## Original Article

# Etiology and clinical profile of pleural effusion in a teaching hospital of south India : A descriptive study.

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## Abstract:

**Background & objectives:** Etiological diagnosis of Pleural effusion (PE) is really challenging to physician. Knowledge of common etiologies of pleural effusion helps us in planning the approach when such a case is encountered. The study was an attempt to identify the common etiologies causing PE in a teaching institute and their clinical profile.

**Materials and Methods:** A prospective evaluation of 100 consecutive cases of PE. Detailed history and physical examination, thoracocentesis and pleural fluid analysis were done in all cases and closed pleural biopsy using cope needle, ultrasound examination and computerized tomography in indicated cases.

**Results**: PE occurred more among males (68%) and in the age group between 46 to 60 years (33%). Majority of the cases (95%) were having exudative effusion. Tuberculosis was the commonest cause of exudative effusion (41%) followed by malignancy (38%). Majority of tuberculous PE (63%) was right sided whereas malignant effusion was left sided (57%). The Mantoux test, pleural fluid protein, pleural fluid ADA and age of patients had statistically significant correlation when PE due to tuberculosis and malignancy were compared.

**Conclusions:** Tuberculosis and malignancy are the two major causes for PE in the hospital. Tuberculous PE predominates slightly than malignant effusion. Tuberculous PE occurred in younger age group. Pleural biopsy should be done in patients with negative pleural fluid cytology. Thoracoscopy should be done if all the other investigative modalities fail to yield a confirmatory result. Knowledge of etiological pattern helps to plan relevant investigations in patients with PE and reduces the delay in diagnosis.

**Key words:** Pleural effusion, tuberculosis, malignancy, adenosine deaminase, needle biopsy, etiology

## Introduction:

Pleural effusion can occur as complication of many diseases. They are classified broadly in to exudative and transudative effusion based on Light's criteria. Common causes of transudative effusions are congestive cardiac failure, cirrhosis, nephrotic syndrome, superior venacava obstruction, peritoneal dialysis, glomerulonephritis, myxoedema, pulmonary emboli and sarcoidosis whereas exudative PE is caused by neoplastic diseases, infections, pulmonary embolism, gastrointestinal diseases, collagen vascular diseases, drug induced, iatrogenic, hemothorax and chylothorax. In an epidemiological study from Czech Republic it was found that four leading causes of PEs were congestive heart failure, malignancy, pneumonia and pulmonary embolism in the order of frequency.[1] When pleural fluid is detected, an effort should be made to determine which among the conditions listed above is responsible and is a challenge to the physician.

Needle biopsy of the pleura is also useful in the diagnosis of malignant PE. The incidence of positive pleural biopsy result ranges from 39-75%.[2] When no pleural fluid is present, but the pleura is thickened, needle biopsy of pleura can still be used to establish the diagnosis of tuberculosis or malignant disease. 20% of PEs remain

undiagnosed even after all investigations. The study was to identify the relative proportion of different etiological conditions and clinical profile of PE encountered in our institute which is a teaching hospital.

## Materials and methods:

**Objectives:** To study the clinical profile and identify the common etiologies of PE in a tertiary care center.

**The design of the study**: A prospective descriptive study.

Hundred consecutive adult cases of PE attending the outpatient clinic of Institute of Chest Diseases, Medical College Calicut for one year were studied. All cases were subjected to detailed clinical examination which included history and physical examination. Symptomatology included chest pain, cough and dyspnoea on exertion (DOE). Physical examination was done with particular attention to hemi thoracic size, tactile vocal fremitus, percussion, auscultation for decreased intensity of breath sounds and pleural rub. Other systemic examinations included assessing cardiomegaly, neck veins distension or peripheral edema, signs of joint diseases or subcutaneous nodules.

A diagnostic thoracocentesis was done. Gross appearance like colour, turbidity, viscosity and odors were noted. The fluid was sent for various investigations. They include total and differential cell counts, pleural fluid protein and sugar with corresponding serum values and cytological examinations. Pleural fluid was submitted for Gram as well as acid fast bacilli (AFB) staining, aerobic bacterial and AFB culture. Serum adenosine deaminase (ADA) estimation was done in all cases. Pleural biopsy specimens were sent for histopathological examination and mycobacterial culture in indicated cases where other diagnostic clues were lacking. Ultrasound thorax and abdomen, computed tomography (CT) scan thorax and fiber-optic-bronchoscopy (FOB) were done in indicated cases.

## Results:

Of the 100 patients studied, 68 patients were males, 32 were females. 18 patients were below 30 yrs, 28 of them between 30 and 45 yrs, 33 patients were between 46 and 60 and 21 patients above 60 yrs.

Basis of diagnosing tuberculous effusion were

1. High ADA level in pleural fluid >70 IU/L
2. Pleural biopsy showing caseating granuloma
3. Positive Mantoux test

Malignant PE was diagnosed on following criteria:

1. Malignant cells in pleural fluid
2. Pleural biopsy suggestive of malignancy
3. Evidence of malignancy in FOB / CT thorax

Of the 100 patients, 41 patients had diagnosis of tuberculosis and 38 patients had malignant PE. The rest belonged to para-pneumonic effusion (n=12), transudative effusion (n=5) and inconclusive (n=4). All transudative PEs were due to cardiac failure (n=5). PEs in which no definite diagnosis was evident with all the investigations, a diagnosis of inconclusive PE was made.

Of the malignant PE (n=38), 23 had diagnosis of adenocarcinoma, 4 squamous cell carcinoma, 4 lymphoma, 5 mesothelioma and 2 small cell carcinoma. 21 patients were male and 17 patients were female. 16 patients belonged to age group 46-60, 10 patients between 31 and 45, 2 patient below 30, and 10 patients above 60 years. (Table 1)

Among the patients with tuberculous PE (n=41), 30 patients were male and 11 patients were females. 27 patients were below 45 years of age and rest above 45 years.

Analysis of symptoms showed that DOE was present in 28 patients with tuberculous PE and 30 patients with malignant effusion, absent in 13 patients and 8 patients respectively. Cough was present in 34 patients with tuberculous effusion and 26 patients with malignant effusion. Chest pain was present in 36 patients with tuberculous effusion and 25 patients with malignant PE. Fever was present in 28 patients with tuberculous effusion where as absent in 13 patients. Fever was present in 20 patients with malignant effusion and 18 patients of this group had no fever. 19 patients with tuberculous effusion and 16 patients with malignant effusion were smokers whereas 22 patients with tuberculous effusion and 22 patients with malignant effusion were nonsmokers. (Table 2)

Colour of effusion was straw in 38 patients with tuberculous effusion and 9 patients with malignant effusion.

PE was hemorrhagic in 3 patients with tuberculous effusion and 29 patients with malignant effusion. (Table 3)

Duration of illness when studied showed 29 patients of tuberculous effusion had more than 1 month history of chief complaints, 12 had duration of less than 1 month. 27 patients with diagnosis of malignant effusion had duration of illness more than 1 month but 11 patients had duration less than 1 month. Out of remaining 21 patients with diagnoses other than tuberculous and malignant effusion, 15 patients had duration of symptoms less than 1 month. When side of effusion were compared between two diagnostic groups 26 patients of tuberculous effusion had right sided effusion and 15 patients had left sided effusion. Malignant effusion group (n=38), 16 patients had right sided effusion and 22 patients left sided effusion.

All patients had undergone pleural fluid gram staining and AFB staining, routine culture and AFB culture (n=100). Gram positive organisms were demonstrated in 2 cases and gram negative organisms in 2 cases. Others were not showing any positive or negative result in gram staining. Routine culture revealed growth of Streptococcus Pneumonia in 2 cases and Acinetobacter in 1 case. One case which showed gram negative organisms in gram staining was found to be sterile on routine culture. AFB smear and culture were negative in all cases. Fibre optic bronchoscopy and CT thorax were done only in cases of PE where diagnosis was not evident by other investigations. CT thorax was done in 1 case and fibre optic bronchoscopy was done in 5 cases and all were suggestive of malignancy. Lymph node fine needle aspiration was positive for malignancy in 3 cases.

Using unpaired 't' test equality of means was measured between the two diagnostic groups. The Mantoux test, protein of pleural fluid, ADA of pleural fluid and age of patients had statistically significant correlation. Other tests did not have any statistical significance in differentiating these two groups. (Table 6)

Pleural fluid cytological examination for malignant cells was done in all cases. 10 cases of adenocarcinoma, 5 cases of mesothelioma, and 2 cases of lymphoma were diagnosed. 3 patients had atypical cells in pleural fluid. Those having malignant cells in pleural fluid were considered as positive, no malignant cells in pleural fluid as negative and those with atypical cells in pleural fluid as inconclusive.

Pleural biopsy was done in 32 cases which revealed 12 cases of adenocarcinoma, 4 cases of squamous cell carcinoma, 5 cases of mesothelioma, 3 cases of lymphoma, and one case of small cell carcinoma. Tuberculous granuloma was demonstrated in 4 pleural biopsy specimens of suspected tuberculous PE. Neutrophilic infiltration was seen in 2 cases.

Comparing pleural biopsy with corresponding pleural fluid cytology in cases of suspected malignancy, positive results were obtained in 25 (96%) cases by pleural biopsy, 17 (65%) cases by pleural fluid cytology, out of total 26 cases. 1 (4%) case was negative by pleural biopsy whereas 6 (23%) were negative by pleural fluid cytology. 3 (12%) cases were inconclusive in pleural fluid cytology; none were inconclusive by pleural biopsy.

## Discussion:

Of the 100 patients studied, 68% were male and 32% were female. The age group between 30 and 60 were predominantly affected. Tuberculous effusion occurred in younger age group (n=27 below 45 yrs). This is concordant with various other studies.[2,3] In a study by Berger and Mejia in 1973, they reported that of their 49 patients with tuberculous pleuritis, 15% of the patients were above the age of 70, and 40% were above the age of 35.[3]

While analyzing the frequency of occurrence of each type of PE, tuberculous effusion predominated. In many areas of the world, tuberculosis remains the most common cause of PEs in the absence of demonstrable pulmonary disease. A study from Rwanda by Batungwanayo J et al, tuberculosis was diagnosed in 110 of 127 patients (86%) who presented with PE.[4] Similar result was reported by Khan FY from Qatar.[5]

Male sex predominated in both tuberculous and malignant effusion (n=30) and (n=21) respectively. Duration of illness in cases of tuberculous and malignant effusions was more than 1 month, but in other cases like para-pneumonic effusion it is less than 1 month. In one series, out of 71 patients with tuberculous PE, 50 (62%) had been symptomatic for less than a month.[6]

## Tables

**Table 1: Etiologies of pleural effusion**

| Diagnosis | Frequency | Percentage |
|---|---|---|
| Tuberculosis | 41 | 41 |
| Adenocarcinoma | 23 | 23 |
| Squamous cell ca | 04 | 04 |
| Lymphoma | 04 | 04 |
| Mesothelioma | 05 | 05 |
| Para-pneumonic effusion | 12 | 12 |
| Transudative effusion | 05 | 05 |
| Small cell carcinoma | 02 | 02 |
| Inconclusive | 04 | 04 |
| Total | 100 | 100 |

**Table 2: Frequencies of major symptoms in 2 major diagnostic groups**

| Symptoms | Tuberculous effusion | | Malignant effusion | |
|---|---|---|---|---|
| | Present (%) | Absent (%) | Present (%) | Absent (%) |
| DOE | 28 (68.3) | 13 (31.7) | 30 (78.9) | 8 (21.1) |
| Cough | 34 (82.9) | 7 (17.1) | 26 (68.4) | 12 (31.6) |
| Chest pain | 36 (87.8) | 5 (12.2) | 25 (65.8) | 13 (34.2) |
| Fever | 28 (68.3) | 13 (31.7) | 20 (52.6) | 18 (47.4) |
| H/o smoking | 19 (46.2) | 22 (53.7) | 16 (42.1) | 22 (57.9) |

**Table 3: Comparison of color of effusion in both diagnostic groups**

| Diagnostic group | Colour of effusion | | Total |
|---|---|---|---|
| | Straw coloured | Hemorrhagic | |
| Tuberculosis | 38 | 3 | 41 |
| Malignant | 9 | 29 | 38 |
| Total | 47 | 32 | 79 |

| Table 4: Duration of illness versus various diagnoses | | | | |
|---|---|---|---|---|
| Duration of illness | TB | Malignant | Others | Total |
| <1 month | 12 | 11 | 15 | 38 |
| 1 - 12 months | 29 | 27 | 4 | 60 |
| >12 months | - | - | 2 | 2 |
| Total | 41 | 38 | 21 | 100 |

| Table 5: Side of effusion | | |
|---|---|---|
| Diagnosis | Right | Left |
| Tuberculosis effusion (n=41) | 26 (63.4) | 15 (36.6) |
| Malignant effusion (n=38) | 16 (42.1) | 22 (57.9) |

| Table 6: Comparison between tuberculous and malignant pleural effusion | | | | | |
|---|---|---|---|---|---|
| Diagnostic group | | N | Mean | Std. Error mean | P value |
| Mantoux test | Tuberculous | 41 | 21.17 | 1.32 | 0.000 |
| | Malignant | 38 | 5.74 | 1.29 | |
| Pleural fluid protein | Tuberculous | 41 | 5.005 | 0.168 | 0.006 |
| | Malignant | 38 | 4.332 | 0.172 | |
| ADA-PF | Tuberculous | 41 | 75.06 | 5.72 | 0.006 |
| | Malignant | 38 | 35.23 | 4.27 | |
| Age | Tuberculous | 41 | 40.44 | 2.78 | 0.001 |
| | Malignant | 38 | 53.16 | 2.34 | |

| Table 7: Pleural fluid cytology report | |
|---|---|
| Adenocarcinoma | 10 |
| Mesothelioma | 5 |
| Lymphoma | 2 |
| Atypical cells | 3 |
| No malignant cells | 80 |
| Total | 100 |

| Table 8: Histopathology results of pleural biopsy specimens | |
|---|---|
| Adenocarcinoma | 12 |
| Mesothelioma | 5 |
| Lymphoma | 3 |
| Squamous cell carcinoma | 4 |
| Small cell carcinoma | 1 |
| No abnormality | 1 |
| Tuberculosis | 4 |
| Neutrophilic infiltration | 2 |
| Total | 32 |

| Table 9: Comparison of results of pleural biopsy and corresponding pleural fluid cytology in malignant PE | | |
|---|---|---|
| Result | Pleural biopsy | Pleural fluid cytology |
| Positive | 25 (96%) | 17 (65%) |
| Negative | 1 (4%) | 6 (23%) |
| Inconclusive | 0 | 3 (12%) |
| Total | 26 | 26 |

Predominant symptoms were fever, cough, chest pain and dyspnoea, of which dyspnoea predominated in malignant effusion; cough, chest pain and fever in tuberculous effusion. In one study by Berger and Mejia in 1973, most patients with tuberculous PE (~70%) had cough, usually nonproductive, and most (~50-75%) had chest pain, usually pleuritic in nature. 7 of 49 patients (14%) were afebrile.[3] In another series, Chernow & Sahn reported that the most common symptom in malignant PEs is dyspnoea, which occurs in more than 50%. Weight loss occurred in 32%, malaise in 21% and anorexia in 14% of patients.[7] Temperature elevation is significantly more common in patients with benign disease (73%) than in patients with malignant disease (37%).[8]

Colour of effusion is diagnostic. Tuberculous effusion was predominantly straw coloured where as malignant effusion was hemorrhagic. But straw coloured malignant and hemorrhagic tuberculous effusions were also seen.

Diagnostic tests like Mantoux test, pleural fluid protein, ADA estimation showed statistical significance in differentiating tuberculous and malignant PE ($P<0.05$).[9] Tuberculin test was negative in majority of diagnosed cases of tuberculous PE. In one Indian study by Hira HS et al. 30% of tuberculous PE were having negative tuberculin test.[10] Ocana and associates measured the pleural fluid ADA level in 221 pleural or peritoneal effusions. All patients with a pleural fluid ADA level above 70 IU/L had tuberculosis, whereas no patient with pleural fluid ADA level below 40 IU/L had tuberculous pleuritis.[11] Fontan Bueso and colleagues reported similar results in a group of 138 patients with PE, which included 61 with tuberculosis and 42 due to malignant disease.[12]

In this study AFB staining and culture of pleural fluid did not yield any positive result. Routine smear for mycobacteria are not indicated because they are almost always negative, unless the patient has a tuberculous empyema.[2] In most series of patients with tuberculous pleuritis, the pleural fluid cultures are positive for mycobacteria in less than 25%.[13]

In the present study, while comparing pleural biopsy and pleural fluid cytology, pleural fluid cytology has low sensitivity than pleural biopsy in case of malignant effusion. Similar studies have shown contradictory results.[14,15] In one series by Levine H et al, the initial pleural biopsy revealed granulomas in approximately 60% of patients with tuberculous pleuritis. If three separate pleural biopsies are obtained the yield increases to approximately 80%. When culture of a biopsy specimen is combined with microscopic examination, the diagnosis can be established in approximately 90% of cases.[16]

In this study pleural biopsy and corresponding pleural fluid cytology were compared and it was found that pleural biopsy is superior in diagnosing malignancy. It has a positive result in 88% when compared to fluid cytology which has a positive result of 32% only. In other studies the pleural fluid cytology was more yielding. In study by Beuno CE et al. the result is consistent with the present study.[2] The proportion of positive pleural biopsy in patients with malignant PEs ranges from 39-75%, according to Bueno et al. In series by Canto A et al, in 1983, pleural biopsy has a lower diagnostic yield than pleural fluid cytologic examination because, in 50% of patients with malignant pleural disease, the costal pleura is not involved.[17] James P et al. reported a diagnostic yield of closed pleural biopsy of 62.2% in all cases of exudative PE.[18] Image guided tru-cut pleural biopsy also increased the yield of this diagnostic test.[19]

## Conclusions:

Tuberculosis and malignancy are the two major causes for PE in the hospital. Tuberculous PE predominates slightly than malignant effusion. Tuberculous PE occurs in younger age group and has fever, cough and chest pain as predominant symptoms. DOE is more commonly seen in malignant effusion. Pleural biopsy should be done in patients with negative pleural fluid cytology. Mantoux test, ADA, pleural fluid protein and age has statistical significance in diagnosing PE. Closed pleural biopsy is useful and should be attempted in indicated cases of PE. Thoracoscopy should be done if all the other investigative modalities fail to yield a confirmatory result. Knowledge of etiological pattern helps to plan relevant investigations in patients with PE and reduces the delay in diagnosis.

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