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Monaldi Archives for Chest Disease

Monaldi Archives for Chest Disease 2026; 96:3233
doi: 10.4081/monaldi.2025.3233

The role of medical thoracoscopy in the diagnosis of exudative lymphocytic pleural effusions: an observational study

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Abstract

Diagnosis of pleural effusion remains challenging despite extensive microbiological and radiological investigations. Pleural histopathological examination (HPE) is often needed to ascertain the etiology. Medical thoracoscopy (MT) is surpassing the other modalities of pleural biopsy on account of its high diagnostic yield. We aim to estimate the yield of MT in undiagnosed exudative lymphocytic pleural effusion and also intend to correlate gross thoracoscopy findings with HPE results. This retrospective observational study was conducted in a tertiary respiratory care center. Medical records of undiagnosed exudative lymphocytic predominant pleural effusion patients who underwent MT during the study period of 24 months were retrieved from the Medical Records Department. The clinico-demographic profile, radiological images, gross thoracoscopy findings, HPE reports, and post-procedure complications were recorded and analyzed using analysis of variance and chi-square test. The study comprised 62 patients with a mean age of 52 years at presentation. HPE of MT-guided biopsy confirmed tuberculosis in 22 (35.3%), malignancy in 18 (29%) cases, and 22 (35.5%) cases had chronic nonspecific inflammation. The most commonly observed MT finding in malignancy was pleural nodules (14.70%), followed by thickened pleura (10.50%) and growth (2.10%). In tuberculosis, the most common MT finding was adhesions in all, followed by nodules (5.28%). We also diagnosed a case of pleural amoebiasis and ependymoma, which are rare. Macroscopic findings had a significant correlation with the final histopathologic diagnosis, with a diagnostic yield of 66.1%. Gross thoracoscopic findings correlate well with the histopathological diagnosis of pleural effusion etiology, with a correlation coefficient of 0.73. Pleural nodules were the most common finding in malignancy, while adhesions were common in benign pathology like tuberculosis. A good diagnostic yield underscores the utility of MT in undiagnosed exudative lymphocytic pleural effusions.

Key words: medical thoracoscopy, pleural biopsy, undiagnosed pleural effusion, pleural amoebiasis, pleural ependymoma.

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Introduction

Pleural effusion, an entity characterized by the accumulation of fluid in the pleural cavity, is one of the most common respiratory diseases encountered by pulmonologists. Pleural effusion accounts for around 25% of the total respiratory diseases presenting to the hospital. The preliminary step in the evaluation of pleural effusion is to categorize the effusion into exudative and transudative effusion based on the biochemical reports of pleural fluid analysis. Despite pleural fluid analysis and radiological investigations, around 25% of pleural effusion cases remain undiagnosed, which require pleural biopsy for establishing a diagnosis [1]. Closed pleural biopsy techniques, computed tomography or ultrasound-guided biopsy, or thoracoscopic guided biopsy are the various modalities for pleural biopsy.

Closed biopsy has overall poor sensitivity in the diagnosis, and around 10-27% of cases may still remain inconclusive after closed pleural biopsy [2]. Radiological image-guided biopsy, though, has good overall sensitivity (around 87%), demands expertise and is expensive, thus may not be feasible at all centers. Medical thoracoscopy (MT) is a minimally invasive procedure that can be performed under mild-moderate sedation and local anesthesia. Direct visualization of the target biopsy site enhances its positive diagnostic rate. The positive diagnostic rate of MT, as per available literature in the diagnosis of malignancy and tuberculosis, is around 91-95% and 93-100%, respectively [3]. MT is replacing closed biopsy on account of its high sensitivity and favourable safety profile. Our study is planned to assess the yield of MT in undiagnosed exudative lymphocytic pleural effusion and to correlate the gross thoracoscopic findings with HPE findings in various etiologies and to enumerate the post-thoracoscopy complications.

Materials and Methods

This descriptive retrospective study was conducted in a tertiary respiratory care center between March 2022 and March 2024 after

obtaining approval and clearance from the Institutional Ethics Committee, SDS Tuberculosis Research Centre & Rajiv Gandhi Institute of Chest Diseases as per the document no. SDS/PG/01/2023-24 dated 21/2/2024**.** All cases aged above 18 years who underwent MT for undiagnosed exudative lymphocytic pleural effusion (described as exudate as per Light's criteria but cytological, microbiological, and biochemical tests failed to yield a diagnosis) during our study period were included, and cases with incomplete data were excluded. Data from the 62 cases fulfilling our inclusion criteria were retrieved from the Medical Records Department of our hospital. The details were recorded in a pre-formatted case proforma. Detailed clinical history, including sociodemographic data, symptomatology, comorbidities, significant medical and surgical illness in the past, drug intake if any, *etc*., was recorded. All the required laboratory hematological and radiological investigations, pleural fluid analysis including microscopic and biochemical analysis reports [sugar, protein, gram stain, ZN stain and culture, adenosine deaminase (ADA) level, and pleural fluid cytology] were collected and recorded. MT procedure details and gross thoracoscopic findings were noted. Post-procedure complications and histopathological examination (HPE) reports were documented.

Procedure details

Informed written consent was obtained from all cases before the procedure. Patients were MT was performed under conscious sedation using injection midazolam 1 mg and injection fentanyl 50-100 microgram Patients were positioned on the contralateral lateral decubitus. After site marking under ultrasound guidance, the ipsilateral hemithorax was cleaned and draped. Injection lignocaine was instilled to the skin, subcutaneous tissue, muscle, and parietal pleura, and the fluid presence was reconfirmed. After systemic exploration of the pleura and pleural cavity using artery forceps, a trocar was inserted into the pleural cavity, MT was directed through the trocar, and the lung, costal diaphragmatic pleura were visualized thoroughly. Biopsies were taken from the abnormal sites with alligator jaw forceps and sent for histopathological analysis and microbiological investigations, including cartridge-based nucleic acid amplification test for *Mycobacterium tuberculosis*. Intercostal drainage tube (ICD) was fixed *in situ* post-procedure. Patients were monitored for procedure-related complications. The thoracoscope used was the Evis Exera Pleuravideoscope Olympus LTF Type 160 (Olympus, Tokyo, Japan).

Statistical analysis

All the data collected were entered in a Microsoft Excel spreadsheet and data analysis was done. The data collected were analyzed statistically using descriptive statistics in terms of mean, standard deviation, median, and range or frequencies (number of cases), percentages, tables, and graphs wherever applicable. Stratified analysis was performed wherever necessary using 95% confidence Interval. Chi-square test and analysis of variance were used to analyze correlations in the data obtained. A p-value of <0.05 was considered significant.

Results

The study comprised 62 patients of undiagnosed exudative lymphocyte predominant pleural effusion who underwent MT. There were 49 (79%) males and 13 (21%) females, with a mean age of 52 years. The histopathological diagnosis from MT showed tuberculosis in 22 (35.5%) patients, malignancy in 18 (29%), and chronic non-specific inflammation in 22 (35.5%) patients. Confirmed etiological diagnosis after thoracoscopy was obtained in 41 of 62 (66.1%) patients. In our study, there was a significant difference in the average age, gender, and past medical history across different groups. The average age of patients with malignancy was more than the average age of those with tuberculosis and chronic inflammation, which was statistically significant. Additionally, we observed that males had more chronic inflammation and tubercular effusion, while females had more malignant pleural effusion. Comorbidities were noted in 25 (40.32%) patients, of which systemic hypertension was the most common. Comorbidities had no impact on the etiological diagnosis. The mean duration of presenting complaints was 4 weeks. Breathlessness was the most common presenting complaint in 52 (83.8%) patients, followed by cough in 38 (61.3%) and chest pain in 26 (41.9%). History of alcohol intake or smoking had no significant influence on the etiological diagnosis. A previous history of tuberculosis or a past history of malignancy had a statistically significant influence on being diagnosed with tuberculosis or malignancy as the cause for the current pleural effusion. Baseline sociodemographic characteristics of all the cases are enumerated in Table 1.

Radiologically, on contrast-enhanced computed tomography (CECT), pleural effusion was the only radiological abnormality in 42 patients (67.7%). Loculations were the commonly observed find-

Table 1. Baseline socio demographic characteristics of the study population

Variables		TB (n=22)	Malignancy (n=18)	Chronic inflammation (n=22)	Total (n=60)	p-value tuberculosis *vs.* malignancy	p-value malignancy *vs.* chronic inflammation	p-value tuberculosis *vs.* chronic inflammation
Age	51.5±13.2	65.6±9.2	56.3±17.7	57.3±15.0	0.0005	0.0511	0.3137	
Gender	Male	18 (81.8)	8 (44.4)	17 (77.3)	43 (69.4)	0.013	0.032	0.708
	Female	4 (18.2)	10 (55.6)	5 (22.7)	19 (30.6)			
Comorbidity		8 (36.4)	7 (38.9)	11 (50.0)	26 (41.9)	0.869	0.482	0.361
Smoking history		9 (40.9)	7 (38.9)	7 (31.8)	23 (37.1)	0.896	0.641	0.531
Alcohol history		11 (50.0)	10 (55.6)	8 (36.4)	29 (46.8)	0.726	0.949	0.361
Past h/o TB		6 (27.3)	0 (0.0)	3 (13.6))	9 (14.5)	0.024	0.235	0.295
Past h/o malignancy		0 (0.0)	7 (38.9)	0 (0.0)	7 (11.3)	0.001	0.001	1.000

TB, tuberculosis; h/o, history of; A p-value of <0.05 is considered significant. Thus, there is significant difference in the average age, gender, and past medical history in different groups.

ings along with effusion in 40 patients (64.5), pleural nodules and mass were observed in 11 patients (17.7%) each. Pleural thickening and loculations were more often noted in tubercular effusion (72.7%), while pleural nodules and parenchymal mass lesions were frequent (77.7%) in malignant effusion (Table 2). Diagnostic thoracocentesis was suggestive of exudative lymphocytic predominant with low ADA level below 40 units/L in all our cases.

On performing MT, we observed adhesions in 48 (77.4%) cases, nodules in 19 (30.6%), growth in 2 (3.2%), and grossly normal pleura in 6 (9.6%). HPE of MT guided biopsy confirmed malignancy in 18 cases (29%). Among these, adenocarcinoma was observed in 13 cases, and 2 were poorly differentiated carcinoma, 1 was mesothelioma, 1 was metastatic squamous cell carcinoma, and 1 was a rare case of pleural ependymoma. Nonspecific chronic inflammation was reported in 22 cases (35.5%), and 1 case of chronic inflammation was diagnosed as pleural amoebiasis on microscopy. The biopsy sample was positive for *M. tuberculosis* by GeneXpert in 4 of 22 (18.18%) patients with HPE-confirmed tuberculosis, and all were rifampicin sensitive. Most commonly observed MT finding in malignancy was nodules in 14 (77.8%), followed by adhesions with thickened pleura in 10 (55.6%) and growth in 2 (11.1%). In tuberculosis, the most common MT finding was adhesions in all 22 patients, followed by nodules in 5 (22.7%) patients. Those with chronic inflammation had adhesions in 16 (72.7%) and grossly normal pleura in almost 6 (27.3%) patients (Table 3). Pleural amebiasis had thick septation and whitish slough covering the entire pleura, and pleural ependymoma had multiple papilloid growth in the parietal pleura. The gross thoracoscopic findings had a significant correlation (correlation coefficient 0.73) with the final histopathological diagnosis.

Post-procedure complications were reported in 14 (22.5%) patients, but none were major. Chills were observed in 9 (14.5%) patients, chest pain in 3 (4.8%), and fever and breathlessness in 1 (1.61%) each (Table 4). The mean duration of post-procedure intercostal tube placement was 2 days in our study group.

Discussion

Establishing the cause of exudative pleural effusion in the context of inconclusive pleural fluid analysis requires pleural sampling *via* invasive procedures. Even closed pleural biopsies fail to reach the right diagnosis in up to 40% of exudative effusion [4]. MT has replaced the conventional pleural biopsy in many centres. In the present study, we obtained histopathological abnormal pleural findings in all 62 patients, but a final etiological diagnosis was obtained in only 41 of 62 patients. Thus, our study reports 66.1% diagnostic yield of MT in undiagnosed exudative lymphocyte predominant pleural effusion. Various factors are known to influence the yield of MT like method of sampling, inadequate sampling, pathological techniques, the presence of dense adhesion masquerading the pathological sites, *etc*.

Table 2. Radiological findings (CECT thorax) of the study population

Features on computed tomography thorax	Tuberculosis (n=22)		Malignancy (n=18)		Chronic inflammation (n=22)	
	N	%	N	%	N	%
Effusion only	1	4.6	1	5.6	4	18.2
Effusion + septations	16	72.7	2	11.1	15	68.2
Effusion + pleural nodules	5	22.7	8	44.4	0	0
Effusion + mass	0	0	6	33.3	0	0
Effusion+ septations+ pleural thickening	0	0	1	5.6	3	13.6

Table 3. Correlation of thoracoscopic findings and histopathological diagnosis among 3 groups (i.e., tuberculosis, malignancy and chronic inflammation).

MT findings	Tuberculosis (n=22)	Malignancy (n=18)	Chronic inflammation (n=22)	p
Nodules	5 (22.7)	14 (77.8)	0 (0.0)	<0.0001
Adhesions	22 (100.0)	10 (55.6)	16 (72.7)	0.003
Growth	0 (0.0)	2 (11.1)	0 (0.0)	0.0801

MT, medical thoracoscopy. A p-value of <0.05 is considered significant. A statistically significant correlation coefficient 0.73 was observed between the gross thoracoscopy findings and the histopathological results suggesting a strong association between them.

Table 4. Complications after thoracoscopy observed in our study population

Complications after procedure	Number	%
Nil	48	77.4
Chills	9	14.5
Chest pain	2	3.2
Fever	1	1.6
Breathlessness	1	1.6

The yield in our study is slightly lower than the available literature of more than 90% positive diagnostic rate [5,6]. Few of these studies with >90% yield included all cases of exudative pleural effusions and not only those with lymphocytic effusions like ours. The diagnostic yield of thoracoscopy in exudative lymphocytic pleural effusions done by Law *et al.* and Mootha *et al.* was 78.57% and 74.28%, respectively [7,8]. An Indian study with patients of inconclusive pleural effusion who underwent flex-rigid thoracoscopy, biopsy was positive in 12 of the 18 patients (66.7%), which was similar to our study [9]. The discrepancy in yield may also be secondary to the non-consideration of chronic inflammation, which constitutes 35.5% of HPE diagnoses as a final etiological diagnosis in yield calculation in our study, unlike a few other studies. Nonspecific chronic inflammation can suggest the occurrence of a sampling error or genuine benign pleural disease. However, our study was limited by the inability to perform advanced molecular or immunohistochemical analyses on samples of chronic inflammation and by the lack of long-term follow-up for these patients. In a study on the long-term outcome of patients with nonspecific pleurisy (NSP) on MT, most of them were found to have a benign etiology (23/31 patients, 74.2%). Specific histopathological changes in the pleura are not expected in cases of pulmonary embolism, heart failure, or treated parapneumonic effusion. Even in the case of tuberculous effusion, the reaction occurring in the pleura may cause effusion in the absence of granulomatous inflammation [10]. Although the diagnosis of most NSP is a benign disease, malignant disease is also a possibility, especially in patients with nodules or plaques following MT and the recurrence of pleural effusion. Another update on the long-term outcome of patients with NSP at MT, of the 154 patients diagnosed with NSP with available follow-up data,19 patients were subsequently diagnosed with pleural malignancy, including lung cancer and malignant pleural mesothelioma, which were the most common. The more difficult disease to diagnose is pleural mesothelioma because the lesion is difficult to access using MT [11].

Thoracoscopy can be performed using a rigid or semi-rigid thoracoscope. We used a semi-rigid thoracoscope and not a rigid one, as in some previous studies with high diagnostic yield. Generally, larger biopsy specimens are obtained *via* rigid thoracoscopy, which may influence the yield obtained [5,12]. A randomized controlled trial comparing the two techniques by Dhooria *et al.* found that the diagnostic yield of biopsies obtained was almost similar (100% with rigid *vs.* 94.3% with semi-rigid), but when they conducted intention-to-treat analysis, including cases where a successful biopsy was not obtained, rigid thoracoscopy had a significantly higher yield compared to semi-rigid (100% *vs.* 73.3%, p=0.02) [13]. Thus, the instrument used and the technique also play a significant role in obtaining a positive yield. Adhesions were the predominant gross thoracoscopy findings found in 77.4% of all cases and 72.7% of those with chronic nonspecific inflammation. The presence of dense adhesions may impair the ease of mobility and restrict access to the pathological site. Also, all patients in our study were treated elsewhere and later referred to us, which might have obscured the actual diagnosis. Especially,8 of 22 patients (36.4%) with chronic nonspecific inflammation on HPE were on empirical ATT prior to thoracoscopic procedure, which could lead to absence of specific findings on MT, non -specific histopathological findings, and hence lower diagnostic yield.

The most common etiology of pleural effusion worldwide is malignancy; regional discrepancies to this are noted, especially in high tuberculosis burden countries. In India, tuberculosis represents the top cause of pleural effusion [14]. Pleural fluid ADA has been widely used to diagnose tuberculosis in resource-limited settings. Though pleural fluid ADA has good sensitivity of 86% in the diagnosis of tuberculosis, false positive results reported in the literature are around 1.7% [14,15]. Moreover, many tubercular pleural effusions will have lower levels of ADA than the accepted cut-offs. In a study by Kim *et al.* on tubercular pleural effusion, 18.8% of their study population had low ADA levels [16]. Decreased ADA levels in tubercular pleural effusion are linked with advanced age, active smoking, multiorgan dysfunction, and critical illness [16]. These observations foreground tissue diagnosis for apt diagnosis. In the present study, tuberculosis remains the common histopathological diagnosis, and all those cases had lower ADA levels. The second common cause was chronic inflammation, followed by malignancy. Malignancy and tuberculosis were the commonest histopathological diagnoses in several studies, of which malignant effusion tops the list. Adenocarcinoma was the commonest histopathological type of malignancy diagnosed, which is similar to other studies [17,18]. It is notable that the present study reports one case of pleural amoebiasis, which is reported to occur in 7-20% cases of hepatic amoebiasis [19]. Also, pleural ependymoma is a rare cause of metastatic pleural effusion that we have encountered.

Among 62 cases, the majority were found to be in the age group of 33 to 70 years, which is a similar observation as observed in a study by Swarnakar *et al*. [20]. Age has a significant impact on the etiology of the pleural effusion. Malignant effusion was more common in the advanced age group in our study. Males were more preponderant to the development of pleural effusion in our study. The majority of females undergoing MT were diagnosed with malignancy, which explains adenocarcinoma being the commonest histopathological type in our study. Neither comorbidities nor smoking history influenced the diagnosis in our study, similar to the observations done by Chen *et al.* [6]. A previous history of tuberculosis or a past history of malignancy had a statistically significant influence on being diagnosed with tuberculosis or malignancy as the cause for the current pleural effusion. 14.5% (9) of the patients had a previous history of being diagnosed with tuberculosis, of which 27.6% were diagnosed as tuberculous pleural effusion on MT.

Most of the patients who were enrolled in this study had breathlessness followed by cough and chest pain as presenting complaints, which is comparable with other studies [21-23], in which breathlessness is the most common presenting symptom in 86.3%, 75.4%, and 67.4% patients, respectively, followed by cough.

Radiologically, on CECT, pleural thickening and loculations were more often noted in tubercular effusion (72.7%), while pleural nodules and parenchymal mass lesions were frequent (77.7%) in malignant effusion. Even the majority of patients with a previous history of tuberculosis had a typical presentation of moderate to large pleural effusion with pleural thickening, loculations with underlying consolidation/collapse, while a few had associated pleural nodules.

The presence of grossly abnormal thoracoscopy findings will increase the probability of histopathologic diagnosis. Knowledge of macroscopic findings will guide physicians about the nature of the disease they are dealing with. The most common gross thoracoscopic finding in our study is adhesions over the pleural surface in 48 (61%), followed by nodules in 19 (35%) and growth in 2 (6%), contrary to several studies which reported more nodules than adhesions [24,25]. This disparity is due to the higher number of tuberculosis and chronic inflammation cases than malignancy in our study. In tuberculosis, the most common MT finding that we

noted was adhesions between visceral and parietal pleura, and they were present in 22 cases (71%), which is similar to the observations made by Chen *et al.* [6]. The most common thoracoscopic finding we observed in malignancy was a pleural nodule, followed by adhesions and growth. Among the patients with chronic nonspecific inflammation in our study, the majority had adhesions (67%), followed by normal pleura (33%), which are comparable with similar studies [6,26]. We observed a significant correlation between macroscopic findings and the histopathological diagnosis. In our study, 14 out of 18 (77%) pleural nodules turned out to be malignant. Yousef *et al.* reported nodules in 27(75%) of their study population, of which 22 (81.48%) were malignant [27]. In a study by Arif *et al.*, they reported nodules in 23 cases of their study population, and the majority (82.6%) were malignant [25]. Other common thoracoscopic findings reported in the literature are adhesions and pleural thickening. 79.16% (38/48) of patients with adhesions on macroscopy turned out to be benign in our study. In a study by Prabhu *et al.,* 96% of pleural adhesions turned out to be benign [23]. Helala *et al*. reported that all their cases with gross adhesions on MT were of benign etiology [28]. In the study by Chen *et al.,* 77% (48) had adhesions, of which 80% were benign, and 20% had malignant pathology [6]. We observed pleural growth only in 2 cases, which turned out to be malignant. Thus, the presence of pleural nodules or growth would increase the possibility of malignancy, while benign etiologies are usually associated with adhesions, pleural thickening, and irregularities.

Though MT is a relatively safe procedure, a very few minor complications like persistent air leak, chest pain, and subcutaneous emphysema are reported to occur. We report complications in only 22.6% (14 cases), of which chills were the most frequent (14.5%), followed by chest pain in 2 cases (3.2%). Complications after thoracoscopy reported in the reference studies were 20%, 3.70%, and 4.41% of patients, respectively [11,23,29]. Subcutaneous emphysema and pneumothorax were the reported post-procedure complications by Kapadia *et al.* in their study [24]. Marwah *et al.* reported fever as the most common complication in their study [30]. The mean duration of ICD in our study was 2 days post-procedure, whereas Ranganatha *et al.* reported a median duration for ICD removal post-procedure of 4 days and often more prolonged in parapneumonic effusions [31].

Limitations

Our study is a single-center study with a small sample size, and hence, the results cannot be generalized. The retrospective and observational nature of the study might have introduced patient selection bias due to referral patterns, prior treatment, and missing data. Thoracoscopy was performed by different pulmonologists with varied skills and experience that might have affected the yield. Advanced molecular or immunohistochemical analysis was not done on chronic inflammation samples, which could have influenced the diagnosis. Most cases were referred at a later stage of disease, which might also have influenced the yield.

Conclusions

MT has a very high diagnostic yield in undiagnosed exudative lymphocytic pleural effusions with negligible complications. Presence of pleural nodules would increase the probability of malignancy, while adhesions and pleural thickening favor benign pathologies.

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Received: 20 October 2024; Accepted: 21 January 2025; Early view: 20 March 2025..

Contributions: Swathi Karanth MP: concept and designing. Pradeep Naik G, Aravind Ram: performing and interpretation. Akshata JS, Raghu BP: manuscript preparation. Nagaraja C: manuscript review and editing. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that no conflict of interest.

Ethics approval and consent to participate: the study was approved by the Institutional Ethics Committee of SDS Tuberculosis Research Centre & Rajiv Gandhi Institute of Chest Diseases as per the letter SDS/PG/01/2023-24 dated 21/2/2024. The committee assessed the planned project as ethically unobjectionable.

Informed consent: written consent to participate from study participants was waivered by the IEC as it is a retrospective observational study

Patient consent for publication: not applicable.

Availability of data and materials: all data generated or analysed during this study are included in this published article.

Acknowledgments: the authors acknowledge the support of all the staff at SDS Tuberculosis Research Centre & Rajiv Gandhi Institute of Chest Diseases, Bengaluru for all the direct and indirect contributions to this study. Without their support this would not have been possible.