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# To evaluate the efficacy of histopathological analysis in diagnosing undiagnosed pleural effusions.

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**ABSTRACT**

**Background:** The most typical pleural pathology manifestation is still pleural effusion. Despite routine biochemical and cytological examination of the pleural fluid, it can sometimes be challenging to distinguish between tubercular and malignant pleural effusion.

**Aims-** This study aims to assess the value of pleural biopsy in identifying the cause of pleural effusion and correlating it with cytological and biochemical pleural fluid parameters.

**Methods:** thirty consecutive patients of pleural effusion were selected from the out patient and indoor department of a tertiary hospital of central India. Biochemical, cytological and microbiological evaluation of pleural fluid was done in all cases. Those with exudative pleural effusions underwent pleural biopsy. Subsequently, the etiology of effusion was determined.

**Results:** Malignancy was the most common etiology, followed by tuberculosis. Pleural biopsy was done in 30 patients. Malignancy was diagnosed in 13, tuberculosis in 10 and 7 cases were remain undiagnosed , on histopathological examination. Mean value of pleural fluid ADA in malignancy patients is 11.5, whereas in tuberculosis patients its 28.6.

**Conclusions:** In our study, malignancy is more common than tuberculosis. pleural fluid cytology and pleural biopsy can give definite diagnosis.

**KEY WORDS:** Malignancy, pleural biopsy, pleural effusion, tuberculosis

## INTRODUCTION

There are a number of potential causes of pleural effusion, which is the abnormal buildup of fluid in the pleural cavity. For instance, malignancies (either primary or secondary pleural tumours), infections like pneumonia or tuberculosis, systemic diseases like congestive heart failure, kidney failure, and connective tissue abnormalities, drug use, and pulmonary embolism (1). When a unilateral pleural effusion is found, the patient needs to undergo a thorough investigation using both minimally invasive and invasive techniques (2). Despite significant clinical effort, at least 15-20 percent of pleural effusions remain misdiagnosed (3).

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Thoracocentesis with pleural fluid cytology and microbiological analysis is the easiest and least invasive way to diagnose undiagnosed exudative pleural effusion (EPE), but this procedure has a high rate of false-negative results, with a sensitivity of around 60% (range, 40-87%), so especially in patients with a high suspicion of neoplastic or infectious disease, further exams must be taken into consideration (4). Consequently, obtaining pleural tissue samples for pathological and microbiological analysis is the next step in the treatment of undetected EPE. Currently, there are two methods for obtaining tissue samples from the pleura: medical thoracoscopy or closed pleural biopsy (CPB) (MT). CPB is a procedure that involves taking a transthoracic biopsy of the pleura and was first described in 1955 by De Francis and colleagues (5,6). If the procedure is carried out blindly, the diagnostic accuracy is slightly less than 60%, but it increases if the pleural biopsy is taken image-guided (using ultrasound or a CT scan) (7). It can be done in an outpatient setting, but there are some restrictions to the procedure, including the inability to perform multiple biopsies and the difficulty of biopsying abnormalities in the apical or diaphragmatic region. Complications of CPB include pain, pneumothorax, vasovagal reaction, haemothorax, hematoma, and transient fever. The origins of MT may be traced back to the early 1900s. Using this technique, the majority of the pleural cavity can be viewed, allowing for pleural biopsy with direct vision as well as therapeutic procedures like talc pleurodesis. MT is currently regarded as the gold standard since it has a diagnostic yield of 91% to 95% for malignant pleural effusions (MPE) and 100% for tuberculous pleural effusions (TPE) (8). (9). Thoracoscopy is not frequently offered in community health centres because to the exorbitant cost, requirement for specialist equipment, and requirement for specialised training of doctors and medical staff.

We conducted this study in order to evaluate the diagnostic yield and safety of closed pleural biopsy in difficult to diagnose exudative pleural effusion.

**METHODS-** This is a Prospective (Observational) study designed to evaluate the role of closed pleural biopsy in undiagnosed exudative pleural effusion. The study was done at the Department of Respiratory Medicine, MGM Medical College & MY Hospital Indore (M.P.). study duration 12 months , Patients with exudative pleural effusion remain undiagnosed after pleural fluid analysis. Proforma was designed and ethical clearance was obtained. Written informed consent was obtained from all the patients included in the study after explaining in detail the nature and purpose of the study. Patients with undiagnosed Exudative pleural effusion after complete radiological, cytological and biochemical evaluation, Age >18 years and patients who have given informed consent for pleural biopsy were included while Patients with Transudative effusion and Diagnosed cases of pleural effusion were excluded from study. Patients with undiagnosed exudative pleural effusion, fulfilling Inclusion criteria were admitted in the Department of Respiratory Medicine, MGM Medical College & MY Hospital Indore (M.P.).

**RESULTS**

In this study, the pleural biopsy was done in undiagnosed cases of pleural effusion and the results of histopathology with pleural fluid routine microscopic findings, ADA (Adenosine

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Deaminase level), cytology, and pleural fluid CBNAAT (Cartridge based nucleic acid amplification test) were analyzed and the results of my study are as follows.

**TABLE 1**
**Demographic and clinical characteristics of patients**

| Particulars | Sub-Particulars | No. of participants | Percent (%) |
|---|---|---|---|
| **Sex** | **Male** | 17 | 56.7 |
| | **Female** | 13 | 43.3 |
| **Age group** | **30-40** | 4 | |
| | **41-50** | **7** | |
| | **51-60** | 11 | |
| | **>60** | 8 | |
| **CASES DIAGNOSED** | **Diagnosed** | 23 | 76.7 |
| | **Undiagnosed** | 7 | 23.3 |
| **HPE** | **Tuberculous** | 10 | 33.3 |
| | **Malignancy** | 13 | 43.3 |
| | **Undiagnosed** | **7** | 23.3 |

During our study period, Pleural biopsy was done in 30 patients of undiagnosed exudative effusions out of which there were 13 females and 17 males. There is a slight male predominance. The study population included the patients of age more than 18 years. The youngest patient in our study is 33years old. Majority (36.67%) of the patients in our study were in the age group of 51-60 years. Majority (76.9%) of females in our study belongs to more than 50 years of age group. The mean age of the study group was 54.53 years. About 76.7% of cases were diagnosed with Histopathological Examination on Pleural biopsy specimen and 23.3% of cases were left undiagnosed Histopathological Examination diagnosed 33.3% of biopsy specimens as Tuberculosis and 43.3% as Malignancy. The rest 23.3% of case was left undiagnosed after Histopathological Examination of Pleural biopsy.

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**Table 2**
**INCIDENCE OF PLEURAL MALIGNANCIES**

| Malignancy | Frequency (n=13) | Percent (%) |
|---|---|---|
| **Adenocarcinoma** | **5** | **38.5** |
| **Squamous Cell carcinoma** | **1** | **7.7** |
| **Lymphoma** | **1** | **7.7** |
| **Mesothelioma** | **2** | **15.4** |
| **Poorly undifferentiated malignancy** | **4** | **30.8** |
| **Total** | **13** | **100.0** |

Out of the malignancies proved in the study Adenocarcinoma topped the list with 38.5% followed by undifferentiated Malignancies with 30.8% followed by mesothelioma with 15.4% and then by Lymphoma and squamous cell carcinoma with 7.7% each.

**Table 3**
**RELATION OF BIOCHEMICAL PARAMETERS OF PLEURAL FLUID WITH HPE DIAGNOSIS.**

| PARAMETER | GROUP | N | MEAN | SD | P-VALUE |
|---|---|---|---|---|---|
| **PROTEIN** | **Malignancy** | 13 | 3.162 | 0.2219 | **0.026** |
| | **Tuberculous** | 10 | 2.940 | 0.1897 | |
| | **Undiagnosed** | 7 | 3.229 | 0.2690 | |
| **NEUTROPHIL Percentage** | **Malignancy** | 13 | 23.462 | 6.8874 | **0.827** |
| | **Tuberculous** | 10 | 23.500 | 13.5503 | |
| | **Undiagnosed** | 7 | 26.429 | 13.4519 | |
| **Lymphocyte Percentage** | **Malignancy** | 13 | 76.538 | 6.8874 | **0.827** |
| | **Tuberculous** | 10 | 76.500 | 13.5503 | |
| | **Undiagnosed** | 7 | 73.571 | 13.4519 | |
| **ADA** | **Malignancy** | 13 | 11.538 | 4.2547 | **<0.0001** |
| | **Tuberculous** | 10 | 28.600 | 8.8969 | |
| | **Undiagnosed** | 7 | 20.857 | 12.3751 | |

Mean Pleural Fluid protein value is on slightly higher side in malignancy (3.16) cases compared to tuberculosis (2.94). Mean differential neutrophil count value is almost similar in diagnosed cases of malignancy (23.462%) and tuberculosis (23.5%). Pleural Fluid Lymphocyte mean value is almost similar in both malignancy and tuberculosis cases. Mean value of pleural fluid ADA in malignancy patients is 11.5, whereas in tuberculosis patients its 28.6.

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Table 4 depict the yield of malignancy out of 30 cases 43.3% were diagnosed with the malignancy while 56.7% were negative.

**Table 4**
**YIELD OF MALIGNANCY**

| HPE | Frequency | Percentage (%) |
|---|---|---|
| **Diagnosed** | 13 | 43.3 |
| **Negative** | 17 | 56.7 |

There were no False positive results with Histopathological Examination making the Specificity and Positive predictive value as 100%. The Sensitivity was 65.00% and Negative predictive value was 58.82%.

**Table 5**
**MALIGNANCY**

| HPE | Percentage (%) |
|---|---|
| **Sensitivity** | 65.00% |
| **Specificity** | 100.00% |
| **Positive Predictive Value** | 100.00% |
| **Negative Predictive Value** | 58.82% |

**DISCUSSION-** Pleural effusion is defined as a collection of fluid in the Pleural space/cavity. It's not a disease but rather a complication of some underlying illness. Multiple entities can be responsible for pleural effusion. Pleural Fluid is classified as transudative or exudative on basis of lights criteria. Pathophysiology and etiological factors are distinctive and peculiar for both transudative and exudative pleural effusion. Transudative effusion ordinarily develops because of systemic factors that increase the vascular permeability that ultimately leads to fluid accumulation. Transudative as the name signifies protein content in pleural fluid is quite less. Whereas if local factors are involved it results in exudative pleural effusion. The two most common causes for exudative pleural effusion are TB and malignancy. Other less common causes include pulmonary embolism, collagen vascular conditions (RA, SLE), oesophageal perforation, pancreatitis, etc. The confirmatory diagnosis of tuberculous pleuritis depends on the demonstration of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimen or the demonstration of granuloma in the pleural biopsy. Another method of establishing the diagnosis is with elevated values of ADA (adenosine deaminase) and interferon-gamma in the pleural fluid. Around 30% of cases still remain undiagnosed even after these investigations. Recently, there has been an emphasis on image-guided or direct visualizing procedures like thoracoscopy for better safety and increased yield, especially in malignant pleural effusion cases. The limit to this notion happens to be the resource constraints in developing countries like India. The higher cost increased hospital stays and increased intercoastal tube drainage-related morbidity also favors the closed needle biopsy by

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Abram's needle. Moreover, the different epidemiological profiles of TB in developing countries and the increased yield via pleural biopsy for the same also add to the point for this procedure. In our study malignancy was diagnosed in 43.34% of cases. There happens to be slight discordance with previous studies with a sensitivity of Abram's needle biopsy ranging from 46-72%. (10) In one study with 414 patients, they showed an additional diagnosis of only 7% as compared to pleural fluid cytological analysis. Whereas, Mungall et al in their study showed the highest diagnostic rates, i.e., 72% for malignant pleural effusion and 88% for tubercular exudative pleuritis.(11) Another study by Zhang et al with 644 patients, showed the sensitivity of closed pleural biopsy for malignant pleural effusion as 51.5% (with lung adenocarcinoma as the most common pathological type) and for tubercular pleural effusion as 68.7%.(12) We diagnosed 2 cases of mesothelioma (1 confirmed case and 1 case of solitary fibrous tumour with high possibility of mesothelioma) in our study. Beauchamp et al showed the highest sensitivity in his study, while Boutin et al in his series showed Abram's biopsy yield to be 20.7%.(13,14) In our study tuberculosis was diagnosed in 10 cases (33.34%). In one study with 248 patients, the biopsy of pleura via needle was having its own yield of almost 80%, which increased to 91% when staining and culture of the fluid was added.(15) Separate or multiple pleural biopsies samples may also increase the yield.(16,17) Though thoracoscopy have an added advantage of direct visualization and identification of biopsy site, the added yield is not convincing possibly due to relative uniformity of the lesion as compared to the skip lesions in malignant effusion.(18) In our study, adequate pleural biopsy with pleura tissue on histopathology was obtained in almost 93% of cases. This was in line with the findings of Cowie et al, whose series almost succeeded in obtaining 90% of the pleural tissue. Walshe et al. reported slightly lower rates (71%) but were conducted by non-respiratory experts.(19,20) In our study, haemorrhagic effusion is more common in malignancies, especially in older age people. Out of 13 patients with malignant pleural effusion in our study nine patients (69.2%) have haemorrhagic pleural effusion. Lending et al diagnosed haemorrhagic malignant pleural effusion (HMPE) in 47-50% of all malignant pleural effusions (MPE).(21) Whereas the majority of patients with tuberculous pleuritis had straw colour fluid. In our study, ADA levels are quite on the lower side with a mean value of 11.53 in malignant pleural effusion compared to tubercular pleural effusion with a mean value of 28.7. In our study, we had done thoracocentesis in thirty other patients where we got the diagnosis on pleural fluid routine investigations or fluid is transudative. As they will fall in exclusion criteria, we had taken them as a control group. We are able to diagnose almost 78% of the undiagnosed cases with closed pleural biopsy, which can draw an inference of alleviation of costly, higher setup procedures and morbidity related to them. Even the burden for the radiology department can be reduced with this procedure. Moreover, the complications rate attributable to the procedure is minimal, which no incidence of pneumothorax in our study. This can have an economic as well as a quality-of-life advantage in developing countries like India, where TB is still endemic.

**CONCLUSION-** Diagnosis of exudative pleural effusion can be established with various investigational measures like pleural fluid routine microscopic examination, pleural fluid cultures, pleural fluid ADA and interferon- gamma levels, pleural fluid CBNAAT testing along cytological examination. Around 40% of cases still remain undiagnosed. Closed pleural biopsy is one of the oldest procedures for pleural pathologies. As it is a blind procedure, it is replaced by newer image guided biopsy techniques (USG Guided, CT-guided, thoracoscopy, VATS or open biopsy) at most of the well-equipped and higher centres. In our study we diagnosed 23 cases out of 30 with closed needle biopsy by Abram's needle without any significant complication. This study suggests that tuberculosis and malignancy are the two common aetiologies for exudative pleural effusion. Malignancy is more common than

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tuberculosis notably in elderly patients with haemorrhagic effusion. Haemorrhagic pleural effusion increases the probability of malignant pleural effusion. This shows that closed pleural biopsy is still of value as a diagnostic procedure, and should be carried out prior to invasive procedures such as thoracoscopy or open pleural biopsy. Closed Pleural Biopsy can be used as an easy, quick, cost effective and relatively safe method to diagnose an exudative effusion not diagnosed by pleural fluid analysis. In conclusion, our study advocates the use of blind pleural biopsy using the Abram's needle in our country whenever pleural fluid analysis is nondiagnostic considering the acceptable yield of the procedure, its safety, limited resources and increased burden of the patients on the healthcare and the endemicity of TB.

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