

## STUDY OF EXUDATIVE PLEURAL EFFUSION IN THE AGE GROUP OF 15-40 YEARS WITH SPECIAL REFERENCE TO ADENOSINE DEAMINASE AND TUBERCULIN SKIN TEST IN THE DIAGNOSIS OF TUBERCULOUS ETIOLOGY

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### Abstract

**Background:** A tubercular pleural effusion can either be a sequel to a primary infection acquired 3 to 6 months previously or represent reactivation tuberculosis.

Two different pathogenic mechanisms can lead to tuberculous pleural effusion. By far the more common is the entry of only a few *M. tuberculosis* into the pleural space; in the presence of specific cell mediated immunity, tubercle bacilli provoke an intense hypersensitivity reaction and outpouring of fluid. Chest radiograph may or may not reveal associated parenchymal involvement. In the second variety, a subpleural caseous focus or cavity ruptures into the pleural space and results in a pleural effusion. In this case chest radiograph nearly always shows parenchymal abnormalities.

A definitive diagnosis of TBPE can be difficult to make because of the low sensitivity and / or specificity of noninvasive traditional diagnostic tools.

In most series of patients with TBPE the result of pleural fluid staining for acid fast bacilli are virtually always negative and pleural fluid cultures are positive for mycobacteria in <35% of cases. Without underlying lung parenchymal lesion sputum examination may be positive in 4% to 11% of patients with TBPE. On the other hand, pleural biopsy specimen will demonstrate granulomatous pleuritis in 50% to 80% of patients.

This study was taken whether pleural fluid ADA and tuberculin skin test has any role in the diagnosis of tubercular pleural effusion.

**Methods and Materials:** In the present study 120 cases of exudative pleural effusion in the age group of 15-40 years of varying etiology are taken who attended the pulmonary medicine department of Burdwan Medical College and Hospital.

The study was conducted the period of March 2017 to February 2018 apart from relevant history taking a detailed clinical examination, full investigation was done to reach a complete and final diagnosis.

**Result:** In our study 120 patients of aged 15-40 years were taken. Different aetiological groups and their frequency as diagnosed by various means were Tuberculous – 85%, Paraneumonic effusion – 10%, Malignant effusion – 10%.

There was male preponderance in all groups of pleural effusion. History of contact was present in 34% cases of tuberculous effusion. Sputum for AFB was found in 10.78% cases of tuberculous effusion. These patients also had pulmonary lesions. 80.39% cases of tuberculous effusion had pale yellow coloured effusion but 13.72% cases had haemorrhagic fluid. 66.66% malignant effusion had haemorrhagic fluid and 33.37% of malignant effusion had pale yellow coloured fluid. Pleural fluid for malignant cells was positive in 66.67% of malignant effusion. Pleural fluid for Z-N stain detected 1.96% cases of tubercle bacilli in TBPE group. Pleural biopsy was found positive in 68.18% cases of TBPE and 60% cases of MPE.

Pleural fluid ADA level was significantly higher ( $P < 0.001$ ) in patients of tuberculous effusion than non-tuberculous effusion. Taking a cut off value of 70 U/L sensitivity and specificity is 95.09% and 33.33%. But when parapneumonic effusion was excluded, the specificity increases. Lymphocytic pleural effusion below the age group of 40 years with cut off value of ADA <40 U/L can be used as a screening test for malignant effusion.

In TBPE tuberculin skin test was positive in 74.50% cases. Taking a cut off value of 10 mm or more induration of tuberculin skin test, "P" value is less than 0.001. Sensitivity and specificity of tuberculin skin test in tuberculous pleural effusion is 74.50% and 50%.

If we compare the efficacy of ADA > 70 U/L and tuberculin skin test positivity to diagnose tuberculous pleural effusion the former is superior statistically to the latter (P value is less than 0.01) specificity of tuberculin skin test is low because it may be positive with infection with NTM and prior BCG vaccination.

**Conclusion:** Maximum incidence of tuberculous pleural effusion occurs in the age group of 20-30 years. Malignant pleural effusion is less likely below the age group of 30 years.

Increased ADA level >70 U/L in pleural fluid is a sensitive, minimally invasive, cost effective, easy method for diagnosis of tuberculous pleural effusion.

Lower level of pleural fluid ADA level (<40 U/L) is a sensitive, specific, minimally invasive, cost effective easy method for suspecting malignant effusion. Its value is much more important when younger patients (<40 years of age) present with malignant effusion, especially so when the pleural fluid is also appeared pale yellow. A low ADA level will guide us to look for malignancy in this age group.

Tuberculin skin testing with intermediate strength PPD has a high sensitivity in patients with pleural tuberculosis. It was seen negative in 1/3<sup>rd</sup> cases of TBPE. This negative tuberculin skin test in TBPE may be due to recent tuberculous infection or may be due to sequestration of PPD reactive T-lymphocytes in the pleural space or patient may be anergic. Our study is insufficient to comment this negative result. More precise study need to comment.

## Introduction

The pleural space is bounded by two membranes, the visceral pleura covering the lung and the parietal pleura covering the chest wall and diaphragm. These two pleural membrane meet the hilar root of the lung.

The normal pleural space is approx. 18 to 20  $\mu\text{m}$  in width, although it widens at its most dependent part. It is likely that the primary function of the pleural membranes is to allow extensive movement of the lungs relative to chest wall. If the lung adhered directly to the chest wall, its expansion and deflation would be more limited. The visceral pleura may also provide mechanical support for the lung; contributing to the shape of the lung, providing a limit to expansion and contributing to the work of deflation. Pleura pressure is subatmospheric and mediates inflation of the lung. The actual pleural pressure in human is approx. - 5 cm of H<sub>2</sub>O at mid chest at functional residual capacity and -30 cm. H<sub>2</sub>O at total lung capacity.

The parietal pleura is supplied by intercostal arteries whereas visceral pleura in humans like that in sheep is exclusively supplied by bronchial circulation which drains into pulmonary veins.

The visceral pleura has extensive lymphatics but they do not connect to the pleural space whereas parietal pleural lymphatics connect to the pleural space via stomas, holes of 8 to 10  $\mu\text{m}$  in diameter that are formed by discontinuities in the mesothelial layer.

By non-invasive studies of the equilibration of radiolabelled albumin, the entry rate of pleural liquid is approximately 0.01 ml / kg / hour in a sheep or about 0.5 ml hourly in a grown man. The half time of pleural liquid turnover in sheep and rabbit is 6 to 8 hours.

For pleural liquid to accumulate, either the entry rate of liquid must increase to a sustained rate more than 30 times normal (to exceed the reserve lymphatic removal capacity), the exit rate of liquid must decrease, or both rates must change. The lymphatic exit rate may be decrease by obstruction of the parietal stomas, inhibition of lymphatic contractility, infiltration of draining parasternal lymph nodes, or elevation of systemic venous pressure into which the

lymph drains. Decrease in lymphatic clearance have been confirmed in patient with tuberculous and malignant effusions and those with the yellow nail syndrome.

Among the different diagnostic modalities the first one is whether the effusion is a transudates or exudates by using Light's criteria.

If the fluid is a transudate, systemic causes like congestive heart failure or hypoalbuminemic states should be search for. But an exudates demand details pleural analysis and some other measures to arise an aetiological diagnosis. In an exudative pleural effusion the fluid should be analysed for appearance of pleural fluid, glucose level, cytology and differential cell count, pleural fluid markers for tuberculosis.<sup>26</sup> In a bloody pleural effusion haematocrit is measured and in cloudy fluid, chylous and pseudo-chylous effusion must be excluded.

The principal causes of exudative pleural effusion are infectious diseases including tuberculous and parapneumoic effusion, neoplastic disease, collagen vascular disease, pulmonary thromboembolism, some gastro-intestinal disease, haemothorax, chylous and drug induced pleural disease!

Of the various condition that causes exudative pleural effusion, tuberculosis is the single most important factor. Tuberculous pleural effusion accounting for 25% to 37% of all pleural effusion. - is one of the endemic region for tuberculosis. Every third tuberculous patient reside here. Everyday more than 20,000 people become infected and more than 5,000 develop some form of tuberculosis.

About 4.9% of tuberculous patient develops TBPE typically three to seven months following initial infection with Mycobacterial tuberculosis and therefore was usually seen in children and young adults.<sup>11</sup>

Pleural effusion due to tuberculosis has been likened to a primary chancre as a manifestation of syphilis. Both are self-limited and of little immediate concern, but both may lead to serious disease many years later. Most instances of pleural effusion secondary to tuberculosis resolves spontaneously, however if patients are not treated with antituberculous therapy, they have about a 50%, likelihood of

developing active tuberculosis in the subsequent 5 years.<sup>20</sup>

Two different pathogenic mechanisms can lead to tuberculous pleural effusion. By far the more common is the entry of only a few *M. tuberculosis* into the pleural space; in the presence of specific cell mediated immunity, tubercle bacilli provoke an intense hypersensitivity reaction and outpouring of fluid. Chest radiograph may or may not reveal associated parenchymal involvement. In the second variety, a subpleural caseous focus or cavity ruptures into the pleural space and results in a pleural effusion. In this case chest radiograph nearly always shows parenchymal abnormalities.<sup>20</sup>

As just mentioned, delayed hypersensitivity appears to play a large role in the pathogenesis of TBPE. In animal models, the intrapleural injection of tuberculous protein in sensitized animals results in the rapid appearance of an exudative pleural effusion. When the animals are given antilymphocyte serum, the development of the effusion is suppressed. It is probable that delayed hypersensitivity also plays a large role in the development of tuberculous pleural effusion in humans. The Mycobacterial burden in the pleural space is very low, so that pleural fluid cultures are positive for mycobacteria in <35% of cases.<sup>20</sup>

A definitive diagnosis of TBPE can be difficult to make because of the low sensitivity and / or specificity of noninvasive traditional diagnostic tools.

In most series of patients with TBPE the result of pleural fluid staining for acid fast bacilli are virtually always negative and pleural fluid cultures are positive for mycobacteria in <35% of cases. Without underlying lung parenchymal lesion sputum examination may be positive in 4% to 11% of patients with TBPE. On the other hand, pleural biopsy specimens will demonstrate granulomatous pleuritis in 50% to 80% of patients.

Although other disorders including fungal disease, sarcoidosis, rheumatoid pleuritis, tularaemia may produce granulomatous pleuritis. But when culture of a biopsy specimen combined with histological examination, the diagnosis can be established in approximately 90% cases.<sup>5</sup>

Pleural biopsy is an invasive procedure, its overall sensitivity is approx. 65%. It has not become routine medical procedure due to its invasive nature and some complications like pneumothorax and bleeding. Moreover, culture of specimens like sputum, pleural fluid or pleural biopsy takes long time, i.e., about 4-6 weeks.

So these clinical, biochemical and bacteriological tests for diagnosis of tuberculous pleural effusion are less sensitive and time consuming. This causes the diagnostic problem as there are several other causes of pleural effusion. In most of these situations therapeutic trial of anti-tuberculous drug is given. So there is a need for an ideal test for TBPE which should be economic, minimally invasive, of high accuracy and quick to perform.

Four relatively new markers have been reported to help the diagnosis of TBPE: adenosine deaminase (ADA), lysozyme, interferon gamma and polymerase chain reaction (PCR). Surprisingly, PCR has a relatively low sensitivity in pleural fluid (0.42 to 0.81) and is fairly expensive.<sup>30,31,32</sup> The sensitivity of an elevated interferon gamma level appears better (0.89 to 0.99) but this is also expensive. The test with the most data to support its use is the pleural fluid ADA level.

Adenosine is widely distributed in animal and human tissues. The highest activity is found in intestinal mucosa and spleen, lower activity is found in liver, skeletal muscle, kidney and serum. The ADA increase has been attributed to cell mediated response to mycobacterial antigens.

The enzyme is also released during tuberculous process in the pleura and its detection is useful in the diagnosis of tuberculous pleural effusion.

ADA analysis is a simple and inexpensive colorimetric test that can be performed on body fluids.<sup>4</sup> ADA is an enzyme of purine catabolism leading to hydrolytic deamination of adenosine to inosine and ammonia. It is found ten times higher concentration in lymphocytes than in erythrocytes.<sup>35</sup> This enzyme is predominantly present in T-lymphocytes of CD4 + variety. Its plasma activity is high in disease in which cellular immunity is stimulated.

ADA is an essential enzyme for the differentiation and proliferation of T lymphocytes and the monocyte-macrophage system. High serum ADA activity has been reported in various diseases including infection, malignancy and liver diseases. ADA level in pleural fluid is significantly high in TBPE, PNE / Empyema, rheumatoid pleural effusion, SLE, O-fever, some lymphomas.<sup>5</sup> Its deficiency is known to produce severe combined immunodeficiency disorder (SCID).

There are two molecular forms of ADA - ADA1 and ADA2. ADA1 is found in all cells but has its greatest activity in lymphocytes and monocytes.<sup>37</sup> ADA2 is found only in monocytes and majority of ADA in

tuberculous pleural effusion is ADA2, whereas majority of ADA in other pleural effusion is ADA1. Use of isoenzyme assay is more expensive and not readily available.

Several reports have suggested that an elevated pleural fluid ADA level predicts tuberculous pleuritis with a sensitivity of 90 to 100% and a specificity of 89 to 100%.

The reported cut-off value for ADA to diagnose tuberculous pleural effusion differs in different studies. The most accepted level above which a diagnosis of tuberculous effusion is essentially diagnostic is 70 U/L if empyema and rheumatoid arthritis is excluded. The specificity of increased ADA level in pleural fluid to diagnose tuberculous effusion is increased if pleural fluid lymphocyte to neutrophil ratio of 0.75 or more is combined.

Moreover pleural fluid ADA level is significantly low in malignant pleural effusion. Ocana et al measured the ADA levels in 221 pleural and peritoneal effusions and showed that ADA level was <40 U/L in most of the malignant patients.

Murray and Nadel's (4th edition)<sup>2</sup> stated that the ADA can be useful test to exclude the diagnosis of TBPE when the ADA level is low (40 U/L).

In the past, tuberculin skin test was an important diagnostic aid in patient suspected of having TBPE. However, a negative skin test does not rule out the diagnosis of tuberculous pleuritis. In one recent series from Spain the PPD was positive in only 66.5% of 254 patients with TBPE. If the patient with a negative tuberculin skin test and tuberculosis pleuritis is skin tested more than 8 weeks after the development of symptoms, the skin test will almost always be positive.<sup>5</sup> Therefore in patient with undiagnosed exudative pleural effusion with a negative tuberculin skin test and the repeat testing performed after 8 weeks of development of Symptom which if negative can be used to exclude the diagnosis of TBPE

Occasionally, the immunosuppression may result from a relative depletion of the circulating PPD reactive lymphocytes as they sequester in pleural space or more commonly immunosuppression is thought to be due to suppressor cells that are found in the blood not in the pleural space.<sup>20</sup>

#### **AIMS AND OBJECTIVES**

1. To observe the clinical profile of the cases with TBPE in the age group of 15 to 40 years.
2. To study the etiological profile of pleural effusion.

3. To study the values of pleural fluid ADA as a parameter for early diagnosis of pleural effusion and its sensitivity and specificity.

4. Comparative study of ADA level in pleural fluid and tuberculin skin test in the diagnosis of tuberculous pleural effusion.

**STUDY AREA:** Department of Pulmonary medicine, Burdwan medical collage and hospital, Burdwan.

**STUDY PERIOD:** One year. (March 2017-February 2018)

**STUDY POPULATION:** Patient of age 15 to 40 years having exudative pleural effusion and fulfill the inclusion and exclusion criteria, attending OPD or undergoing in patient treatment at pulmonary medicine department of Burdwan medical collage and hospital, Burdwan.

Total 120 patient with pleural effusion were taken.

#### **INCLUSION CRITERIA:**

1. Medical history and other evidences compatible with exudative pleural effusion.
2. Pleural effusion with protein/serum protein >.5, LDH/Serum LDH >.6 and effusion LDH level >2/3<sup>rd</sup> of upper limit of laboratory reference range of serum LDH(Light's criteria)

#### **EXCLUSION CRITERIA:**

1. Age <15 years and >40 years.
2. Patient refusal pleural fluid aspiration.
3. Transudative pleural effusion
4. Haemothorax following trauma to the chest.
5. Any contraindication to thoracentesis.
6. Haemodynamically unstable moribund patient.

#### **METHODS OF STUDY:**

##### **CLINICAL EXAMINATION:**

A thorough clinical examination and relevant history was taken according to the plan schedule. Careful clinical examination of the respiratory system were done in each case. Other Systemic examinations were done to detect other system or organs were involved or not.

##### **INVESTIGATION:**

**Blood:** Complete haemogram, FBS, blood urea, creatinine, LFT, HIV screening done.

**Sputum:** Examination sputum for AFB done in all cases in our RNTCP department.

**Radiological Examination:** Chest X ray in PA view were taken in all cases. Lateral view and/or deep penetrating view were taken in selected cases.

**CT scan of Thorax and CT guided FNAC:** Done in where under line lung shows space occupying lesion or any mediastinal involvement was suspected.

**Lymph node FNAC:** Fine needle aspiration cytology was done in our FNAC clinic of our pathology department.

**Pleural Fluid Study:** A necessary consent was taken from the patient or near relatives and diagnostic thoracentesis was performed under sonographic guidance.

A minimum of 20 to 25 ml pleural fluid was aspirated and sent for physical analysis, biochemical test (sugar, protein, LDH and ADA) and microbiological test (gram stain, Z-N stain, aerobic culture & mycobacterial culture) in tube without anticoagulant (brown topped). Pleural fluid for cell type, cell count and malignant cell were sent in EDTA treated vial.

**TUBERCULIN SKIN TEST: (Mantoux Test):** Mantoux test is an one procedure of tuberculin skin test which is performed in our chest dept. It is done in all patient. The test is done using 5 TU.

**PLEURAL BIOPSY:** It was done by Abram’s punch biopsy needle. The tissues were fixed in 10% formalin solution then examine under microscope for H/P examination.

**RESULT AND ANALYSIS**

In the present study 120 cases of exudative pleural effusions in the age group of 15 to 40 years of varying etiology were taken who attended the Pulmonary medicine Department, Burdwan Medical College and Hospital, Burdwan.

The study was conducted during the period March 2017 to February 2018. Apart from relevant history taking a detail clinical examination, full investigation were done to reach a complete and final diagnosis. Exudative pleural effusions were subdivided mainly into three groups

1. Tuberculous Pleural effusion (TBPE)
2. Parapneumonic Pleural effusion (PNE)
3. Malignant pleural effusion (MPE)

**Analysis of clinical data :**

Table 1 shows the different aetiological diagnosis of all the 120 cases of pleural effusion.

**Table 1: Subdivision of cases according to aetiology**

Group	Aetiological diagnosis	No. of cases	Percentage
1	Tubercular pleural effusion (TBPE)	102	85
2	Parapneumonic effusion (PNE)	12	10
3	Malignant Pleural effusion (MPE)	6	5

**Table 2: Age distribution in tuberculous pleural effusion**

Age Group	No. of cases	% of total TBPE
15-20 years	18	17.64
21-25 years	34	33.33
26-30 years	25	24.50
31-35 years	15	14.70
36-40 years	10	9.80

The mean age was 26.27 years. The youngest one is aged 15 years and the oldest was 40 years. The maximum patients were in the age group between 21-25 years.

**Table 3: Age distribution in parapneumonic effusion**

Age Group	No. of cases	% of total TBPE
15-20 years	1	8.33
21-25 years	1	8.33
26-30 years	2	16.66
31-35 years	3	25.0
36-40 years	5	41.66

The mean age was 32.41. Lowest age was 18 years and the oldest was of 40 years. Maximum incidence was in between 36-40 years of age group.

**Table 4: Age distribution in Malignant Pleural effusion**

Age Group	No. of cases	Total MPE Percentage
15-20 years		
21-25 years		
26-30 years		
31-35 years	2	33.33
36-40 years	4	66.66

The mean age was 37.16. This was considerably higher than tuberculous group and parapneumonic group. The highest number of patients in the age group of 36-40 years.

**Table 5: Sex Incidence Groups**

GROUPS	Male		Female	
	NO.	Percentage	NO.	Percentage
Tuberculous	77	75.59	25	24.50
Parapneumonic	10	83.34	2	16.66
Malignant	5	83.34	1	16.66

From the above table it was evident that incidence of pleural effusion in this series more in male in all groups.

**Table 6: Residence of the patients**

GROUPS	Urban		Rural	
	NO.	Percentage of total	NO.	Percentage of total
Tuberculous	65	63.73	37	36.27
Parapneumonic	8	66.67	4	33.33
Malignant	4	66.66	2	33.34

63.73% of Tubercular pleural effusion patients were residing in urban area. The more urban distribution might be due to easy accessibility of the hospital for urban population.

Section-II

A. Symptomatology: Five chief complaints in respiratory disease, i.e., cough, fever, dyspnoea, haemoptysis and chest pain were assessed in all the groups of the patients as shown in the table below.

**Table 7: Sex Incidence Groups**

Symptoms	TBPE	PNE	MPE
Cough	78 (76.46%)	10 (83.34%)	4 (66.67%)
Fever	86 (84.30%)	12 (100%)	2 (33.34%)
Chest Pain	70 (68.60%)	9 (75.00%)	3 (50.00%)
Haemoptysis	9 (8.82%)	2 (16.6%)	3 (50.00%)
Dyspnoea	49 (48.03%)	7 (58.34%)	5 (83.34%)

**Cough:** Both dry cough and cough with expectoration were taken into account. This was found maximally in PNE group (10 patients 83.34%). In TBPE and MPE it was found 76.46% and 66.67% respectively.

**Fever:** Any type of fever whether irregular, intermittent or continuous was taken into account. The range of fever was from 99°F to 105°F. Fever was associated with all cases of PNE group. Also in this group fever was over 100°F in all cases.

**Chest pain:** It was found in 70 (68.60%) cases of TBPE. Maximum incidence in PNE i.e., 9 (75%) cases. Chest pain was found in 3 (50%) cases of MPE. One patient had chest pain and had ST depression in lateral chest lead in ECG and chest pain is due to cardiac cause.

**Dyspnoea:** maximally assessed in MPE i.e., 5 (83.34%) cases). TBPE group dyspnoea noted in 49 (48.03%) cases and in PNE group dyspnoea noted in 7 (58.34%) cases.

**Haemoptysis:** This include from streaky haemoptysis to massive expectoration of blood. In TBPE group it was noted in 9 (8.82%) cases. In PNE group it was noted in 2 (16.60%) cases. In MPE group it was noted in 3 (50.00%) cases.

In the whole series, most common presentation was fever followed by cough, chest pain, dyspnoea and haemoptysis.

**History of Contact:** This is an important history in tuberculous pleural effusion patients. Out of 102 cases only 35 (34.31%) cases were gave a history of contact with tuberculous patients.

**History of Alcohol intake:** It means 40-80 gm / day for 5 days in a week for at least 10 years taken into consideration.

In TBPE group, history of alcohol intake was found in 16 (15.68%) cases. In PNE group, history of alcohol intake was found in 4 (33.34%) cases.

In MPE group, history of alcohol intake was found in 2 (33.34%) cases.

**GENERAL SURVEY:**

Section II

**Pallor:** In TBPE group: Pallor was noticed in 11 (10.78%) cases. In PNE group: Pallor was noticed in 1 (8.33%) case. In MPE group: Pallor was noticed in 2 (33.33%) cases.

**Clubbing:** It was not observed in any patient of TBPE group. Clubbing was noticed in 2 (16.66%) cases of PNE group. In MPE group, clubbing was present in 2 (33.34%) cases.

**Cyanosis and Oedema:** Both cyanosis and oedema were absent in three groups of patients.

**Blood Pressure:** Blood pressure noted in all patients. It was within normal limit of all patients.

**Lymph node Enlargement:** In TBPE group, cervical lymph node enlargement seen in 15 (14.70%) cases. In MPE group: 2 cases had cervical lymph node enlargement and one case had both cervical and axillary lymph node enlargement i.e., 3 (50.00%) cases. No lymph node enlargement is seen in any patient of PNE. **Pulse Rate :** Pulse rate varied between 80-120 per minute. Tachycardia i.e., pulse rate >100 / minute was seen in 85 (83.30%) cases of TBPE. Tachycardia was noticed in all patient of PNE group and in MPE it was seen in 5 (82.34%) cases.

**Jaundice:** It was not seen in any patient.

**Respiratory rate:** It was varied between 16 and 32 per minute. Tachypnoea i.e., respiratory rate >20 / minute was noticed in all cases of PNE group (100%). In TBPE group, it was noticed in 66 (64.70%) patients out of the 102 patients. In MPE group, it was noticed in 4 (66.67%) cases out of 6 patients.

**BCG Scar mark:** It was noticed 60 (50%) patients out of 120 pleural effusion cases. In TBPE group, it was noticed in 52 (50.90%) cases and 8 (66.66%) cases in PNE group and no patient in MPE group

**HIV Screening:** HIV screening done in all cases in our VCTC Department. Patient whose blood showed HIV positive by ELISA screening test, were not included in our study group.

**Examination of sputum:**

a. **Sputum for AFB:** It was collected by the patient in our DOTS center. Sputum sample was stained with

Ziehl Neelsen (Z. N.) stain. In TBPE patient 11 cases (10.78%) were AFB positive.

b. Culture of sputum for mycobacterium tuberculosis : This method was employed to confirm the diagnosis of tuberculous etiology in pleural effusion patients associated with radiological pulmonary infiltration

where sputum for AFB and pleural biopsy for histopathology was found negative. 5 cases of TBPE whose sputum for mycobacterial culture done. 4 cases whose sputum culture were positive for mycobacterial tuberculosis.

**Table 8: Radiological Examination**

CXR findings	TBPE	PNE	MPE
Rt. Sided pleural effusion	52 (55.91%)	8 (66.66%)	4 (66.66%)
Lt sided pleural effusion	41 (44.08%)	4 (33.33%)	2 (33.33%)
Pleural effusion with parenchymal lesion (infiltration, cavity, fibrosis)	23 (22.54%)	0	0
Pleural effusion with mediastinal LN enlargement	12 (11.76%)	0	1 (16.6%)
Pleural effusion with mass lesion	0	0	2 (33.33%)
Pleural effusion with consolidation	0	5 (41.66%)	0
Pleural effusion with metastatic lesion	0	0	0
Massive pleural effusion	17 (16.66%)	3 (25%)	2 (33.33%)
Bilateral pleural effusion	9 (8.82%)	0	0

From the table it is seen that right-sided pleural effusion are more common than the left side in all groups. Pleural effusion involving the right side - in TBPE : 52 (55.91%) cases and in PNE : 8 (66.66%) cases and in MPE : 4(66.66%) cases.

In TBPE, bilateral pleural effusion seen in 9 (8.82%) cases.

In TBPE, parenchymal involvement in the form of infiltration, cavity, fibrosis occurs in 23 (22.54%) cases. In such patients, the effusions is almost always on the side of parenchymal lesions and invariably indicates active parenchymal disease.

Pleural effusion with mediastinal lymph node enlargement - in TBPE -12 (11.76%) cases and in MPE - 1 (16.6%) case noted.

Pleural effusion with mass lesion seen in 2 (33.33%) cases of MPE.

Pleural effusion with consolidation seen in 5 (41.66%) cases of PNE.

Massive pleural effusion involving more than 2/3rd of hemithorax or entire hemithorax seen in 17 (16.66%) cases of TBPE and 3 (25%) cases of PNE and 2 (33.33%) cases of MPE.

CT Scan of Thorax : done in 10 cases of pleural effusion, where underlying mass or mediastinal enlargement was suspected by chest x-ray and in patients where diagnosis was in doubt.

CT guided FNAC : done in patient with pleural effusion where mass lesion are noted in chest x-ray and they were situated peripherally and diagnosis is not confirm otherwise. 7 cases are performed. Of which 2 cases are diagnosed as malignancy and 1

case as tubercular granuloma and 4 cases shows nonspecific inflammation.

Lymph node FNAC : FNAC of lymph node were done where LN were enlarged and approachable. In the whole series 18 patients had enlarged peripheral LN. FNAC was done in all the cases the results are given below.

- i) Tuberculous caseation 11
- ii) Metastatic carcinoma 2
- iii) Nonspecific inflammation 5

In TBPE - 15 (14.70%) cases shows lymph node enlargement. FNAC of this lymph node done, 11 cases shows caseating granuloma, 4 cases shows nonspecific inflammation.

In MPE - 3 (50%) cases shows lymph node enlargement. FNAC of these 3 cases done. 2 cases are diagnosed as metastatic carcinoma. One case shows nonspecific inflammation.

**Table 9: Examination of pleural fluid**

Colour	TBPE	PNE	MPE
Clear fluid	6 (5.88%)	0	0
Pale yellow	82 (80.39%)	3 (25%)	2 (33.33%)
Reddish	14 (13.72%)	0	4 (66.66%)
Turbid	0	9 (75%)	0
White or Milky	0	0	0

From these observations, we found TBPE 80.39% cases the colour of fluid is pale yellow and slightly hazy.

In MPE 33.33% cases the pleural fluid colour is pale yellow. In PNE 25% cases the pleural fluid colour is pale yellow. In TBPE reddish colour is noted in 14 (13.72%) cases. In MPE reddish colour is noted in 4 (66.66%) cases.

In PNE Turbid colour is noted in 9 (75%) cases whereas pale yellow noted in 3 (25%) cases.

**Table 10: Cell count and cell type**

Cell Count Per Cmm	TBPE	PNE	MPE
0-500	15 (14.70%)	-	1 (16.66%)
501-1000	51 (50%)	-	4 (66.66%)
1001-1500	21 (20.58%)	2 (16.66%)	1 (16.66%)
>1500	15 (14.70%)	10 (83.33%)	6

**Table 11: Lymphocyte Count In Different Group**

LYMPLIOCYTE %	TBPE	PNE	MPE
Less than 50%	-	12(100%)	-
50-60%	-	-	-
61-70%	3 (2.94%)	-	-
71-80%	11 (10.78%)	-	1 (16.66%)
81-90%	18 (17.64%)	-	1 (16.66%)
91-100%	70 (68.62%)	-	4 (66.66%)

Most of the cases of TBPE and MPE predominant cell is lymphocyte. In TBPE and MPE total lymphocyte count 500 to 1000. Whereas in PNE cell count greater than 1500 in 83.33% cases and predominant cells are neutrophils.

In TBPE - Differential count Predominantly lymphocytes mostly 90-100% is seen in 68.62% cases whereas in MPE - predominantly lymphocytes which varies 90-100% cases seen in 66.66% cases

Whereas in PNE lymphocyte count was noted less than 50% preferably below 20% noted in 100% cases. Eosinophil count was noted less than 5% in all cases.

Microscopic Study of Pleural Fluid:

Z-N stain for AFB: In our series only 2 (1.96%) cases were found positive for AFB in the tuberculous group. Gram Stain: It was done in all cases only 4 cases was positive for pyogenic organism. Ultimately these four cases were diagnosed PNE group.

**Papanicolaou's stain:** It was done to detect malignant cells. Done in all cases. It was positive in 4 (66.66%) cases. These four cases were diagnose MPE.

**Culture of pleural fluid for mycobacteria :** It was done in selected cases of pleural effusion.

**Biochemical examination of pleural fluid :**

Blood was drawn in fasting condition from each patient and pleural aspiration was also done within close interval in the same day. Pleural fluid for glucose and protein and serum for FBS and protein was estimated. The results obtained are shown below.

The mean blood glucose in the various groups are as follows : -

Tubercular group: 77.84 (±21.42)

Paraneumonic group: 117.08 (±39.24)

Malignant group: 90.66 (±26.97)

**Table 12: Pleural fluid glucose**

Pleural fluid glucose mg%	TBPE	PNE	MPE
0-40	3 (2.94%)	6	2
41-60	44 (43.73%)	6	4 (66.66%)
61-90	50 (49.01%)		
Above 90	5 (4.90%)		
Mean	59.05±11.49	38±6.04	47.16±10.16

From the above table, it is seen that mean glucose in pleural fluid in tubercular group was 59.05 ± 11.49 mg%. In TBPE pleural fluid glucose in the range between 61-90 mg% were 50 cases, and 41-60 mg% were 44 cases, and 0-40 mg% were 3 cases, and above 90 mg% were 5 cases.

In PNE - it was noted that pleural fluid glucose level was quite lower PNE group.- It is 100% cases in below 50 mg%. In MPE mean pleural fluid glucose in 47.16±10.16. Majority in the range of 41- 60 mg%.

**Table 13: Pleural fluid Protein estimation**

Total Pleural fluid protein gm%	TBE	PNE	MPE
Less than 3	0	0	0
3.1-4.0	16 (15.68%)	2 (16.66%)	1
4.1-5.0	26 (25.49%)	7 (58.33%)	2
>5	60 (58.82%)	3 (25%)	3 (50%)
Mean Protein	5.37 ± 0.98	4.6 ± 0.74	4.83 ± 0.89

In TBPE - Mean pleural fluid were 5.37±0.98. Pleural fluid protein greater than 5 gm% noted in 60 (58.82%) cases.

In PNE Pleural fluid protein in the range of 4.1-5.0 gm% is noted in 7 cases out of 12 cases, i.e., 58.33%.

In MPE - Pleural fluid protein greater than 5 gm% noted in 3 out of 6 cases, i.e., 50%.

Results of observations of ADA activity in Pleural fluid:

In all cases of pleural effusion in the age group of 15-40 years, thoracentesis was done and ADA level of pleural fluid measured along with other parameters.

In TBPE Mean ADA = 89.23 ± 28.18

In PNE Mean ADA = 115.24 ± 229.99

In MPE Mean ADA = 32.34 ± 4.98

**Table 14: For comparison the ADA values in different groups are tabulated Below**

Group No	No of patients	Pleural fluid ADA values			
		Mean	S.D.	Range	
1	Tuberculous	102	89.23	28.18	42.2-169.3
2	Parapneumonic	12	115.27	22.99	72.8-152.0
3	Malignant	6	32.34	4.98	26.03-38.6

**Statistical significance of pleural fluid ADA level :**

In our study pleural fluid ADA level more than 70 U/L was taken as the upper limit above which tuberculous effusion is almost diagnostic as per previous references. Pleural fluid ADA level less than 40 U/L was considered as the lower limit below which tuberculous effusion is less likely and if clinically suspected a malignant effusion must be excluded.

So now it will be seen statistically whether ADA measurements in these ranges are significant to diagnose tuberculous effusion.

Here Chi-Square Test (x<sup>2</sup>) will be applied to determine the statistical significance of pleural fluid ADA level > 70 U/L to diagnose tuberculous effusion. Table below shows the pleural fluid ADA level > 70 U/L and < 70 U/L in cases of tuberculous effusion and non-tuberculous effusion.

Applying the x<sup>2</sup> test, x<sup>2</sup> = 14.85. So the probability (P) value will be much <0.001. So the test i.e., pleural fluid ADA level >70 U/L is accepted to diagnose tuberculous effusion.

Determination of sensitivity and specificity :

Sensitivity and specificity of pleural fluid ADA levels >70 U/L to diagnose tuberculous pleural effusion.

1. Sensitivity = 95.09%
2. Specificity = 33.33%
3. Predictive Value of a +ve test = 88.99%
4. Predictive value of a -ve test = 54.54%
5. Percentage of False Positive = 66.66%
6. Percentage of False Negative = 4.90%

In our study specificity of the test (ADA > 70 U/L for diagnosis of TBPE) is 33.33%. This is because in our study age group is mention (15to40 years) and in this age group, we found only 6 cases of pleural effusion due to malignant process (taken as a control) where ADA is lower.

The other aetiology apart from TBPE in which ADA level were found more than 70 U/L is most cases of PNE which can be differentiated from tuberculosis effusion clinically and by pleural fluid appearance and

its cytological and bio-chemical examination. So, if we exclude the cases of PNE the specificity of ADA > 70 U/L will be increased to diagnose TBPE.

Sensitivity and specificity of pleural fluid ADA level > 70 U/L to diagnose TBPE when Empyema cases are excluded.

1. Sensitivity = 95.09%
2. Specificity = 100%

**Tuberculin skin test (Mantoux test) :**

Results of observations of Mantoux Test in pleural fluid in the age group of 15-40 years. In all cases of pleural effusion tuberculin skin test (5TU) was done and induration measured after 72 hours.

**Table 15: Mantoux Test in different group**

Group	No. of patients	Tuberculin skin Test		
		Mean	S.D.	Range
Tuberculous	102	13.34	5.60 mm	3-24
Parapneumonic	12	6.75	3.46 mm	2-14
Malignant	6	5.83	4.01	0-12

**Table 16: Mantoux test in different ranges in different aetiologies**

Tuberculin test (5TU)	TBPE	PNE	MPE
0-4	3= 2.94%	2	2
5 – 9	23= 22.54%	7 =58.33%	3 =66.66%
10- 14	43= 42.15%	3	1
15-19	24= 23.52%	-	-
Above 20	9= 8.82%	-	-
Total	102	12	6

**Statistical significance of Tuberculin skin test in a patient of tubercular pleural effusion :**

In our study tuberculin skin test results 10 mm or more was taken as the upper limit above which the results is positive as per previous references. Tuberculin skin test results below 10 mm were considered negative which denotes tuberculous infection is less likely. So now it will be seen statistically whether tuberculin skin test in these ranges are significant to diagnose tuberculous infections or not.

Here "Chi-Square Test" (x<sup>2</sup>) applied to determine the statistical significance of tuberculin skin test results greater than 10 mm to diagnose the tuberculous infections. Table below shows tuberculin skin test results >10mm and <10 mm in cases of tuberculous effusion and non-tuberculous effusion.

**Table 17:**

Test	TBPE	Non-TBPE	Total	%+ve of TBPE
Tuberculin skin test result $\geq 10$ mm	76	4	80	95
Tuberculin skin test result $< 10$ mm	26	14	40	65
Total	102	18	120	

Let us first consider that tuberculin skin test result  $>10$  mm and  $<10$  mm has no difference to diagnose tuberculous effusion. Proportion of tuberculous pleural effusion will be = 0.85. Proportion of Non-TBPE will be = 0.15

From the above, in the group of Tuberculin skin test result  $>10$  mm

1. Expected number of TBPE will be  $0.85 \times 80 = 68$ .
2. Expected number of Non-TBPE will be  $0.15 \times 80 = 12$ .

In the group where tuberculin skin test  $<10$  mm,

1. Expected number of TBPE will be  $0.85 \times 40 = 34$ .
2. Expected number of Non-TBPE will be  $0.15 \times 40 = 6$ .

**Table 18: We shall now rewrite the previous table showing the observed (O) and expected (E) values in each group.**

Mantoux Test	TBPE	Non-TBPE
$\geq 10$ mm	Observed Value: 76 Expected Value: 68	Observed Value: 4 Expected Value: 12
$< 10$ mm	Observed Value: 26 Expected Value: 34	Observed Value: 14 Expected Value: 6

Applying the X2 Test,  $x^2 = 18.8233$ . So the probability (P) value is much  $<0.001$ . So the test i.e., Mantoux  $\geq 10$  mm is accepted to diagnose tuberculous infections.

Determination of Sensitivity and Specificity

1. Sensitivity = 74.50%
2. Specificity = 50%.
3. Predictive Value of a +ve test = 95%.
4. Predictive value of a -ve test = 35%.
5. Percentage of False Positive = 14.28%.
6. Percentage of False Negative = 25.49%

Statistical difference between ADA  $\geq 70$  U/L and tuberculin skin test 10 mm to diagnose tuberculous infections.

**Table 19:**

Parameters	Positive	Negative	Total	% of Positive
ADA $> 70$ U/L	97	5	102	95.09
Mantoux test $\geq 10$ mm	76	26	102	74.50

Apparently it is seen that ADA  $> 70$  U/L is a more effective method to diagnose tuberculous effusion. Now applying x2 method, we will determine if this apparent superiority is statistically significant or not. We shall now re-write the table showing the O and E values in each cell.

**Table 20:**

Test	Positive	Negative
ADA $> 70$ U/L	Observed Value: 97 Expected Value: 92.35	Observed Value: 12 Expected Value: 16.35
Mantoux test $>10$ mm	Observed Value: 76 Expected Value: 68	Observed Value: 4 Expected Value: 12

Now applying the X2 Test,  $x^2 = 7.62$ . So P value is much  $<0.01$ . Hence we can conclude that ADA  $> 70$  U/L is a superior test than Mantoux test  $\geq 10$  mm to diagnose tuberculous infections as per statistical significance is concerned.

### Pleural Biopsy

Pleural biopsy is an invasive procedure and its overall sensitivity is about 50 - 80%. In our study we had not performed pleural biopsy in every cases because it is an invasive procedure requires hospitalization. Some patients deny invasive procedure.

We performed 27 cases which are doubtful about the diagnosis. Abram's needle was used for this purpose. The results obtained for the two groups, i.e., tuberculous and malignant group are shown below.

**Table 21:**

Groups	No. of patients	Pleural Biopsy +ve	Pleural Biopsy -ve	% of +ve Biopsy
TBPE	22	15	7	68.18
MPE	5	3	2	60

From the table it is evident that positive biopsy was found 68.18% cases of TBPE and 60% cases of MPE. In tuberculous group presence of granuloma with or without caseation was taken as positive. In Malignant group, most cases result shows carcinomatous deposit, type not mention.

### DISCUSSION

In our study, 120 cases of pleural effusion in the age group of 15 to 40 years were taken. Clinical, radiological, biochemical, cytological parameters were observed in all cases. Pleural biopsy was done in 27 cases to reach confirmed diagnosis. Special attention was paid to determine the pleural fluid ADA level. Tuberculin skin test using mantoux procedure

done in all cases of pleural effusion in this age group. Only the aetiological confirmed cases were included in this study. Different approaches were considered as relevant in each case.

Three groups of patients were observed in this study. Tuberculous, Malignant and Parapneumonic prevalence of different groups in these age groups were TBPE 85%, PNE 10% and MPE 5%.

#### **Clinical Study:**

1. **Age:** In tuberculous group mean age was 26.27 years. Majority of the cases in the age range of 21 to 30 years.

The mean age in the PNE group was 32.41 years. Majority case was in the range of 31 to 40 years.

In the malignant group mean age was 37.16 years. Majority case was in the range of 35 to 40 years.

Different studies have shown that tuberculous pleural effusion affects younger age group. Kraft (1949)<sup>104</sup> reported that the maximum patients (92%) of tuberculous pleural effusions belongs in the age range of 18 - 30 years.

Roper and Warling (1955)<sup>120</sup> showed that most of the patients (75%) of TBPE remains in the age group of 18-25 years. Ghosh (1964)<sup>105</sup> reported that 74% of the cases remain in the age range of 11-30 years.

In our present study we found that 57.83% of tuberculous effusion lies in the age group of 21 to 30 years.

In our study, pleural effusion in the age group of 15 - 40 years, of 120 cases of pleural effusion we found only 6 cases of malignant pleural effusion. Mean age was 37.16 years. All cases lies in the age group of 31 to 40 years. Robson (1952)<sup>118</sup> and Grant (1954) reported that majority of cases of malignant pleural effusion were above 40 years.

In PNE group mean age was noted in 32.41 years. PNE patient seen in all age group with maximum incidence occurs in 31 to 40 years of age.

2. **Sex Incidence:** In our studies in all the three aetiological groups, male patients were predominant. In MPE group incidence of male patient was 83.34%.

In PNE group incidence of male patient was also 83.34%.

In TBPE group incidence of male patient was 75.50% and female incidence was 24.50%.

Bonilla (1942)<sup>121</sup> showed 50.02% incidence in males. Reddy and Indira (1963)<sup>116</sup> found 58.6% incidence in males while Ghosh (1964)<sup>105</sup> indicated a male preponderance of 76%.

3. **Residence:** In our series, we found that in all the three groups urban distribution was more than rural

distribution. It was probably related to easy accessibility of this hospital to urban population.

4. **History of Contact:** In the tuberculous effusion patients, contact history was found in 35 cases (34.31%) out of 102 patients.

This was comparable to the findings of Bonilla (1942)<sup>121</sup>, Erwin (1944), Thompson (1946), Karon and Purves (1947)<sup>114</sup> and Sibley (1950)<sup>122</sup>, JM, Marino et al (1999)<sup>6</sup> history of contact was found 25.7% cases.

The adult population does not confine themselves into home and many patients deny family history of tuberculosis. Consequently elicitation of history of contact is difficult.

5. **Smoking Habit:** It is an important history in cases of malignant group. All patients in this group had smoking habit (100%).

#### **Analysis of Symptoms:**

1. **Fever:** In the tubercular group we observed fever 86(84.30%) cases and in neoplastic group fever was noticed in 33.34% cases. Fever was present in 100% cases of parapneumonic group.

Mestitz and Pollard (1959)<sup>123</sup> reported an incidence of fever in 82.2% in tuberculous effusion. Richard W. Light stated in his book "Pleural Diseases" that most patients are febrile with tuberculous effusion, but normal temperature does not rule out the diagnosis.<sup>5</sup> Epstein et al (1985)<sup>14</sup> reported an incidence of fever in 69.56% in tuberculous group. Ghosh (1964)<sup>105</sup> observed fever in 50% cases with MPE.

2. **Cough :**It was the presenting feature in 78 (76.46%) cases of TBPE and 4 cases (66.67%) of MPE patients. Here cough was predominantly dry, But in PNE group, cough with expectoration was predominant found in 10 (83,34%) cases. Epstein et al (1985)<sup>14</sup> found 14 of 23 cases (60.86%) of tuberculous group presented with cough. Richard W. Light in his book "Pleural Diseases" (4th edition)<sup>5</sup> stated that most patients (- 70%) with TBPE had cough.

3. **Chest Pain:** In our series chest pain was found 70 (68.60%) cases of TBPE, 9 (75%) cases of PNE and 3 (50%) cases of MPE group. Epstein et al (1985)<sup>14</sup> noted chest pain was present in 52.17% cases of TBPE patients. Light (4th edition)<sup>5</sup> describe most patients of TBPE had chest pain (-75%).

4. **Dyspnoea :** In our study dyspnoea was observed maximally in MPE group, 5 cases out of 6 patients (83.34%) In TBPE group and PNE group it was noted 48.03% and 58.34% respectively.

Karon and Purves (1947)<sup>114</sup> reported an incidence of dyspnoea in TBPE patients of 25% and Ghosh

observed in 38% of their series. Epstein et al (1985) found dyspnoea in their 23 cases of TBPE, patient (47.82%). Dyspnoea was relieved by therapeutic aspiration.

5. Haemoptysis : In our series haemoptysis was observed maximally in MPE 3 (50%) cases followed by PNE 2 (16.6%) cases and TBPE 9 (8.82%) cases. Erwin (1944) and Karon (1947)<sup>114</sup> reported an incidence of haemoptysis in TBPE 6-7% and Ghosh<sup>105</sup> mentioned an incidence of 2%.

6. Examination of sputum for Z-N stain and MTB culture : Sputum for AFB staining done in all cases of pleural effusion in our DOTS Centre. 11 cases (10.78%) were seen AFB positive by Z-N stain.

Sputum for Mycobacterial culture was employed to confirm the diagnosis of tuberculous etiology in pleural effusions patients associated with radiological pulmonary infiltration where sputum for AFB stain and pleural biopsy was found negative. Sputum culture for MTB was done in 5 cases only, 4 cases yielded positive culture.

Sputum for Mycobacterial culture and sputum for Z-N stain were positive in patients mostly in those patients where chest x-ray shows parenchymal lesion.

7. **Radiological examination:** Routine chest x-ray (PA view) confirmed the clinical diagnosis in all cases of pleural effusion.

In our series right sided pleural effusion more common than left sided pleural effusion. Pleural effusion involving right side

In TBPE group: 55.91%

In PNE group: 66.66%

In MPE group: 66.66%.

Rom and Garay<sup>109</sup> 2nd edition stated that in TBPE, plain chest radiograph most often reveal unilateral pleural effusion, more often involving right Pleural cavity.

Epstein et al (1985)<sup>14</sup> stated that tuberculous pleural effusion was more common in right side of 23 TBPE patient 15 had pleural effusion in right side and 8 had pleural effusion on left side.

In our series massive pleural effusion involving more than 2/3rd of hemithorax noted in 17 cases (16.66%) of TBPE, 3 cases (25%) of PNE and 2 cases (33.33%) of MPE.

Lights (4th edition)<sup>5</sup> stated that pleural effusion secondary to tuberculosis are usually unilateral and can be of any size. In one series the effusion occupied more than 2/3rd of hemithorax in 18%, between 1/3

and 2/3 of hemithorax in 47% and less than 1/3rd of hemithorax in 34% cases.

In our series, in TBPE parenchymal involvement in the form of infiltration, cavity, fibrosis noted in 23 (22.54%) cases. Pleural effusion with mediastinal lymph node enlargement seen in 12 (11.76%) cases of TBPE and one case of MPE. Pleural effusion with mass lesion seen in 2 (33.33%) cases of MPE. Pleural effusion with consolidation seen in 5 (41.66%) cases of PNE. Bilateral pleural effusion seen in 9 cases (8.82%) of TBPE.

Murray and Nadel (4th edition)<sup>20</sup> stated that about 1/3rd of patient have coexisting parenchymal disease. In such patients the effusion is almost always on the side of parenchymal lesions and invariably indicates active parenchymal disease.

Murray and Nadel (4th edition)<sup>20</sup> stated that approx. 20-40% of patients with bacterial pneumonia have an accompanying pleural effusion.

Rom and Garay (2nd edition) stated that bilateral pleural effusion may also noted as many as 10% cases of TBPE.

8. **Lymph node FNAC:** In our series 18 patients had enlarged superficial LN. Tuberculous caseation necrosis was found in 11 cases. Metastatic carcinoma was detected in 2 cases by FNAC. Nonspecific inflammation noted in 5 cases.

#### **Study of pleural fluid**

1. **Appearance:** Most of the tuberculous effusion was pale yellow coloured (80.39%) but reddish fluid was observed in 13.72% cases.

In malignant pleural effusion reddish appearance was found in 66.66% cases but pale yellow colour fluid noted in 33.33% cases.

In PNE group appearance of pleural fluid was mostly turbid (75%).

From this series it is seen that pale yellow coloured pleural fluid favours diagnosis of tuberculous aetiology but in 13.72% cases it is seen in reddish colour.

2. **Cytological examination:** Cell type, cell count were performed in all cases.

In TBPE group - TLC varies between 250 and 3,800 cells/cmm of pleural fluid. Most cases 70.58% cases TLC in the range of 500 to 1,500. Less than 500 noted in 14-70% cases. Predominant cells are lymphocytes. Lymphocytes percentage noted more than 60% cases in 100% cases. Range varies 60% to 100%. 91-100% noted in 68.20% cases.

In MPE group - total leukocyte count varies between 350 and 1,500 cells/cmm of pleural fluid. Most cases in the range of 500 to 1,000 seen in 66.66% cases. Most cases lymphocytes count noted more than 70% cases.

In PNE group - all patients had cell count >1000/cmm. All patients had neutrophil count >50%.

Rom and Garay (2nd edition)<sup>109</sup> stated that in TBPE fluid leukocyte counts usually range from several hundred to approximately 5,000/cmm. Cytological analysis usually reveals lymphocyte predominance and in many instances 90% to 95%.

Luis Valdes, David Alvarez (1997)<sup>13</sup> found in tuberculous pleural effusion, 93.5% of the effusion, more than 50% leukocytes are lymphocytes and almost all had the biologic characteristic of exudates.

Berger Et Mejia (1973)<sup>15</sup> reported 88% of tuberculous effusion had more than 50% lymphocytes.

3. Microscopic study of pleural fluid : Only 2 cases were found positive for AFB (1.96%) in tuberculous effusion. Z-N stain of pleural fluid for AFB done in all cases.

Gram staining of pleural fluid done in all cases. Only 4 cases were positive from pyogenic organism. These four cases diagnosed PNE.

PAP stain to detect malignant cells done in all cases. 4 cases were positive. This four cases were diagnosed MPE.

#### 4. Biochemical examination of pleural fluid :

i) Protein: Pleural fluid protein was found more than 3 gm /dL in all cases in our series.

In our series in TBPE, Mean pleural fluid was noted  $5.37 \pm 0.98$  gm%, Range 3.4 to 6.7 gm%. Pleural fluid protein greater than 5 gm% noted in 58.82% cases.

In MPE, Mean pleural fluid protein  $4.83 \pm 0.89$  gm%, range 3.5 to 6.1 gm%.

In PNE group, Mean pleural fluid protein was  $4.6 \pm 0.74$  gm%, range 3.4 to 6.3 gm%, mostly (58.33%) in the range 4.1 to 5.0 gm%.

Nadel and Murray's (4<sup>th</sup> edition) stated that if the pleural fluid protein is above 5.0 gm/dl, the likelihood of the diagnosis of tuberculous pleurisy is increased.

Rom and Garay (2<sup>nd</sup> edition) stated that serous pleural effusion with total protein in the range of 4 to 5 (or more) gm /dl are characteristic of tuberculous pleural effusion, although lower protein extent may be found with AIDS.

Seibert et al (1988)<sup>38</sup> stated that in TBPE mean pleural fluid was  $5.2 \pm 0.2$  gm/dl (range 3.0 to 7.6).

Luis Valdes et al (1998)<sup>13</sup> found 98.8% had high total protein extent in TBPE. Our findings corroborate with this finding.

ii) Sugar: Pleural fluid glucose level was estimated in all patient along with their fasting blood sugar level.

In our series in TBPE mean pleural fluid glucose was observed  $59.05 \pm 11.49$  mg% range 32 to 110 mg% and below 60 mg% noted in 46.07% and above 60 mg% noted in 53.91% cases.

In PNE group, mean value  $38 \pm 6.04$  mg%, range 33 to 70 mg% and <60 mg% noted in 100% cases.

In MPE group, mean pleural fluid glucose  $47.16 \pm 10.16$ , range 31 to 60 mg%, less than 60 mg% noted in 100% cases.

Calnan et al (1951)<sup>111</sup>, Barbar et al (1957), Mishra (1965) were of Opinion that pleural fluid glucose level were diminished in tuberculous effusion.

Clarkson (1964), Barger and Maher (1971)<sup>110</sup> opined that low glucose level in pleural fluid was found in malignant effusion.

Alevert (1962), Ciana (1971) and Carr (1963) observed low pleural fluid glucose level in parapneumonic effusion.

Light's pleural disease (4th edition) stated that measurement of the pleural fluid glucose level is useful in the differential diagnosis of exudative pleural effusions because a low pleural fluid glucose level (<60 mg/dl) indicates that patient probably has one of four disorders, namely parapneumonic effusion, malignant disease, rheumatoid disease or tuberculous pleuritis. Our observation was corroborative with these findings.

**Pleural biopsy:** In our series, we performed pleural biopsy 27 cases, where the diagnosis was in doubt and there was no contraindication.

It was done in 22 patients of TBPE, of which 15 cases showed caseating or non-caseating granuloma so the positive yield in TBPE is 68.18%.

Pleural biopsy diagnosed 3 cases of malignant pleural effusion out of 5 cases performed. So the positive yield in MPE is 60%.

So positive yield of pleural biopsy to diagnose tuberculous effusion was almost similar to the findings of Diana Autonikis et al (1972) which were 72%.

Allan F Seibert (1988)<sup>38</sup> et al showed that positive pleural biopsy obtained in 66.7% in tuberculous effusion.

Inma Ocana, Jose M (1983)<sup>8</sup> yield positive biopsy specimen in 37 cases (88.9%) of tuberculous pleural effusion

Murray and Nadel (4th edition) stated that needle biopsy of the pleura has its greatest utility in diagnosing tuberculous pleurisy. The initial biopsy is positive for granulomas in 50% to 80% of patients. But in malignant pleural disease the needle biopsy of the pleura will be positive in 40% to 60% of patients. In malignant pleural effusion the positive yield was far low than tuberculous effusion. This difference was possibly due to the fact that tuberculous pleuritis involves the parietal pleura diffusely, whereas malignant deposits are relatively localized.

**Observation of ADA activity in pleural fluid :**

The first significant study of ADA activity in pleural fluids was undertaken by Piras, Gakis et al (1978)<sup>1</sup>. In their series they found that ADA concentration was significantly higher in tubercular effusion as compared to parapneumonic and malignant effusion. The mean ADA in tubercular effusion was 83.0 ± 25.51 as compared to malignant effusion 15.54 ± 6.56 U/L.

Maritz FJ, Malan C, Roux et al (1982)<sup>91</sup> estimated ADA activity in 368 cases of pleural effusion. They found high activity in tuberculous effusion (92.11+ 37.05 U/L) as compared to malignant effusion (23.23 ±13.15). They also found very high values of 97.55 ± 82 .

Blake (1982) indicated that ADA levels greater than 30 U/L in pleural fluids pointed towards tuberculosis. Singh R.P. et al (1986)<sup>92</sup> studied ADA in 65 cases of pleural effusion.

They found the following on ADA activity.

1. Tuberculous: 72.5 137.01 U/L
2. Malignancy: 10,0 - 26.3 U/L
3. Transudates:6,5 - 10.0 U/L

Strankinga, Nauta and other (1987)<sup>94</sup> concluded from their studies of ADA activity in pleural effusion that it was high in patients with tuberculosis and empyema. Specificity (87%) and sensitivity (100%) of this test for tuberculosis is high, when a reference limit of 53 U/L was taken.

In our study of 120 cases of pleural effusion the following results were obtained as regards of ADA activity in pleural fluids.

Table showing the results of ADA activity in pleural fluid in our series:

Aetiological group	Mean	S.D.	Range
Tuberculous pleural	89.23	28.18	42.2
Parapneumonic	115.24	22.99	72.8 - 152.0
Malignant effusion	32.34	4.98	26.03 - 38.6

In our study pleural fluid ADA level more than 70 U/L was taken as the upper limit as one which tuberculous effusion is almost diagnostic as per previous references. Pleural fluid ADA level less than 40 U/L was considered as the lower limit below which tuberculous effusion is less likely. It correspondence with above studies.

**Table 22: Cut off value of pleural fluid ADA level to diagnose tuberculous effusion by different study:**

Year	Workers	Mean Pleural fluid ADA value / cut off value
1978	Piras and Gakis	83.0 ± 25.51
1982	Maritz, Malon	92.11 ± 37.05
1982	Blake	46.03 ±13
1983	Inma Ocana	92.43 ± 29.43
1984	Patterson	83.3 ± 7.3
1987	Strankinga	11 6.5
1990	Gupta DE	77.61 U/L
1991	Banales	70.0 U/L cut off value
1992	Prasad R	64.67 ± 21.68
1992	MV Nagaraja	137.0 ± 53.23
1994	De Oliveira	40 U/L (cut off value)
1995	Valdes	47 U/L (cut off value)
1996	Burgess	50 U/L (cut off value)
1998	Khan	40.2± 10.82 (mean value)

**Tuberculin skin test (Mantoux test) in patient with pleural effusion:**

In our study tuberculin skin test using intermediate strength done in all patients of pleural effusion in the age group of 15 to 40 years. After 72 hours reading was taken. Induration 10 mm or more taken as positive and induration less than 10 mm taken as negative which denotes tuberculous infection is less likely.

In TBPE mean value is 13.34 ± 5.60 mm, range 3-24 mm.

In PNE group mean value is 6.75 ± 3,46, range 2-14 mm.

In MPE group mean value 5.83 4.01, range 0-12 mm.

In TBPE tuberculin skin test ≥ 10 mm was found in 76 cases (74.50%).

In PNE group tuberculin skin test ≥10 mm was found in 3 cases (25%).

In MPE group Tuberculin skin test ≥ 10 mm was found in one case out of 6 cases (16.66%)

This goes in conformity with the observation of other workers.

Wallgren (1930) carried out the first large comprehensive study in 264 cases of pleurisy in

children of whom all except two were tuberculin positive. This observation of Wallgren proved to be valid also in young adults who were followed from the tuberculin negative stage or from the stage of primary infection with clinical manifestation.

This observation was verified by Farber (1943) and Fildman and Lewis (1946) who however included a few tuberculin negative patients although the diagnosis in these cases were based on clinical picture alone. Eberle (1949) in Queen Mary's Hospital found 97 tuberculin positive cases in 1 : 10,000 dilution and 32 tuberculin positive cases in 1 : 1,000 dilution out of 132 cases.

Berry in 1954 found positive results in 19 out of 23 cases. The 2 out of 4 negative cases were seriously ill. Mertitz et al (1959) in 66 cases and Deshmukh et al (1968) in 70 cases of tuberculous pleural effusion performed tuberculin test and was found to be positive in all.

Allan F. Seibert (1991)<sup>38</sup> et al tuberculin skin test by intradermal injection of 5 TU of PPD. Induration was measured after 48 to 72 hours and recorded in mm. 10mm. of palpable induration was used as the criterion for positive test. They performed 43 cases of tuberculous pleural effusion and found positive in 40 cases (93%). The three patients with negative (<10 mm) skin test actually had no palpable induration (0 mm) They concluded that skin testing with intermediate strength PPD has a high sensitivity in patients with pleural tuberculosis.

David M. Epstein et al (1987)<sup>14</sup> studied 26 adults patient with TBPE. Of which 15 patients were injected with 1 TU of PPD and results are noted after 48 to 72 hours. They found 11 patients were reactors and four were anergic (73.3%).

Berger and Mejia (1973) studied 36 patients with tuberculous pleural effusion and found positive tuberculin skin test in 25 patients (69.44%).

Jose M. Merino (1999)<sup>6</sup> et al studied 175 children <18 years were diagnosed having primary pulmonary tuberculosis of which 39 showed pleural effusion. Tuberculin skin test was done in 39 patients using intradermal injection of 2 tuberculin units of PPD, induration measured after 48 to 72 hours and >5 mm regarded as positive. They found 38 patients positive (97.4%).

## SUMMARY AND CONCLUSION

### Summary:

Involvement of pleural surfaces by tuberculous is one of the two most common extra Pulmonary manifestation of tuberculosis, the other being

lymphatic involvement. Tuberculous pleural effusion accounting for 25% to 37% of all pleural effusion. India is one of the endemic region for tuberculosis. Every third tuberculous patient reside here. In a 20 year retrospective review, pleural tuberculosis represented 4.9% of the 1738 cases of tuberculosis reported from Alabama. Typically, tuberculous pleural effusion was described to occur 3 to 7 months following initial infection with Mycobacterial tuberculous and therefore was usually seen in children and young adults.

Different modes are being used to diagnose the aetiology. But apart from pleural biopsy, sensitivity of other tests is very low. Pleural biopsy is an invasive procedure and facilities are not widely available. So, in our clinical setting antituberculous drugs are often prescribed empirically in young patients with a lymphocytic predominant exudative pleural effusion. ADA in pleural fluid is now an established biochemical worker for tuberculous effusion. It can substantiate the diagnosis of tuberculous effusion in most of the cases.

In our study 120 patients of aged 15 to 40 years with pleural effusion were taken. Different aetiological groups and their frequency as diagnosed by various mean were –

1. Tuberculous: 85%
2. Parapneumonic effusion: 10%
3. Malignant effusion: 5%

Thy observations are summarized below

1. Mean age was youngest in tuberculous group, 26.27 years compared to malignant group 37.16 years. Parapneumonic effusion can occur in any age group.
2. There was male preponderance in all three groups of pleural effusion.
3. History of contact was present in 34.31% cases of tuberculous effusion.
4. Smoking was an important association for malignant effusion.
5. Fever was most common symptoms (84.30%) following by cough (76.46%), chest pain (68.60%) and dyspnoea (48.03%) in tuberculous pleural effusion. In PNE group, fever was most common (100%) followed by cough (83.34%), chest pain (75%). In MPE group, dyspnoea was most common presenting symptoms (83.34%). Haemoptysis is a rare symptom in pleural effusion in our study group.
6. Tachycardia and tachypnoea were the predominant signs in whole series.

7. BCG scar mark noted in 50% cases of tuberculous pleural effusion
8. Sputum for AFB was found 10.78% cases of tuberculous effusion. These patients also had pulmonary lesions.
9. Chest X-ray revealed additional findings in 34.31% cases of TBPE group
10. Lymph node examination was very much important. It was palpable in 18 cases (15%).
11. 80.39% cases of tuberculous effusion had pale yellow coloured effusion but 13.72% cases had haemorrhagic fluid.
12. 66.66% of malignant effusion had haemorrhagic fluid and 33.37% of malignant effusion had pale yellow coloured pleural fluid. 25% of patient with PNE group had pale yellow coloured pleural fluid.
13. Most of the patients of tuberculous effusion and malignant effusion had predominant lymphocyte count in pleural fluid. Neutrophil count in pleural fluid was raised in parapneumonic effusion. Pleural fluid for malignant cells was positive in 66.67% of malignant effusion.
14. Pleural fluid for Z-N stain detect 1.96% cases tubercle bacilli in TBPE group.
15. Pleural fluid protein was raised in all three group. In TBPE mean protein  $5.37 \pm 0.98$  gm%, in MPE  $4.83 \pm 0.89$  gm% and in PNE group,  $4.6 \pm 0.74$  gm%. Glucose level was markedly low in parapneumonic effusion.
16. Pleural biopsy was a quite sensitive and specific method to diagnose tuberculous effusion. It was found positive in 68.18% cases of TBPE and 60% cases of MPE.
17. Pleural fluid ADA level was significantly higher ( $P < 0.001$ ) in patients of tuberculous effusion than non-tuberculous effusion. Taking a cut off value of 70 U/L sensitivity and specificity is 95.09% and 33.33%. But when parapneumonic effusion was excluded, the specificity increases. Lymphocytic pleural effusion below the age group of 40 years with cut off value of ADA  $< 40$  U/L can be used as a screening test for malignant effusion.
18. In TBPE tuberculin skin test was positive in 74.50% cases. Taking a cut off value of 10 mm or more induration of tuberculin skin test, "P" value is less than 0.001. Sensitivity and specificity of tuberculin skin test in tuberculous pleural effusion is 74.50% and 50%.
19. If we compare the efficacy of ADA  $> 70$  U/L and tuberculin skin test positivity to diagnose tuberculous

pleural effusion the former is superior statistically to the later (P value is less than 0.01) specificity of tuberculin skin test is low because it may be positive with infection with NTM and prior BCG vaccination.

#### **Conclusion:**

1. Maximum incidence of tuberculous pleural effusion occurs in the age group of 20-30 years. Malignant pleural effusion is less likely below the age group of 30 years.
2. Increased ADA level  $> 70$  U/L in pleural fluid is a sensitive, minimally invasive, cost effective, easy method for diagnosis of tuberculous pleural effusion.
3. Lower level of pleural fluid ADA level ( $< 40$  U/L) is a sensitive, specific, minimally invasive, cost effective easy method for suspecting malignant effusion. Its value is much more important when younger patients ( $< 40$  years of age) present with malignant effusion, especially so when the pleural fluid is also appeared pale yellow. A low ADA level will guide us to look for malignancy in this age group.
4. Tuberculin skin testing with intermediate strength PPD has a high sensitivity in patients with pleural tuberculosis. It was seen negative in  $1/3^{\text{rd}}$  cases of TBPE. This negative tuberculin skin test in TBPE may be due to recent tuberculous infection or may be due to sequestration of PPD reactive T-lymphocytes in the pleural space or patient may be anergic. Our study is insufficient to comment this negative result. More precise study need to comment.
5. Pleural biopsy is a sensitive and specific method for diagnosis of tuberculous effusion. Though it is an invasive method, it will give the histological diagnosis. It should be done when there is any confusion regarding diagnosis of tuberculous effusion on the basis of ADA level and tuberculin skin testing.
6. To diagnose malignant pleural effusion, pleural fluid for malignant cells and pleural biopsy for H/P examination both can be performed in same sitting which give us more than 90% cases of positive result.

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