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Original Research Article

The study of pleural diseases with special reference to cytopathology and histopathology

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Abstract

Diagnosis of pleural diseases creates difficulty due to overlapping cytopathological and histopathological feature of various benign and malignant conditions. However pleural fluid cytology and histopathology of closed pleural biopsy specimen are most commonly used procedure to diagnose various pleural diseases in developing country like India.

In present study, we gave emphasis on histopathological and cytopathological characteristic of various pleural diseases and evaluated the efficacy and correlated the pleural fluid cytology and histopathology of pleural biopsy in diagnosing various pleural diseases.

Keywords: Pleural disease, pleural fluid, cytology, histology.

1. Introduction

Primary and metastatic pleural neoplasms, and non-neoplastic pleural diseases, can have similar clinical, radiographic and gross features. However, treatment and prognoses of these diverse pleural conditions vary greatly. Accurate diagnosis of pleural disease is therefore extremely important, and histological interpretation of pleural lesions is vital to rendering an accurate diagnosis. Metastatic pleural neoplasm is the most common pleural neoplasm. Diffuse malignant mesothelioma, the most common primary pleural neoplasm, is extremely rare in India. Solitary fibrous tumour is the most common benign primary pleural neoplasm.[1] Pleural diseases most commonly manifeste as pleural effusions.

Pleural effusions have classically been divided into transudates and exudates with the help of biochemical analysis by applying Light's criteria.[7] By definition, a transudative pleural effusion develops when the systemic factors influencing the formation or absorption of pleural fluid are altered [2], In contrast, an exudative pleural effusion develops when the pleural surfaces or the capillaries in the location where the fluid originates are altered. The primary reason to differentiate transudates and exudates is that, if the fluid is a transudate, no further diagnostic procedures are necessary and therapy is directed to the underlying congestive heart failure, cirrhosis, or nephrosis. Alternately, if the effusion proves to be an exudate, a more extensive diagnostic investigation is indicated.

The following tests are useful in determining the cause of an exudative pleural effusion: appearance of the pleural fluid; smears and cultures of the pleural fluid; haematocrit and differential cell count of the pleural fluid; cytology of the pleural fluid; levels of adenosine deaminase, glucose, amylase and LDH in the pleural fluid; needle biopsy of the pleura; thoracoscopy; and perfusion lung scans.

The gross appearance of the pleural fluid should always be noted. Bloody pleural fluid suggests one of three diagnoses: malignancy, pulmonary embolization or trauma [3]. If the pleural fluid is turbid or milky or if it is bloody, the supernatant of the pleural fluid after centrifugation should be examined. If pleural fluid was turbid when it was originally withdrawn, but the supernatant is clear,

then the turbidity was due to cells or debris in the pleural fluid. Alternatively, if the turbidity persists after centrifugation, the turbidity was due to high lipid content.

The differential cell count is useful in determining the aetiology of the pleural fluid. When polymorphonuclear cells predominate, the patient has an acute process affecting the pleural surfaces. If there are concomitant parenchymal infiltrates, then the most likely diagnoses are parapneumonic effusion, pulmonary embolus or bronchogenic carcinoma. If there are no parenchymal infiltrates, the most likely diagnoses are pulmonary embolus, viral infection, gastrointestinal disease, asbestos pleural effusion or acute tuberculous pleuritis.[4] When mononuclear cells predominate in the pleural fluid, the patient has a chronic process involving the pleura. If there are more than a few mesothelial cells in the pleural fluid, it is quite unlikely that the patient has tuberculous pleuritis[5][6]. If the patient has predominantly small lymphocytes in the pleural fluid, tuberculosis and malignancy are the two most likely diagnoses [5][7].

If a patient has malignancy, cytological examination of the pleural fluid is a fast, efficient and noninvasive means by which to establish the diagnosis. The percentage of malignant pleural effusions which are diagnosed with cytology has been reported to be 40–87%[8-10]. There are several factors that influence the diagnostic yield with cytology. If the patient has a malignancy, but the pleural effusion has another aetiology, such as heart failure, pulmonary embolism, pneumonia, lymphatic blockade or hypoproteinaemia, the cytology will be negative. The frequency of positive cytological results also depends upon the tumour type. The yield is less with squamous cell carcinoma, Hodgkin's disease and sarcomas. The yield will be increased if both cell blocks and smears are prepared [10] and if more than one specimen is submitted[7]. Measurement of the ADA level in pleural fluid is diagnostically useful because ADA levels tend to be higher in tuberculous pleural effusions than in other exudates.

The primary two diagnoses that can be established with needle biopsy of the pleura are tuberculosis and malignancy. With tuberculous pleuritis, the initial needle biopsy is positive for granulomas in 50–80% of patients[11-13]. A specimen of the pleural biopsy should also be cultured for mycobacteria, since the cultures may be positive when microscopy of the biopsy is negative[14]. The combination of microscopy and culture of the pleural biopsy should provide a positive diagnosis in more than 80% of patients with tuberculous pleuritis. If the initial biopsy is nondiagnostic and the patient has tuberculous pleuritis, a second biopsy will be positive 10–40% of the time [12] As mentioned above, the diagnosis of tuberculous pleuritis can also be made noninvasively by demonstrating a high (>45 $U \cdot L^{-1}$) level of ADA in the pleural fluid[15].

Cytological examination of the pleural fluid establishes the diagnosis of pleural malignancy more frequently than does needle biopsy of the pleura. The reported incidence of positive pleural biopsies ranges 39–75% [12,16,17], and probably averages about 45%. The explanation for the relatively lower yield with pleural biopsy than with cytology is that the parietal pleura is involved later in the course of the disease than is the visceral pleura, and the involvement of the parietal pleura is frequently patchy[18].

Metastases to the pleura occur much more frequently than primary pleural neoplasms. Metastases to the pleura exhibit characteristics, including pleural effusions, pleural thickening and pleural-based masses, found with primary pleural neoplasms and reactive pleural processes. Common metastases to the pleura include lung cancer, lymphoma and breast cancer; however, malignancies from any primary may metastasize to the pleura.[2] Adenocarcinoma represents the most frequent histologic type of lung cancer to result in a malignant pleural effusion presumably because adenocarcinomas comprise a greater proportion of peripheral cancers than the other histologic types[19] followed by squamous, small cell, and large cell undifferentiated carcinomas. Depending on the anatomic site of the primary tumor, infiltration of the pleura can result from direct invasion of the visceral pleura by an underlying lung cancer or, alternatively, infiltration into the subpleural lymphatic plexus or from invasion of small branches of the pulmonary artery, with embolism of tumor cells to the periphery of the lung where they can then invade the visceral pleura. In general, pleural metastatic deposits are a marker of advanced disease.[20] It is noteworthy that the most recent (7th edition), American Joint Committee on Cancer (AJCC) Staging Manual has reclassified lung cancer patients with pleural invasion from stage IIIB (T4) to stage IV (M+). It further separates metastatic lung cancer into two groups, pleural metastases (M1a) and other visceral metastases (M1b). The AJCC Cancer Staging Manual's reclassification is based on significant survival differences; it notes that patients with pleural dissemination of lung cancer, either as a pleural nodule or as a malignant pleural effusion, exhibit similar survival as patients with contralateral lung nodules; and that patients with distant metastases exhibited significantly worse survival.[21]

In developing countries, TB pleuritis is significantly more common than in the developed

countries. As pleural effusion is the most common manifestation of pleural diseases, thoracocentesis is the first diagnostic procedure employed for evaluation of pleural fluid. Thoracocentesis usually not performed in patients with secure diagnosis like congestive heart failure except clinical situation worsens or is atypical. A definitive diagnosis can only be established by pleural fluid analysis in a limited number of diseases that include empyema, malignancy, chylothorax, rheumatoid pleurisy etc.[18]

In the present study, malignant pleural involvement was more common than tuberculosis. Pleural fluid cytology and closed needle pleural biopsy are most commonly used procedure to diagnose various pleural diseases in developing country like India, where the facilities of thoracoscopy and imaging guided cutting needle pleural biopsies are not easily available.

The present study evaluates the efficacy of pleural fluid cytology and closed neddle pleural biopsy in diagnosing pleural diseases and according to our study both the investigations had moderate to high diagnostic yield especially when performed together

2. Materials and Methods

This study was carried out in indoor patients who were presented with pleural disease (clinically and radiologically) and sample of pleural fluid and/or pleural tissue were sent to department of pathology, I P G M E & R, Kolkata. Cytopathological examination of pleural fluid and histopathological examination of pleural tissue was performed to achieve an etiological diagnosis. A total 100 patients were evaluated. Profile of various pleural diseases was analysed by descriptive statistics. Cytopathology and histopathology in etiological diagnosis of various pleural diseases was determined and compared using appropriate statistical analysis.

3. Results and Analysis

The present study includes total 100 cases with pleural diseases.

3.1 Clinical Parameters

Table 1: Age and Sex Distribution

Age Group	Male	Female	Total	Percentage
<11 Yrs	1	0	1	1%
11-20 Yrs	3	6	9	9%
21-30 Yrs	3	4	7	7%
31-40 Yrs	2	7	9	9%
41-50 Yrs	9	6	15	15%
51-60 Yrs	16	11	27	27%
61-70 Yrs	13	7	20	20%
71-80 Yrs	8	2	10	10%
81-90 Yrs	2	0	2	2%
Total (%)	57 (57%)	43 (43%)	100	100%

From Table-1, it can be stated that, there were 57 male and 43 female patients that means among total patients 57% were male and 43% were female. The male female ratio was 1.33:1. Youngest patient and oldest patient of the study were an 8 months old male and 90 years old male. Most common age group with pleural diseases were 51 to 70 years. Total 47 patients (47% of total population) were in this group.

Table 2: Presenting symptoms

Symptoms	No. of Patients (n = 100)	Percentage
Chest pain	44	44%
Cough	63	63%
SOB	60	60%
Fever	28	28%
Hoarseness of voice	5	5%
Heaviness of chest	6	6%
Dysphagia	1	1%
Weight loss	13	13%
Loss of appetite	8	8%
Puffiness of face	5	5%
Lower limb swelling	10	10%
Hemoptysis	3	3%

Cough (63%) and shortness of breath (60%) were the most common symptoms followed by chest pain (44%) and fever (28%). Weight loss, lower limb swelling, loss of appetite were seen in minority of patients. In majority of cases presence of multiple symptoms were seen.

3.2 Radiological parameters

Table 3: Pleural lesion by site and sex

Sex	Site			Total (%)
	Right Sided Pleura (%)	Left Sided Pleura (%)	Bilateral Pleura (%)	
Male	29 (29%)	19 (19%)	9 (9%)	57 (57%)
Female	18 (18%)	16 (16%)	9 (9%)	43 (43%)
Total	47 (47%)	35 (35%)	18 (18%)	100 (100%)

In this study the most of the pleural lesions involved the right side (47%) alone in both sex. The left side is involved in 35% of cases and bilateral involvement was seen in 18% of cases.

Table 4: Radiological presentation of the lesions

Type of pleural lesion	No. of cases	Percentage (%)
Pleural effusion	85	85%
Hydropneumothorax	5	5%
Pleural thickening	16	16%
Pleural nodule	7	7%
Pleural deposit	3	3%
Pleural mass	3	3%

In this study, the most common type of lesion radiologically was pleural effusion (85%). Pleural thickening and pleural nodule were found in 16% and 7% cases respectively. 3% of cases were presented with pleural mass. Some cases have more than one pleural lesion.

Table 5: Gross appearance of pleural fluid (n=90)

Age (years)	Appearance of pleural fluid				Total (%)
	Haemorrhagic (%)	Straw (%)	Pus (%)	Clear (%)	
≤ 20	1 (1.11%)	5 (5.56%)	3 (3.33%)	0	9 (10%)
21-40	5 (5.56%)	4 (4.44%)	1 (1.11%)	0	10 (11.11%)
41-60	14 (15.56%)	24 (26.67%)	1 (1.11%)	1 (1.11%)	40 (44.45%)
61-80	12 (13.33%)	17 (18.89%)	0	0	29 (32.22%)
≥ 81	2 (2.22%)	0	0	0	2 (2.22%)
Total	34 (37.78%)	50 (55.56%)	5 (5.56%)	1 (1.1%)	90 (100%)

Table 5 shows distribution of pleural fluid according to their appearance in different age groups. Majority of the pleural fluids were straw in colour (55.56%) followed by haemorrhagic pleural effusions (37.78%). Pus was aspirated in only 5 cases (5.56%). Majority of straw colured effusions (26.67%) were seen in between the age of 41 to 60 years. Occurrence of haemorrhagic effusion is almost similar in both the age groups of 41 – 60 years (15.56%) and 61 – 80 years (13.33%).

Table 6: Type of pleural effisions (n=90)

Type of pleural effusion	Sex		Total
	Male	Female	
Exudative	51 (57%)	38 (42%)	89 (99%)
Transudative	1 (1%)	0 (0%)	1 (1%)
Total	52 (58%)	38 (42%)	90 (100%)

Table 6 shows distribution of type of pleural effusions that means exudative or transudative by applying light's criteria. 99% of pleural effusions were exudative as local pleural disease causes exudative pleural effusions and only one (1%) case was transudative pleural effusion which was not responding to treatment and turned out to be a case of tuberculosis.

Table 7: Spectrum of pleural Diseases

Diagnosis					No. of Patients	Percentage
Non-neoplastic	Tuberculosis				18	18%
	Non-specific inflammation				10	10%
	Bacterial infection				2	2%
	Parapneumonic effusion				1	1%
	Pleural fibrosis				1	1%
Neoplastic	Primary	MPNST			1	1%
		Schwannoma			1	1%
		Castleman's Disease			1	1%
	Secondary	Metastasis	Lung CA	Adenocarcinoma	32	32%
				Squamous cell carcinoma	6	6%
				Large cell carcinoma	2	2%
				Pleomorphic carcinoma	1	1%
				Type not ascertained	8	8%
			Lymphoma		3	3%
			Hepatocellular CA		1	1%
			breast CA		1	1%
			ovarian CA		1	1%
			oesophageal CA		1	1%
			unknown primary		3	3%
		Direct Involvement		Malignant clear cell epitheloid tumor with myoepithelial phenotype	1	1%
				Large cell carcinoma lung	1	1%
				Mucinous bronchogenic carcinoma	1	1%
				Pleomorphic carcinoma lung	1	1%
Diagnosis not made					2	2%
Total					100	100%

Table 7 reveals spectrum of pleural diseases in the study population (n = 100). Ultimate diagnosis was achieved either by microscopic exanimation of pleural fluid, pleural tissue or by other means of investigations like guided FNAC or biopsy of associated lung lesion, response to therapy specially in cases of tuberculosis, microbiological investigations etc.

32% cases were diagnosed as non-neoplastic pleural lesion among them tuberculosis (18%) was the most common followed by non specific inflammation

of pleura (10%). Pleural fibrosis was noted in one case.

66% cases showed neoplastic involvement of pleura. Secondary involvements either by metastasis or by direct involvement were the most common among pleural neoplasia. Adenocarcinoma lung was the most common (32%) primary which leads to secondary involvement of pleura. This is followed by SQUAMOUS cell carcinoma lung (6%) and large cell carcinoma lung (2%). Lymphoma was the second most common primary following lung carcinoma which causes secondary pleural neoplasm. Among others secondary from breast carcinoma (1%), ovarian carcinoma (1%), oesophageal carcinoma (1%) and hepatocellular carcinoma (1%) were also reported. Type of primary in case of secondary involvement of pleura was unknown in 3% cases. 4% cases showed direct involvement of pleura by adjacent tumors, among them 3 cases were lung carcinoma and one case was mediastinal neoplasm (Malignant clear cell epitheloid tumor with myoepithelial phenotype). Primary pleural neoplasm was seen in only 3% cases. Primary pleural lesions were primary pleural malignant spindle cell neopasm, Schwannoma, and Castleman Disease each comprising of single case. Ultimate diagnosis was not achieved in 2% cases.

Table 8: Distribution of pleural disease and appearance of pleural fluid

Appearance of pleural fluid	Pleural disease			Total
	Tuberculosis	Malignancy	Others	
Haemorrhagic	3	28	3	34
Straw coloured	12	31	7	50
Pus	2	1	2	5
Clear	1	0	0	1
Total	18	60	12	90

Among 90 cases of pleural effusion (including 5 cases of hydropneumothorax) 60 cases were diagnosed as malignant effusions and 18 cases were diagnosed as tuberculosis. Out of 34 haemorrhagic pleural effusions 28 (82.35%) cases were malignant effusions and among 56 cases of non haemorrhagic pleural effusion 32 (57%) were malignant. 3 cases of tuberculosis presented as haemorrhagic pleural effusion.

Table 9: Distribution of pleural fluid total WBC count in pleural diseases

Total WBC count (/cumm)	Malignant pleural effusion	Tubercular effusion	others	Total
0-500	21 (23.3%)	6 (6.7%)	9(10%)	36 (40%)
501-1000	22 (24.4%)	4(4.4%)	1(1.1%)	27(30%)
> 1000	17(19%)	8(9%)	2(02%)	27(30%)
Total	60 (66.67%)	18 (20%)	12 (13.33%)	90 (100%)

Table 9 shows distribution of total wbc count in various pleural diseases. Cases of malignant pleural effusion had almost equal distribution in the three group of total WBC count range. 8 cases (44.44%) out of 18 cases of tubercular effusion showed total WBC count >1000. Benign conditions other than tuberculosis in most of the cases (75%) had total leukocyte count within the range of 0 – 500/cumm.

Table 10: Distribution of pleural fluid lymphocyte percentage in pleural diseases

Lymphocyte count (%)	Pleural diseases			Total
	Malignant effusion	Tubercular effusion	Others	
0-50%	13	2	5	20
51-70%	14	3	4	21
71-100%	33	13	3	49
Total	60	18	12	90

Among 18 cases of tuberculous pleural effusion 13 cases (72%) had > 70% lymphocyte differential count in pleural fluid, whereas most of the non-tubercular benign pleural effusions (75%) had differential lymphocyte count <70%. 33 cases (55%) out of 60 cases of malignant pleural effusions showed > 70% lymphocytes in pleural fluid.

Table 11: Pleural fluid cytology in malignant pleural effusion (n = 60)

Pleural fluid cytology interpretation	No. of patients	Percentage
Positive for malignancy	28	47%
Suspicious of malignancy	11	18%
Negative for malignancy	21	35%

Table 12: Diagnostic yield of pleural fluid cytology in cases of malignant pleural effusion

Pleural fluid cytology		95% Confidence interval
Sensitivity	65%	51.6%-76.9%
Specificity	96.67%	82.8%-99.9%
Positive predictive value	97.5%	86.8%-99.9%
Negative predictive value	58%	43.2 %-71.8%
Diagnostic Accuracy	75.56%	65.16%-83.74%

In present study pleural fluid cytology was positive for malignancy in 47% cases and suspicious of malignancy in 18% cases of malignant pleural effusion and it had 65% sensitivity, 96% specificity and 75.56% accuracy in diagnosing malignant pleural effusion.

Table 13: Result of closed needle pleural biopsy in pleural diseases (n = 32)

Pleural biopsy yield in malignant pleural diseases	95% confidence interval
Sensitivity	72.7%	49.78%-89%
Specificity	100%	69%-100%
Positive predictive value	100%	79.4%-100%
Negative predictive value	62.5%	35.4%-84.8%

Table 14: Yield of closed needle pleural biopsy histopathology in malignant pleural diseases (n = 22)

Pleural biopsy yield in tubeucular pleural diseases	95% confidence interval
Sensitivity	85.70%	42%-99.6%
Specificity	100%	86.2%-100%
Positive predictive value	100%	54%-100%
Negative predictive value	96.15%	80%-99.9%

Table 15: Yield of closed needle pleural biopsy in tubercular pleural involvement (n= 7)

Pleural Biopsy Result	Pleural diseases			Total
	Tuberculosis	Malignancy	Non-specific inflammation	
Positive	6	16	3	25
Negative	1	6	0	7
Total	7	22	3	32

Table 16a: Results of pleural biopsy and fluid cytology in malignant pleural diseases where both were performed

		Pleural biopsy	
		Positive	Negative
Pleural fluid cutology	**Positive**	**12**	**3**
	Negative	**5**	**2**

Closed needle pleural biopsy was performed in total 32 cases. Among them 7 cases were tuberculosis, 22 cases were malignancy and 3 cases were non-specific inflammation. Out of 7 cases of tuberculosis in 6 cases granulomatous inflammation was noted in pleural biopsy and out of 22 cases of malignancy in 16 cases pleural biopsy histopathology showed metastatic deposit in pleura. 3 cases showed non-specific inflammation in pleural biopsy.

Closed needle pleural biopsy had 72.2% sensitivity in diagnosing malignant pleural disease and 85.7% sensitivity in diagnosing tubercular pleural involvement. Pleural biopsy had 100% specificity in both the cases. In cases of malignant pleural diseases where both closed needle pleural biopsy and pleural fluid cytology were performed, together they had 90.9% sensitivity.

Table 16b: Correlation of Pleural fluid cytology and pleural biopsy (n = 32)

		Closed needle Pleural biopsy	
		Non-malignant	malignant
Pleural fluid cytology	Non-malignant	12	5
	malignant	3	12

Cytopathology-histopathology correlation	
Kappa statistics	95% confidence interval
0.5	0.2 -0.8

Pleural fluid cytopathology – histopathology correlation statistic showed moderate agreement (Cohen's kappa = 0.5).

4. Discussion

In developing countries, TB pleuritis is significantly more common than in the developed countries.` As pleural effusion is the most common manifestation of pleural diseases, thoracocentesis is the first diagnostic procedure employed for evaluation of pleural fluid. Thoracocentesis usually not performed in patients with secure diagnosis like congestive heart failure except clinical situation worsens or is atypical. A definitive diagnosis can only be established by pleural fluid analysis in a limited number of diseases that include empyema, malignancy, chylothorax, rheumatoid pleurisy etc.[47] DeFrancis *et al* first described pleural biopsy for etiological diagnosis of pleural effusion in 1955 by using vim-silvarman needle.

In the present study, malignant pleural involvement was more common than tuberculosis.Pleural fluid cytology and closed needle pleural biopsy are most commonly used procedure to diagnose various pleural diseases in developing country like India, where the facilities of thoracoscopy and imaging guided cutting needle pleural biopsies are not easily available.

The present study evaluates the efficacy of pleural fluid cytology and closed neddle pleural biopsy in diagnosing pleural diseases and according to our study both the investigations had moderate to high diagnostic yield especially when performed together.

4.1 Age and sex distribution profile (Table no. 1)

In present study most of the study population were in between the age group of 51 to 70 years, (mean age 51.3 years and median age 56 years) and male: female ratio was 1.33:1. This is quite similar with the other study shown in table 17.

Table 17: Age and sex incidences from different study as compared to present stydy

Name of Study	Mean Age / Age Group	Male to female Ratio
Hierholzer J *et al*.	55.9	1.6: 1
Valdès L *et al*.	57.1	1.66: 1
Porcel J *et al*.	65	1.46: 1
Liangping L *et al*.	58.7	1.46: 1
Present study	**51 – 70 yrs (mean 51.3 years, median – 56 years)**	**1.33 : 1**

We also evaluate the male: female ratio in malignant pleural involvement and it is 1.2:1 in present study. This is corroborating with Roncella S *et al* study (M: F – 1.38: 1). Mean age of malignant pleural cases is 54.5 years in the present study. In Reshad K *et al* study among 200 malignant pleural diseases 99 was female and 101 was male (M: F 1.02: 1) and mean age was 60.4 years.

4.2 Symptoms (Table No. 2)

In the present study, cough (63%) and shortness of breath (60%) and chest pain (44%) were the most common symptoms followed by fever (28%). Weight loss, lower limb swelling, loss of appetite were seen in minority of patients. Fa al-alusi study and Heidari B *et al* study showed similar symptomatology. Table 18 shows percentage of various clinical symptoms in different studies including present study.

Table 18: Presenting Features of pleural diseases in various studies

Symptoms	Fa al-alusi *et al* study	Heidari B *et al* study	Present study
Dyspnoea/ shortness of breath	87%	67%	60%
Cough	86%	68%	63%
Chest pain	67%	59%	44%
Fever	79%	Not reported	28%

A thorough history may provide clues to aetiology and provides a measure of disability. According to Judson *et al*, Dyspnoea is a common and non-specific symptomof pleural disease, causes are multifactorial and reflect a combination of reduced chest wall compliance, depression of the diaphragm and reflexes stimulated by a reduction in lung volume. Chest pain implies involvement of the pleura, ribs or chest wall, suggesting an exudative process (e.g. malignancy, pleural infection, pulmonary infarction). Cough is also a non-specific symptom, although the production of purulent sputum suggests an infective aetiology. Constitutional symptoms such as weight loss, night sweats, anorexia and malaise may occur in association with pleural infection, tuberculous pleurisy or pleural malignancy. (Judson MA, Sahn SA (1995) Pulmonary physiologic abnormalities caused by pleural disease. Semin Respir Crit Care Med, 16: 346–53).

4.3 Radiological Presentation (Table – 3 & 4)

In the present study, most of the pleural lesions presented as pleural effusion (90%) (along with the 5 cases of hydropneumothorax) and involved the right side (47%) alone in both sex. The left side is involved in 35% of cases and bilateral involvement was seen in 18% of cases.

Similar findings are noted in valdes *et al*. study. In their study, 46.7% cases pleural effusion

occurred only on the right side, in 38.2% cases only on the left, and in 15.1% cases both sides were affected. Heidari B *et al* study showed that pleural effusion was right sided in 51% of cases, left sided in 44% and bilateral in 5% of patients.

Yilmaz U *et al*. study showed that 144 cases out of 146 cases (98.6%) presented as pleural effusion. In this study pleural thickening (16%) was the second most common radiological presentation following pleural effusion. Hussein-Jelen *et al*. also stated that pleural thickening is the second most common pleural abnormality after pleural effusion.

4.4 Spectrum of pleural lesions (Table 7)

In the present study non-neoplastic pleural involvement was noted in 32% cases and neoplastic pleural diseases were seen in 66% cases. Prakash UB *et al*. study showed similar findings.

In this study, secondary involvements either by metastasis or by direct involvement by adjacent neoplasm (63%) were the most common pleural lesion followed by tuberculosis (18%). In Heidari B *et al* study, malignant diseases accounted for 41% and tuberculosis for 33% of the 100 cases of exudative pleural effusion. Salyer *et al*, study showed among 176 cases 53.97% cases were malignancy and 31.8% cases were tuberculosis. These studies supported our findings. Yilmaz U *et al* study showed that among 146 cases of pleural disease 40.9% cases were malignant pleural disease and 41% cases were tuberculosis. But Valdès *et al* study showed that most common lesion especially in area where tuberculosis was prevalent, most common was tuberculosis (25%) followed by malignancy (22.9%). This finding contradicts our finding even though tuberculosis is prevalent in our area. As stated above this may be due to the fact that present study was conducted at tertiary centre in Kolkata and all of our study population were indoor patients. The patients in this hospital are mostly complicated cases and referred from primary or secondary health care facility and straight forward cases of tuberculosis are mostly treated in outdoor basis.

In the malignant group, Carcinoma lung (52%) was the most common primary which leads to secondary involvement of pleura and among them Adenocarcinoma lung (32%) was the most frequent followed by squamous cell carcinoma lung (6%). Studies conducted by Hsu C, Salyer *et al*, Reshad K *et al*. supported these findings. (Table – 20)

Table 19: Spectrum of pleural diseases in different studies

Diagnosis			Present study	Salyer *et al.*	Weissberg *et al.*	Valdès *et al*
Non-neoplastic			32%	46%	37.8%	77.1%
	tuberculosis		18%	31.8%	-	25%
Neoplastic			66%	54%	54.3%	22.9%
	Secondary	Lung carcinoma	52%	23.8%	-	7.5%
		lymphoma	3%	6.2%	-	2.5%
		Breast carcinoma	1%	6.2%	-	2.6%
	Primary pleural neoplasm		3%	0.57%	1.6%	0.8%

Table 20: Histologic type of primary lung carcinoma causing secondary pleural involvement in various studies

Histology of primary lung carcinoma	Present study (n = 52)	Salyer *et al.* study(n = 42)	Reshad *et al.* study(n = 123)	Johnston WW study(n = 167)
Adenocarcinoma	61.5%	42.85%	57.7%	41.3%
Squamous cell carcinoma	11.5%	23.8%	19.5%	20.3%
Large cell carcinoma	5.77%	-	5.7%	9.6%
Pleomorphic carcinoma	3.85%	-	-	-
Broncioloalveolar cell carcinoma	1.9%	-	4%	-
Type not ascertained	15.4%	-	-	-

Lymphoma (3%) was the second most common primary following lung carcinoma which causes secondary pleural neoplasm. Among others secondary from breast carcinoma (1%), ovarian carcinoma (1%), oesophageal carcinoma (1%) and hepatocellular carcinoma (1%) were also reported. Primary pleural neoplasm was seen in only 3% cases. These findings are almost similar to studies by different authors as shown in table – 19.

Primary pleural lesions were Primary pleural malignant spindle cell neoplasm, schwannoma, and Castleman's Disease each comprising of single case. Ultimate diagnosis was not achieved in 2% cases.

Primary neoplasm of pleura is rare. Although mesothelioma is the most common malignant pleural primary, it is a rare tumor even in Western world and still rarer in India. In our study, we got no case of pleural mesothelioma. Kini *et al*

reported only 15 cases over 25 years study from south India. From eastern India, there are few case reports.

Intrathoracic castleman's disease mostly involves mediastinum and hila. There was only a limited documented cases of pleural castleman's disease. Ko SF *et al*, repoted 8 cases of pleural castlemann disease and that was probably the largest case series of pleural castleman's disease till date[4]. Pleural castleman's disease predominantly affects young women. Pleural castleman's disease may be asymptomatic or may be present with dyspnoea, cough, chest discomfort. In our case 26 year female was presented with shortness of breath and chest pain. On chest radiograph pleural CD usually present as well defined lesion and CT shows contrast enhancing lesion with variable hyperintensity.[4] Definitive diagnosis of Castleman disease usually relies on detailed histopathologic examinations after excision of the mass. Ko SF *et al* theorize that intrapleural Castleman disease may arise from the subpleural lymph nodes and grow toward the pleural space.[4]

Pleural schwannoma is also a very rare neoplasm. Hu S *et al*. reported clinical and CT manifestation of eleven pleural schwannoma cases. In the present study, pleural schwannoma was resected along with the rib and sent to the pathology department. On gross examination the mass was well circumscribed and histopathologically diagnosed as schwannoma.

In the present study, a case of multiple neurofibroma presented with chest pain, and on chest x-ray there was a homogenous round mass in left lower lung zone. Left thoracotomy showed a pleura-pericardial mass (6x4 cm) occupying 6^{th}-8^{th} intercostals space. Histopathological examination revealed a malignant spindle cell neoplasm of pleura, separated from the superficial mesothelial lining with areas of necrosis. Provisional diagnosis was malignant peripheral nerve sheath tumour and differential diagnosis was malignant solitary fibrous tumour, monophasic synovial sarcoma etc. the tumour recurred at resection site after 6 months and involved pleura, chest wall with intra and extra-thoracic extension. For definitive diagnosis immunohistochemistry was required. Patients with neurofibromatosis have increased risk of MPNST (Evans DG). Ordonez NG *et al*. reported one case of pleural MPNST.

4.5 Appearance of pleural fluid (table – 5 & 8)

In present study, majority of the pleural fluids were straw in colour (55.56%) followed by haemorrhagic pleural effusions (37.78%). This finding is similar to the study conducted by Villena V *et al*. Among 34 haemorrhagic pleural effusion, in the present study, 82.35% were malignant effusion and among 56 non-haemorrhagic pleural effusion 57% were malignant. We calculate the p value for predicting haemorrhagic pleural effusion to be malignant and it was <0.05. According to Villena *et al* and Martensson *et al*, bloody pleural effusion had strong predictability for malignancy. But the authors (Villena V *et al*.) concluded that the appearance of the fluid should not be overemphasized as a diagnostic test. However, Ozcakar *et al* study contradicts these findings though they conducted their study in patients with malignant pleural effusion.

4.6 Pleural fluid type, cell type, cell count (Table – 6, 9 & 10)

In present study 99% of cases, pleural fluids are exudative and there is only 1 case of transudative pleural effusion as local disease causes exudative pleural effusion. This one cases of transudative pleural effusion was refractory to initial treatment and on further investigations (pleural biopsy), tuberculosis was detected. In Kushwaha R *et al* study 82% and in Porcel JM *et al* study 87% of their cases were exudative pleural effusion. As stated before if the diagnosis is straight forward and if there is no atypical presentation in cases of trasudative pleural effusions, thoracocentesis is usually not performed.

In this study, total leukocyte count in malignant effusions showed almost equal distribution in three groups (<500/cumm, 501 – 1000/cumm, >1000/cumm). 44.44% cases of tuberculosis showed total leukocyte count >1000/cumm. In present study, among 18 cases of tuberculous pleural effusion 13 cases (72%) had >70% lymphocyte differential count in pleural fluid, whereas 50% of the non-tubercular pleural effusions had differential lymphocyte count >70% (p value not significant). 33 cases (55%) out of 60 cases of malignant pleural effusions showed > 70% lymphocytes in pleural fluid. We can conclude from these findings that total leukocyte count and differential leukocyte count had no usefulness in differentiating the etiology of pleural effusions. These findings were supported by Dines DE *et al* study.

4.7 Pleural fluid cytology (Table 11, 12)

In present study pleural fluid cytology was positive for malignancy in 47% cases and suspicious of malignancy in 18% cases of malignant pleural effusion and it had 65% sensitivity, 96% specificity and 75.56% accuracy in diagnosing malignant pleural effusion. According to various author sensitivity of pleural fluid cytology ranges from 50% to 72% and specificity ranges from 84.6% to 100% in diagnosing malignant pleural effusions.

Table 21: Yield of pleural fluid cytology in diagnosing malignant pleural effusion (Various Studies)

Study	Pleural fluid Cytology		
	Sensitivity	**Specificity**	**Diagnostic accuracy**
Present study	**65%**	**96%**	**75.56%**
Motherby *et al*.	50%	97%	-
Gour *et al*.	68.4%	84.6%	77.8%
Shrestha *et al*.	62.5%	100%	-
Salyer *et al*.	72.6%	-	-
Prakash *et al*	57.6%	-	-

4.8 Closed needle pleural biopsy (Table 13-16)

In present study, Out of 7 cases of tuberculosis in 6 cases granulomatous inflammation was noted in pleural biopsy and out of 22 cases of malignancy in 16 cases pleural biopsy histopathology showed metastatic deposit in pleura. Closed needle pleural biopsy had 72.2% sensitivity in diagnosing malignant pleural disease and 85.7% sensitivity in diagnosing tubercular pleural involvement. Pleural biopsy had 100% specificity in both the cases. Table 22 showed sensitivity of pleural biopsy in different studies ranges from 54% – 86% in cases of malignancy and 70% to 87.1% in cases of tuberculosis.

Table 22: Yield of closed needle pleural biopsy in various study

Study	Closed needle pleural biopsy sensitivity	
	Malignancy (%)	**Tuberculosis(%)**
Present study	**76.20**	**85.7**
Heidari *et al*.	54	70
Gour *et al*.	68.4	77.8
Prince *et al*.	86	76.1
Antonangelo L	62.1	87.1

4.9 Pleural fluid Cytology and closed needle pleural biopsy (Combined yield and correlation) [Table – 16 & 17]

Present study showed that pleural fliud cytology had less sensitivity than closed needle pleural biopsy in malignant pleural effusions. These findings are similar to the james *et al* study. But most of other studies contradict these findings. This may be due to pleural fluid cytology was performed in 60 malignant cases whereas closed needle pleural biopsy was performed in 22 malignant cases in the present study. Pleural fluid cytology yield is also dependent on the method of processing. In present study, cases of malignant pleural diseases (n = 22) where both closed needle pleural biopsy and pleural fluid cytology were performed, together they had 90.9% sensitivity. This finding was in aggrement with 64.7%-90% sensitivity as reported by other researcher. (Table 23)

Table 23: Yield of pleural fliud cytology and closed needle pleural biopsy in different study

Studies	Pleural fluid cytology	Closed needle pleural biopsy	Combined pleural fluid cytology and pleural biopsy
Present study	**65% (n = 60)**	**76.2% (n = 22)**	**90.9% (n = 22)**
Salyer *et al*.	72%	55%	90%
Prakash UB *et al*.	57.6%	43%	64.7%
Kuaban C *et al*.	66.67%	59.26%	88.9%
James P *et al*.	50%	85.7%	-

In present study we correlated pleural fluid cytology and closed needle pleural biopsy findings and it showed moderate correlation (Cohen's kappa = 0.5). Gour DS *et al*, found 68.4% cyto-histological correlation in malignant pleural effusion.

5. Summary and Conclusion

Diagnoses of pleural diseases create difficulty due to overlapping cytological and histopathological feature of various benign and malignant conditions. However, In developing countries like ours, where investigations and health facilities are inadequate and cost of treatment is often un-affordable, pleural fluid analysis and cytology should continue to be a first line investigation to screen out the suspiciously malignant pleural effusion cases, as it is a very convenient, cost-effective and safe investigation. It shows good sensitivity, specificity and accuracy in diagnosing primary as well as metastatic pleural malignancies. Its combination with pleural closed needle biopsy can further enhance its usefulness in diagnosing pleural lesions.

Figure 1: Pleural fluid cytology (pap stain, x400): metastatic deposit from adenocarcinoma

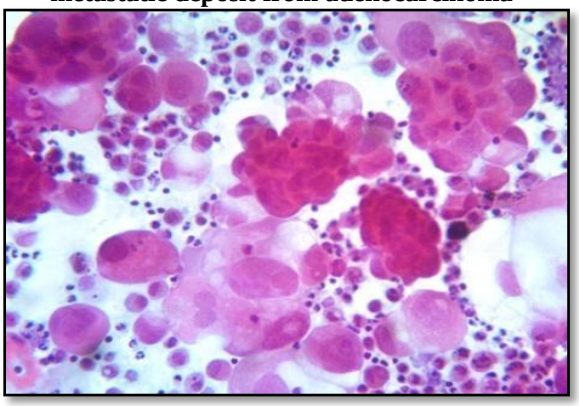


Figure 2: Pleural biopsy (H&E stain, 100X) – metastatic mucinous adenocarcinoma.

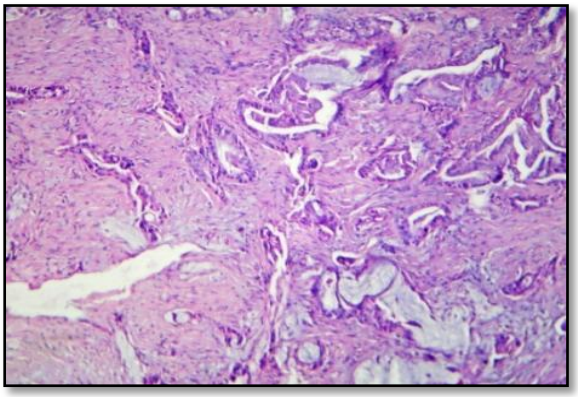


Figure 3: Pleural biopsy (H&E stain, 400X) – metastatic mucinous adenocarcinoma

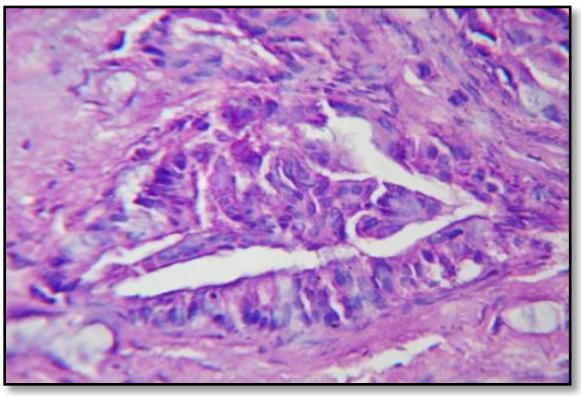


Figure 5: Pleural biopsy (H&E stain, 100 X) – metastatic deposit from poorly differentiated carcinoma [case no: 66]

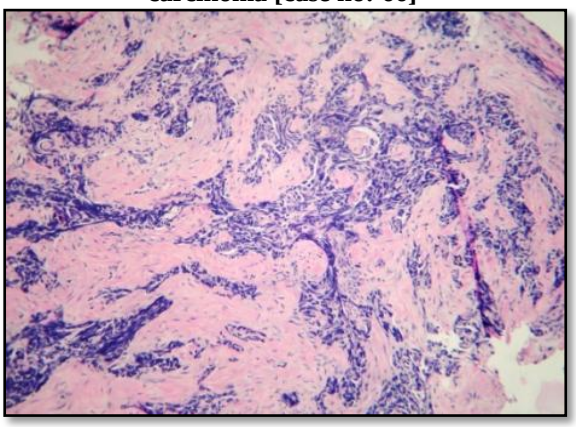
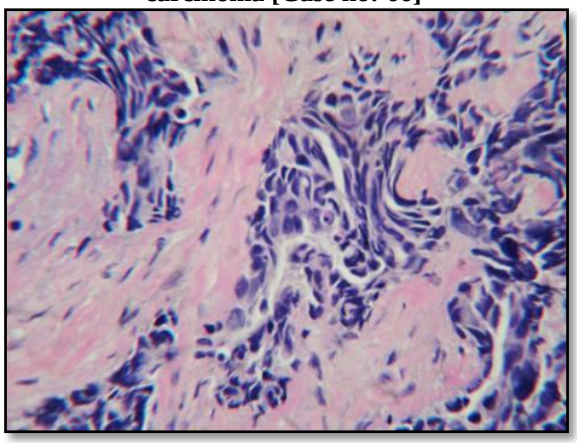


Figure 6: Pleural biopsy (H&E stain, 400X) – Metastatic deposit from poorly differentiated carcinoma [Case no: 66]



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