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Diagnostic Yield of Closed Pleural Biopsy in Undiagnosed Exudative Pleural Effusions

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ABSTRACT

Introduction: *In our practice, etiological diagnosis of pleural effusion is sometimes difficult despite cytological, biochemical and microbiological tests. The aim of the present study was to make an etiological diagnosis by means of closed pleural biopsy in undiagnosed pleural effusions.*

Methods: *The study group consisted of patients with exudative pleural effusion where etiology was not determined by means of conventional cytological, biochemical and microbiological investigations. Pleural tissue was obtained by Abrams pleural biopsy needle. Pleural biopsy was subjected to histopathology, Ziehl-Neelsen (Z-N) staining and mycobacterial culture.*

Results: *Four hundred fifty eight patients with pleural effusion were screened over three years and 82 of them were found to have undiagnosed exudative effusion after investigations, as mentioned in the Method section. The age of the 82 subjects [56 (68.29%) men and 26 (31.71%) women] ranged from 15 to 65 years (mean 32.6). Histopathology showed epitheloid granuloma with caseation necrosis in 50 (60.9%) patients and non-specific chronic inflammation in 14 (17.1%) subjects. Ziehl-Neelsen stain was positive for acid fast bacilli (AFB) in 10 (12.2%) patients and culture of pleural tissue showed the presence of* Mycobacterium tuberculosis *in 18 (21.9%) patients.*

Conclusions: *In the era of thoracoscopy, percutaneous closed needle pleural biopsy still holds a significant role in cases of undiagnosed exudative pleural effusions where thoracoscopy is not available, being also a cost effective approach for developing countries. It can achieve specific diagnosis among 86.6% of cases with undiagnosed exudative pleural effusions.*

Keywords: Abrams, closed needle, pleural biopsy, undiagnosed, pleural effusion.

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INTRODUCTION

Exudative pleural effusions are frequently encountered in clinical practice of pulmonology. Etiological diagnosis in of those cases is a diagnostic challenge to the clinician because even after all cumbersome work-ups some cases remain undiagnosed. Given that 15-20% of exudative effusions remain undiagnosed even after extensive efforts (1), invasive diagnostic procedures are needed for diagnosis in such cases, among which percutaneous needle biopsy of pleura is a cost-effective approach. By closed pleural biopsy, up to 49% of missed cases may be diagnosed (2). Closed pleural biopsy provides highest diagnostic yield in pleural tuberculosis and malignancy, which are the two most common causes of exudative pleural effusions (3).

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

MATERIALS AND METHODS

The study was conducted in a tertiary care hospital of Kolkata, West Bengal, India, over a period of three years (January 2009 – January 2012). It was a cross-sectional descriptive study. Written and informed consent was taken from all patients. The academic board and ethical committee of the institution approved the study protocol. All patients aged over 12 with exudative pleural effusion were included in our study.

A detailed clinical history was taken and physical examination was done. Chest x-ray, followed by diagnostic thoracocentesis was performed in each case to get pleural fluid for analysis. Cytological examination included total leukocyte count (TLC), differential leukocyte count (DLC), red blood cell count (RBC), mesothelial cells and malignant (M) cells. Biochemical tests included pleural fluid protein, lactate dehydrogenase (LDH), glucose, adenosine deaminase (ADA), rheumatoid (RA) factor and anti nuclear antibody (ANA). Serum protein and serum LDH were measured too. Microbiological tests included pleural fluid for Gram stain, Ziehl-Neelsen (Z-N) stain with culture for acid-fast bacilli (AFB) and pyogenic culture. Mantoux test was also done by 5 units of purified protein derivative (PPD). If the etiological diagnosis was reached by these tests, then they were excluded from the study. Tubercular pleural effusion was diagnosed by high ADA (> 40 U/L) with positive Z-N stain or CBNAAT (cartridge based nucleic acid amplification test) for MTB in a case of lymphocytic (lymphocyte count more than 60% in pleural fluid) exudative effusion.

During the study period, 458 consecutive patients with exudative pleural effusions were screened for etiological diagnosis by the above mentioned tests.

Pleural biopsy was done for cases that remained undiagnosed after using the above mentioned tests. Before pleural biopsy, we checked prothrombin time, bleeding time, clotting time and enzyme linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) 1 & 2 antibodies. Patients with bleeding diathesis and HIV positive status were excluded from our study.

Closed pleural biopsy using Abrams needle

The site (two intercostal spaces below the fluid level) was selected by using chest x-ray and clinical percussion. After local anaesthesia with 2% lignocaine injection, a small incision parallel to the ribs was made using a surgical blade. Abrams needle was inserted, fluid was aspirated to confirm the position and then, minimum four to five biopsy specimens were taken. Biopsy samples were divided into two halves, of which one was delivered to 10% formaldehyde filled container and the other to normal saline filled container. All specimens were accurately labelled. We sent specimen in formaldehyde container for histopathological examination and specimen in normal saline filled container for AFB staining and mycobacterial culture.

Statistical analysis

Collected data were compiled on Microsoft Excel worksheets (Microsoft, Redwoods, WA, USA). Categorical data were expressed in proportions and continuous data in mean values. Dispersion of data was expressed in terms of standard deviation (SD). SPSS software version 16.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA) was used for statistical analysis. Sensitivity and specificity of pleural bi-

TABLE 1. Clinical, biochemical and cytological characteristics of patients with undiagnosed pleural effusions

Characteristics		Males (N=56)	Females (N=26)	Overall (N=82)
Mean age		34.74 ± 10.56	30.64 ± 11.65	32.69 ± 12.25
Mean body mass index (BMI)		19.45 ± 3.45	18.65 ± 3.86	19.05 ± 3.75
Smoker		46 (82.14%)	4 (15.39%)	50 (60.98%)
Co-morbidities	DM	8 (14.29%)	5 (19.23%)	13 (15.85%)
	HTN	17 (30.36%)	9 (34.62%)	26 (31.71%)
Symptoms	Fever	40 (71.43%)	14 (53.84%)	54 (65.85%)
	Cough	52 (92.86%)	22 (84.62%)	74 (90.24%)
	Pleuritic chest pain	32 (57.14%)	17 (65.39%)	49 (59.76%)
	Shortness of breath	30 (53.57%)	15 (57.69%)	45 (54.87%)
Side of effusion	Left sided	36 (64.29%)	17 (65.39%)	53 (64.63%)
	Right sided	19 (33.93%)	9 (34.62%)	28 (34.15%)
	Bilateral	1 (1.79%)	0	1 (1.22%)
Amount of effusion	Minimal effusion	24 (42.86%)	12 (46.15%)	36 (43.91%)
	Moderate effusion	22 (39.29%)	10 (38.46%)	34 (41.46%)
	Massive effusion	10 (17.86%)	4 (15.39%)	12 (14.63%)
Gross appearance of fluid	Yellow coloured	38 (67.86%)	22 (84.61%)	60 (73.17%)
	Hemorrhagic	18 (32.14%)	4 (15.39%)	22 (26.83%)
Biochemical parameters of pleural fluid (PF)	Mean pH	7.29±0.21	7.32±0.24	7.31±0.22
	Mean LDH (U/L)	480.50±90.65	472.35±92.70	476.43±90.90
	Mean ADA (U/L)	24.25±8.55	22.55±9.15	23.40±8.90
	Mean protein (gm/dL)	5.65±1.08	5.34±0.95	5.49±1.05
	Mean glucose (mg/dL)	68.58±14.68	62.45±15.74	65.52±14.98
Biochemical parameters of serum (S)	Mean total protein (gm/dL)	7.84±1.24	7.56±1.14	7.7±1.18
	Mean LDH (U/L)	768.65±118.84	780.76±120.65	774.71±120.24
Ratio of biochemical parameters	PF:S protein	0.72±0.13	0.71±0.11	0.71±0.12
	PF:S LDH	0.63±0.21	0.60±0.24	0.61±0.22
Cellularity of pleural fluid	Mean lymphocyte count	68.65%	69.45%	69.05%
	Mean polymorph count	29.15%	29.25%	29.2%
	Mean mesothelial cell count	2.20%	1.30%	1.75%

opsy to reach a etiological diagnosis was analysed.

RESULTS

The study included 82 patients with exudative pleural effusions in whom no etiological diagnosis was made despite cytological, biochemical and microbiological study of pleural fluid (Table 1). Among them, 56 (68.3%) were men (mean age 34.74 years) and 26 (31.7%) women (mean age 30.64 years). Out of the 82 subjects, 82.14% of men and 15.4% of women were smokers. Diabetes mellitus was associated in 14.3% of male patients and 19.23% of female ones. Cough was the predominant symptom among all participants. Left sided pleural effusion was present in 64.6% of patients and bilateral pleural effusion was found in only one male patient. Only 12 patients had massive effusion, of which eight were diagnosed with malignant effusion, one patient was diagnosed with tuberculosis and three subjects remained undiagnosed. Yellow colour fluid was present in 60 patients (among them, 50 subjects had tubercular etiology), and 22 patients had hemorrhagic effusion (among them, 15 patients had malignant etiology).

All cases were exudative pleural effusions. The pleural fluid had a mean pH of 7.31, ADA of 23.40 U/L, a mean level of glucose and protein of 65.5 mg/dL and 5.6 mg/dL, respectively; also, the mean value of serum and pleural fluid LDH was 476.4 and 774.71 U/L, respectively. Effusions were predominantly lymphocytic. The mean value of neutrophil and lymphocyte count was 29.2% and 69%, respectively. In 60 out of 82 patients there were no RBCs in the pleural fluid. In 22 patients, the fluid was frankly hemorrhagic. The mean±SD was 0.71±0.12 for pleural fluid to serum protein ratio 0.61±0.22 for pleural fluid to serum LDH ratio.

The average number of passes to obtain pleural biopsy was 6.1 (minimum 5, maximum 8) and 4.7 (range 4-6) samples were obtained. Histopathology showed epithelioid granuloma with caseous necrosis in 50 (60.2%) cases, which confirmed the diagnosis of pleural tuberculosis (Table 2). Histopathology showed metastatic adenocarcinomatous deposit in 12 (14.6%) cases, squamous cell carcinoma in six (7.3%) cases and chronic non-specific inflammation in 14 (17.1%) cases. Ziehl-Neelsen (Z-N) staining of pleural tissue was positive in 10 (12.2%) cases. Mycobacterial culture of pleural tissue revealed mycobacterial growth in 18 (21.9%) cases. Among undiagnosed pleural effusions, tubercular pleural effusion was diagnosed in 53 (36 men and 17 women) (64.6%) cases, malignant effusion in 18 (14 men and four women) (21.9%) cases and 11 (six men and five women) (13.4%) patients remained undiagnosed after closed pleural biopsy (Table 3). Sensitivity of the test to reach an etiological diagnosis in cases of exudative undiagnosed pleural effusion was 86.6%, with a positive likelihood ratio of 0.87, while specificity could not be evaluated because tests were only done in diseased patients. Among patients with diagnosed malignant effusion, all male subjects and two female ones were smokers.

There were immediate complications after closed pleural biopsy in nine (10.2%) patients (Table 4), hydropneumothorax in three subjects, vaso-vagal attack in two patients, fever in two

Investigations		Cases (n = 82)	Percentage
Histopathology	Epithelioid granuloma with caseation	50	60.98%
	Adenocarcinoma	12	14.63%
	Squamous cell carcinoma	06	7.32%
	Non-specific inflammation	14	17.07%
Ziehl-Neelsen staining positive		10	12.2%
Positive mycobacterial culture		18	21.95%

TABLE 2. Results of pleural biopsy investigations

TABLE 3. Diagnostic yield of closed pleural biopsy by Abrams needle

Diagnosis	Mode of diagnosis	Cases
Tubercular pleural effusion (64.63%), n = 53	Caseating epithelioid granuloma	35 (66.04%)
	Caseating epithelioid granuloma + MTB culture	5 (9.43%)
	Caseating epithelioid granuloma + MTB culture + Z-N staining	10 (18.87%)
	Non-specific inflammation + MTB culture	3 (5.66%)
Malignant pleural effusion (21.95%), n = 18	Adenocarcinoma on HP examination	12 (66.67%)
	Squamous cell carcinoma on HP examination	6 (33.33%)
Undiagnosed effusion (13.42%), n = 11	Non-specific inflammation in HP examination	11 (100%)

TABLE 4. Immediate complications developed after closed pleural biopsy by Abrams needle

Complications	Cases (n)	Percentage
Hydropneumothorax	3	3.66%
Vaso-vagal attack	2	2.44%
Fever	2	2.44%
Local site sepsis	1	1.22%
Local site subcutaneous emphysema	1	1.22%
Total	9	10.98%

subjects, local site sepsis in one case and subcutaneous emphysema at the biopsy site in one case. Hydropneumothorax cases required intercostal tube drainage. Subcutaneous emphysema resolved on the third postoperative day after moist oxygen inhalation at high flow. Local site sepsis was managed by regular dressing and antibiotics. ❑

DISCUSSION

Pleural effusion is one of the most common problems for which patients come to see a pulmonologist. Despite cytological, biochemical and microbiological studies of pleural fluid, 18% of cases remain undiagnosed.

Regarding the diagnosis of pleural tuberculosis, pleural fluid smear for Z-N stain is positive in less than 5% of cases, and around 40% for MTB cultures, but the yield can be increase up to 76% when pleural biopsy specimens are also sent for culture. In the pleural fluid, Gene Xpert sensitivity is low (25%–50%) across a number of studies, but specificity is high. In nearly 50%-80% of patients, the histopathological diagnosis of TB pleuritis can be made by finding of pleural necrotizing caseating granulomas. Histopathology with MTB culture of the pleural biopsy is the gold standard for diagnosis of TB pleuritis, with up to 95% sensitivity.

Currently, needle biopsy of the pleura is used less than in the past, because the diagnosis of tuberculous pleuritis can be made by measuring ADA or interferon-gamma level in the pleural fluid and the diagnosis of pleural malignancy is usually established by pleural fluid cytology or thoracoscopy (4). A needle biopsy of the pleura is currently recommended when tuberculous pleuritis is suspected and the pleural fluid ADA or interferon-gamma levels are not definitive. A needle biopsy of the pleura is also recommended when malignancy is suspected, but pleural fluid cytology is negative and thoracoscopy is not readily available (4). The main contraindication to a pleural biopsy is a bleeding diathesis. The presence of empyema is another contraindication (5).

Three types of pleural biopsy needle, including Abrams needle, Raja needle and Cope needle, are currently available. The rate of success in obtaining a pleural biopsy specimen depends more on the skill of the operator than on the

choice of instruments (6). Morrone *et al.* reported that virtually, the diagnostic yield of both Abrams and Copes needle is identical (7). In a recent study, Manju *et al.* found that there was no statistically significant difference between Abrams and Copes needles with regard to the diagnostic yield (8). Hence, Abrams and Copes needles are equally efficacious. In our set up, Abrams needle was available. So, we had done all biopsies by using Abrams needle.

According to various studies, the diagnostic yield of pleural biopsy in pleural effusion is about 60 to 80% in all cases (9, 10). In our study, it was 86.58% even in difficult to diagnose exudative effusions. The diagnosis of tuberculosis based on histopathological finding of epithelioid granuloma with caseation was made in 94.34% cases, which is better than the study by Valdes *et al.* (11). In 18.87% of patients with tubercular effusions, AFBs were seen in histological section of pleural tissue by Ziehl-Neelsen staining. One series had not seen AFB on pleural tissue smear but another series has comparatively reported the same percentage (11, 12). Mycobacterial culture of pleural tissue was positive in 33.96% of patients with tubercular pleural effusions, which is much higher than in other published reports (11-14). This discrepancy may be attributed to small pleural biopsy specimen, single sample for mycobacterial culture and technical fault. One study has also revealed that more than one sample increased the diagnostic yield of pleural tissue mycobacterial culture (15). Non-specific inflammation on pleural biopsy was found in 17% of our patients. In one study, non-specific inflammation with varying degree of fibrosis was found in 68% of patients (16).

In our study, among the difficult to diagnose exudative effusions, 21.95% of cases were identified as malignant pleural effusion by closed pleural biopsy using Abrams needle, where pleural fluid cytology for malignant cells was negative. In a recent study from India, conducted by Prince James *et al.*, pleural biopsy was found to be the only diagnostic test in 50% cases of malignant pleural effusion (3), but the authors sent only one sample for pleural fluid for cytological evaluation of malignant cells, while we sent three samples for pleural fluid for cytology of malignant cells, which failed to detect malignant cells.

Pneumothorax is the most frequent complication after a closed pleural biopsy. However, the incidence of pneumothorax and the requirement for tube thoracostomy are comparable after thoracocentesis and pleural biopsy (17). This is probably because more experienced individuals usually perform the pleural biopsy. In the literature, bleeding causing hemothorax is the second most common complication (5, 9). There was also one case report of an arteriovenous fistula from an intercostal artery to an intercostal vein developing after pleural biopsy (18). But in our study, hydropneumothorax was the most common complication (3.66%); other minor complications included fever, local site sepsis and vaso-vagal attack, and local site subcutaneous emphysema. Hydropneumothorax cases required intercostal tube drainage. All that is required is the technical expertise for reducing the complication rates of closed pleural biopsy. A recent study from Northern India, conducted by Hira *et al.*, concluded that closed pleural biopsy by Copes needle may fetch diagnosis in 76% of cases with undiagnosed exudative pleural effusion, which is less than our study, where we found 86.58% (19).

Study limitations

Closed pleural biopsy cannot reach diagnosis in a subset of patients [in our study, 11 (13.5%) patients] and therefore, thoracoscopic biopsy should be the procedure of choice for pleural biopsy. Also, closed pleural biopsy cannot be done in small cases of effusions, while in mesothelioma it can give false impressions of metastatic adenocarcinoma. ❑

CONCLUSIONS

In this thoracoscopic era, percutaneous closed needle pleural biopsy still holds a significant role in cases of undiagnosed exudative pleural effusions where thoracoscopy is not available, being also a cost-effective approach for developing countries. It can achieve specific diagnosis among 86.5% of cases of undiagnosed exudative pleural effusions. ❑

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