

Utility of medical thoracoscopy in patients with undiagnosed pleural effusion in chest department in Beni-Suef University

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Introduction Pleural diseases involve the parietal and visceral pleura and may be of either inflammatory or malignant origin, with pleural effusions. Medical thoracoscopy (MT) is a procedure involving internal examination and biopsy of masses within the pleural and thoracic cavity. It is a valuable tool that enables a wide variety of diagnostic and therapeutic procedures.

Aim The aim of this work was to assess the role of MT in patients with exudative undiagnosed pleural effusion.

Patients and methods A total of 42 patients with undiagnosed exudative pleural effusion were admitted to Chest Department, Faculty of Medicine, Beni-Suef University. They were subjected to written informed consent, full history, clinical examination, sputum analysis, chest radiography, chest computed tomography, ECG, routine liver and kidney functions tests, complete blood count, coagulation profile, viral markers, and Tuberculin test. Diagnostic thoracentesis was done. The pleural fluid was subjected to testing for sugar, protein, lactate dehydrogenase, adenosine deaminase, cytopathology, Gram's stain, and acid-fast bacilli smear and culture. Patients in whom the pleural effusion remained undiagnosed were subjected to MT.

Introduction

Undiagnosed recurrent pleural effusion is a frequently encountered problem in clinical practice. Thoracoscopy is a safe and valuable tool for diagnosis of undiagnosed exudative pleural effusion (EPE), particularly for patients with a high probability of malignancy [1]. Medical thoracoscopy (MT) has consistently been demonstrated to be superior to fluid cytology and 'blind' closed needle biopsy [2] with a sensitivity of up to 95% [3]. One study comparing MT with computed tomography (CT)-guided Abrams needle biopsy demonstrated no significant difference with the two techniques, although the advantage of thoracoscopy remains that pleurodesis can be performed after pleural fluid removal during the procedure [4]. It can be useful as well to provide large biopsies required for the application of molecular techniques, such as the use of molecular markers, for example, epidermal growth factor receptor; these markers participate in the modern staging of malignant diseases and provide possibilities for potential therapies [5]. Other nonroutine and more complex applications of MT are in the treatment of empyema, in lung biopsy with forceps, and in cervical sympathectomy; these procedures are considered advanced, need more experience, and should definitely be performed by experts and highly trained thoracoscopists [6].

Results This study was applied on 42 patients with inconclusive cytological results: 20 were malignant (nine malignant pleural mesothelioma and 11 metastases), five had tuberculous pleurisy, eight had empyema, and nine had nonspecific pleurisy. Regarding pleural fluid cytological analysis, five cases were positive for atypical mesothelial cells.

Conclusion MT is a valuable tool in the diagnosis of undiagnosed exudative pleural effusion. It is simple and safe, with high diagnostic yield and lower complication rates.

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The present study investigated the usefulness of MT in diagnosing the undiagnosed cases of EPE.

Aim

This study investigated the usefulness of Medical Thoracoscopy in pleural effusion patients with inconclusive cytology results, as a first experience in Chest Department of Beni-Suef University.

Patients and methods

A total of 42 (30 males and 12 females) patients with a mean age of 54 years with undiagnosed EPE admitted to Chest Department, Faculty of Medicine, Beni-Suef University between January 2015 and September 2016 were included in the study. All patients and healthy controls included in this study gave their informed consent and approval upon participating in the study. All patients in this study gave their informed written consent (there were not healthy control subjects).

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Study design

This is a prospective observational study.

Inclusion criteria

Patients with EPE and/or pleural thickening of unknown etiology after repeated inconclusive thoracentesis were included in this study.

Exclusion criteria

The exclusion criteria were general contraindications to thoracoscopy – for example, unstable angina, left ventricular failure, uncontrolled hypertension, and bleeding tendency. Patients with poor lung function, and patients with intractable cough or respiratory failure, were also excluded.

Prethoracoscopic investigations

All patients gave written informed consent and were subjected to full history and clinical examination, sputum analysis, chest radiography (posteriolateral and lateral), chest CT, ECG, routine liver and kidney function tests, complete blood count, coagulation profile, and viral markers (HIV and hepatitis C viral antigen). Diagnostic thoracentesis was done. The pleural fluid was subjected to testing for sugar, protein, lactate dehydrogenase, adenosine deaminase (ADA), cytopathology, Gram's stain, acid-fast bacilli smear, culture, and Tuberculin test, which was done routinely in each pleural exudative effusion cases especially in endemic areas. Patients in whom the pleural effusion remained undiagnosed were subjected to MT. Multiple biopsy samples (usually 2–6) were obtained under direct vision from any abnormal areas in the parietal or visceral pleura with the biopsy forceps. The samples were subjected to histopathological examination and culture for *Mycobacterium tuberculosis*.

Medical thoracoscopy*Equipment*

In the present study, MT was done using a KARL-STORZ rigid thoracoscope (Karl Storz GmbH & Co., Tuttlingen, Germany) that consists of various equipment including trocar, telescope, light source, and biopsy forceps. The rigid telescope is made of stainless steel and is 27 cm in length with a diameter of 7 mm. The rigid telescope can be straight (0°) or oblique (typically 30° and 50°) angle of vision. A metallic trocar 8 mm in inner diameter, autoclavable, is used. A cold (Xenon) light source with camera (Telecam) is attached to the eyepiece of the telescope.

Technique

Patients were kept fasting for 6 h before the procedure. An intravenous cannula was secured in the upper limb

on the opposite side of thoracoscopy. Patient was placed in lateral decubitus position with the affected side up and the arms of the patient placed above the head to prevent the arms from interfering with the procedure. A finger probe was attached to monitor the pulse rate and the arterial oxygen saturation of the patient. Oxygen via nasal cannula was administered during the entire procedure to maintain SpO₂ more than 90%. All cases were performed using local anesthesia (lidocaine 2%) under conscious sedation using pethidine 100 mg (50 mg was given by intramuscular injection and 50 mg was given by intravenous injection). Lidocaine 2% was used for local anesthesia of the skin, subcutaneous tissues, and periosteum of ribs.

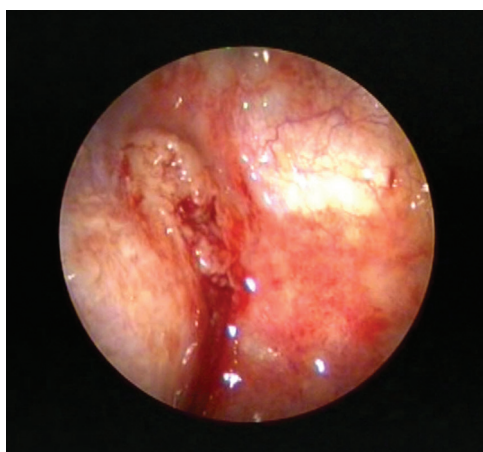
The needle was advanced carefully over the superior aspect of the rib, first aspirating and then injecting small amounts of the lidocaine while slowly advancing toward the pleura, until the pleural fluid was drained. The puncture site is usually in the mid-axillary zone between the fourth and sixth intercostal spaces. The single-port entry technique for thoracoscopy was used in all cases. Skin incisions of 1.5 cm were made with a scalpel, which was followed by blunt dissection of intercostal muscles by curved artery forceps until reduction of resistance is felt and the costal pleura is reached. Then the rigid trocar, which is 8 mm in inner diameter, was inserted in a corkscrew motion slowly and carefully. The inner part of the trocar was then withdrawn and the thoracoscope was introduced inside the trocar. Pleural fluid was suctioned through the cannula until the pleural surfaces were clearly visible. The thoracoscope was rotated within the pleural cavity to visualize the costal, diaphragmatic, and the visceral pleura. Dense fibrin strands were cut with cutting forceps. An adequate biopsy of the parietal pleura was taken from an abnormal and infiltrated area on the parietal pleura by means of the biopsy forceps – two to six biopsies. When no obvious tumoral lesions are present, multiple biopsies should always be taken, especially at the lower costophrenic area, especially in patients with a history of asbestos exposure and recurrent pleural exudates with diffuse thickening of the pleura [7]. After obtaining satisfactory biopsy specimens, the thoracoscope was removed followed by the trocar, and chest tube (28–32 Fr) connected to underwater seal was introduced in the same place. Chest radiography was done after the thoracoscopic procedure. All the pleural biopsy specimens were sent for histopathological analysis. The chest tube was removed as soon as the lung is clinically and radiologically re-expanded with minimal amount of pleural fluid drainage. The indications for removal of

chest tubes placed for various pathological processes are as varied as the indications for tube placement. In general, the absence of air leakage and cessation of fluid flow (100–150 ml daily) are reasonable guidelines [8].

Results

The present study included 42 patients who underwent MT for EPE with inconclusive cytology results. They were selected from the Chest Department inpatient wards in Beni-Suef University during the period from January 2015 to September 2016. As regards the histopathological results of the thoracoscopic pleural biopsy among the studied population, out of 42 patients, nine (21.4%) patients were diagnosed with malignant pleural mesothelioma (MPM), 10 (23.8%) patients with metastatic adenocarcinoma primary from breast, lung, and liver, one (2.3%) patient with undifferentiated carcinoma, five (11.9%) patients with caseating tuberculous granuloma, nine (21.4%) with nonspecific pleurisy (NSP), and eight (19.04%) with empyema (Table 1). The descriptive criteria of the involved patients are given in Table 2; there were 42 patients aged 30–78 years, with a mean of 50.3 ± 12.86 years (30 males and 12 females) all from rural areas. Most of the thoracoscopic gross pictures were nodules of variable sizes, some were small nodules and others were of large sizes and masses; pleural plaques and adhesions were detected (Figs. 1–4), as well as adhesions and septic pyogenic membrane with collection of pus (Table 4). As regards pleural effusion, out of 42 cases, 59.5% were right sided, 35.7% were left sided, and 4.8% were bilateral. As regards gross appearance, 38% were hemorrhagic, 47.6% were turbid, 11.9% were straw in color, and 2.4% were chylous; there was a female patient with a history of blunt trauma 2 years ago who developed

Figure 1



Large nodule over visceral pleura.

Table 1 The histopathological diagnosis for the involved patients (n=42)

Histopathological pattern	n (%)
Malignant pleural mesothelioma	9 (21.4)
Metastatic adenocarcinoma	10 (23.8)
Undifferentiated carcinoma	1 (2.3)
Caseating granuloma	5 (11.9)
Nonspecific pleurisy	9 (21.4)
Empyema	8 (19)

Table 2 Descriptive characteristics of the involved patients

	n (%)
Age [mean±SD (range)] (years)	50.3±12.86 (30–78)
Sex	
Male	30 (71.4)
Female	12 (28.6)
Smoking	
Positive	22 (52.4)
Negative	20 (47.6)

Table 3 Pleural fluid characteristics of the involved patients (n=42)

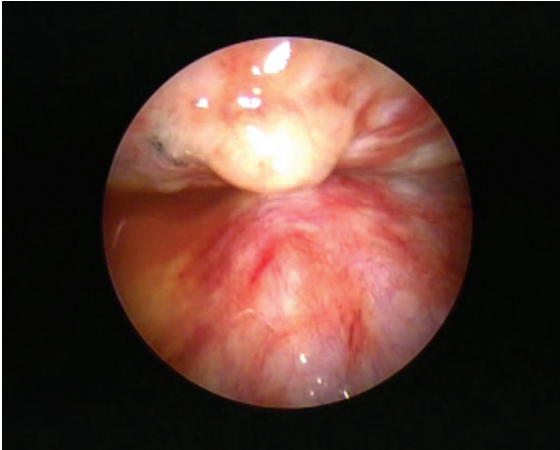
Site	
Right	25 (59.5%)
Left	15 (35.7%)
Bilateral	2 (4.8%)
Appearance	
Hemorrhagic	16 (38%)
Turbid	20 (47.6%)
Chylous	1 (2.4%)
Straw	5 (11.9%)
Pleural fluid cytology	
Negative	36 (85.7%)
Positive for atypical cells	6 (14.3%)
Pleural fluid Gram staining	
Positive	8 (19) (streptococci, Gram negative cocci)
Negative	34 (81%)
Adenosine deaminase	
>40	15 (35.7%)
<40	27 (64.3%)

Table 4 Distribution of studied patients in relation to thoracoscopic findings

Thoracoscopic finding	Final diagnosis
Small nodules	Caseating tuberculous granulomas (n=5)
Masses	MPM (n=4), metastatic adenocarcinoma (n=2)
Variable-sized nodules	Malignant (MPM, adenocarcinoma, and undifferentiated carcinoma) (n=12)
Septic pyogenic membrane, adhesion, and collected pus	Empyema (n=8)
Adhesion and fibrous strands	NSP (n=9)
Diffuse thickened pleura and plaques	MPM (n=2)

MPM, malignant pleural mesothelioma; NSP, nonspecific pleurisy.

Figure 2



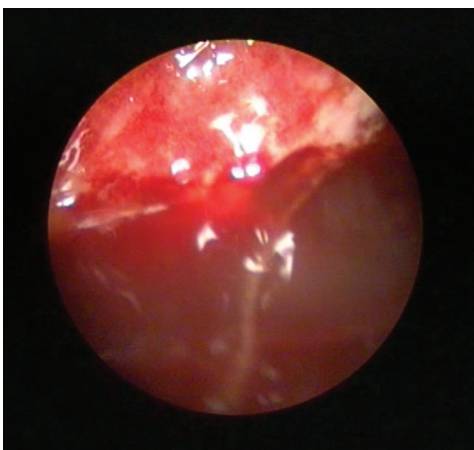
A gig mass over visceral pleura and small scattered nodules over both visceral and parietal pleurae, biopsies were taken revealed malignant mesothelioma.

Figure 3



Pleural plaques and nodules.

Figure 4



Hemorrhagic effusion with thin fibrin strand.

chest pain – radiologically there was right-sided pleural effusion and multilocular osteolytic lesions in the posterior aspect of ribs from 6 to 9 on the right side. Thoracocentesis revealed chylous fluid; cytologically the sample revealed proteinaceous material entangling many small lymphocytes, neutrophils, and few reactive mesothelial cells. ADA was $34\mu\text{l}$, and tuberculin test was negative. Thoracoscopically there were adhesions and biopsy revealed chronic NSP and pleural fibrosis, and surgical biopsies from ribs revealed fibrocystic benign lesion. As regards pleural fluid cytology, 14.3% were positive for atypical cells but inconclusive, and 85.7% were negative. In all, 19% of cases were positive for Gram staining and 81% were negative for Gram staining (35.7% with $\text{ADA}>40\text{ IU/l}$, and 64.3% with $\text{ADA}<40\text{ IU/l}$, Table 3). Generally most of the patients' hospital stay ranged from 15 to 30 days (18.5 ± 6.33 days), until the results of the biopsy were obtained and the intercostal tube was withdrawn. Only one patient died 1 day after thoracoscopy, as the patient developed vomiting after the procedure. Refractory hypoxemia and acute respiratory distress syndrome developed. Otherwise, three cases developed surgical emphysema.

Discussion

Pleural effusions are a common problem in pulmonary practice. The epidemiology of pleural effusions varies depending on the population studied; however, the most common causes worldwide of EPEs include tuberculosis and malignancy [9]. Pleural fluid analysis and 'blind' pleural biopsy are the initial investigations in patients with EPE [10]. Between 20 and 40% of patients with EPEs remain undiagnosed despite these investigations [11]. The yield of CT scans and bronchoscopy in pleural disease is abysmally low [12]. Thus, the next step in undiagnosed EPEs is to obtain pleural tissue under vision. Thoracoscopy has been demonstrated to increase the diagnostic yield in undiagnosed EPE, as it allows inspection of the pleural surfaces and permits pleural biopsy under direct visualization [13]. The diagnostic yield of thoracoscopy in malignant and tuberculous pleural effusion ranges from 91 to 94% and 93 to 100%, respectively [14]. The British Thoracic Society guidelines recommend MT as a next step for cases of EPE after inconclusive thoracocentesis [15]. The following prospective study was carried out on 42 patients with undiagnosed EPEs, in the Chest Department of Faculty of Medicine in Beni-Suef University during the period from January 2015 to September 2016, aiming to study the diagnostic role of MT in undiagnosed

EPE. In the current study, MT gave a definitive diagnosis of all the patients, with a diagnostic yield of 100%. Malignancy was diagnosed in 20 patients: nine MPM, 10 metastatic adenocarcinoma, and one undifferentiated carcinoma. Five patients were diagnosed with tuberculosis, eight patients with empyema, and nine patients with NSP. This is in agreement with a prospective study by Mohamed and Shaban [16], which was conducted on 117 patients with undiagnosed EPEs admitted to the Chest Department of the Faculty of Medicine, Cairo University, during the period from January 2012 to December 2012. MT gave a definitive diagnosis in 117 out of 117 patients with a diagnostic yield of 100% [16]. In addition, Ahmed *et al.* [17] in their study on 50 patients with undiagnosed pleural effusion admitted at Abbassia Chest Hospital MT gave a definitive diagnosis in 48 out of 50 patients with a diagnostic yield of 96%. In addition, in the study by Helala *et al.* [18], which was conducted in Kobri El-Kobba Military Chest Hospital on 40 patients with undiagnosed EPEs during the period from March 2010 to October 2012, MT gave a definitive diagnosis in 38 out of 40 patients with a diagnostic yield of 95%. Other studies that were conducted on patients with undiagnosed pleural effusion like Prabhu and Narasimhan [19], who performed thoracoscopy for 68 patients at the Department of Respiratory Medicine, Apollo Hospitals, Chennai, India, which gave a definitive diagnosis in 66 out of 68 patients and was nondiagnostic in two patients, with a diagnostic yield of 97%. Guo *et al.* [20] obtained similar results; they performed thoracoscopy for 47 patients with pleural effusion and thickening of unknown etiology. The diagnosis was obtained for 44 patients, whereas negative result was obtained for three (6.4%) cases. The diagnostic accuracy rate reached 93.6% [20]. In the present study, the histopathological results of thoracoscopic pleural biopsy among the study population revealed that the most common diagnosis was malignancy in 20 (47.6%) patients followed by chronic NSP in nine (21.4%) patients, empyema in eight (19%) patients and, last, tuberculous pleurisy in five (11.9%) patients. This is in agreement with a study by Mohamed and Shaban [16], who found that the most common diagnosis was malignancy in 87/117 (74.3%) patients, followed by chronic NSP in 16/117 (13.6%) patients, tuberculous pleurisy in five (4.27%) patients, septic empyema in six (5.13%) patients, sarcoidosis in two (1.7%) patients, and systemic lupus erythematosus in one (0.85%) patient [16]. In addition, Ahmed *et al.* [17] found that the most common diagnosis was malignancy in 46

(92%) patients, followed by chronic NSP in two (4%) patients, tuberculous pleurisy in one (2%) patient, and fibrotic pleurisy in one (2%) patient. Malignant pleural effusion (MPE) is considered a very common cause of EPE. The overall diagnostic sensitivity of thoracentesis is around 60% [21]. The yield of pleural fluid cytology from the first specimen is 51%, which increases an additional 7% from the second specimen and only 2% from the third [22]. Thus, additional investigation is clearly needed in such a situation of a nondiagnostic thoracentesis in which MPE is a consideration (or is suspected). In the present study, metastatic pleural effusion was more evident than malignant mesothelioma in the group of patients studied: 23.8% metastatic adenocarcinoma, 2.3% undifferentiated carcinoma, and 21.4% malignant mesothelioma. The results agreed with the study performed by Jiang *et al.* [23] who showed pleural metastases in 37.8%, and primary pleural mesothelioma in only 18.4%. In addition, Wang *et al.* [24] found that out of 27 patients who underwent MT, 15 patients had malignancy among them, 12 patients had metastatic carcinoma, two patients had only mesothelioma, and one patient had non-Hodgkin's lymphoma. MT is of great help in diagnosis and accurate staging of MPE, which therapeutic management and prognosis rely on. In the present study, thoracoscopic findings included the presence of pleural masses in four cases of MPM and two cases of metastatic adenocarcinoma, multiple variable-sized nodules in 12 cases malignant (MPM, adenocarcinoma, and undifferentiated carcinoma). Small nodules or sago-grain appearance was seen in all cases of tuberculous pleurisy. Septic pyogenic membrane, adhesion, and collected pus were observed in eight cases of empyema, and diffuse thickened pleura and plaques were observed in two cases of MPM. Adhesion and fibrous strands were seen in nine cases of NSP (Table 4).

The superiority of MT over cytological analysis or blind pleural biopsy is explained by the improved direct visualization and visually directed (and larger, especially in case of mesothelioma) biopsy samples. In all, 14.3% of cases are positive for atypical cells as cytological analysis of fluid may be negative because of insufficient exfoliation of malignant cells from the pleural surfaces into the pleural fluid or because of a lack of cytological characteristics to make an accurate diagnosis (Table 3). Pleural tuberculosis is diagnosed in 75–95% of cases using pleural fluid analysis with or without closed pleural biopsy, and thus pleuroscopy is rarely indicated up front to establish its diagnosis [25].

The pleuroscopic appearance of tuberculosis is characterized by a diffuse pachypleuritis, multiple adhesions, and a (micro) nodular aspect of parietal and visceral pleura. In the present study, five cases were diagnosed with tuberculous pleurisy with pleuroscopic small nodules scattered over visceral and parietal pleura - the so-called sago-grain appearance. ADA can be a useful marker for diagnosis of tuberculosis. There were many debates about ADA level in pleural fluid; the level was high among both cases with tuberculous pleurisy and some of malignant cases (>40 IU), which was in disagreement with Verma *et al.* [26] (>36 IU/l), Niwa *et al.* [27] (>38 IU/l), and Mohamed and Shaban [16], who found higher levels of ADA in cases of tuberculous pleural effusion. However, Verma and colleagues stated that ADA level in malignancy was up to 87.6 IU/l. ADA level more than 100 IU/l was observed only in cases of tubercular pleural effusion, so they concluded that if ADA level of more than 100 IU/l is taken as a cutoff point it is exclusively seen in cases of tubercular pleural effusion. MT has also been widely used in the diagnostic workup of tuberculous pleural effusion with a sensitivity of 93% in developed countries and increasing to 98% in endemic countries [28]. Moreover, MT can provide larger quantities of tissues for culture in suspected multidrug-resistant tuberculosis.

In the present study, eight patients were diagnosed with empyema. Gram staining of the pleural fluid samples during thoracentesis was positive for streptococci and Gram-negative organism. Early thoracoscopy is effective and less invasive than thoracotomy, and was shown to provide significant benefit compared with classic treatment in two small, nonblinded, randomized studies [29,30]. In addition, early minimal intervention with pleuroscopy for breakdown loculations and adhesions has shown excellent results in recent reports. MT was successful in 86–91% of patients, and 6–14% required further surgical interventions such as video-assisted thoracoscopic surgery and thoracotomy [31]. Nine patients were diagnosed with NSP. NSP/fibrosis is defined if the histology report of the pleural tissue revealed any of the following: reactive fibrous pleural thickening, fibrinous pleurisy, fibrosis, florid reactive change, fibrous connective tissue, chronic inflammation, benign change or dense fibrous tissue, in the absence of malignant pleural infiltration, granulomata, pleural vasculitis, or evidence of bacterial infection [32]. Many studies were applied on cases of chronic NSP; Davies *et al.* [32] reported that, in their study on 142 patients, 44 patients were diagnosed with NSP/

fibrosis on histological analysis. Patients were followed up until death or for a mean period of 21.3 ± 12.0 months. Five (12%) were subsequently diagnosed with malignant pleural disease after a mean interval of 9.8 ± 4.6 months. All five patients had histologically confirmed mesothelioma. In 26 patients with 'NSP/fibrosis', no cause for the pleural effusion was discovered. Clinical guidelines recommend close observation of patients with undiagnosed exudative effusions, although the length and follow-up regime is not defined [33]. MT is a safe and easy procedure in trained hands. Loddenkemper [11] reported that the most serious, but rare, complication is severe hemorrhage caused by trauma to the blood vessel. Other reported complications are empyema, prolonged air leakage, subcutaneous emphysema, postprocedure fever, wound infection, cardiac arrhythmias, hypotension, and seeding of the chest wall from mesothelioma [34]. In the present study, one patient died 1 day after the procedure, as she developed vomiting and aspiration, profound refractory hypoxemia, and acute respiratory distress syndrome. Three patients developed surgical emphysema and were managed successfully. Prabhu and Narasimhan [19] found that, out of 68 patients who underwent MT, there were no major complications; only four patients had minor complications such as subcutaneous emphysema (three patients) and prolonged air leak (one patient). Özgül *et al.* [35] found that out of 27 patients who underwent MT, three patients had expansion defects during the postoperative period. Hemothorax occurred in one patient who died of respiratory failure on day 34 of hospitalization.

Conclusion

MT is a valuable tool in the diagnosis of undiagnosed pleural effusion. It is a simple and safe method with a high diagnostic yield and lower complication rates.

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Conflicts of interest

There are no conflicts of interest.

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