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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 **Original Research Article**

Tuberculosis (TB) is one of the most common cause of exudative pleural effusion in India and pleural effusion is the second most common site of extrapulmonary TB after lymph node. Main aim of this study to evaluate the role of ADA and L/N ratio in the diagnosis of tuberculous pleural effusion in patients with exudative pleural effusion. A prospective observational study is done on 120 patients visiting govt chest hospital, hyderabad with exudative pleural effusion age more than 12. Hemodynamically unstable patients were excluded from the study. 84 patients were males and 36 were females. Maximum number of patients was seen in age group 21-30 years. Total ada was found to be >40 u/l in all tubercular effusion with l/n ratio >0.75. When ada> 40U/L is considered alone in diagnosing tubercular effusion the sensitivity, specificity, positive predictive value, and negative predictive values are 100%, 82.6%, 96% and 100% respectively. Combination of ADA along with L/N ratio increased sensitivity and specificity to100% and 91.3%respectively.

Keywords: Adenosine deaminase, exudative pleural effusion, tubercular pleural effusion, lymphocyte/neutrophil ratio.

INTRODUCTION

Tuberculosis (TB) is one of the most common causes of exudative pleural effusion in India and pleural effusion is the second most common site of extrapulmonary TB after lymph node. A lot of newer diagnostic methods have come up in recent years to aid in the diagnosis of TB like the Xpert mycobacterium TB (MTB)/resistance to rifampicin (RIF) which is available as a cartridge-based nucleic acid amplification test (CBNAAT) and it can identify MTB DNA and RIF simultaneously. Although its specificity is very good, its sensitivity is less. Pleural biopsy and histopathological examination is an invasive test, requires great skill and has many complications. Hence, a rapid test which is relatively inexpensive and has good sensitivity and acceptable specificity is needed for diagnosis of tuberculous pleural effusion. Adenosine deaminase (ADA) is considered a valuable tool in the diagnosis of extra-pulmonary Tuberculosis. Various studies using ADA as a diagnostic tool for tuberculous pleural effusion quote that the sensitivity and specificity of ADA in pleural fluid ranges between 47.1%-100% and 50%-100% respectively. A Cochrane meta-analysis review of forty articles on ADA in pleural fluid shows that the test results for ADA with cutoff value > 40 U/L derived from the summary receptor operator curve (SROC) was 92.2% for both sensitivity and specificity. ADA value> 40 U/L with a lymphocytic effusion Lymphocyte/Neutrophil (L/N) ratio >0.75 is considered diagnostic of TB pleural effusion. Very few studies investigated the combined utility of pleural fluid ADA plus routine and microscopy examination, and so this study is done to bridge the gap in knowledge.

AIMS AND OBJECTIVES

To evaluate the role of ADA and L/N ratio in the diagnosis of tuberculous pleural effusion in patients with exudative pleural effusion, to analyze the causes of nontuberculous exudative pleural effusion

METHODS

A Prospective observational study is done on 120 patients admitted in Government general and chest hospital with exudative pleural effusion.

Duration of the study

8 months, March 2019-October 2019

INCLUSION CRITERIA

Cases of Exudative pleural effusion Age >12yrs

EXCLUSION CRITERIA

Cases of Transudative pleural effusion

Age<12yrs

Haemodynamically unstable patients

Light's criteria [1] were used to diagnose exudative pleural effusion.

A thorough history, clinical examination, hemogram, esr, sputum afb, chest x ray, pleural fluid analysis for proteins, ada, cell counts was done

RESULTS

Out of 120 patients 84 were males and 36 were females. Maximum number of cases was seen among age group 21-30years. The lowest age was 14 years and highest age was 81 years. Left sided effusion was seen in 59 cases (49.1%), right sided effusion in 57 cases (47.5%) and bilateral effusion in 4 cases (3.3%). Of those cases with bilateral effusion all four were due to tuberculosis.

ADA was done in all samples of pleural fluid. Total ADA was done. ADA 1 &2 isoforms was not done. The range of ADA was between 4 to 249 U/L***(a)*** with a mean ADA value of 92.15 U/L (Table 4). ADA was > 40 U/L in 101 cases. L/N ratio was done in all cases. L/N ratio was >0.75 in 99 cases (Table 6). Based on ADA and L.N ratio 97 cases were classified to have Tuberculous pleural effusion. Other causes of exudative effusion noted are 1 cases of pancreatic effusion, 4 parapneumonic effusions, 14 malignant effusions, 1 rheumatoid pleurisy, 2 empyema, and 1 case of liver abscess with exudative effusion.

Total ADA was done and found to be > 40 U/L in all the cases with tuberculous pleural effusion. The mean ADA was 155.2 U/L. the highest value noted in our study was 249 U/L, and the lowest was 40.7 U/L (Table 8). ADA value > 100U/L was noted in 38 cases.

In exudative effusion due to other causes, total ADA was done. It was found that the ADA value ranged between a lowest of 4 U/L to a highest of 145U/L. The mean ADA value was 27.2 U/L. Of 23 cases, 4 cases had ADA >40 U/L (1 Rheumatoid arthritis with pleural effusion, 2 empyema and 1 pancreatic pleural effusion), rest 19 cases had ADA< 40 U/L.

All cases of tuberculous pleural effusion had ADA>40 U/L and L/N ratio>0.75. Of 23 cases with nontuberculous pleural effusion, Ada was < 40 U/L in 19 cases and L/N ratio was <0.75 in 21 cases.

When ada> 40U/L is considered alone in diagnosing tubercular effusion the sensitivity, specificity, positive predictive value, and negative predictive values are 100%, 82.6%, 96% and 100% respectively. Combination of ADA along with L/N ratio increased sensitivity and specificity to100% and 91.3%respectively.

Table-1: Gender distribution

Male	Female	Total
84(70%)	36(30%)	120

Table-2: Age wise distribution

Age in years	Male	Female	Total	Percentage
13-20	6	4	11	9.1%
21-30	30	10	40	33.3%
31-40	23	11	34	28.3%
41-50	16	4	20	16.6%
51-60	5	4	9	7.5%
>60	4	2	6	5%

Table-3: Clinical features-symptoms

Symptom	Total	Percentage
Pleuritic chest pain	90	75%
Dyspnea	74	61.6%
Fever	73	60.8%
Cough	70	58.3%
Weight loss	38	31.6%
Appetite loss	47	39.1%

Table-4: Total ada range and mean

ADA range(U/L)	4 – 249
ADA mean(U/L)	92.15

Table-5: ADA

	ADA < 40 U/L	ADA > 40 U/L
No of cases	19	101

Table-6: L/N RATIO

	L/N ratio > 0.75	L/N ratio< 0.75
No of cases	99	21

Table-7: Genderwise distribution of etiology of pleural effusion.

Etiology	Male	Female	Total
Tuberculous effusion	71	26	97
Parapneumonic effusion	2	2	4
Malignant effusion	8	6	14
Rheumatoid pleurisy	0	1	1
Empyema	1	1	2
Pancreatic pleural effusion	1	0	1
Liver abscess	1	0	1
TOTAL	84	36	120

Table-8: Past h/o and contact with tb

Past H/O TB	7(7.2%)
H/O contact with TB	14(14.5%)

Table-9: Mantoux and sputum afb in tubercular pleural effusion

	Tested	Positive
Mantoux	97	50(51.5%)
Sputum AFB	30	3(10%)

Table-10: Ada in exudative effusion

ADA(U/L)	Tuberculous effusion	Nontuberculous effusion
Range	40.7 – 249	4 – 145
Mean	155.2	27.2

Table-11: l/n ratio in exudative effusion

L/N Ratio	Tuberculous effusion	Nontuberculous effusion
>0.75	97	2
<0.75	0	21

Table-12: Ada and l/n ratio

Etiology	ADA >40U/L	L/N ratio >0.75
Tuberculous	97	97
Non tuberculous	4	2

DISCUSSION

Tuberculosis is a common infection in India and the commonest cause of exudative pleural effusion. Definitive diagnosis of TB pleural effusion is difficult. Pleural fluid Acid Fast Bacilli (AFB) demonstration is virtually always negative, culture of fluid could be positive in <25%, histology (HPE) of pleural biopsy could be positive in 80% whereas HPE and culture of pleural biopsy increases diagnostic efficacy to 90%. Because of the non-availability of confirmatory tests (Pleural biopsy and HPE) in all centres, the confirmation of diagnosis is difficult. In India, an exudative pleural effusion is considered Tuberculous and started on Antituberculous Treatment (ATT).

ADA is considered a valuable tool in the diagnosis of Extra-pulmonary Tuberculosis. The measurement of the pleural fluid ADA level could be used to rule out a tuberculous etiology of lymphocytic pleural effusions.

All the 97 tb effusion cases had Lymphocyte predominant pleural effusion with a L/N ratio >0.75. Total ADA was done in all cases and found to be >40 U/L in all the cases. The range of ADA was between 40.7 – 249 U/L with a mean of 155.2 U/L. Four of non-tubercular cases also had ADA value more than 40 U/L, but the l/n ratio was <0.75.

Combining both ADA and lymphocyte neutrophil ratio the sensitivity and specificity has increased to 100% and 95% respectively. These results are in agreement with those of P.C. Mathur *et al.*[2]. Our study also correlates with study done by Rahman *et al*. [3] where 84 cases were tubercular and had high level of ADA in comparision to rest of 16 non-tubercular cases.

1 case of exudative pleural effusion due to Rheumatoid Arthritis was seen. Pleuritic chest pain and cough are noted. The level of pleural fluid glucose in our study was noted in rheumatoid pleurisy, the value being 13 mg/dl. In this 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*. [4].

The ADA was 69 U/L. The effusion was Lymphocyte predominant but did not achieve L/N ratio >0.75.

4 cases of Pneumonia with pleural effusion were analysed. The presentation was like acute illness and presenting complaints were fever (80%), coughs with sputum production (100%), pleuritic chest pain (60%) and dyspnea (60%).

The mean WBC count was 12,400 and peripheral blood neutrophilia was noted in line with the observation of Light RW *et al*. [1]. Pneumococci were grown in sputum of 3 cases and klebsiella along with E coli in 1 case. This observation is consistent with the study of Varkey B *et al*. [5] and Bartlett JG *et al.* [6] who stated that Pneumococci and S aureus account for approximately 70% of all aerobic gram-positive isolates and E coli along with Klebsiella sp account for approximately 75% of all aerobic gram-negative empyemas.

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

Empyema was noted in 2 cases. The most common presenting symptom was fever (100%), The mean WBC count was 25,600 with predominant neutrophils. Gross appearance of pleural fluid was purulent in both the cases. Mean pleural fluid glucose concentration was 50 mg/dl. In our study ADA value was more than 40 IU/L and L/N ratio <0.75.in both the cases.

1 patient, an alcoholic presented with pain right hypochondrium and jaundice and pleuritic chest pain. Evaluation revealed tender hepatomegaly and pleural effusion on right side. USG abdomen revealed multiple liver abscess and pleural fluid was high coloured. Effusion was exudative with ADA value of 6.7U/L and L/N ratio <0.75.

Malignant effusion was noted in 14 cases. ADA in pleural fluid was less than 40 IU/L in all 14 cases. Mean ADA was 20.3 U/L. The effusion was lymphocyte predominant with Mesothelial cells >10% and L/N ratio < 0.75 in all the cases except two.

CONCLUSION

In developing countries like India where investigations and health facilities are inadequate and cost of treatment is often high, pleural fluid analysis with high ADA with lymphocyte predominance justifies treatment initiation as both investigations combined together increases the specificity

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