A Cross Sectional Hospital-Based Study to Assess Various Outcomes Among Undiagnosed Exudative Pleural Effusion Patients Through Medical Thoracoscopy at PBM Hospital, Bikaner

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Abstract

Background: Undiagnosed pleural effusions remain a diagnostic challenge for pulmonologists. Medical thoracoscopy should be considered in patients with undiagnosed pleural effusions, particularly those lymphocytic exudative effusions where TB and malignant pleural effusion are clinical possibilities and initial pleural fluid analysis is inconclusive. In Indian scenario, there are fewer studies that have been done on the role of thoracoscopy in cases of pleural effusion. Therefore, this study has been chosen for the diagnostic evaluation for moderate to massive pleural effusion attending the Department of Respiratory Diseases, S.P. Medical College, Bikaner. **Materials & Methods:** This is a hospital based descriptive type of observational study done on 50 patients those presented with recurrent moderate to massive exudative pleural effusion at department of respiratory disease at S.P. Medical College, Bikaner. Once we consider the patient for thoracoscopic procedure, we record detailed history including smoking habits, history of anti tubercular treatment, occupational history, exposure to asbestos, previous history of pleurocentesis, along with detailed respiratory and other systemic examinations in a proforma. All patients having exudative pleural effusion were further evaluated. When these investigations of pleural fluid failed to provide the diagnosis, it was labelled as undiagnosed exudative pleural effusion and patient were selected for Medical thoracoscopic guided pleural biopsy. **Results:** The mean age of subjects was 56.0±12.06 years and male to female ratio was 2.12 :1. In case of moderate to massive pleural effusion, shortness of breath was most common pulmonary symptoms. In thoracoscopy of pleural cavity the appearance of pleural surface, mostly nodular pleural surface seen in 29 patients (58%), followed by thickened 16 cases (32%) and smooth surface seen only in 5 cases (10%).Out of 50 cases that remained undiagnosed after repeated biochemical & cytological analysis, 47 patients (94%) were diagnosed by means of thoracoscopic pleural biopsy and 3 patients remained undiagnosed (couldn't arrive at specific diagnosis to initiate treatment) and thus the sensitivity of medical thoracoscopy in undiagnosed pleural effusion was 94%.
Conclusion: We concluded that medical thoracoscopy should be considered in patients with undiagnosed exudative pleural effusions, particularly those lymphocytic exudative effusions where TB and malignant pleural effusion are clinical possibilities and initial pleural fluid analysis is inconclusive. In this study the sensitivity of medical thoracoscopy in undiagnosed exudative pleural effusion was 94%.
Keywords: Thoracoscopy, Pleural Effusion, Exudative, Undiagnosed**.**

Introduction

Pleural effusion is an abnormal accumulation of fluid within the pleural cavity. Pleural effusion is one of the most common clinical conditions encountered in pulmonary practice. Accumulation of pleural fluid is not a specific disease but reflects an underlying pathological process. In India common causes of pleural effusion are tuberculosis, bacterial pneumonia, malignancies, congestive heart failure, renal failure, connective tissue disorders and pulmonary embolism.

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In spite of good history, thorough clinical, radiological and cytochemical examination of aspirated fluid, it is possible to establish the diagnosis in not more than 20% of the cases[1]. Percutaneous closed pleural biopsy is also of great value in diagnosis of granulomatous and malignant disorders of pleura and is usually reserved in patients having undiagnosed exudative pleural effusion, where fluid cytological examination is not diagnostic and whatever there is strong urge to differentiate the diagnosis of tuberculosis from malignancy[2]. However the diagnostic accuracy with closed pleural biopsy is approximately 60%[3].

Undiagnosed pleural effusions remain a diagnostic challenge for pulmonologists. In a patient with an undiagnosed pleural effusion, the first question to answer is whether the fluid is an exudate or a transudate[4].

Recurrent and persistent pleural exudates are common in clinical practice, and in a large number of patients, thoracocentesis and blind pleural biopsy procedures do not provide a definitive diagnosis. In the Western world, the majority of these exudates are malignant.

Thoracoscopy guided pleural biopsy today remains the gold standard technique in providing diagnosis and management in these cases[5]. Thoracoscopy is a minimally invasive procedure that allows visualization of the pleural space and intrathoracic structures. It enables the taking of pleural biopsies under direct vision, therapeutic drainage of effusions and pleurodesis in one sitting[6].

Medical thoracoscopy should be considered in patients with undiagnosed pleural effusions, particularly those lymphocytic exudative effusions where TB and malignant pleural effusion are clinical possibilities and initial pleural fluid analysis is inconclusive[7].

Thoracoscopy is the gold standard for the diagnosis and treatment of pleural diseases. Its diagnostic yield is 95% in patients with malignant pleural disease, with approximately 90% successful pleurodesis for malignant pleural effusion and 95% for pneumothorax[8].

The semirigid thoracoscope achieves a diagnostic yield similar to that of the conventional rigid instrument despite the smaller biopsy size. Both instruments remain valuable in the evaluation and management of pleural disease[9]. Thoracoscopy with flex-rigid thoracoscope is a useful diagnostic tool in the evaluation of pleural effusions with negative blind pleural biopsy and cytology[10]. In Indian scenario, there are fewer studies that have been done on the role of thoracoscopy in cases of pleural effusion. Therefore, this study has been chosen for the diagnostic evaluation for moderate to massive pleural effusion attending the Department of Respiratory Diseases, S.P. Medical College, Bikaner.

Materials & methods

This is a hospital based descriptive type of observational study done on 50 patients those presented with recurrent moderate to massive exudative pleural effusion at department of respiratory disease at S.P. Medical College, Bikaner. Once we consider the patient for thoracoscopic procedure, we record detailed history including smoking habits, history of anti tubercular treatment, occupational history, exposure to asbestos, previous history of pleurocentesis, along with detailed respiratory and other systemic examinations in a proforma.

Inclusion Criteria
1. Patient willing for participation in the study
2. All moderate to massive exudative pleural effusions remaining undiagnosed on initial & repeated cytobiochemical analysis of pleural fluid and not falling in exclusion criteria.

Exclusion Criteria
1. AGE <12 yr and >80 yr
2. Non co-operative patients
3. Mild pleural effusion
4. Bleeding diathesis
5. Hemodynamic unstable and intractable cough patients
6. Transudative pleural effusion
7. Local skin infection
8. Major psychiatric illness
9. Pregnancy & lactation
10. Patients having cardiac instability and other serious co-morbid illness.

Study Protocol

The hospital based descriptive type of observational study, patient presenting with pleural effusion willing to participate were included in the study. Each patient having pleural effusion underwent diagnostic thoracocentesis and pleural fluid biochemical analysis. On the basis of which according to predefined criteria's e.g. lights criteria, patients were further divided in to two groups first having transudative pleural effusion and second having exudative pleural effusion. Those having transudative pleural effusion were excluded from study. All patients having exudative pleural effusion were further evaluated. When these investigations of pleural fluid failed to provide the diagnosis, it was labelled as undiagnosed exudative pleural effusion and patient were selected for Medical thoracoscopic guided pleural biopsy. All the data were collected and analysed performing as per standard statistical tests.
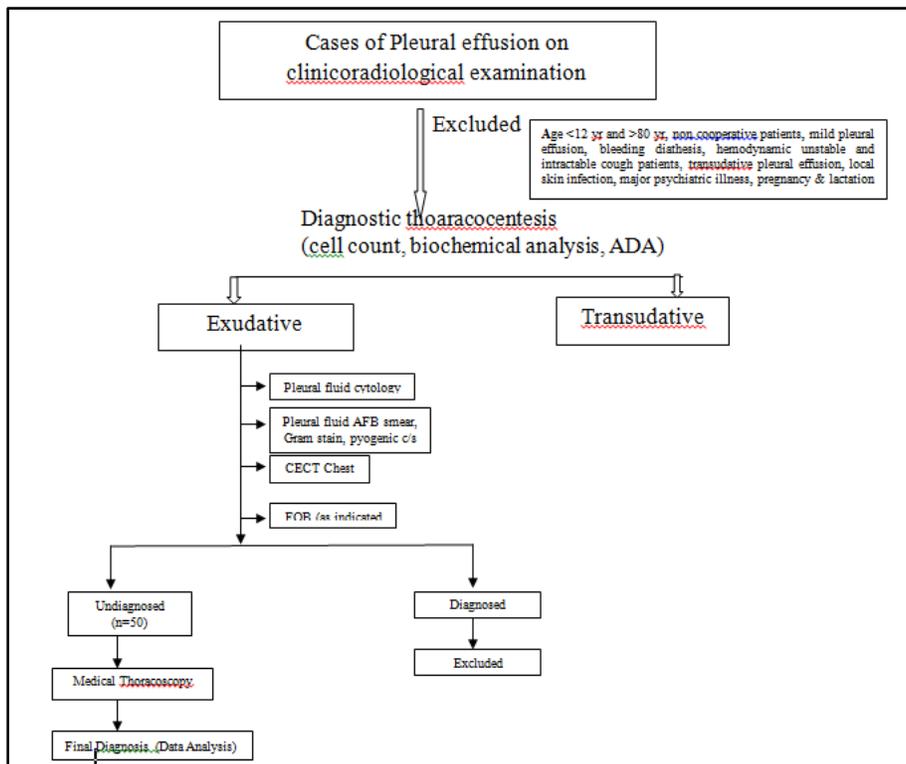

Figure 1: Flow chart of material & Methods

Results

Our study showed that majority of patients were above 50 years of age, 13 patients were between the age group 41-50 years and 12 patients were between 61-70 years of age group. Mean age of subjects was 56.0±12.06 years. Male:female ratio was 2.12 :1 (table 1).

Shortness of breath being the most common pulmonary symptoms in cases of moderate to massive pleural effusion, present in 49 patients (98%), followed by chest pain in 46 cases (92%) and cough in 45 cases (90%) (table 1).

Twenty-one (42%) patients had no addiction, 29 patients had history of addiction (58%). Among whom, 23 (46%) were alcoholic and 19 (38%) were both smokers along with alcohol takers. The total no. of smokers (n=29) was taken more than 30 pack years (table 1).

Table 1: Age Group Distribution Of Study Population

Demographic data	No. of patients (N=50)	Percentage (%)
Age group (yrs)		
11-20	1	2.0%
21-30	1	2.0%
31-40	3	6.0%
41-50	13	26.0%
51-60	16	32.0%
61-70	12	24.0%
71-80	4	8.0%
Gender		
Male	34	68%
Female	16	32%
Symptoms		
Shortness of breath	49	98%
Significant Weight Loss	25	50%
Fever	23	46%
Chest Pain	46	92%
Anorexia	30	60%
Cough	45	90%
Expectoration	28	56%
Addiction		
No addiction	21	42.0%
Pack years (>30)	29	58.0%
Only Smoking (bidi/cigarette)	29	58.0%
Only alcohol	23	46.0%
Alcohol and smoking	19	38.0%

In this study total mean value of TLC, Neutrophil, Lymphocyte, Protein, Sugar and ADA were 1808±844.5 (per cu. Mm), 14.04±7.672 (%), 85.68±8.004 (%), 4.558±0.567 (mg/dl), 85.39±20.09 (mg/dl) and 34.11±3.304(IU/L) respectively (table 2).

Table 2: Shows The Cytochemical Analysis In Study Population

Cytochemical Analysis	Mean Value	SD
TLC (per cu.mm)	1808	844.5
Neutrophil (%)	14.04	7.672
Lymphocyte (%)	85.68	8.004
Protein (mg/dl)	4.558	0.567
Sugar (mg/dl)	85.39	20.09
ADA (IU/L)	34.11	3.304

The appearance of pleural surface in CECT of chest, Mostly nodular pleural surface seen in 32 patients (64%), followed by thickened 13 cases (26%) and smooth surface seen only in 5 cases (10%). The mediastinal lymph node present in 29 cases (58%) (table 3).

Table 3: Distribution of Study Population According To CECT of Chest

CECT		No. of patients	Percentage (%)
Pleural Surface	**Nodule**	32	64.0%
	Smooth	5	10.0%
	Thickening	13	26.0%
Mediastinal Lymph node		29	58.0%

In thoracoscopy of pleural cavity the appearance of pleural surface, mostly nodular pleural surface seen in 29 patients (58%), followed by thickened 16 cases (32%) and smooth surface seen only in 5 cases (10%) (Graph 1).
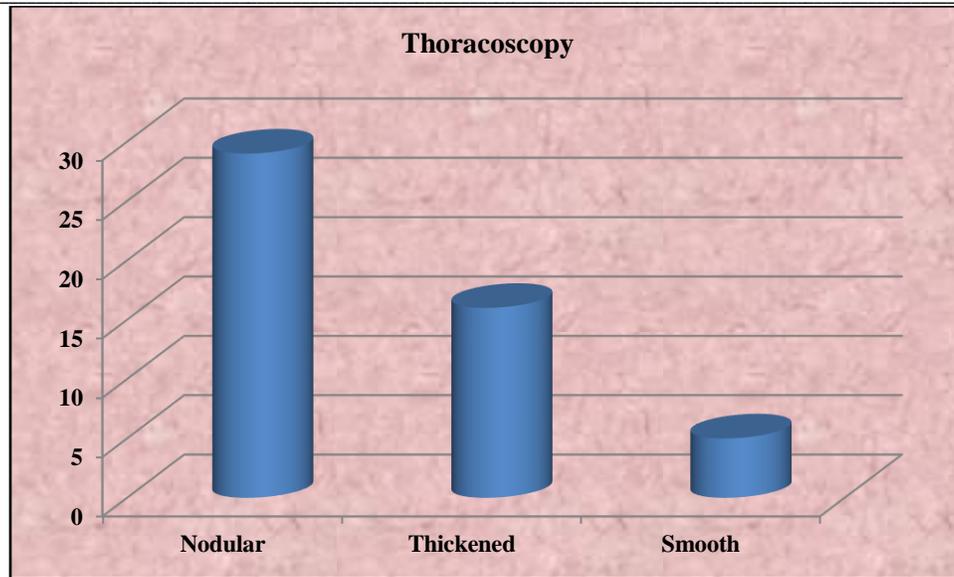
Figure 2: Distribution of Study Population According ToThoracoscopy of Pleural Cavity

The study population according to the characteristics of pleural fluid, hemorrhagic fluid in 28 patients (56%), serosanguinous in 14 patients (28%), straw coloured fluid seen in 6 patients (12%) and serous fluid seen in 2 patients (4%) (table 4).

Table 4: Distribution of Study Population According To Gross Appearance of Pleural Fluid By Thoracoscopy

Colour	No. of patients	Percentage (%)
Serosanguinous	14	28%
Hemorrhagic	28	56%
Serous	2	4%
Straw	6	12%
Total	50	100%

In table no. 5 showed the comparison of left and right pleural effusion by histopathological examination. Undiagnosed cases (6%) were seen only in left side and squamous cell carcinoma (4%) & Non-Hodgkin's lymphoma (2%) seen in right side of pleural effusion. Maximum metastatic carcinoma (22%) & malignant mesothelioma (14%) were seen in right side and tubercular granuloma (20%) seen in left side of pleural effusion.

Table 5:Distribution of Study Population in Left And Right Effusion According To Histopathological Examination

Histo-pathological Examination	Left	Right
undiagnosed	3 (6%)	0 (0%)
Malignant Mesothelioma	5 (10%)	7 (14%)
Metastatic Adenocarcinoma	6 (12%)	11 (22%)
Non-Hodgkin's Lymphoma	0 (0%)	1 (2%)
Squamous cell Carcinoma	0 (0%)	2 (4%)
Tubecular Granuloma	10 (20%)	4 (8%)

Out of 50 cases that remained undiagnosed after repeated biochemical & cytological analysis, 47 patients (94%) were diagnosed by means of thoracoscopic pleural biopsy and 3 patients remained undiagnosed (couldn't arrive at specific diagnosis to initiate treatment) and thus the sensitivity of medical thoracoscopy in undiagnosed pleural effusion was 94% (table 6).

Table 6: Total Diagnosed Yield of Thoracoscopy Based On Histopathological Results

Pathological Results	No. of Patients	Percentage (%)
Definitive diagnosis by Thoracoscopy	47	94%
Remained undiagnosed	3	6%
Total	50	100%

Discussion

Pleural effusion is a common presentation in clinical practice and can be caused by a variety of malignant or benign cause[11]. Investigation of a pleural effusion evident on chest radiographs should follow a stepwise approach to diagnosis. Diagnosis begins with the clinical history, physical examination, and chest radiography and is followed by thoracocentesis when appropriate.

In our study fifty patients were included in which 34 (68%) male and 16 (32%) female, most of the patient had age more than 50 year, the mean age of study population was 56 years and male:female ratio was 2.12 :1.Mostafa Mahmoud Abdel Mageid Shaheen et al (2014)[12] did a study to evaluate the diagnostic role of medical thoracoscopy in undiagnosed exudative pleural effusion and showed the mean age of patients was 53 years and female to male ratio was 5:3and another study done by Laila A et al[13] on diagnostic yield of medical

thoracoscopy in cases of undiagnosed pleural effusion and shows the mean age of 51.3±16.3 years & male to female ratio was 7:3.

In the case of a proven exudate with nonconclusive cytology after (repeated) thoracocentesis, an additional procedure to obtain pleural tissue biopsy is the next step. This can be done with a minimal invasive procedure in four ways: closed pleural biopsy (CPB; Abrams biopsy), thoracoscopy guided pleural biposy, ultrasound (US)-guided pleural biopsy, and computed tomography (CT) - guided pleural biopsy[14]. Thoracoscopy is a safe and valuable tool for diagnosis of undiagnosed pleural effusion, particularly for patients with high probability of malignancy. Overall cost effectiveness of thoracoscopy is better in view of its better yield and lesser duration of hospital stay[14].

The shortness of breath being the most common pulmonary symptom in cases of moderate to massive pleural effusion, present in 49 patients (98%), followed by chest pain in 46 cases (92%), cough in 45 cases (90%), anorexia in 30 cases (60%), Cough with expectoration in 28 cases (56%), significant weight loss in 25 cases (50%) and fever occurred only 23 cases (46%). A thorough history may provide clues to aetiology and provides a measure of disability. Chest pain implies involvement of the pleura, ribs or chest wall,[15] suggesting an exudative process (e.g. malignancy, pleural infection, pulmonary infarction). Up to 75% of patients with effusions secondary to pulmonary emboli have a history of pleuritic pain, and dyspnea is often out of proportion to the size of the effusion (which is usually less than one-third of a hemithorax)[16]. Cough is also a non-specific symptom, although the production of purulent sputum suggests an infective aetiology. Constitutional symptoms such as weight loss, night sweats, anorexia and malaise may occur in association with pleural infection, tuberculous pleurisy or pleural malignancy.

Our study shows that 21 patients had no addiction (42%), 29 patients had history of addiction (58%). Among them, 23 (46%) were alcoholic and 19 (38%) were both smokers along with alcohol takers. According to Rooth Vasantha M et al[17] and Albanes D et al[18] shows that association with smoking and alcoholic in tuberculosis & malignancy. A study done by Jindal SK on the habits and attitude aspects of tobacco smoking, shows the total no. of smokers (n=29) was take more than 30 pack years. In a study on smoking habits, they found that 17.7% of cigarette smokers and 9.7% of bidi smokers with SI above 300[19]. These ratios were important while calculating relative risk ratios for smoking related diseases. There were very few lung cancer patients amongst smokers with SI less than 100 while 91.3% of those with cancer, were heavy smokers (SI>300)[20].

In our study the majority of patients (56%) with haemorrhagic pleural effusion were finally diagnosed malignant and other were diagnosed 14 (28%) tuberculosis & 3 (6%) were non-specific. According to Mostafa Mahmoud Abdel Mageid Shaheen et al (2014)[12] the gross appearance of pleural fluid, 19 patients presented with hemorrhagic effusion (47.5%), 20 (50%) presented with straw coloured and one (2.5%) presented with green coloured pleural effusion. The majority (79%) of patients with hemorrhagic effusions were finally diagnosed as malignant, other diagnoses were tuberculous and parapneumonic effusions. So, the haemorrhagic appearance of the pleural fluid narrowed the differential diagnosis predicting the malignant nature of the effusion in most of the patients.

The present study observed the mean value of ADA of study population was 34.11 IU/L. Although, lymphocytic predominant fluid is usually seen in tubercular pleural effusion but it is also seen in case of malignancy also. In our study ADA <40 IU/L patients were 30 (60%) and ADA > 40 IU/L patients were 4 (8%) were malignant. Adenosine deaminase (ADA) is an essential enzyme in the metabolism of purine nucleosides. Pleural fluid ADA estimation is quick and relatively inexpensive. The most widely accepted cut-off level of ADA for the diagnosis of tubercular pleural effusion (TPE) is 40 IU/l[21,22]. In present study we took ADA≤ 40 IU/l as in agreement with other studies. Previous studies showed that less than 3% of patients suffering from non-tuberculous lymphocytic pleural effusions have reported ADA levels over the diagnostic cut-off of 40 IU/l[23].

In our study majority of patients (32/50, 64%) having nodular pleural surface followed by thickened (13/50, 26%) by CECT procedure. Majority of patients having nodular pleural surface (28/32, 87.5%) diagnosed as malignant and rest (4/32, 12.5%) were tubercular. Those having thickened pleural surface diagnosed as tuberculosis (6/13, 46.15%) followed by malignant (5/13, 38.46%) and rest were undiagnosed (2/13, 15.38%). There are features of contrast enhanced thoracic CT scanning which can help differentiate between benign and malignant disease. In a study of 74 patients, 39 of whom had malignant disease, Leung et al[24] showed that malignant disease is favoured by nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening greater than 1 cm, and circumferential pleural thickening. Scott et al[25] evaluated these criteria in 42 patients with pleural thickening; 32 of the 33 cases of pleural malignancy were identified correctly on the basis of the presence of one or more of Leung's criteria. When investigating a pleural effusion a contrast enhanced thoracic CT scan should be performed before full drainage of the fluid as pleural abnormalities will be better visualized[26]. CT scanning has been shown to be superior to plain radiographs in the differentiation of pleural from parenchymal disease.

In our study observed that the appearance of pleural surface in thoracoscopy of pleural cavity, nodular pleural surface (29/50, 58%), followed by thickened (16/50, 32%) and smooth surface (5/50, 10%). A compelling support to the present study was given by Prabhu and Narasimhan (2012)[27] who performed pleuroscopy in a total of 68 patients (55 males and 13 females; mean age 49 years), nodules were found in 33 patients, 26 patients had adhesions, 8 patients had sago grain appearance, and one patient had normal pleura. They reported that, the direct visualization of the pleural surfaces had an advantage in arriving diagnosis. When the pleuroscopic findings were compared with the final histopathological examination reports, it was found that >70% of patients who had nodules had malignant lesion, >96% of patients who had adhesion had chronic or sub-acute inflammation (non-malignant lesion) and 100% of patients who had sago grain nodules had tuberculosis.

In present study it is observed that most of pleural nodules turned to be malignant in biopsy. Mostly metastatic carcinoma occurred in 18 cases (36%) followed by tubercular granuloma in 14 patients (28%), malignant mesothelioma in 12 patients (24%), undiagnosed in 3 cases (6%), squamous cell carcinoma in 2 patients (4%) and non-hodgkin's lymphoma occurred in 1 patients (2%).A study done by Abhishek Agarwal et al in 2014,[28] observed that 128 patients with pleural effusion who were studied, pleural fluid examination established the diagnosis in 81 (malignancy 33, tuberculosis 33, pyogenic 14 and fungal 1); 47 patients underwent closed pleural biopsy and a diagnosis was made in 28 patients (malignancy 24, tuberculosis 4). The remaining 19 patients underwent medical thoracoscopy and pleural biopsy and the aetiological diagnosis could be confirmed in 13 of the 19 patients (69%) (adenocarcinoma 10, poorly differentiated carcinoma 2 and mesothelioma 1) and concluded that medical thoracoscopy is a useful tool for the diagnosis of pleural diseases. The procedure is safe with minimal complications.

In our study observed that the sensitivity of medical thoracoscopy in undiagnosed exudative pleural effusion was 94%. Other studies showed variable diagnostic yield; in a prospective study on 40 patents from South Africa, thoracoscopy had a diagnostic yield of 98%[29]. Kendall[30] reported yield of thoracoscopic pleural biopsy to be 83% in their study in the United Kingdom. Tscheikuna[31] reported that thoracoscopy was diagnostic in 95% of 34 patients.

Conclusion

We concluded that medical thoracoscopy should be considered in patients with undiagnosed exudative pleural effusions, particularly those lymphocytic exudative effusions where TB and malignant pleural effusion are clinical possibilities and initial pleural fluid analysis is inconclusive. In this study the sensitivity of medical thoracoscopy in undiagnosed exudative pleural effusion was 94%.

Medical thoracoscopy should be performed as early as possible in all cases of undiagnosed exudative pleural effusion. It is a simple and safe method with high diagnostic yield and with low complication rates. Physicians should extend its access to proper patients if the facilities for medical thoracoscopy are available.

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Conflict of Interest: Nil   Source of support: Nil