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Role of Medical Thoracoscopy in undiagnosed exudative pleural effusion with low Adenosine Deaminase level: Prospective Observational study in a tertiary care hospital from Eastern India

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Abstract

Background: Establishing the etiology of exudative pleural effusions in low ADA level (<40IU/L) often requires biopsies from the pleura. Medical thoracoscopy (MT) is a minimally invasive procedure performed under local anesthesia.

Aim: To assess diagnostic yield of medical thoracoscopy in undiagnosed exudative pleural effusion with low ADA (<40 IU/L). To detect the association of pleural fluid ADA in different thoracoscopic diagnosis.

Methods: This was a prospective observational study over a period of one year. Patients with undiagnosed exudative pleural effusion were enrolled in the study. MT was performed with rigid thoracoscope (OptymetCE0197) under local anesthesia. ADA level of pleural fluid was noted. Pleural biopsy material was subjected to histopathology examination and culture for mycobacteria along with cartridge-based nucleic acid amplification test for TB. Incidence of percentage of tuberculosis and malignancy in low ADA level was calculated.

Results: 106 patients with undiagnosed exudative pleural effusion underwent thoracoscopy of which were 56 male and 50 female. MT was able to establish the diagnosis in 96 cases, providing a diagnostic yield of 90.5%. Pleural TB contributed to 35.8% of undiagnosed pleural effusions in the present study. The mean ADA value was 33.9 and 19.6 in tuberculosis and malignant pleural effusion respectively which was found to be statistically significant. Among patients diagnosed as tuberculosis Mycobacterial Tuberculosis was detected on CBNAAT in 18%, while CBNAAT was negative in 82% cases. A cut off 28.5 IU/L for pleural fluid ADA, the sensitivity and specificity were 88.5% and 76.7% respectively based on receiver-operating characteristic analysis (AUC0.88).

Conclusion: Medical Thoracoscopy is a valuable diagnostic tool for undiagnosed exudative pleural effusion. It is a simple and safe procedure without significant morbidity and mortality. Thoracoscopy should be done as soon as possible in low ADA value whenever it is available. As significant number of tuberculosis patients are seen in even in low ADA(<40IU/L) setting.

Keywords: Adenosine deaminase levels; Medical thoracoscopy; Pleural tuberculosis; Malignancy; Undiagnosed exudative effusion

1. Introduction

Pleural effusion is one of the most common entities in pulmonary medicine and can be due to varying etiology. Establishing the etiology of pleural effusion is of paramount importance, as the treatment and prognosis of pleural

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effusion largely depend on its cause [1]. Understanding the nature and composition of pleural effusions is crucial for accurate diagnosis and effective management [2]. Timely and accurate diagnosis of the etiology of pleural effusion is critical for appropriate treatment planning and patient care.

Approximately in one-fourth patients (20-25%) with the pleural pathology, clinicians are unable to diagnose a specific etiology even after substantial work up that includes pleural fluid analysis (cyto-biochemical and microbiological) and closed pleural biopsy [3, 4]. The two most important causes of lymphocyte predominant pleural effusion are tuberculosis and malignancy. Among the biochemical parameters used for differentiating between these two, ADA has important clinical application value. In undiagnosed pleural effusion, pleural biopsy is the gold standard and it reveals malignancy, tubercular and non-specific pleuritis. More than half of these patients are eventually diagnosed as malignant [5].

Medical thoracoscopy (MT) is a minimally invasive procedure which helps the interventional pulmonologist to enter the pleural cavity and take pleural samples under direct visualization. Medical thoracoscopy (MT) is commonly performed by respiratory physicians for diagnostic as well as therapeutic purposes and has now come to the forefront as an important diagnostic aid for the evaluation of undiagnosed pleural effusion [6]. The earliest use of thoracoscopy dates to 1865 and 1866 by Francis Richard Cruise and Samuel Gordon, respectively [7, 8]. It was described for diagnostic purpose by Jacobaeus in 1910. Semirigid thoracoscope was evaluated as a new instrument for the examination of thoracic cavity for the first time in 1998 [3]. Two type two thoracoscopy available; video-assisted thoracoscopic surgery (VATS) and Medical Thoracoscopy (MT) [9].

The present study investigated the diagnostic yield and safety of medical thoracoscopy for undiagnosed exudative pleural effusions with low ADA level (<40IU/L) over one year period. Simultaneously we have tried to find out cut off value of ADA in differentiating tubercular from malignant pleural effusion.

2. Materials and methods

An Observational study was conducted in the Department of Pulmonary Medicine, IPGMER, Kolkata from January 2023 to January 2024.

Aims and objectives

- To assess diagnostic yield of medical thoracoscopy in undiagnosed exudative pleural effusion with low ADA (<40 IU/L).
- To detect the association of pleural fluid ADA in different thoracoscopic diagnosis.

2.1. Inclusion criteria

- Age ≥18 yrs.
- Patients with undiagnosed exudative pleural effusion [10] defined as 2 consecutive pleural fluid cytology or cell block reports are negative.

2.2. Exclusion criteria

- Patients who are not willing to give consent.
- Sputum positive PTB patients and patients of parapneumonic effusion.
- Pleural fluid positive for acid-fast bacilli [AFB] smear and cartridge-based nucleic acid amplification test [CB-NAAT] for M Tb.
- pleural fluid ADA levels >40 IU/L.
- platelet count <75000/cc or P Time or APTT >4 seconds above normal.
- Hemodynamically unstable
- Evidence of mass lesion, or cavitary lesion in CT chest.

Sample size: all patients fulfilled inclusion and exclusion criteria patients were enrolled in the study.

2.3. Data collection and interpretation

All cases of undiagnosed exudative (as per Light's criteria) pleural effusion with ADA level < 40IU/L as per inclusion and exclusion criteria were enlisted for medical thoracoscopic biopsy. Meticulous history taking, detailed clinical

examination with subsequent laboratory, radiological and necessary interventional studies have been performed before medical thoracoscopy. During thoracoscopy, pleural biopsy was taken from suspected lesions and was sent for histopathological examinations (in formalin) and CBNAAT / M Tb culture (in normal saline). We calculated the incidence of tuberculosis in low ADA pleural effusion and assessed the association of different thoracoscopic diagnosis with ADA with proper statistical analysis.

2.4. Procedure: Thoracoscopy

Thoracoscopy was conducted under conscious sedation with intravenous midazolam (0.5mg/kg body weight) and analgesia (IV Fentanyl 100–200 mcg). The thoracoscope used was the rigid thoracoscope of OptymetCE0197. Informed consent and USG assessment was done before the procedure.

For rigid thoracoscopy in patients with small pleural effusion, one liter of normal saline was injected into pleural cavity just prior to the procedure. This allowed lung to collapse and reduced the chances of lung being injured while introduction of trocar. Patients was positioned in lateral decubitus with diseased side up. A 1.5cm to 2cm long skin incision along the line of intercostal space was given in 5th intercostal space in anterior-axillary line. Thoracoscope was maneuvered to see visceral, costal, diaphragmatic surface as well as the costophrenic recess. After selecting suitable site on parietal pleura for biopsy, biopsy forceps were introduced through working channel of the thoracoscope. Pleura was grasped under vision and biopsy was taken with a shearing movement of the thoracoscope.

Multiple pleural biopsies (about 10 to 12 biopsy samples) were taken. The samples were collected in formalin (for histopathological examination plus immunohistochemistry) and in saline (for CBNAAT and Mycobacterial cultures).

After the procedure a chest radiograph was obtained and intercostal tube was removed following the procedure usually within 3–10 days depending on lung expansion.

2.5. Outcome parameters

Patients were grouped into malignant pleural effusion (MPE), tuberculous pleural effusion (TBPE), Non-specific inflammation (NSI) and Inconclusive according to the diagnosis. The thoracoscopic findings and complications of the four groups were compared. Finally, we analyzed the significant predictive factors for diagnosis between the MPE and TBPE groups.

2.6. Statistical analysis

All the data were collected, tabulated, and analyzed using the statistical package for the social sciences (SPSS version 25). The results were presented as mean ± SD or percentage. Differences in categorical data were compared using the chi-square test of the Fisher exact test for two variables and for more than two variables ANOVA. A p value of < 0.05 was considered statistically significant. ROC curve was used for calculating cut off value of ADA, for predicting Tuberculosis.

3. Results

A total of 106 patients were enrolled in the study. Out of 106, 56 (52.8%) were male and 50 (47.1%) were female. So, the proportion of male and female patients was comparable. The mean age of the study population was 54.6 years.

The most common symptom observed in the study group was a cough, which was seen in 74.5% of patients, followed by chest pain in 38.5% and breathlessness in 36.5% cases.

In our study 58.5 were smokers and 41.5 were non-smokers.

Table 1 Distribution of study participants based on demographic characteristics n=106

Variable	Category	Frequency	Percent
Age (in completed years) [$]		54.6 (14.4)	
Sex	Female	50	47.1
	Male	56	52.8

Smoker	No	44	41.5
	Yes	62	58.5
Symptoms[&]	Cough	79	74.5
	Chest pain	44	42.3
	Fever	8	7.7
	Shortness of breath	38	36.5
	Haemoptysis	3	2.8
Total		106	100.0

[$] Mean (SD); [&] total numbers may be more than 104 because of more than one symptom in a single patient; Diagnostic yield

A final diagnosis is made in 96patients (n= 106) who underwent MT, thus providing a diagnostic yield of 90.5%. Pleural TB contributed to 35.8% (38 out of 106) of undiagnosed exudative effusions, 45.2% of effusions (48 out of 106) were due to malignant disease involving the pleura. Non-specific inflammation and inconclusive were observed in 11.3% and 7.5% patients respectively (Table-2)

Table 2 Diagnostic yield of thoracoscopic biopsy (n=106)

Thoracoscopic Diagnosis	**Categories**	**Total**	**Percentage**
Malignancy (45.2%)	Adenocarcinoma lung	35	33.0
	Squamous cell carcinoma lung	6	5.8
	Pleural Mets (other than lung)	3	2.8
	Mesothelioma	1	1.0
	Malignancy (not specified)	3	2.9
Tuberculosis (35.8%)		38	35.8
Nonspecific inflammation		12	11.3
Inconclusive		8	7.5
Total		106	100.0

Most patients in the study population had moderate pleural effusion (69.4%) in total and irrespective of the diagnosis. Massive pleural effusions were seen in 47.7% of patients with malignancy.

Malignant pleural effusion consisted of 47.7% massive, 54.3% moderate effusion where tuberculous pleural effusion consisted of 85%moderate, 10% mild and only 5% of massive effusion ($p<0.000$).

It is a well-known fact that malignancy and tuberculosis are characteristically present with haemorrhagic (59.3%) and straw-coloured (90.5%) effusion respectively, which was also seen in our study.

Pleural fluid LDH level is high in malignancy compared to tubercular pleural effusion.

In routine pleural fluid biochemical evaluation, all parameters were comparable between the two groups, except for ADA levels, which were significantly higher in the tuberculosis group (mean = 33.9) than in the malignancy group (mean 17.6). (Table-3)

Table 3 Compare between mean serum LDH, pleural fluid LDH and ADA of patients based on the thoracoscopic diagnosis (n=106)

Variables	Total Mean (SD)	Tuberculosis Mean (SD)	Malignancy Mean (SD)	NSI Mean (SD)	Inconclusive Mean (SD)	p value
Serum LDH	483.7 (236.2)	351.1 (124.9)	485.7 (305.5)	381.1 (136)	296.5 (98.3)	0.005*
Pleural fluid LDH	724.4 (398.9)	465.4 (290.3)	670.9 (475.4)	354.3 (233.8)	462.6 (163.7)	0.003*
ADA	25.3 (9.4)	33.9 (5.4)	19.6 (7.0)	23.7 (9.4)	29.3 (11.9)	0.001*

*Statistically significant, SD-standard deviation

The most common gross thoracoscopic findings in patients of tuberculosis was pleural nodules (91.5%) followed by sago grain (35.5%) and adhesions (27.5%). Whereas in malignancy, it was nodules (80.7%) followed by pleural plaques (44.3%) and adhesions (22.6%). Post hoc analysis shows no significant difference between malignancy and tuberculosis (p=0.001). Among patients diagnosed as tuberculosis Mycobacterium Tuberculosis was detected on CBNAAT in 18%, while CBNAAT was negative in 82% cases.

Prediction of TB using ADA values

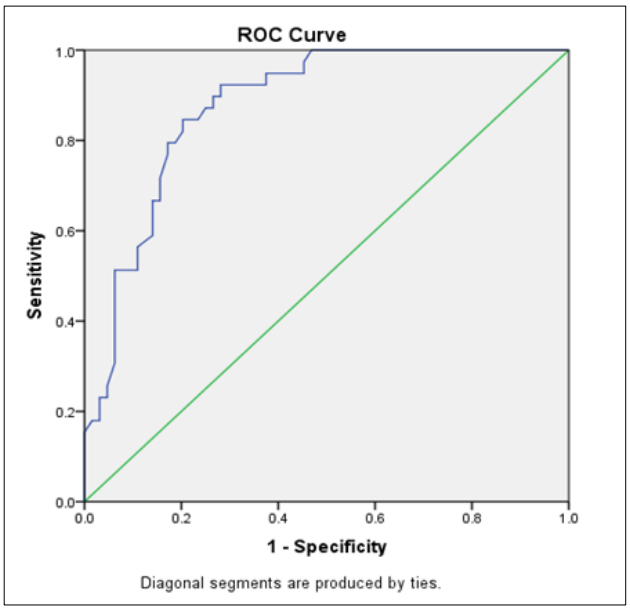

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Figure 1 ROC curve showing the predictive value of pleural fluid ADA for tuberculosis (n=104)

Table: 4 AUC of ROC curve

Area under the curve	P value	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
0.897	0.000*	0.872	0.931

AUC of 0.897 signifies a good model. Using a cut off 28.5 for pleural fluid ADA, the sensitivity and specificity was 88.5% and 76 .7% respectively.

3.1. Complications

Complications were seen in 24 (22.6%) cases. 5 patients (7.6%) had persistent air leak. Major post-procedure bleeding requiring PRBC transfusion were seen in 2 patients. No mortality was seen in our study. Minor complications like chest pain, fever, sub cut emphysema were seen in 14(15.3%), 3(1.9%) and 6 (3.8%) patients respectively.

4. Discussions

In our study, a total of 106 patients were enrolled as per our inclusion and exclusion criteria.

The mean age of patients was 54.6 years. In this study, the mean age of patients of malignancy was higher (57.7 years) than that of tuberculosis patients (51.9 years) (P< 0.646). The most common symptoms observed were dry cough followed by chest pain and shortness of breath that is also seen in other studies [11].

4.1. Diagnostic yield

In our study, a final diagnosis was made in 96 patients (n= 106) who underwent MT, thus providing a diagnostic yield of 90.5%. Pleural TB contributed to 35.8% (38 out of 106) of undiagnosed exudative effusions, 45.2 % of effusions (48 out of 106) were due to malignant disease involving the pleura. Non-specific inflammation and inconclusive were observed in 11.3% and 7.5% patients respectively. These findings are like other published studies. We have compared our studies with different published literatures [Table 4]. In various studies, the diagnostic yield of thoracoscopy varied from 74.3 to 99.2% [12,13,14].

Table 4 Comparison of results of our study with similar studies

Variables	Our study 2024	Sobh E et al. 2020 [13]	Tousheed SZ et al. 2022 [22]	Kumar H et al. 2023 [16]
Sample size (n)	106	542	373	160
Male%	52.8	58.3	65.9	55.6
Female%	47.1	41.7	34.1	44.4
Mean Age(yrs)	54.6	57	51.9	57.3
Diagnosis achieved	96	476	370	158
Diagnostic yield (%)	90.5	87.8	99.2	98.7
Malignancy	45.2	60.7	32.2	75
TB	35.8	20.7	33.5	16.9
NSI	11.3	6.5	11.2	6.3
other	---	---	22.3	0.6

In contrast to the studies mentioned above, there was a low prevalence of malignancy in our study. A probable explanation for this could be the rising incidence of tuberculosis in low ADA (<40IU/L) and we exclude known case of malignancy and imaging showing lesions suggestive of malignancy.

Adenosine deaminase (ADA) is the enzyme that catalyses the conversion of adenosine to inosine. ADA is a predominant T-lymphocyte enzyme. It has been extensively studied as a biochemical marker in pleural fluid for tubercular pleuritis. Despite its widespread use, there is no definitive cut-of value of ADA for the diagnosis of tuberculosis. In general, a positive test improves post-test probability of tuberculous effusion to a much lower extent in high prevalence than in low prevalence settings, and a negative test performs much better at excluding TPE in low prevalence settings. In our study, there is a significant difference in pleural fluid ADA levels with mean ADA levels in malignant and tubercular pleural effusion were 17.6 and 30.9 IU/L respectively (p<0.000). A study conducted by Hemant Kumar et al. [16] reported significant difference in pleural fluid ADA levels with mean ADA levels in malignant and tubercular pleural effusion were 19.2 and 37.28 IU/L respectively. Maturu VN et al. [17] compared 104 malignant and 76 patients with tubercular pleural effusions and found out mean ADA level in malignant and tubercular pleural effusion is 26 and 47 IU/L respectively. Mehta AA et al. [18] studied 171 exudative pleural effusions and found the median ADA value as 45.3 and 18 in tubercular and malignant pleural effusion respectively. All the studies showed higher values of ADA in tubercular pleural effusion. The most widely accepted cut-of level of ADA for the diagnosis of tubercular pleural effusion is 40 IU/l [19]. In general, ADA levels higher than 70 IU/L are highly suggestive of TBE, whereas levels less than 40 IU/L are more helpful in excluding disease.

In our study, 35.8% of patients had tuberculosis in the low ADA group (ADA<40 IU/L). (Table 2). In our study, ADA cut off 28.5 will give a sensitivity of 88.5% and a specificity of 76.7% specificity for the diagnosis of tuberculosis (AUC 0.897) (fig. 1).

ADA values need to be coupled with clinical judgment, imaging findings, and other ancillary tests to make a non-invasive diagnosis of tuberculous pleural effusion.

Table 5 ADA level in different studies for tuberculous pleural effusion

Study	ADA Level(mean)	Sensitivity	Specificity
Our study	28.5	88.5	76.7
Verma et al. [20]	36	89	78
Niwa et al. [21]	38	91	85
Rodriquizet al. [7]	37	93	80

4.2. Complications

The chest drains usually removed when less than 50 ml pleural fluid drain out in last 24 hrs with complete radiological expansion and no air leak. It takes 3-4 days in case of tubercular pleural effusion and in malignant effusion average6-12 days [22]. In our study mean duration for removal of ICT in tuberculosis was 3.2 days and in malignancy it was 9.8 days (p<0.000). Medical thoracoscopy is a safe procedure without significant morbidity or mortality. Complications of thoracoscopy are usually procedure-related like post procedure pain, minor bleeding (not requiring blood transfusion), fever, sub cutaneous emphysema. Major complications like persistent air leak beyond 3 days was more common in malignancy. Complications in our study were comparable with other studies [22, 23, 24].

Limitations of the study

Our study has several limitations.

- single centric study.
- Number of patients were small.
- The spectrum of pleural diseases that has been seen in our study limited to pleural malignancy and pleural TB.

5. Conclusions

Medical thoracoscopy was able to diagnose 90.5% cases in undiagnosed exudative pleural effusion. It is relatively safe and simple procedure without significant morbidity. Thoracoscopy should be done as soon as possible in low ADA value whenever it is available. As incidence of tuberculosis is high in our country even in low ADA(<40IU/L). Pleural fluid ADA levels >28.5IU/L is statistically significant in differentiating between TB and malignant effusion (p<0.0001).

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

Ethical approval was taken from the Institutional Ethics Committee.

Statement of Informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Jany B, Welte T. Pleural effusion in adults-etiology, diagnosis, and treatment. Dtsch Arztebl Int 2019; 116:377-86.

[2] D'Agostino HP, Edens MA: Physiology, pleural fluid. StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL; 2023.

[3] Menzies R, Charbonneau M. Thoracoscopy for the diagnosis of pleural disease. Ann Intern Med 1991; 114:271–6

[4] Loddenkemper R. Thoracoscopy - state of the art. Eur Respir J 1998; 11:213–21.

[5] Jiménez D, Pérez-Rodriguez E, Diaz G, et al. Determining the optimal number of specimens to obtain with needle biopsy of the pleura. Respir Med 2002; 96:14–7

[6] haw JA, Koegelenberg CFN. Pleural tuberculosis. Clin Chest Med2021; 42:649-66.

[7] Rodríguez-Panadero F. Medical thoracoscopy. Respiration 2008; 76:363-72.

[8] Gordon S. Clinical reports of rare cases, occurring in the Whitworth and Hardwicke hospitals. Dublin Q J Med Sci 1866; 41:83–90.

[9] Shojaee S, Lee HJ. Thoracoscopy: Medical versus surgical-in the management of pleural diseases. J Thorac Dis 2015;7(Suppl 4): S339-51.

[10] Light RW. Clinical practice. Pleural effusion. N Engl J Med. 2002 Jun 20;346(25):1971-7. doi: 10.1056/NEJMcp010731. PMID: 12075059.

[11] Dubin S, Grifn D et al. Lung cancer in non-smokers. Mo Med, 2020. 117(4):375–379.

[12] Saguil AA, Wyrick KR, Hallgren J. Diagnostic approach to pleural efusion. Am Fam Physician 2014;90:99–104.

[13] Sobh E, Elsawy SB, Ahmed ME. Yield of medical thoracoscopy in undiagnosed exudative pleural efusion: a 3-year retrospective multicentre study. Al-Azhar Assiut Med J 2020; 18:203–208.

[14] Patil CB, Dixit R, Gupta R, Gupta N, Indushekar V.Thoracoscopic evaluation of 129 cases having undiagnosed exudative pleural efusions. Lung India 2016; 33:502–506.

[15] DS, Punitha M, Sagar C, Dutt TS, Murali Mohan BV, Zuhaib M, Annapandian VM. Role of medical thoracoscopy in the diagnosis of pleural efusions. Indian J Tuberc 2022; 69(4):584–589.

[16] Kumar H, Mohammad A, Kumar S et al. The Egyptian Journal of Bronchology.2023; 17:60.

[17] Maturu VN, Dhooria S, Bal A, Singh N, Aggarwal AN, Gupta D, Behera D, Agarwal R. Role of medical thoracoscopy and closed-blind pleural biopsy in undiagnosed exudative pleural efusions: a single-center experience of 348 patients. J Bronchology Interv Pulmonol 2015; 22(2):121–129.

[18] Mehta AA, Gupta AS, Ahmed S, Rajesh V. Diagnostic utility of adenosine deaminase in exudative pleural efusions. Lung India 2014; 31(2):142–14.

[19] Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. Respir Med 2008; 102:744–754.

[20] Verma A, Abisheganaden J, Light R. W. Identifying Malignant Pleural Effusion by A Cancer Ratio (Serum LDH: Pleural Fluid ADA Ratio. Lung (2016) 194:147–153 DOI 10.1007/s00408-015-98316.

[21] Y. Niwa, H. Kishimoto, K. Shimokata. Carcinomatous and tuberculous pleural effusion, Chest.1985;351–355

[22] Chawla RK, Kumar M, Madan A, Dhar R, Gupta R, Gothi D, et al. NCCP-ICS joint consensus-based clinical practice guidelines on medical thoracoscopy. Lung India 2024; 41:151-67.

[23] Rodriguez-Panadero F, J.P. Janssen and P. Astoul. Thoracoscopy: general overview and place in the diagnosis and management of pleural effusion. Eur Respir J 2006; 28: 409–421 DOI: 10.1183/09031936.06.00013706

[24] Tousheed SZ, Ranganatha R, Hemanth Kumar M, Manjunath PH, Philip DS, Punitha M, Sagar C, Dutt TS, Murali Mohan BV, Zuhaib M, Annapandian VM. Role of medical thoracoscopy in the diagnosis of pleural effusion. Indian J Tuberc 2022; 69(4):584–589.