Medical Thoracoscopic Pleural Biopsy and Clinico-Pathological Study - A Tertiary Center Experience

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ABSTRACT

BACKGROUND

Medical thoracoscopy is a nominally invasive procedure practised in diagnostic and therapeutic approaches for pleural diseases. We report a series of patients who underwent thoracoscopic pleural biopsy and clinicopathological analysis presenting to our center.

METHODS

A prospective study of thoracoscopic pleural biopsy was carried out in 117 cases over a period of one year. Clinical diagnosis, age and gender distribution, smoking habit, pleural fluid analysis, types of lung lesions, subtypes of histological data of the patients were collected prospectively and analysed.

RESULTS

Male to female ratio was 1.8 : 1. The most common symptom among patients was shortness of breath. Above 60 years age group was usually affected, particularly patients who were smokers. Histopathological diagnosis confirmed malignancy in 57.2 % patients, tuberculosis in 15.4 %, others including solitary fibrous tumour, non - tubercular granulomatous lesion, foreign body type multinucleate giant cell reaction, non-specific chronic inflammatory lesion in 27.4 % patients. Metastatic adenocarcinoma of pleura was the most common histological finding.

CONCLUSIONS

Medical thoracoscopy is a relatively safe, highly compatible technique which decreases the need of diagnostic thoracotomy. It decreases the time interval in achieving the final diagnosis and to initiate the treatment without delay.

KEYWORDS

Adenocarcinoma, Metastatic, Squamous Cell Carcinoma, Thoracoscopic Pleural Biopsy, Tuberculosis

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BACKGROUND

Medical thoracoscopy also known as pleuroscopy is a medical technique of internal examination, biopsy of masses within the thoracic cavity and pleural cavity. It is a minimally invasive procedure that was first performed by Sir Francis Cruise in 1865, significantly improved by Hans Christian Jacobaeus a Swedish internist in 1910 for treatment of tubercular intra-thoracic adhesions. Biopsies from pleura, diaphragm, mediastinum and pericardium are taken for diagnosis and staging of pleural malignancies. Therapeutic procedures like blebectomy and / or pleurodesis used for recurrent pneumothorax and pleural effusion. In developing nations, as well as India, thoracoscopy is not readily accessible. The concept of medical thoracoscopy is simplification of video-assisted thoracoscopic surgery. It is performed in moderate sedation under local anaesthesia by trained pulmonologist.

Objective of this study was to analyse the present clinico-pathological data of patients who have undergone thoracoscopy pleural biopsy for diagnostic evaluation of undiagnosed exudative pleural effusion at our center and evaluate their outcomes.

METHODS

This is a prospective study on 117 cases of undiagnosed exudative pleural effusion, (described as failure to establish a diagnosis by preliminary pleural fluid examination), who underwent medical thoracoscopic pleural biopsy at S.C.B. Medical College and Hospital, Cuttack between July 2018 and June 2019.

In these cases, demographic profile of the patient consisting of age, gender, addiction to smoking, clinical diagnosis, pleural fluid examination containing total and differential count, protein, glucose and ADA values were collected. Data was presented in tables. Pleural fluid was categorized as exudative or transudative according to Light's criteria. Patients with transudative pleural effusion, pyothorax, chylothorax were excluded. The pleural fluid was collected. Cytological smears were made and stained with H&E and Pap stain. Medical thoracoscopic pleural biopsy was done in same patients. The biopsy specimens were received at the Department of Pathology. Tissue was processed and stained with H&E stain for histopathological examination. In some cases IHC markers were evaluated for confirmatory diagnosis and searched for primary malignancies. The data was then studied and presented in the form of tables.

RESULTS

During the study period out of 117 patients, 76 (65 %) were male and 41 (35 %) were female with male: female ratio of 1.8 : 1. According to age, patients were again subdivided within following groups : 16 - 30 years, 31 - 45 years, 46 - 60 years and above 60 years. Majority i.e 90 patients (76.9 %) were seen after the age of 45 years [Table 1].

Age group	No. of Patients	Male	Female	(%)
16 - 30	11	6	05	9.4
31 - 45	16	10	06	13.7
46 - 60	43	31	13	36.7
>60	47	29	17	40.2
Total	**117**	**76**	**41**	**100**

Table 1. Age and Gender Wise Grouping of Cases

Clinical presentation of patients with their addiction to smoking data were collected. Most common clinical presentation was shortness of breath (68 cases=58.1 %) followed by fever (21 cases=17.9 %), chronic cough (15 cases=12.8 %), chest pain (13 cases=11.2 %). Out of total cases majority were found to be smoker i. e in 86 patients (73.5 %) and were mostly males.

Clinical Diagnosis	Histological Diagnosis	Number (n)	Percentage (%)	Diagnostic Yield of Thoracoscopic Biopsy
Malignant pleural effusion (n=69)	Malignancy	47	68.1	(53 / 69) 76.8 %
	Tuberculosis	6	8.7	
	Others	16	23.2	
Tuberculosis (n=23)	Malignancy	6	26.1	(16 / 23) 69.6 %
	Tuberculosis	10	43.5	
	Others	17	30.4	
No diagnosis (n=25)	Malignancy	14	56	(16 / 25) 64 %
	Tuberculosis	2	8	
	Others	9	36	
Total (n=117)	Malignancy	67	57.2	(85 / 117) 72.6 %
	Tuberculosis	18	15.4	
	Others	32	27.3	

Table 2. Clinical and Pathological Diagnosis

Pleural Fluid Analysis	Histology Diagnosis: Tuberculosis (n=18) Mean	Tuberculosis (n=18) Range	Malignant Effusion (n=67) Mean	Malignant Effusion (n=67) Range	Others (n=32) Mean	Others (n=32) Range
Cytology						
Total cell count	1234	586 - 2184	740	230 - 1214	2238	694 - 4236
Differential count						
Neutrophil %	18.4	10 - 46	1.3	5 - 24	54.6	26 - 92
Lymphocyte %	80.2	62 - 94	76	64 - 90	46.3	5 - 92
Malignant cell	0	0	0	0	0	0
Acid fast bacilli	0	0	0	0	0	0
Biochemical						
Adenosine deaminase activity (ADA) (U / L)	54.5	42 - 56	20.3	10 - 60	28	8-96
Glucose (mg / dL)	57.2	11 - 94	68.4	19 - 92	56	12 - 110
Protein (g / L)	47.2	30 - 72	62.3	34 - 112	52.4	30 - 280

Table 3. Pleural Fluid Analysis and Correlation with Histology

Among 117 patients of undiagnosed exudative pleural effusion, clinical diagnosis was malignant pleural effusion in 69 (59 %) cases and 23 (19.7 %) patients within clinical suspect of TB. In 25 (21.3 %) patients, even though pleural fluid and radiographic studies, no clinical diagnosis could be done. ADA value of pleural fluid was not raised (>70 IU / L) in neither of the cases with malignant pleural effusion or else tubercular effusion patients. The result of thoracoscopic pleural biopsy following, early clinical diagnosis identified that in 53 cases out of the 69 patients (76.8 %) among initial diagnosis of malignant pleural effusion had a conclusive diagnosis. We could confirm 10 cases of tuberculosis out of 23 patients with initial clinical diagnosis of tuberculosis. Among 25 patients without any initial clinical diagnosis was made, 14 cases had pleural malignancy, two had tuberculosis and nine had others including benign conditions of pleura (Table 2). Malignancy was proven in 67 (57.2 %) cases, 18 (15.4 %) cases were tubercular lesion and 32 (27.4 %) cases were others, including solitary fibrous

tumour, granulomatous lesion, foreign body type multinucleate giant cell reaction, non-specific chronic inflammatory lesion of pleura (Table 2).

Consisting of 67 cases of malignancies, 58 cases (86.6 %) was ADA level <40 IU / L and nine cases (13.4 %) was ADA level >40 IU / L. Out of total 18 cases of tuberculosis; 12 cases (66.7 %) showed ADA level >40 IU / L. Just six cases (33.3 %) showed ADA level <40 IU / L. Other cases of non - specific pleural lesions showed ADA value <40 IU / L. In this study none of the case recorded ADA level >70 IU/L (Table 3). Total cell count range of the pleural fluid was 230-1214 cells / cmm with a mean of 740 cells / cmm in 67 cases of malignant pleural effusion, in 18 cases of tubercular lesion range was 586 - 2184 cells / cmm with a mean of 1234 cells / cmm. Other 32 cases including non - specific lesions have range 694 - 4236 cells / cmm and a mean of 2238 cells / cmm. The total cell count in 62.4 % case of malignant and 54.6 % cases tubercular effusion showed > 500 cells / cmm (Table 3). Differential count of pleural fluid showed lymphocyte range of 64 - 90, 62 - 94, 5 - 92 cells / cmm and mean of 76, 80.2, 46.3 in case of malignant effusion, tubercular effusion and other non - specific pleural lesions respectively. Neutrophil count range of 5 - 24, 19 - 46, 26 - 92 cells / cmm and mean of 1.3, 18.4, 54.6 in case of malignant effusion, tubercular effusion and other non - specific pleural lesions. Similarly glucose and protein levels of pleural fluid shown in table 3. The differential count of 80 % of tubercular and 52 % of malignant effusions cases showed lymphocyte count > 50 %.

Diagnosis	No. of Patients	(%)	Age Group (Years)			
			16 - 30	31 - 45	46 - 60	>60
Malignant						
Adenocarcinoma	45	38.5	04	05	15	21
Squamous cell carcinoma	18	15.4	00	01	07	10
Small cell carcinoma	03	2.6	00	01	01	01
Mesothelioma	01	0.8	00	00	00	01
Non malignant						
Tuberculosis	18	15.4	03	04	07	04
Solitary fibrous tumour	03	2.6	01	00	02	00
Non-tubercular granulomatous lesion	06	5.1	01	03	02	00
Foreign body type multinucleate giant cell reaction	08	6.9	01	02	03	02
Nonspecific chronic inflammatory lesion	15	12.8	03	04	07	01
Total	**117**	**100**				

Table 4. Histopathological Subtypes of Thoracoscopic Pleural Biopsy

The histopathological subtypes were of following types; metastatic squamous cell carcinoma 18 (15.4 %) cases, small cell carcinoma 3 (2.6 %) cases and malignant mesothelioma 01 (0.8 %) cases. Metastatic adenocarcinoma was found in 45 (38.5 %) cases out of 117 cases with male to female ratio is 1 : 4 and most commonly seen in more than 46 years age group. Four cases were seen in the age group of 16 - 30 years (Table 4). 18 (15.4 %) cases out of 117 cases were metastatic squamous cell carcinoma with male to female ratio is 5 : 1 and mostly seen in male those who are addicted to smoking and above 60 years age group. Metastatic small cell carcinoma and malignant mesothelioma of pleura were three and one case each respectively. Among non-malignant findings, tuberculosis were 18 (15.4 %) cases out of 117 cases and others 32 (34.1 %) cases including solitary fibrous tumour 03 (2.6 %) cases, non - tubercular granulomatous lesion 06 (5.1 %) cases, foreign body type multinucleate giant cell reaction 08 (6.9 %) cases, non - specific chronic inflammatory lesions 15 (12.8 %) cases. Immunohistochemistry (IHC) was done on selected cases (Table 5). Of 45 cases diagnosed with adenocarcinoma, IHC was done in 32 cases. CK7 was positive in all the cases on which it was done (30 / 30), followed by TTF - 1 in 87.5 % (28 / 32). Positivity for p63 in 33.3 % (6 / 18), CK5 / 6 in 44.4 % (8 / 18) and CK20 in 16.1 % (5 / 31) cases was also observed although staining was focal and/ or weak in most cases. Of 18 cases diagnosed with squamous cell carcinoma. IHC was done on 10 cases, CK5 / 6 was positive in all the 10 cases followed by p63, which was positive in 80 % (8 / 10). Positivity for CK7 in 50 % (5 / 10) cases was also observed. The staining intensity of TTF1 was weak.

There were three cases of small cell carcinoma, of which IHC was done on two cases. Neuroendocrine markers were positive in all cases. TTF - 1, CK5 / 6 were positive in 50 % (1 / 2) and 50 % (1 / 2) cases respectively. One case of malignant mesothelioma showed positivity for calretinin and CK5 / 6.

IHC Marker	CK 5/6	CK 7	CK 20	TTF1	p63	Calretinin	Synaptophysin	Chromogranin A
Adenocarcinoma (n = 32/45) (%)	8 / 18	30 / 30	10 / 32	28 / 32	6 / 18	0 / 32	0 / 32	0 / 32
Squamous cell carcinoma (n=10/18) %	10 / 10	5 / 10	2 / 10	3 / 10	8 / 10	0 / 6	0 / 3	0 / 2
Small cell carcinoma (n=2/3)%	1 / 2	0 / 2	0 / 2	1 / 2	0 / 2	0 / 2	2 / 2	2 / 2
Malignant mesothelioma (n=1/1)%	1 / 1	0 / 1	0 / 1	0 / 1	0 / 1	1 / 1	-	-

Table 5. Immunohistochemical Profile of Different Histological Types

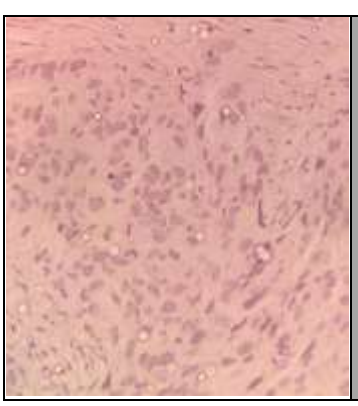

Figure 1e. Metastatic Squamous Cell Carcinoma, H and E x 400

DISCUSSION

A total of 117 cases included with negative for malignant cell in pleural cytology and exudative pleural effusion by Light's criteria were studied over a period of one year. In our study, pleural malignancy was mostly seen in patients belonging to

more than 60 years age group. The earlier studies have stated the same age group Warnisher et al.[1] The sex ratio (male: female) in present study was 1.8 : 1. The sex ratio mentioned in different Indian studies varied from 1.7 : 1 to 7 : 117. Smoking is associated with most of the pleural malignancies Lawrence et al.[2] In the current study, we detected 73.5 % patients were smokers. Shortness of breath was the commonest symptom followed by fever and chronic cough which is comparable to various studies Buchheri et al.[3] In this study, total cell count in exudative pleural effusions showed almost equal distribution between malignant and tubercular effusion. More than 50% of lymphocyte count seen in both tubercular and malignant pleural effusion in our study and comparable with Kushwaha et al[4] study. ADA level exceed 40 IU / L known to well correlate with tuberculosis in various studies and help to differentiate between tuberculosis and malignant exudative pleural effusion. Pandit et al[5] survey showed that ADA level > 70 associated with tuberculosis. Similarly in malignant pleural effusions ADA levels in different studies have been reported <40 IU / L Maldhure et al.[6,7] Metastasis to pleura is the most common reason of malignant pleural effusions over mesothelioma. Merely a case of mesothelioma reported while 66 cases out of the 67 cases were because of pleural metastasis.

In this study, we detected metastatic adenocarcinoma of pleura was the most common histological subtype, attribution for 41 % of total cases. During the last few years, a shift of histological pattern towards adenocarcinoma globally took place Meyer et al.[8] Despite that, mostly Indian various studies still record metastatic squamous cell carcinoma remain the most common subtype Malik et al.[9] Other less common non - malignant conditions were tuberculosis of pleura, chronic non-specific inflammatory lesion, solitary fibrous tumour, granulomatous lesion and foreign body type multinucleate giant cell reaction which is similar with the study by Clara et al.[10] The yield of thoracoscopic pleural biopsy was 72.6 % (85 / 117) patients in this study. Identical observation seen with medical thoracoscopy has been explained from others institution. Kendall et al[11] described yield of thoracoscopic pleural biopsy was 83 % in their study. Tscheikuna et al[12] had described thoracoscopy was diagnostic in 95 % patients with undiagnosed exudative pleural effusion. The possible reason for variation in the diagnostic yield of thoracoscopic biopsy in different studies has been analysed in depth by Lodenkemper et al.[13] The important factors that contribute to this variation include inadequate sampling, pathological errors not taking deeper cut.

In this study we found 57.3 % (67 / 117) of patients along with undiagnosed exudative pleural effusions possessed pleural malignancies. Metastatic to pleura is the more commonly reason of malignant pleural effusion. Only one case of malignant mesothelioma detected. Out of the patients diagnosed with metastatic pleural malignancy, lung was the most frequent site for primary malignancy. Actually, in 53.7 % (36 / 67) of patients, the primary cancer was carcinoma lung and in 10.4 % (7 / 67) patients, the primary was breast and in 35.8 % (24 / 67) of cases, the primary site remained unknown. Adenocarcinoma was the most prevalent histological diagnosis within the patients had metastatic pleural effusion from lung cancer followed by squamous cell lung cancer and small cell lung cancer was less often diagnosed. From 117 cases of undiagnosed exudative pleural effusion in 18 (15.4 %) patients found pleural tuberculosis on pleural biopsy. Our results are comparable with the findings of Agarwal et al, Groove et al, Saha et al.[14,15,16] Different IHC markers had been assessed to distinguish between primary lung adenocarcinomas and metastatic adenocarcinomas. TTF - 1 and Napsin - A each have revealed high sensitivity and specificity in favor of primary lung adenocarcinoma. CK7 along with CK20 and CDX2 is helpful to distinguish primary lung adenocarcinoma (CK7+ / CK20- / CDX2-) from metastatic colon cancer (CK7- / CK20+ / CDX2+) exception to the primary mucinous adenocarcinoma of lung. Markers for squamous differentiation generally assessed in carcinomas of lung contain p63, CK5 / 6. Markers like chromogranin - A, synaptophysin are expressed with small cell carcinoma. Mesothelial markers for example calretinin, CK5 / 6, WT - 1, and D2 - 40 are being applied for diagnosis of malignant mesothelioma.

A rationalized approach, starting with histomorphological assessment, the algorithmic use of a small and actual panel of immunohistochemistry markers and the specific selection of molecular or other adjuvant tests, is essential for the accurate diagnosis of pleural metastasis. The tissue or tumour specific IHC markers comprising particular latest generations of immunomarkers, help to achieve primary of unknown pleural metastasis.

CONCLUSIONS

The data suggests that thoracoscopic pleural biopsy is a secure, highly compatible technique enabling the precise diagnosis of pleural pathology. In addition to determining the underlying cause, it also provides the prospect to deliver distinctive therapeutic methods. Therefore, thoracoscopy should be done in patients with non-diagnostic exudative pleural effusion where underlying malignancy is strongly suspected. It helps in early diagnosis and early treatment to minimize the morbidity and mortality related with pleural malignancies.

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