed by squamous cell carcinoma, small cell carcinoma and large cell carcinoma and metastasis also occurred from other sites like: breast cancer, cervical cancer, ovarian cancer, colon cancer, gastric cancer, oesophageal cancer, testicular malignancy and lymphoma.

The present study showed that pleural fluid cytology in malignancy had yield of 39.29%. In malignancy cases pleural biopsy had 93.62% yield in our study. In the context of earlier studies pleural biopsy had 45-80% yield[12]. This high yield in our study is probably due to focussed selection of cases, taking six or more biopsy samples (in comparison with previous studies where 4-6 samples were taken) and use of IHC for confirmation of pathological subtypes in selected cases.

In malignancy, image guided (CT or USG) FNAC or Tru-cut biopsy from lung mass had 75% yield, FNAC or biopsy from peripheral lymph node or other nodules had 83.33% yield, and flexible bronchoscopsy guided biopsy had yield of 75%. Maji et al.[9] had shown the yields as 77.6% in CT guided FNAC and 84.6% in FOB biopsy. This finding is comparable.

Diagnostic modalities used in our study had minimal complication rate. Mild haemoptysis was seen following flexible bronchoscopy in 14.28% cases and none required any major management. Iatrogenic hydropneumothorax was seen in 6.81% cases following pleural biopsy, one case needed palliative aspiration. However none of these patients required tube thoracostomy for management of complication. The other complication included development of empyema following pleural biopsy in 1 patient (2.27%) who was an immunocompromised case of CKD being treated with maintenance haemodialysis.

In literature it is stated that the most frequent complication after a closed pleural biopsy is pneumothorax. However, the incidence of pneumothorax and the requirement for tube thoracostomy are comparable after thoracentesis and pleural biopsy[13]. Second most complication is bleeding causing haemothorax[14]. There is also one case report of an arteriovenous fistula from an inter-costal artery to an intercostal vein developing after pleural biopsy[15]. In our study we did not observe any such complication.

V. Conclusion

To conclude, neoplastic pleural effusions require multiple diagnostic modalities to reach the etiology. Closed pleural biopsy using Cope needle revealed high yield in evaluation in neoplastic pleural effusion. Complication rate is low. Average time of diagnosis is 8.5 days.

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