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Original Research Article

Role of adenosine deaminase and lymphocyte/neutrophil ratio in the diagnosis of tuberculous pleural effusion in patients with exudative pleural effusion

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ABSTRACT

Background: Present study was conducted with an objective to evaluate the role of ADA and lymphocyte/neutrophil ratio in the diagnosis of tuberculous pleural effusion in patients with exudative pleural effusion and to analyze the cause of non-tuberculous exudative pleural effusion.
Methods: This hospital based observational study was conducted from August 2011 to September 2013 with a total number of 120 patients of exudative pleural effusion who were admitted in medical wards of MKCG Medical College Hospital, Berhampur, Odisha, India. Patients with transudative pleural effusion, age less than 12years and those who were haemodynamically unstable were excluded from the study. Statistical analysis was done using standard statistical techniques.
Results: A total number of 120 patients with exudative pleural effusion were analyzed. 83 patients were males and 37 patients were females. Maximum no of patients were seen in the age group of 21-40 years. Total ADA was found to be >40 U/L in all cases of TB effusion. All cases of TB effusion were lymphocyte predominant with L/N ratio > 0.75. In case of exudative pleural effusion due to non-tuberculous etiology L/N ratio was <0.75. P Value <0.0001 was considered extremely significant for L/N ratio for TB effusion.
Conclusions: ADA value more than 100 U/L was observed only in patients of tuberculous effusion. L/N ratio was >0.75 in 97 patients of tuberculous effusion and none of the non-tuberculous effusion. Combined use of ADA and L/N ratio is more efficient means for diagnosing tuberculous pleural effusion than the use of ADA alone.

Keywords: Adenosine deaminase, Exudative pleural effusion, Transudative pleural effusion, Lymphocyte/Neutrophil ratio

INTRODUCTION

Pleural effusion is the abnormal collection of fluid in the pleural space. It is classified into exudates and transudates based on Light's criteria.[1-3] The common exudative effusions encountered in clinical practice are tuberculosis, malignancy, para pneumonic or associated with collagen vascular disease. TB pleural effusion is seen in more than 90% cases. TB pleural effusion may be sequel to a primary infection acquired 6-12weeks previously or it may represent reactivation of TB.[4]

Adenosine deaminase (ADA) is considered a valuable tool in the diagnosis of extra pulmonary tuberculosis. A Cochrane meta-analysis review of forty articles on ADA in pleural fluid shows that test results for ADA with cut off value >40U/L derived from the summary receptor operator curve (SROC) was 92.2% for both sensitivity and specificity. ADA value >40U/L with a lymphocytic

effusion and Lymphocyte/Neutrophil (L/N) ratio >0.75 is considered diagnostic of TB pleural effusion.[5]

A TB pleural effusion is typically clear and straw colored; however, it can be turbid or serosanguinous, but is virtually never grossly bloody and effusion is virtually always an exudate.[6-8]

METHODS

The present study was conducted from August 2011 to September 2013 in the department of General Medicine, MKCG Medical College Hospital, Berhampur, Odisha, India. Observational study was design, with a sample size of 120. The work was carried out after approval from the Institutional Ethics Committee of MKCG Medical College Hospital, Berhampur, Odisha. The data for this study was collected from 120 patients of pleural effusion fulfilling the inclusion/exclusion criteria admitted in MKCG Medical College Hospital, Berhampur using a proforma specially designed for the study.

For tuberculous pleural effusion, diagnosis was made by demonstration of AFB in pleural fluid/sputum and/or ADA >40U/L and L/N ratio >0.75 in pleural fluid. In non-tuberculous pleural effusion evaluation was done for lupus pleurisy, liver abscess, pneumonia, hypothyroidism, malignancy, empyema and rheumatoid pleurisy.

Statistical analysis

Statistical Analysis of data like frequency and percentages were used for categorical variables. Mean and standard deviation were used for describing continuous variables. Inferential statistical tools like Chi-Square test and Student's t-test were used. P-value of <0.05 was considered statistically significant.

Inclusion criteria

- Patients of exudative pleural effusion,
- Age >12years,
- Hemodynamically stable.

Exclusion criteria

- Patients of transudative pleural effusion,
- Age <12years,
- Hemodynamically unstable.

Diagnostic criteria

Light's criteria were used to diagnose exudative pleural effusion. Exudative pleural effusion meets at least one of the following criteria

- Pleural fluid / serum protein >0.5,
- Pleural fluid LDH/serum LDH >0.6,
- Pleural fluid LDH more than two-thirds of normal upper limit for serum.

Criteria taken for diagnosis of tuberculous pleural effusion

- Demonstration of AFB in pleural fluid/sputum and / or
- ADA > 40 U/L and / or
- L/N ration > 0.75 in pleural fluid.

In non-tuberculous pleural effusion evaluation was done for lupus pleurisy, liver abscess, pneumonia, hypothyroidism, malignancy, empyema and rheumatoid pleurisy.

Besides a detailed history and clinical examination, the following investigations were carried out.

Investigations

Complete haemogram, ESR, serum Urea, Serum Creatinine, Liver Function Tests, Mantoux, Sputum AFB, Sputum Culture and sensitivity, HIV ELISA. Diagnostic thoracentesis was done, and fluid sent for analysis of glucose, protein, cytology and cell count, LDH, AFB and gram stain, culture and sensitivity and ADA were done.

Imaging

Plain chest X-ray PA view, USG chest and/or CT chest based on affordability.

Other investigations

Echocardiogram, pericardial fluid analysis, Serum HBsAg, Anti HCV, OGD scopy, serum ANA, dsDNA, RA factor, aCL antibody, serum thyroid function tests, MRI Brain, 24hr. urine protein, CD4 count, CT guided biopsy. ADA in pleural fluid was done by sensitive Giusti and Galanti's colorimetric method, Total ADA was done. ADA 1 and 2 isoforms were not done.

RESULTS

A total of 120 patients of exudative pleural effusion were analyzed out of which 83 (69.1%) were males and 37 (30.9%) were females. They were mostly in the age group of 21-40years. The lowest age was 13years and highest age was 76years. ADA was done in all samples of pleural fluid.

Total ADA in pleural fluid of more than 40U/L with a pleural fluid L/N ratio of more than 0.75 was useful in differenting between tuberculous and non-tuberculous pleural effusion. Tuberculosis was the most common cause of pleural effusion. Peak age of tuberculous pleural effusion was 21-30years. Out of 120 patients of exudative pleural effusion, 97 were tuberculous pleural effusion.

Out of 97 cases of tuberculous pleural effusion, 70 were males and 27 were females. Pleuritic chest pain was noted in 64 cases, followed by fever in 62 cases, dry cough in 59 cases and cough with sputum in 28 cases, hemoptysis in past history of TB was obtained in 7 cases and history of contact with TB patients in 14 cases. Mantoux was reactive (10mm or more) in 52 cases. 50 cases presented with left sided pleural effusion and 54 cases had moderate pleural effusion. Sputum smear for AFB was done in 33 patients who produced sputum and it tested positive only in 3 cases.

Total ADA was found to be >40U/L in all the cases with TB effusion (Table 11). All cases of TB effusion were lymphocyte predominant with L/N ratio >0.75. In cases of exudative pleural effusion due to non-tuberculous aetiology L/N ratio was <0.75 (Table 10). The P value <0.0001, considered extremely significant for L/N ratio for TB Effusion.

Other causes of exudative pleural effusion noted are parapneumonic effusion, connective tissue diseases, malignancy, amoebic liver abscess, empyema and hypothyroidism.

Table 1: Age distribution of 120 cases of exudative plural effusion.

Age in years	Male	Female	Total	%
13-20	5	5	10	8.3
21-30	27	13	41	34.1
31-40	23	11	34	28.3
41-50	17	4	21	17.5
51-60	5	3	8	6.7
>60	5	1	6	5

Table 1 shows the age variation was from 13 to 76years, Majority patients were in the age group of 21-40years.

Table 2: Gender distribution.

Gender	Frequency	%
Male	83	69.1
Female	37	30.9
Total	120	100

Table 2 shows the present study group consisted of 69.1% males and 30.9% females.

Table 3: Clinical features-symptoms.

Symptoms	Total	%
Pleuritic chest pain	88	73.3
Fever	74	61.6
Dyspnoea	73	60.8
Cough	69	57.5
Weight loss	38	31.6
Appetite loss	47	39.1

Table 3 shows the pleuritic type of chest pain is the most frequently noted symptom in 88 cases (73.3%) followed by fever 74 cases (61.6%), dyspnoea in 73 cases (62%) and cough in 69 cases (57.5%) respectively.

Table 4: Gender wise distribution of etiology of pleural effusion.

Etiology	Male	Female	Total
Tuberculous effusion	70	27	97
Parapneumonic effusion	3	2	5
Malignant effusion	3	0	3
Rheumatoid pleurisy	1	1	2
Lupus pleurisy	0	7	7
Emphysema	2	1	3
Hypothyroidism	2	0	2
Liver abscess	1	0	1
Total	83	37	120

Table 4 shows out of 120 cases of exudative pleural effusion most common cause is tuberculous pleural effusion i.e. 97 cases.

Table 5: Total ADA range and mean.

ADA range	Mean
ADA range (u/l)	5-239
ADA mean (u/l)	89.58

Table 6: Total ADA.

	ADA < 40 u/l	ADA > 40 u/l
No. of cases	20	100

Table 7: L/N ratio.

	L/N ratio > 0.75	L/N ratio < 0.75
No. of cases	97	23

Table 8: Mantoux and sputum AFB in tuberculous pleural effusion.

	Tested	Positive
Mantoux	97	52 (53.6%)
Sputum AFB	28	3 (10.7%)

Table 9: ADA in exudative effusion.

ADA (u/l)	Tuberculous effusion	Non-tuberculous effusion
Range	42.19-239	5-76.5
Mean	153.6	25.6

Table 10: L/N ratio in exudative effusion.

L/N ratio	Tuberculous effusion	Non-tuberculous effusion
> 0.75	97	0
< 0.75	0	23

Table 11: ADA and L/N ratio.

Etiology	ADA >40u/l	L/N ratio >0.75
Tuberculous	97	97
Non-tuberculous	3	0

DISCUSSION

Tuberculosis is a common infection in India and the commonest cause of exudative pleural effusion. Because of the non-availability of confirmatory tests like pleural biopsy and HPE in all centers, the confirmation of diagnosis is difficult.

ADA is considered a valuable tool in the diagnosis of extra pulmonary tuberculosis. Pleural fluid Acid Fast Bacilli demonstration is virtually always negative, culture positive in <25%, histopathology of pleural fluid could be positive in 80% whereas HPE and culture increases diagnostic efficacy to 90%.[7] Polymerase chain reaction having a sensitivity of 78% for active disease, has not been found to be an efficient alternative.[9]

Although the rise in ADA in tuberculous effusion was predominantly due to ADA 2, the difference was statistically not significant, and measurement of ADA isoforms is commercially not feasible.[10] An ADA level < 40U/L virtually excludes tuberculosis in lymphocytic pleural effusions.[11]

All the 97 cases of lymphocyte predominant pleural effusion with L/N ratio >0.75 total ADA was found to be >40U/L. The range of ADA was between 42.19-239U/L with a mean 153.6U/L. These results were in agreement of a study conducted by P. C. Mathur et al.[12]

Two cases of exudative pleural effusion due to rheumatoid arthritis were seen. Pleuritic chest pain was noted in both the patients and one patient had cough. Both patients had history of long standing bilateral small joints arthritis. The lowest level of pleural fluid glucose in our study was noted in rheumatoid pleurisy, the value being 13mg/dL. In both the cases pleural fluid LDH level were elevated than plasma levels and Rheumatoid factor (RA) level was >1:320 in pleural fluid. This is in accordance with the observation of Halla JT et al.[13]

The mean ADA value was 42.5U/L and one case had elevated ADA 69U/L. The effusion was lymphocyte predominant but none of them achieved L/N ratio >0.75.

5 cases of pneumonia with pleural effusion were analyzed. The presentation was like acute illness and presenting complaints were fever (80%), cough with sputum production (100%), pleuritic chest pain (60%) and dyspnoea (60%). Haemoptysis was seen in one patient. The mean WBC count was 12,400 and peripheral blood neutrophilia was noted in line with observation of Light RW et al. *Pneuomococci* was grown in sputum in 3 cases and *klebsiella* along with *E. coli* in 2 cases. This observation is consistent with the study of Varkey B et al, and Barlett JG et al, who stated that *pneumococci* and *S. aureus* account for approximately 70% of all aerobic gram-positive isolates and *E. coli* along with *klebsiella* species, account for approximately 75% of all aerobic gram-negative empyemas.[14,15]

The mean glucose level in pleural fluid was 52mg/dL. The pleural effusion was neutrophil predominant with a L/N ratio <0.75. Culture of plural fluid was negative in all cases. The ADA level was <40U/L in all the cases with a mean value of 21.3 U/L.

Malignant effusion was noted in 3 cases of males. The average age of presentation was 65years. The most common symptoms noted were anorexia and weight loss in all the 3 cases. one patient presented with haemoptysis. Gross appearance of pleural fluid was bloody in 3 cases. ADA in pleural fluid was less than 40U/L in 2 cases (7.2 and 30.2U/L) and 42.6U/L in one case. Mean ADA was 20.3U/L. The effusion was lymphocyte predominant with mesothelial cells >10% and L/N ratio <0.75 in all the three cases.

CONCLUSION

From the above discussion, it is concluded that combined use of the total ADA in pleural fluid of >40U/L with a pleural fluid L/N ratio >0.75 is a more efficient means of diagnosing tuberculous pleural effusion than the use of ADA alone.

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