Original Article

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Role of Rigid Medical Thoracoscopy in Diagnosing Exudative Pleural Effusions with Low Adenosine Deaminase

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Abstract

Background: Medical thoracoscopy (MT) performed in the evaluation of undiagnosed exudative pleural effusion (EPE) has a high diagnostic yield. In this study, we describe our experience of rigid MT in the evaluation of undiagnosed exudative pleural effusions (EPE) with low adenosine deaminase (ADA). **Subjects and Methods:**This is a retrospective analysis of RT pleural biopsies performed between July 2012 and June 2015 for diagnosing EPE. These patients had at least two pleural fluid samples negative for malignant cytology and ADA less than 65 IU/L. Here we report the yield and complications of pleural biopsies with RT. **Results:** Our yield of thoracoscopic pleural biopsies was 81% with malignancy as the commonest diagnosis in 46% patients. Malignant pleural effusion was caused commonly by adenocarcinoma (67%) followed by squamous cell carcinoma (17%), small cell lung cancer (8%) and lymphoma (8%). There was no case of mesothelioma. Biopsy revealed tuberculosis in 31%, vasculitis in 4%, nonspecific pleuritis (NSP) in 11% and normal pleural tissue in 8% subjects. The presence of nodules on CT scan and those on MT had no significant correlation ($P > 0.1$). ADA did not significantly differ between various biopsy confirmed diagnostic groups ($P > 0.2$). Minor complications that settled with conservative management developed in 3 patients (11.5%) and were significantly related to comorbidities ($p < 0.05$) but not to the biopsy result ($P = 0.894$). **Conclusion:** Since majority of the EPE turn out to be either malignancy of tuberculosis, a rigid MT evaluation should be considered in all such patients if the facility is available at the center. Rigid MT has high diagnostic yield and acceptable safety.

Keywords: Rigid thoracoscopy, medical thoracoscopy, pleuroscopy, pleural effusion, ADA, tuberculosis, lung malignancy

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Introduction

Medical thoracoscopy (MT) also called as pleuroscopy is a minimally invasive procedure that gives us access to pleural cavity under vision in a spontaneously breathing patient under local anesthesia. This makes MT not only diagnostic but an attractive therapeutic tool as well in the evaluation of exudative pleural effusions (EPE) which remain undiagnosed after pleural fluid analysis (PFA). Jacobaeus introduced thoracoscopy in 1910 for lysis of pleural adhesions by thoracocautery to facilitate pneumothorax treatment of tuberculosis (Jacobaeus operation).[1] Subsequently with the advent of anti-tuberculosis drugs in 1940s, it was abandoned for several decades. However thoracoscopy was revitalized in 1980s with improvements in optical and video technology coupled with better instrumentation and optimal sedation protocols. Thoracoscopy can be done by rigid or semirigid instruments. The yield of thoracentesis (PFA) is 60% in malignant pleural effusions (MPE) and 90% in tubercular pleural effusions (TPE).[2,3] The yield of closed-blind pleural biopsy (CBPB) is 50% to 60% in MPE and 80% to 90% in TPE.[2–5]Pleural biopsy by MT has significantly enhanced the diagnostic yield between 91% to 95% for MPE, and nearly 100% for TPE.[2,6–8] Based on this evidence thoracoscopic pleural biopsy has virtually replaced CBPB in the evaluation of EPE. In addition MT is also used for therapeutic procedures like pleurodesis in MPE and spontaneous pneumothorax and drainage of pus together with adhesion lysis in empyema.[9] In the present study we describe our experience about the outcome of pleural biopsy by rigid (MT) in patients of undiagnosed EPE with low ADA levels.

Subjects and Methods

This is a retrospective analysis of rigid thoracoscopic pleural biopsies that were performed in undiagnosed exudative pleural effusion (EPE) between July, 2012 and June, 2015 at Modern Hospital Rajbagh, Srinagar. Undiagnosed EPE was defined as pleural effusions with at least twice negative pleural fluid cytology for malignancy and ADA less than 65 IU/L. Detailed clinical history was recorded and examination done in all patients. Patient's demographic details including age, sex, comorbidities and pleural fluid analysis reports were all recorded. We categorized pleural effusion in to three categories i.e. mild (occupying <1/3 of the hemithorax), moderate (occupying 1/3 to 2/3 of the hemithorax) and massive (occupying >2/3 of the hemithorax). Patients with loculated pleural effusion on CECT and significantly narrowed intercostal spaces were excluded. Patients with haemodynamic or respiratory instability, intractable cough and those with platelet count less than 70,000/mm3 or PT or aPTT prolonged by more than four seconds above control were not subjected to thoracoscopy.

Written informed consent was obtained from all patients. All patients were advised to fast for six hours prior to the thoracoscopy. Vascular access was achieved with intravenous cannula. Patients were positioned in lateral decubitus with effusion side up. The arm on the side of thoracoscopy was positioned above the patient's head to widen the intercostal spaces and allow better access to pleural cavity. Sedation was induced with intravenous midazolam (0.5mg/kg) and analgesia with intravenous tramadol (5mg) before starting the thoracoscopy and both were repeated as required during the procedure to achieve adequate sedation and analgesia. Skin, intercostal muscle and parietal pleura were injected with 10 to 20 mL of 1% lignocaine to achieve local anesthesia. Using a sterile surgical blade a skin incision 1.5cm to 2cm in length was given in 4th or 5th intercostal space in mid-axillary line. Curved artery forceps was used for blunt dissection of subcutaneous tissue and the intercostal muscles. A 10 mm diameter cannula with blunt trocar was inserted into the pleural cavity and we used a single port for taking pleural biopsies. Rigid thoracoscope (Karl Storz, Germany) then replaced trocar. Pleural fluid was completely aspirated while air was allowed to enter the pleural space to allow ipsilateral lung to collapse and enable clear visualization of pleural surface. Thoracoscope was maneuvered to examine costal, diaphragmatic and mediastinal pleura in a systematic way to end at the apex. Before pleural biopsy, lysis of any adhesions if present was done with RT. Biopsy forceps was introduced through working channel of the RT after selecting the suitable site on parietal pleura for biopsy. Under direct vision pleura was grasped and biopsy taken with a shearing movement of the thoracoscope. Complete hemostasis was ensured before withdrawing thoracoscope and the cannula. Chest tube (24 to 28 F) was inserted at the end and connected to water-seal drainage bag. Chest drain was removed once the lung had expanded on X-ray film and drain output had decreased to less than 50 mL per 24 hours.

Pleural biopsy was send in separate vials for histopathological examination and mycobacterium tuberculosis (MTB) culture. Pleural fluid drained during thoracoscopy was send for analysis including total and differential cell count, protein, glucose, ADA, microbiology, and malignant cytology. We also recorded CT scan findings, thoracoscopic pleural findings and the complications of thoracoscopy. We defined procedure as successful if biopsy was representative of the pleural tissue. If biopsy revealed malignancy it was defined as MPE. If ZN stain showed acid-fast bacilli (AFB), culture grew MTB or if caseating granulomas were demonstrated in pleural tissue it was classified as TPE. We followed all patients up to 12 months after RT. Data are presented in a descriptive manner.

Results

The mean age of 26 participants [Table 1] in the present study that included 17 (65.3%) males and 9 (34.7%) females was 51.12 (±SD16.42). Comorbidities that included diabetes, CKD, CAD, SLE and extra-thoracic malignancy were found in 10 (38.5%) patients. Pleural effusion was right sided in 46%, left sided in 39% and bilateral in 15% of the cohort. Pleural effusion was mostly moderate (58%) and 11% had massive effusion including two patients who presented with respiratory distress and needed therapeutic drainage before thoracoscopy. Pleural fluid analysis revealed predominantly lymphocytic exudate with a mean ADA of 20 IU/L (SD 14.29 and range 5-51). The mean protein and glucose levels in the pleural fluid were 4.2 gm/dL (±SD 0.34) and 68 mg/dL (±SD 9.34) respectively. No pleural fluid sample was positive for either acid fast bacilli or malignant cells.

Only 5 patients (19.2%) had pleural nodules demonstrated on CT scan of chest whereas on thoracoscopic examination, 16 patients (61.5%) had visible pleural nodules that were biopsied. The 5 patients who had nodules demonstrable on CT scan also had nodules on MT and all (100.0%) had pleural malignancy on biopsy. Out of 16 patients with pleural nodularity on MT, 11 (68.7%) patients had tiny nodules that were not visible on CT scan and among these 6 patients (54.5%) had pleural malignancy and 5 patients (45.5%) had tuberculosis on biopsy. Random pleural biopsies on apparently normal looking pleura without any nodularity revealed tuberculosis in 3 patients (75%) and malignancy in one patient (25%). There was no significant correlation ($P > 0.1$) between nodules on CT scan and those on thoracoscopy [Table 2].

Thoracoscopic biopsy revealed pleural malignancy as the commonest diagnosis in 12 (46%) patients [Table 3]. Adenocar-

Table 1: Clinical, radiological andthoracoscopic features of study subjects: N = 26

Chracteristic	NO	Percentage
Age (years)	Mean 51.12	(±SD16.42)
Sex (male / female)	17 / 9	65.3 % / 34.7%
Comorbidities		
Diabetes	5	19.2
CKD	2	7.7
CAD	1	3.8
SLE	1	3.8
Extra-thoracic malignancy	1	3.8
Side of effusion		
Right	12	46.1
Left	10	38.5
Bilateral	4	15.4
Size of effusion on X-ray chest:		
Mild	8	30.8
Moderate	15	57.7
Massive	3	11.5
CT chest showing pleural nodules	5	19.2
MT showing pleural nodules	16	61.5

CKD = Chronic kidney disease, CAD = Coronary artery disease, SLE = Systemic lupus erythematosus, CT = computed tomography, MT = Medical thoracoscopy

Table 2: CT scan pleural nodules vs MT nodules:

		MT-nodules		Total
		No	Yes	
CT- nodules	No	10	11	21
		100.0%	68.8%	80.8%
	Yes	0	5	5
		0.0%	31.3%	19.2%
Total		10	16	26
		100.0%	100.0%	100.0%

P > 0.1, CT: computed tomography, MT: medical thoracoscopy

Table 3: Pleural biopsy result, N = 26

	Number	Percentage
Pleural malignancy	**12**	**46.2**
Adenocarcinoma	**8**	66.7
Squamous cell carcinoma	**2**	16.7
Small cell lung cancer	**1**	8.3
Lymphoma	**1**	8.3
Mesothelioma	**nil**	0.0
Tuberculosis	**8**	30.8
Nonspecific Pleuritis (NSP)	**3**	11.5
Vasculitis	**1**	3.8
Normal pleural tissue	**2**	7.7

Table 4: Correlation of pleural fluid ADA with pleural biopsy diagnosis:

ADA (IU/L)	N	Mean	SD	Range
Malignancy	12	25.17	17.39	8 – 51
Tuberculosis	8	20.38	9.46	6 – 36
Vasculitis	1	6.00		6 – 6
NSP ¥	3	12.00	7.81	7 – 21
Normal	2	7.50	3.54	5 – 10
Total	26	20.08	14.29	5 – 51

P > 0.2, ADA: adenosine deaminase, ¥ NSP: Nonspecific pleuritis

Table 5: Complications of rigid thoracoscopy

	NO	Percentage
Total patients who developed complications¥	3	11.5
Excessive cough	3	100
Desaturation during thoracoscopy	2	66.6
Minor hemorrhage	3	66.6
Empyema	1	33.3
Atrial Fibrillation	1	33.3
Re-expansion pulmonary edema	1	33.3
Hypotension	1	33.3
Hemorrhage requiring blood transfusion	Nil	0.0
Respiratory failure	Nil	0.0
Deaths	Nil	0.0

¥ Some patients developed more than one complication, therefore total complications do not add up.

cinoma was found in 8 (67%), squamous cell carcinoma in 2 (17%) and small cell lung cancer and lymphoma each in one 1(8%) patient. There was no case of mesothelioma. Second common diagnosis was tuberculosis reported in 8 (31%) patients showing granulomatous inflammation consistent with tuberculosis. Three out of 8 tuberculosis patients (37.5%) also had subsequently cultures positive for mycobacterium tuberculosis (MTB). All eight tuberculosis patients responded to anti-tuberculosis therapy both clinically as well as radiologically. Nonspecific pleuritis (NSP) was the final diagnosis in 3(11.5%) patients that included one diabetic and two chronic kidney disease patients. Normal pleural tissue was reported in 2 (7.7 %) patients. A 26 year old female systemic lupus erythematosus (SLE) patient with lymphocytic EPE had vasculitis on pleural biopsy. The two main diagnostic outcomes in our study, pleural malignancy and pleural tuberculosis did not have any significant difference in their mean ages, 55.2 versus 49.6 years (P=0.42). Neither smoking status of the patient nor the presence of comorbidities correlated significantly either with malignancy or tuberculosis (P >0.9). Pleural fluid ADA did not significantly differ (P > 0.2) between various biopsy confirmed diagnostic groups [Tables 4].

Complications [Table 5] that developed in 3 patients (11.5%) were significantly related to underlying comorbidities (p < 0.05).These complications included excessive cough, oxygen desaturation during the procedure, minor bleeding that did not require blood transfusion. Re-expansion pulmonary edema complicated drainage of one massive malignant pleural effusion. Transient atrial fibrillation with hypotension complicated thoracoscopy in a 70 year old diabetic and coronary artery disease patient who also developed significant oxygen desaturation. Post thoracoscopy empyema and fever occurred in one patient. There was no death nor did any patient require mechanical ventilation or surgical intervention. The complications did not differ significantly between various biopsy confirmed diagnostic groups (P= 0.894).

Discussion

The gold standard investigation in the diagnosis of malignant and tubercular pleural effusions is thoracoscopic pleural biopsy. Yield of thoracoscopic pleural biopsy has been reported as high as 95% in malignant pleural effusions and 99% in tubercular pleural effusions which is much more than that of closed pleural biopsy and pleural fluid analysis.[10]

The current study evaluated the yield of rigid thoracoscopy in the diagnosis of 26 patients with undiagnosed exudative pleural effusions (EPE) i.e at least twice negative pleural fluid cytology for malignancy and ADA less than 65 IU/L. Our results suggest that RT is a useful and largely safe tool in the workup of undiagnosed EPE. Our yield of thoracoscopic pleural biopsy was 81% which is close to what has been reported in an ealier study.[11] Our yield is much higher than 45% reported by Ng et al,[12] in a series of 22 patients but less than 95% reported by Tscheikuna[13] in a series of 86 patients.

Present study revealed pleural malignancy as the commonest diagnosis in 46% patients thoracoscoped for evaluation of undiagnosed EPE. Similar observations were reported by V.K. Mootha (45.7%), Tscheikuna et al (45%) and Ng et al (45%).[12–14] We had adenocarcinoma (67%) as commonest pleural metastasis followed by squamous cell carcinoma (17%). None of our patients had mesothelioma but we had one case each of small cell lung cancer and lymphoma.

Second commonest diagnosis after malignant pleural effusion we had was tuberculosis (31%) showing granulomatous inflammation consistent with tuberculosis. Three out these 8 patients subsequently had cultures positive for MTB but in none of the 8 biopsies ZN stain was positive for AFB. In a report by Mootha 23% of their 35 thoracoscopic pleural biopsies were positive for tuberculosis.[14] In sharp contrast to our study and that by Mootha both from India, a recent study from Mayo Clinic, USA by Zachary did not report any case of pleural tuberculosis in 51 patient of EPE who underwent out-patient medical thoracoscopy, possibly due to very low prevalence of tuberculosis in that country.[14,15] These contrasting results emphasize the importance of differentiating tuberculosis from malignancy the two most common causes of EPE in tuberculosis endemic countries. Present study revealed nonspecific pleural inflammation (NSP) on thoracoscopic pleural biopsy in 11% patients with EPE which is significantly less than 45% reported ealier.[15]

Though complications have been reported, thoracoscopy is a relatively safe procedure.[16,17] In our study, thoracoscopic pleural biopsy had a complication rate of 11.5% close to other studies.[18,19] The complications that we encountered included excessive cough, minor bleeding, oxygen desaturation and a case each of empyema, re-expansion pulmonary edema and transient atrial fibrillation and all were managed without significant consequences. We did not have any mortality though it can occur and has been reported previously.[19,20]

Conclusions

Based on our results we conclude that, given its high diagnostic yield and acceptable safety, rigid thoracoscopy should be considered in the evaluation of exudative pleural effusion if pleural fluid analysis is inconclusive, because significant number of these turn out to be either malignant or tubercular. The common practice of starting empirical anti-tubercular drug therapy in all undiagnosed exudative pleural effusions especially in the developing world should be discouraged. Larger studies particularly controlled trials for comparison between semi rigid and rigid MT are required to define the exact role of rigid thoracoscopy in diagnosis of undiagnosed exudative pleural effusion.

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