ORIGINAL ARTICLE

Diagnostic yield of medical thoracoscopy in exudative pleural effusions in a region with high tuberculosis burden

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ABSTRACT

Introduction: Pleural effusion is frequently encountered in respiratory medicine. However, despite thorough assessment including closed pleural biopsy, the cause of around 20% of pleural effusions remains undetermined. Medical thoracoscopy (MT) is the investigation of choice in these circumstances especially if malignancy is suspected. The aim of this study is to evaluate the diagnostic yield of MT in exudative pleural effusions in a single center from East Malaysia.

Methods: Retrospective chart review of all adult patients who underwent MT for undiagnosed exudative pleural effusion in a 24-month duration.

Results: Our cohort comprised of 209 patients with a median age of 61 years old (IQR 48.5-69.5). There were 92 (44%) patients with malignant pleural effusion (MPE) and 117 (56%) benign effusions; which included 85 tuberculous pleural effusion (TBE) and 32 cases of non-tuberculous exudative pleural effusion. Conclusive pathological diagnosis was made in 79.4% of the cases. For diagnosis of MPE, MT had a sensitivity of 89.1% (95% CI 80.4-94.3), specificity of 100% (95% CI 96.0-100.0), and positive predictive value (PPV) of 100% (95% CI 94.4-100) and negative predictive value (NPV) of 92.1% (95% CI 85.6-95.9). For TBE, MT had a sensitivity of 90.5% (95% CI 81.8-95.6), specificity of 100% (95% CI 96.3-100.0) PPV of 100% (95% CI 94.1-100) and NPV of 93.9% (95% CI 88.0-97.2). Overall complication rate was 3.3%.

Conclusions: MT showed excellent sensitivity and specificity in the diagnosis of exudative pleural effusion in this region. It reduces empirical therapy by providing histological evidence of disease when initial non-invasive investigations were inconclusive.

INTRODUCTION

Pleural effusion (PE) is frequently encountered in respiratory medicine. It is a common presentation in a wide range of pleural, pulmonary and systemic diseases. One of the early crucial step in the approach to PE is to categorise it into transudative or exudative type, as the latter usually require further workup until a definite underlying cause is found.[1] In general, the common causes of exudative pleural effusion include malignancy, parapneumonic and tuberculosis.[1] Liam et al demonstrated tuberculous pleural effusion (TBE) to be the most frequent cause of exudative pleural effusions in a West Malaysian cohort of 186 patients, followed by malignant pleural effusions (MPE).[2] TBE is a common cause of PE in regions with high tuberculosis burden.[3] World Health Organization (WHO) estimated that the incidence rate of tuberculosis to be at 92 per 100,000 population in Malaysia.

Despite thorough clinical assessment and initial investigations including closed pleural biopsy, the cause of around 20% of PE may yet remain undetermined.[4] Medical thoracoscopy (MT) (or local anaesthetic thoracoscopy, pleuroscopy) would be the investigation of choice in these circumstances, especially if malignancy was suspected.[1] MT has advanced significantly ever since its introduction in 1910 by Hans-Christian Jacobaeus with better instrumentation and simpler sedation protocols.[5] It is an effective tool in the evaluation of pleural and pulmonary disease when routine pleural fluid analysis and cytology are inconclusive. Besides allowing direct visualization of the pleural cavity and biopsy of visually abnormal areas enhancing the diagnostic accuracy, MT is also able to provide therapeutic options of talc poudrage, adhesiolysis in PE, and even complex procedures such as sympathectomy and splanchnicolysis.[6,7]

The main aim of this study is to evaluate the diagnostic aspects of MT and the baseline demographics, procedural characteristics and the complication rate. We also aimed to calculate the sensitivity and specificity of MT in the diagnosis of exudative PE (including TBE).

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective chart review conducted in the Division of Respiratory Medicine, Sarawak General Hospital, a 900-bedded tertiary referral hospital, between April 2016 and April 2018 (24 months). The study protocol was approved by the Medical Research & Ethics Committee, Ministry of Health Malaysia *(NMRR-18-2205-43052-IIR)*.

Patients

Consecutive adult patients aged more than 18 years old who underwent diagnostic MT for undiagnosed exudative PE during the study period were considered for inclusion.

Diagnostic Criteria for Malignant and Benign Pleural Effusion

All adult patients presented with PE underwent initial diagnostic thoracocentesis in our center as per our protocol. Standard pleural fluid (Pf) workup includes Pf for pH, biochemistry (protein, albumin, lactate dehydrogenase, glucose), bacterial culture, acid fast bacilli, *Mycobacterium*

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tuberculosis culture and cytology. Other than the basic routine blood tests, three consecutive early morning sputum for acid fast bacilli were checked in the initial analysis. If none of the results were conclusive, and the pleural effusion fulfilled Light's criteria for exudative PE, the case is categorized as undiagnosed exudative pleural effusion. Pf adenosine deaminase (ADA), Pf interferon gamma (IFN-γ), sputum and Pf Xpert MTB/RIF were not sent routinely prior to diagnostic MT due to limited resources.

MPE was defined as pleural effusion with histological evidence of malignancy in pleural biopsy and/or in patients with known malignancy with no other obvious alternative diagnosis of an exudative PE.

Benign pleural effusion was defined as pleural effusion in the absence of malignant features in pleural biopsy, and in patients not known to suffer from advanced malignancy. Tuberculous pleural effusion (TBE) and other infective or inflammatory causes of PE were grouped under benign pleural effusions. Definite TBE was defined as the presence of positive *M.tuberculosis* culture from the pleural fluid or pleural biopsy specimens, while presumptive TBE was defined by the presence of chronic necrotizing granulomatous inflammation on pleural biopsy specimen with or without positive staining for acid fast bacilli, positive sputum for acid fast bacilli, Xpert MTB/RIF or culture for *M.tuberculosis* with no alternative explanation for other causes of exudative PE and in patients who demonstrated positive response to empirical anti-tuberculous treatment after a minimum of six months follow up.

Medical Thoracoscopy Procedure

Written consent was obtained from patients prior to the procedure and procedures were performed as in-patient. MT was performed with patient lying in a lateral decubitus position with the affected side facing upward. Supplementary oxygen was given via nasal cannula empirically, vital signs and cardiac rhythm monitored throughout. Transthoracic ultrasound was performed to identify the safe site of entry in all cases by the endoscopist. The area of interest was then cleaned and draped.

Intravenous sedation (midazolam and/or pethidine) was administered at the start of procedure. Local anaesthesia (lignocaine 2%) was infiltrated at the marked entry point. Blunt dissection was performed with dissecting forceps until parietal pleural was breached and pneumothorax induced. In selected cases where effusion was minimal, Verres needle was used for pneumothorax induction prior blunt dissection. An 11 mm metallic or plastic cannula with trocar was then be inserted after dilatation of the track using trocar. MT is then inserted through the trocar into the pleural cavity for our examination. Either semi-rigid thoracoscope *(LTF-160, Olympus Medical, Japan)* or rigid endoscope *(Karl Storz Endoscope, Tuttlinggen, Germany)* with an optical forceps and suction was used in our cohort at the discretion of the endoscopist.

All pleural fluid was aspirated to allow effective examination of the pleural cavity. Under direct vision, abnormal or suspicious areas of the parietal pleural is then biopsied and preserved in formalin solution and transferred immediately to the laboratory for histopathological examination. At the end of the procedure, intercostal chest tube is inserted to allow drainage of residual pleural fluid and air. The intercostal chest tube would be removed once underlying lung re-expanded and minimal fluid drained.

Statistical Analysis

The data analysis was done using SPSS version 21 *(Chicago, IL, USA)*. Descriptive statistics of the variables were expressed with median and interquartile range (IQR). The difference in between variables was assessed with Mann-Whiney U test for continuous variables and Chi-Square or Fisher's exact test for categorical variables. Sensitivity, specificity and predictive values were calculated based on standard definitions. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 210 MTs were performed and 209 cases were included for analysis with one exclusion due to incomplete data. There were 92 (44%) MPE and 117 (56%) benign pleural effusion; which included 85 (72.6%) TBE and 32 (27.4%) cases of non-tuberculous benign pleural effusion.

Basic Demographic and Procedural Characteristic

Overall median age of our patients was 61 years old (IQR 48.5-69.5) with older ones recorded in the malignant group. The laterality of the PE did not differ between two groups. On transthoracic ultrasound, MPE was associated with more uniloculated PE in comparison to benign pleural effusions. Semi-rigid thoracoscope was used in 159 cases (76.1%) while rigid thoracoscope was used in 50 cases (23.9%). Pleural nodules (65.2%) were a predominant thoracoscopic finding in MPE followed by pleural thickening (22.8%). In TBE, sago-like pleural nodules were found in 48.2% while 24.7% patients demonstrated diffuse inflamed pleural with extensive fibrin formation. The majority of non-tuberculous benign PE had thoracoscopic appearance of inflamed and thickened pleura. Majority (96.7%) of the MTs were uncomplicated. However, 2 (0.9%) patients developed prolonged air leak of more than 5 days, which eventually resolved spontaneously, while 1 (0.4%) patient suffered from massive haemothorax requiring emergency thoracotomy. The characteristic of the study population is listed in Table I.

Overall Pathological Diagnostic Yield

We were able to achieve conclusive pathological diagnosis in 79.4% (166/209) of the cases. MPE comprised the majority at 82 cases (49.4%), followed closely by TBE at 77 cases (46.4%), while non-tuberculous benign PE made up the remaining seven cases (4.2%). Adenocarcinoma lung was the commonest histology in MPE group at 60 cases (73.2%), followed by ovarian adenocarcinoma and squamous cell carcinoma at a tie of five (6.1%) each. All 77 TBE cases had chronic necrotizing granulomatous inflammation, with 18 (23.4%) cases staining positively for acid-fast bacilli. Acute inflammatory changes with neutrophilic infiltration were observed in six cases of clinically suspected acute parapneumonic pleural effusion (PPE). Details of pathological results are listed in Table II.

Table I: Characteristic of Overall Study Population (N=209)

		Overall	Malignant	Benign		
				Benign	Subgroup of Benign Group	
					Tuberculous	Non Tuberculous
Number (%)		209	92 (44.0)	117 (56.0)	85 (72.6)	32 (27.4)
Age (Range)		61 (48.5-69.5)	65 (56.0-73.0)	56 (38.5-68.0)	56 (32.5-67.0)	56 (49.5-68.0)
Gender (%)	Male	132 (63.2)	43 (46.7)	89 (76.1)	62 (72.9)	27 (84.4)
	Female	77 (36.8)	49 (53.3)	28 (23.9)	23 (27.1)	5 (15.6)
Side of Effusion (%)	Left	80 (38.3)	34 (37)	46 (39.3)	34 (40.0)	12 (37.5)
	Right	129 (61.7)	58 (63)	71 (60.7)	51 (60.0)	20 (62.5)
Ultrasound (%)	Uniloculated	108 (67.5)	61 (66.3)	47 (51.1)	33 (52.4)	14 (48.3)
	Multiloculated	52 (32.5)	7 (7.6)	45 (48.9)	30 (47.6)	15 (51.7)
Thoracoscope (%)	Rigid	50 (23.9)	18 (19.6)	32 (27.4)	22 (25.9)	10 (31.3)
	Semi-Rigid	159 (76.1)	74 (80.4)	85 (72.6)	63 (74.1)	22 (68.8)
Thoracoscopic	Nodules	74 (35.4)	60 (65.2)	14 (12.0)	13 (15.3)	1 (3.1)
Finding (%)	Sago Nodules	42 (20.1)	1 (1.1)	41 (35.0)	41 (48.2)	0 (0.0)
	Thickening	47 (22.5)	21 (22.8)	20 (17.1)	10 (11.8)	10 (31.3)
	Inflamed & Fibrin	46 (22.0)	6 (6.5)	42 (35.9)	21 (24.7)	21 (65.6)
Complication (%)		3 (1.4)	3 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pathology (%)	Conclusive	166 (79.4)	82 (89.1)	84 (71.8)	77 (90.6)	7 (21.9)
	Inconclusive*	43 (21.6)	10 (10.9)	33 (28.2)	8 (9.4)	25 (78.1)

*Non-specific pleuritic

Table II: Histopathological Finding of Pathological Conclusive Subjects (N=166)

	N (%)
Malignant	**82 (49.4)**
Adenocarcinoma Lung	60 (73.2)
Squamous Cell Carcinoma	5 (6.1)
Adenocarcinoma Ovary	5 (6.1)
Adenocarcinoma Breast	3 (3.8)
Small Cell Carcinoma	2 (2.4)
Diffuse Large B Cell Lymphoma	2 (2.4)
Adenocarcinoma Gastrointestinal	1 (1.2)
Mesothelioma	1 (1.2)
Renal Cell Carcinoma	1 (1.2)
Adenocarcinoma Thyroid	1 (1.2)
Metastatic Adenocarcinoma	1 (1.2)
Tuberculous	**77 (46.4)**
Chronic Granulomatous Inflammation with Negative AFB	59 (76.6)
Chronic Granulomatous Inflammation with Positive AFB	18 (23.4)
Non Tuberculous	**7 (4.2)**
Acute Inflammation (Parapneumonic)	6 (85.7)
Calcified Pleural Nodule (Uremic Pleuritis)	1 (14.3)

*AFB: acid fast bacilli

Table III: Outcome of Pathological Inconclusive (Non Specific-Pleuritis) Subjects (N=43)

	N (%)
Malignant	**10 (23.3)**
Transbronchial biopsy	3 (30.0)
Adenocarcinoma Lung	2
Squamous Cell Carcinoma	1
Endobronchial biopsy	1 (10.0)
Small Cell Carcinoma	1
Percutaneous biopsy	3 (30.0)
Metastatic Sarcoma	2
Adenocarcinoma Ovary	1
Radiologic progression of underlying advanced malignancy	3 (30.0)
Squamous Cell Carcinoma	2
Renal Cell Carcinoma	1
Tuberculous	**8 (18.6)**
Sputum TB culture grew Mycobacterium Tuberculosis	2 (25.0)
Responded to anti-tuberculous therapy	6 (75.0)
Non Tuberculous	**25 (58.1)**
No recurrence with antimicrobial and drainage	13 (52.0)
Parapneumonic pleural effusion	13
No recurrence with antimicrobial and adequate dialysis in renal failure patients	12 (48.0)
Uremic pleuritis	12

Table IV: MT histology results compared to the final diagnosis of MPE

	Final Diagnosis Malignant	Final Diagnosis Not Malignant	Total
MT malignant	82	0	82
MT not malignant	10	117	127
Total	92	117	209

Table V: MT histology results compared to the final diagnosis of TBE

	Final Diagnosis Tuberculous	Final Diagnosis Not Tuberculous	Total
MT tuberculous	77	0	77
MT not tuberculous	8	124	132
Total	85	124	209

The remaining 21.6% (43/209) of cases with inconclusive histopathological results were classified as non-specific pleuritis. Chronic inflammation was reported in 33 cases, necrotic tissue in five cases, fibro-collageneous in four cases and haemorrhagic pleural fragment in one case. Out of these 43 cases, 23.3% (10/43) were eventually diagnosed to be MPE after further invasive diagnostic procedure and 18.6% (8/43) to be TBE. The other 58.1% (25/43) of these non-specific pleuritis cases were categorised under non-tuberculous benign PE with 13 cases of PPE and 12 cases of uremic pleuritis. Median follow up for these 43 cases was 9.9 months (IQR 4.0-15.0). Details of further evaluation of these cases are listed in Table III.

Diagnostic Yield of Medical Thoracoscopy in Malignant and Tuberculous Pleural Effusions

For pathological diagnosis of MPE, MT had a sensitivity of 89.1% (95% CI 80.4-94.3) and specificity of 100% (95% CI 96.0-100.0). Positive predictive value was 100% (95% CI 94.4-100) and negative predictive value 92.1% (95% CI 85.6-95.9). Overall diagnostic accuracy for MPE was 93.7% (Table IV).

For TBE, MT had a sensitivity of 90.5% (95% CI 81.8-95.6) and specificity of 100% (95% CI 96.3-100.0). Positive predictive value was 100% (95% CI 94.1-100) and negative predictive value of 93.9% (95% CI 88.0-97.2). Overall the diagnostic accuracy for TBE was 96.2% (Table V).

DISCUSSION

Diagnostic yield of MT in literature has been reported inconsistently, ranging from 42% to 95%, as the definition of diagnostic yield was not centered on the pathological diagnosis alone.[8] In the largest series to date, Valsecchi et al reported a pathological diagnostic yield of 71% over a span of 30 years in around 2000 patients.[8] Our result is comparable with this reported pathological diagnostic yield at 79.4%, with almost equal numbers of MPE and TBE. MT is a relatively safe procedure. The overall complication rate of 3.3% in our cohort was in agreement with reported minor complication rates of 7.3%, major complications of 1.8%, and mortality rate of 0.3%.[9]

MT has an important role in the diagnosis of MPE. The pooling of multiple case series reported a diagnostic sensitivity of 92.6% for malignant pleural effusion.[9] Our cohort demonstrated 93.7% diagnostic accuracy for MPE with excellent sensitivity and specificity, which is consistent with previous reports.[10-13] The high diagnostic accuracy of MT in MPE is important as a definite diagnosis needs to be secured as early as possible, and repeat of procedures minimized in this group of patients with advanced metastatic disease, who often perform poorly. Among the pathological findings, adenocarcinoma lung remains the major pathology in our cohort at 73.2%, which was slightly higher compared to previous reports at 61-62.8%.[11,14] Moreover, in addition to its diagnostic capabilities, MT also allows simultaneous therapeutic procedures to be performed, such as talc poudrage and indwelling pleural catheter placement. A pilot study conducted by Reddy et al demonstrated MT with talc pleurodesis and simultaneous indwelling pleural catheter placement to be feasible and safe with a success rate of 92% and median duration of 7.54 days for indwelling pleural catheters.[15] However, this remain a limitation in our region as lung expansion cannot be ascertained intra-procedurally to predict pleurodesis success and indwelling pleural catheter may not be readily available due to financial and logistic concerns.

TBE made up 72.6% of our benign PE cohort with overall diagnostic accuracy of 96.2%. Sensitivity of MT in diagnosis of TBE has been quoted to be around 93.3% in areas with low tuberculosis burden and 100% in areas with high tuberculosis burden when pleural biopsy was combined with culture result.[9] Our cohort of patients had a lower sensitivity of 90.5% despite being in a region with high tuberculous burden as pleural biopsy culture was not taken into consideration. Pleural biopsy for the diagnosis of TBE remains pertinent as Casalini et al demonstrated that a diagnosis of TBE can only be achieved in 28.8% via microbiological tests alone.[16] Although closed pleural biopsy had demonstrated good sensitivity of 91.5% for TBE diagnosis, it lacks the capability for direct visualisation of the parietal pleura, which can provide reasonable diagnostic certainty of TBE, allowing immediate initiation of antituberculous therapy, which is important in TB endemic country.[17,18] Sago-like nodules have been reported as the most frequent thoracoscopic appearance (56-70%) of TBE.[16,19] However, these sago-like nodules were only observed in 48% of our TBE cohort. Instead, a significant numbers of our TBE (24.7%) presented with diffuse inflamed pleura with extensive fibrin strands between the lung and the chest wall. This thoracoscopic manifestation highlights the potential therapeutic role of MT, allowing separation of the fibrin strands between lung and chest wall to achieve better drainage during the MT procedure. In multi-loculated TBE, studies had demonstrated that in combination

with large-bore chest tube drainage and streptokinase irrigation, MT significantly shortened chest tube duration, hospital stay and the reduced number of patients needing further treatment.[20]

Despite excellent performance of MT in the diagnosis of MPE and TBE, non-specific pleuritis remains an issue with a reported range of 28.6-31%.[8,10] Our cohort reported 21.6% of non-specific pleuritis. It is of concern as various reports have shown that 5-25% of these patients may eventually turn out to be malignant disease, particularly mesothelioma.[10,21] However, Asian countries report a lower incidence of mesothelioma compared to Europe, North America and Oceania countries. Instead, TBE and infective pleural effusions remain a major concern in this region.[22] Ng et al., reported 36% of non specific pleuritis in a Malaysian cohort, of which 25% eventually turned out to be TBE, while 75% were classified as PPE. Jamsak et al also reported 14.3% of non-specific pleuritis which turned out to be TBE, with no mesothelioma reported in the Thailand cohort.[23,24] Hence, a cautious follow up duration for non-specific pleuritis is usually recommended. Davies et al demonstrated that 12% of patients with non-specific pleuritis were eventually diagnosed as mesothelioma after a mean duration of 9.8 months; while DePew et al reported that 3.5% of their non-specific pleuritis cohort were subsequently diagnosed with mesothelioma within 1 year.[10,21] Although these reports seem to suggest durations of follow-up, these were conducted in regions with high mesothelioma incidence, and may not be feasibly extrapolated to the Malaysian population. Thus, the optimum duration of follow up remains unclear and may depend on the patient population.[13] This is reflected in our current cohort of patients where with a median follow up of 9.9 months, eight (18.6%) of them were eventually diagnosed to be TBE and 25 (58.1%) were PPE and uremic pleuritis. Hence, the continued index of suspicion for tuberculosis should be equal to that of malignancy during follow up of non-specific pleuritis in tuberculosis-endemic regions.

Nonetheless, our study has its limitations. Firstly, the retrospective study design with data collected from a single institution does not allow conclusive conclusions to be drawn from our results. However, to the best of our knowledge, this is one of the largest MT series reported from the region of South East Asia with high tuberculosis burden which report the actual pathological diagnostic yield of MT. Secondly, Pf ADA and IFN-γ were not routinely analyzed in our cohort of patients prior to MT due to financial and resources constraint. Although Pf ADA and IFN-γ provide excellent sensitivity to TBE diagnosis; Sharma et al from India has reported that combining these tests in the diagnosis of TBE in developing countries may not be cost effective as compared to anti TB treatment.[25] This further highlights the role of MT in developing countries which carry the major share of global TB burden. Thirdly, pleural biopsy for *M.tuberculosis* culture was not performed routinely in our cohort and hence a definite diagnosis of TBE cannot be affirmed. However, 92.9% (79/85) of our TBE was diagnosed with robust clinical criteria (i.e., necrotising granulomatous inflammation and positive TB culture from their sputum), furthermore, all patients demonstrated therapeutic response to anti TB treatment. Lastly, another limitation is the duration of follow up in especially for the diagnosis of TBE. Previous reports had described that 65% of patients may progress to pulmonary or extra-pulmonary tuberculosis within up to five years after spontaneous resolution of pleural effusion caused by tuberculosis.[26] Hence, we are unable to conclude confidently that the 58.1% (25/43) of the non-specific pleuritis in our cohort of patients were truly non-tuberculous or benign at the end of this study. Although we believe a median follow up duration of 9.9 months was a practical clinical duration; long term follow up study will help to identify the true negative value of MT in the diagnosis of TBE, especially in a region with high tuberculosis burden.

CONCLUSION

MT has shown excellent diagnostic accuracy in diagnosis of exudative pleural effusion in a region with high tuberculosis burden. MT reduces empirical therapy by providing histological evidence of disease, which in turn may improve patient care especially when the initial non-invasive investigations are inconclusive.

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