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Original Research Article

A Cross Sectional Study on Lung Cancer with Pleural Effusion

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Conflict of interest: Nil

Abstract:

Background: Primary lung cancers are frequently complicated by pleural effusion which can be either malignant pleural effusion (MPE) or paramalignant effusion.

Aim: To study cases of lung cancer with pleural effusion at presentation and to ascertain the etiology of pleural effusion in these cases. The study also attempts to compare these patients with lung cancer cases without pleural effusion at presentation.

Materials and Methods: The present study was an institution based cross-sectional observation study, conducted in a tertiary care hospital in southern India for a period of 6 months. 30 consecutive patients diagnosed to have lung cancer who had pleural effusion at presentation were selected for the study. Another 30 cases of lung cancer but without pleural effusion at presentation were included for comparison with the main group i.e., lung cancer with pleural effusion.

Result: Majority of the cases of lung cancer with pleural effusion at presentation were in the age group of 50-69 years. Most pleural effusions were lymphocytic with low ADA and low glucose. Pleural fluid cytology was positive for malignant cell in 50% cases in our study. Adenocarcinoma and Squamous cell carcinoma were the most common in patients of lung cancer presenting with and without pleural effusions, respectively.

Conclusion: Pleural effusion in malignancy are mostly moderate/massive, homolateral, lymphocytic, exudative with low ADA. Cytological analysis of pleural fluid sample collected on three consecutive days and cell block study increase the yield of malignancy considerably. A pleural effusion in the setting of lung cancer usually implies a malignant pleural effusion however a small percentage of these patients may have a paramalignant effusion or effusion of other causes requiring individualized management.

Keywords: Lung Cancer, Malignant Pleural Effusion, Paramalignant Effusion.

Introduction

Primary lung cancers are frequently complicated by pleural effusion which can be either malignant pleural effusion (MPE) or paramalignant effusion. Paramalignant effusions have no evidence of direct involvement of pleura with tumour and are likely caused by lymphatic obstruction, atelectasis, and trapped lung and rarely due to systemic effects of the tumour and adverse effects of therapy. [1]

According to American Joint Committee on Cancer (AJCC) staging of lung cancer, the presence of a malignant effusion upgrades the staging of a lung tumor of any size to M1a, and thus stage IV. In the few patients with paramalignant effusion, clinical judgment may dictate exclusion of the effusion as a staging element and the tumour be classified as M0 with appropriate management including need for curative surgery.

With this background, the present study was undertaken with the objective to study cases of lung cancer with pleural effusion at presentation and to ascertain the etiology of pleural effusion in these cases. The study also attempts to compare these patients with lung cancer cases without pleural effusion at presentation.

Materials and Methods:

The present study was an institution based cross-sectional observation study, conducted in a tertiary care hospital in southern India for a period of 6 months. 30 consecutive patients diagnosed to have lung cancer who had pleural effusion at presentation were selected for the study. Another 30 cases of lung cancer but without pleural effusion at presentation were included for comparison with the main group i.e., lung cancer with pleural effusion. Patients with pleural effusion due to malignancies other than those of the lung were excluded from the study. Informed consent was taken from all the study participants.

Once included in the study, the patients underwent elaborate history taking and physical examination. The records of all the 60 patients were analyzed with respect to age, sex, addiction status and clinical presentation. Hematological investigations and chest X rays were done in all patients. Two samples of sputum were tested for acid-fast bacilli and sputum samples were sent on three consecutive days for cytology. In patients with clinical or radiological evidence of pleural effusion, the size of the effusion at the time of presentation was classified as mild, moderate and severe, based on chest X ray PA view. Effusion noted upto 4th, upto 2nd& above 2nd rib anteriorly were classified as mild, moderate and massive, respectively. A diagnostic pleural fluid tap was done and analysed for cell type, cell count, protein, sugar, lactate dehydrogenase (LDH) and adenosine deaminase (ADA). 40 - 50 ml pleural fluid was sent on 3 consecutive days for Papanicoulau (PAP) stain and a separate 150 ml sample was sent in each patient for cell block study for malignant cells. Closed pleural biopsy with Abrams needle was done in cases in which the pleural fluid cytology was negative for malignancy.

After repeated therapeutic thoracocentesis, contrast enhanced computer tomography (CECT) of the thorax was done and analysed in three aspects – the lung primary, the pleura and the mediastinum. Histopathological diagnosis was established by relevant sampling (bronchoscopic biopsy, image guided FNAC/biopsy or peripheral lymph node sampling).

In our study, the effusions were segregated into 5 groups based on etiology – malignant pleural effusion (MPE), paramalignant effusion (PME), tubercular (TB), indeterminate and others. The pleural effusions which were secondary to post obstructive pneumonia and those cases of exudative pleural effusion with extensive mediastinal lymphadenopathy and invasion have been grouped as paramalignant effusion[9]. This was so done because autopsies have indicated that impaired lymphatic drainage from the pleural space is the predominant mechanism for the accumulation of fluid associated with malignancy: a strong relationship was found between carcinomatous infiltration of the mediastinal lymph nodes and the occurrence of pleural effusion. Those cases of exudative effusion where there was no extensive mediastinal invasion or any other definitive cause for the effusion have been grouped as indeterminate.

All the data was entered in a Microsoft excel sheet and analysed using the Epi Info 7 software, Centers for Disease Control and Prevention, Atlanta, GA, USA. 95% confidence intervals (CI) are presented where deemed relevant.

Results & Analysis

Majority of the cases of lung cancer with pleural effusion at presentation (n=20, 66.67%) were in the age group of 50-69 years (54.43 ± 13.3 years; range 28-82 years). The male: female ratio was 1.1: 1. Among males, 94% (n=15) were smokers while in females 71.43% (n=10) were non-smokers but 28% (n=4) were addicted to smokeless tobacco forms. Distribution of cancer histology based on smoking status showed that squamous cell carcinoma (SqCC) was the most common (60%) type in tobacco (smoking or smokeless) addicts; while it was Adenocarcinoma (ADC) in case of non-addicts (71%).

The most common presenting symptoms were cough (83.33%), dyspnea (76.67%) followed by chest pain (50%) and hemoptysis (20%) for a mean (± SD) duration of 5.6 ± 2.8 months (median duration 5 months; range 2 – 12 months). A considerable number (n=5, 17%) of the patients had been misdiagnosed to have tuberculosis and prescribed anti tubercular drugs for the illness, prior to presentation at our department. 37% were underweight with hypoalbuminemia in one-third of the cases; Majority (63%) presented with Karnofsky performance status (KPS) ≤ 70 with supraclavicular lymphadenopathy in 47% (n=14), indicating late stage at presentation.

One patient was found to be sputum positive for acid fast bacilli (1+) and thus diagnosed to have dual pathology. Two patients had sputum positive for malignant cells, of which one was a case of centrally located squamous cell carcinoma with intrabronchial extension and the other was a case of Adenocarcinoma who had presented with bronchorrhea.

The findings of the pleural fluid analysis are shown in Table 1.

Table 1: Characteristics of Pleural Fluid in Our Study Population

Characteristic	Result Of Our Study
1. Size	Mild 3 (1%) Moderate 13 (43.33%) Massive 14 (46.67%)
2. Site	Unilateral 28 (93.37%) Bilateral 2 (6.67%)
3. Gross Appear-ance	Serous 12 (40%) Serosanguineous 9 (30%)

<table>
<tr><td></td><td>Hemorrhagic 8 (27%)
Pus 1 (3%)</td></tr>
<tr><td>4. Nature</td><td>Exudative 29 (96.67%)
Transudative 1 (3.33%)</td></tr>
<tr><td>5. Cell Type (Predominant)</td><td>Lymphocytic 26 (86.67%)
Neutrophilic 4 (13.33%)</td></tr>
<tr><td>6. Protein</td><td>Mean 4.6 g/dL (range 3-6.1 g/dL)</td></tr>
<tr><td>7. ADA (in IU/L)</td><td>< 30 23 (76.67%)
30-40 2 (6.67%)
> 40 5 (1.67%)</td></tr>
<tr><td>8. Glucose (in mg/dl)</td><td>Mean Glucose:
Overall (n=30) 61.93 ± 41.89
MPE (n=15) 58.93 ± 42.23
NON-MPE (n=12) 74.27 ± 41.83
Distribution Of Pleural Fluid Based on Etiology and Glucose Level
<table>
<tr><th>Etiology</th><th><60 mg/dl</th><th>>60 mg/dl</th></tr>
<tr><td>Overall</td><td>16 (53.33%)</td><td>14 (46.67%)</td></tr>
<tr><td>MPE</td><td>10 (66.67%)</td><td>5 (33.33%)</td></tr>
</table>
Probability of Mpe Based on Pleural Fluid Glucose Level
<table>
<tr><th>Glucose</th><th><60 mg/dl (n=10)</th><th>>60 mg/dl</th></tr>
<tr><td>MPE Probability</td><td>62.5%</td><td>36% (n=5)</td></tr>
</table></td></tr>
<tr><td>9. Pleural Fluid Positive for Malignant Cell</td><td>15 (50%)
Yield From 3 Consecutive Pleural Fluid Pap Stain Samples and Cell Block Study
<table>
<tr><td>Pleural Fluid Sample</td><td>% Extra Yield for Malignant Cells (N=15)</td></tr>
<tr><td>SAMPLE 1 (S1)</td><td>60 (n=9)</td></tr>
<tr><td>SAMPLE 2 (S2)</td><td>13.33 (n=2) **</td></tr>
<tr><td>SAMPLE 3 (S3)</td><td>6.67 (n=1) **</td></tr>
<tr><td>CELL BLOCK (CB)</td><td>20 (n=3) **</td></tr>
</table></td></tr>
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***After Exclusion of Effusion Due to Post Obstructive Pneumonia, ** excludes those cases which already tested positive for malignant cell in the previous samples.**

Cell block was found to be positive for malignant cell in all but one case where pleural fluid was found to be positive with pap stain. In one case, cell block could identify the cell type as metastatic adenocarcinoma. The CECT thorax findings in pleura which were found to be useful in predicting malignant pleural involvement were pleural nodularity, pleural thickening (>10 mm) and pleural irregularity, in descending order of significance in our study. The sensitivity, specificity and predictive values for malignant pleural involvement for each of these CT findings are tabularized in Table 2.

Table 2: Diagnostic Utility of Various Ct Findings in Pleura

CT Finding	Sensitivity	Specificity	PPV	NPV
Irregularity	13%	87%	50%	50%
Thickening	53%	73%	67%	61%
Nodularity	33%	100%	100%	60%

Appearance of primary and the percentage of cases of each histologic subtype is tabularized in table 3 .Also included are the percentages where CECT findings showed evidence of intrabronchial growth(IBG), bronchus cut off sign(BCS) and mediastinal lymphadenopathy(MLN). Anatomical distribution of the lung primary is shown in tables 3 and 4 (A & B).

Table 3. Radiological Presentation of Lung Cancer Cases with Pleural Effusion Based On Histology*

Histology	Mass Lesion	Nodule	CON/ GGO	HWCL	CAVITY	IBG / BCS	MLN
ADC (n=11)	36%	27%	18%	18%	0	0	45%
SqCC (n=16)	56%	0	0	37%	6%	25%	81%
NSCLC (n=2)	100%	0	0	0	0	0	0
SCLC (n=1)	100%	0	0	0	0	100%	100%

***n=30**

Table 4(A & B): Distribution of the Anatomical Location of the Primary: Central/Peripheral and Lobar Distribution

Table 4(A):

Histology	Central	Peripheral
ADC (n=11)	18%	82%
SqCC (n=16)	87%	13%
NSCLC (n=2)	50%	50%
SCLC (n=1)	100%	0

Table 4(B):

Histology	Upper Lobe	Middle Lobe	Lower Lobe	Whole Lung	Hilar
ADC (n=11)	27%	18%	27%	18%	9%
SqCC (n=16)	25%	6%	31%	25%	12.50%
NSCLC (n=2)	50%	0	50%	0	0
SCLC (n=1)	100%	0	0	0	0

In our study, 15 out of the 30 cases (50%) had malignant pleural effusion. Ten out of the fifteen non-MPE cases were found to have "paramalignant" pleural effusion, majority of which (n=7, 70%) had extensive mediastinal lymphadenopathy and mediastinal invasion and rest (n=3, 30%) had effusion secondary to post-obstructive pneumonia. Of the rest 5 cases, 1 case each were due to associated tuberculosis & congestive heart failure. The etiology could not be determined in 3 cases since they were cytologically and on pleural biopsy negative for malignancy, did not have extensive mediastinal lymphadenopathy or any other obvious explanation for the effusion. Distribution of lung cancer versus etiology of pleural effusion is depicted in table 5(A&B)

Table 5a: Histology-Wise Percentage Distribution of Cases Based on Etiology of Pleural Effusion

Histology	Etiology Of Effusion				
	MPE	PME	TB	CHF	Indeterminate
ADC (n=11)	91%	0	0	0	9%
SqCC (n=16)	31%	56%	6%	6%	0
NSCLC (n=2)	0	50%	0	0	50%
SCLC (n=1)	0	100%	0	0	0

Table 5b: Anatomical Location of Lung Primary In Case Of MPE & Non-MPE Cases

	Central	Peripheral
Overall	**18(60%)**	**12(40%)**
MPE	**5(33%)**	**10(67%)**
Non MPE	**13(87%)**	**2(13%)**

The histologic diagnosis was established by CT guided FNAC/ true-cut biopsy in majority (19 cases; 63.33%), followed by bronchoscopy-guided biopsy in five cases (16.67%), peripheral lymph node FNAC in four cases (13.33%) and lymph node biopsy in two cases (6.67%). The diagnostic yield for malignancy was 100% by the above procedures.

Comparison of Lung Cancer Patients with Pleural Effusion and Without Pleural Effusion

Table 6: Patients Profile

Profile	Lung Cancer + Effusion (N=30)	Lung Cancer – Effusion (N=30)
Age (Mean±SD)	54.43±13.3 Years	60.73±11.3 Years
M : F	1.1: 1	5: 1
U : R	1: 14	1: 6.5
KPS (Median, Mode)	70,70	70,70
% Prescribed ATT	17% (N=5)	23% (N=7)
Smokers: Non-Smokers	1.7: 1 (19: 11)	4: 1 (24: 6)
Smoking Pack Years (Mean)	17.8	17.6
Presenting Symptoms	Cough, Dyspnea, Chest Pain	Similar Presentation
Duration Of Symptoms at Presentation	Mean – 5.6 ± 2.8 Months (Median Duration 5 Months;	Mean- 3.6 ± 1.9 Months (Median Duration 3 Months;

	Range 2 – 12 Months)	Range 1- 9 Months).
Time Since Appearance of First Symptom to Final Histologic Diagnosis Of The Primary	5.2 ± 2.8 Months	3.8 ± 1.9 Months

Table 7: Comparison of Histology of the Lung Cancer in Patients with and Without Pleural

	EFFUSION +	MPE +	EFFUSION -
SqCC (in no.)	16	5	18
ADC (in no.)	11	10	8
SqCC : ADC (ratio)	1.5: 1	1: 2	2.25: 1

Discussion

In most series, lung cancer is the leading cause of malignant pleural effusion [2]. When patients with lung cancer are first evaluated, approximately 15% have a pleural effusion [3]. During the course of the disease, however, at least 50% of patients with disseminated lung cancer develop effusion.

Age distribution of our study sample of lung cancer cases with pleural effusion was similar to that of other Indian studies. However, the male: female ratio of our study population was much lower than the sex ratios of earlier studies [4].

With regards to clinical presentation, hemoptysis was mostly seen in patients who were found to have central lesions with intrabronchial extension. In many cases the supraclavicular lymph node was involved.

The ratio of smokers: non-smokers in the lung cancer with pleural effusion group was 1.7:1. When all 60 cases were considered, the ratio of smokers: non-smokers were 2.5:1 in accordance with previous studies [5].

A pleural effusion ipsilateral to the primary lesion is the rule in carcinoma of the lung. Also in three of four patients who present with carcinomatous involvement of the pleura, the pleural effusion is moderate to large. In our study too, most cases had unilateral moderate to massive effusion on the same side as primary

In our study, the appearance of pleural fluid was not found to have any significance in predicting malignancy [6]. It is often not appreciated that approximately 5% of pleural effusions in malignancy are transudates. These transudates are due either to concomitant congestive heart failure, atelectasis from bronchial obstruction, or the early stages of lymphatic obstruction. Sometimes, the total protein pleural fluid to serum ratio may be low, but the fluid qualifies as an exudate by lactic dehydrogenase (LDH) criteria alone. In our study, according to Lights criteria, all cases were found to be exudative. However one patient had clinical features suggestive of congestive cardiac failure with bilateral pleural effusion and when the serum and pleural fluid protein gradient was measured , it was found to be > 3.1 gm/dL and hence his case was finally classified as transudative . Again in three out of the 29 exudative cases, the ratio of pleural fluid to serum protein was <0.5. However, all three met the exudative criteria according to LDH ratio and absolute LDH value. All these three cases were later established as malignant pleural effusion (MPE). Most pleural effusions that meet exudative criteria by the LDH level but not by the protein level are malignant pleural effusions [7].

Most pleural effusions were lymphocytic with low ADA three out of four cases of neutrophilic effusion and 4 out of 5 cases of high ADA in our study, there were other reasons for the neutrophil predominance and increased ADA. Three of the cases had effusion due to post obstructive pneumonia and one case had effusion due to tuberculosis. The mean ADA is similar to the finding by Agrawal et al [8] and Mehta AA et al [9] reporting the median ADA of 24.12 ± 10.88 U/L and 18 U/L, respectively

In a third of patients with malignant pleural effusions at the time of diagnosis the glucose concentration is low (<60 mg/dL). The low glucose effusions have usually been present for several months, and are associated with a large tumour burden and fibrosis of the pleura and denote decreased survival. In our study, the presence of low glucose greatly increased the chance of having cytology positive for malignant cell.

Pleural fluid cytology was positive for malignant cell in 50% cases in our study, and it was clearly evident that the yield of malignant cells positivity increased significantly by analyzing three consecutive day samples and cell block. In the study on malignant pleural effusions by Agrawal et al [8], pleural fluid cytology was positive for malignant cells in 60% cases.

In CECT thorax the presence of pleural nodularity & pleural thickening indicates possibility of malignant pleural involvement. The distribution of the effusion in the 30 cases in our study according to histology clearly shows that in 50% cases (n=15) the effusion was malignant pleural effusion, with adenocarcinoma being the most common histologic subtype of the primary (66.7%), which is in accordance with earlier studies on malignant pleural effusion [10].

Among the 30 cases of lung cancer presenting with effusion, more than half the cases (60%) had centrally located primary tumor. However majority (67%) of the cases of malignant pleural effusion (n=15) had peripherally located primary and more in lower lobe.

When etiology of the effusion was analyzed according to histology, all but one case of ADC had malignant pleural effusion. Whereas, among SqCC cases, more than half (n=9, 56%) were paramalignant effusion and one (6%) each were due to TB & CCF. Only five cases (31%) were due to MPE & of these two cases had large space-occupying-lesion (SOL) with direct extension to the periphery and pleural space and one case it was a peripherally located SOL. We could not find any earlier study stating the distribution of the etiology of effusion histology-wise. On comparison with lung cancer cases with and without pleural effusion, it was noted that the latter had more female patients, with longer symptom duration and time to histologic diagnosis. Though SqCC was higher in lung cancer patients with pleural effusion, amongst patients with malignant pleural effusion, the number of ADC cases were twice that of SqCC; whereas amongst lung cancer patients without pleural effusion, the histologic predilection is reversed.

Conclusion

Pleural effusion in malignancy are mostly moderate/massive, homolateral, lymphocytic, exudative with low ADA. Cytological analysis of pleural fluid sample collected on three consecutive days and cell block study increase the yield of malignancy considerably. Pleural nodularity on CT increases the likelihood of the effusion being malignant.

Adenocarcinoma is the most common histological type associated with MPE whereas squamous cell carcinoma was more common in cases without effusion. In our study lung cancer cases with pleural effusion had more female patients, with longer symptom duration and time to diagnosis in comparison to those cases without effusion at presentation.

A pleural effusion in the setting of lung cancer usually implies a malignant pleural effusion however a small percentage of these patients may have a paramalignant effusion or effusion of other causes requiring individualized management.

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