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A study of pleural fluid adenosine deaminase levels in tubercular and other exudative pleural effusions

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ABSTRACT

Tuberculosis is among the commonest causes of pleural effusion in India. Adenosine Deaminase (ADA) level in pleural fluid is chemical biomarker that can be employed as a rapid screening tool for tuberculosis. A prospective study was designed to evaluate the importance of pleural fluid ADA level in the diagnosis of tubercular pleural effusion and differentiating it from other causes of exudative pleural effusion. A total of 232 cases of pleural effusion were evaluated, of which 169 (72.85%) were found to be exudative pleural effusion. There were 76 (45%) cases of TB, 32 (19%) of malignancy and 50 (29.6%) of parapneumonic effusion whereas 11 (6.5%) cases belong to other causes or remained undiagnosed. Median ± SD value of ADA for tubercular pleural effusion, malignant pleural effusion and parapneumonic effusion were 62.37 ± 22.63, 24.12 ± 10.88, and 34.55 ± 20.45 U/l respectively. Our study showed that 68 of 76 cases (89.5%) of patients with tubercular pleural effusion had ADA ≥ 40 U/l while only 3 (9.3%) out of 32 cases of malignant pleural effusion had ADA ≥ 40 U/l. Pleural fluid ADA ≥ 40 U/L yielded 89.47% sensitivity, 72.04% specificity, positive predictive value was 72.34% and a negative predictive value was 89.33% for diagnosis of TB. Pleural fluid ADA can be utilized for differentiating TB effusions from those of non-tubercular etiology. Moreover it can obviate the need for pleural biopsy.

INTRODUCTION

Pleural effusion is a common clinical problem. Tuberculosis, pneumonia, malignancies and CHF are the common causes among others. As many as 20% cases remain undiagnosed in spite of all the available investigations including pleural biopsy [1]. Tuberculosis is among the commonest causes of pleural effusion in India [2]. Untreated tubercular pleural effusion can develop into active tuberculosis [3] and as in more than 50% of patients, pleura is the only site of infection, it is important to make early and accurate diagnosis by appropriate tests and early initiation of treatment. Adenosine deaminase (ADA) level in pleural fluid is such chemical biomarker that can be employed as a rapid screening tool for tuberculosis [2-4].

Keeping this in mind, a prospective study was designed to evaluate the importance of pleural fluid ADA level in the diagnosis of tubercular pleural effusion and differentiating it from other causes of exudative pleural effusion.

MATERIALS AND METHODS

The study was conducted in The Department of Pulmonary Medicine over a period of one year. The patients of exudative pleural effusion were included in the study. All the transudative and post-traumatic pleural effusion were excluded from the study. Patients with history of acute viral fever, enteric fever, acute viral hepatitis, active cirrhosis and chronic renal patients were also excluded. Pleural tap was done in all the cases and fluid tested for glucose, proteins, LDH, total ADA, microscopy, cytology and microbial testing (Gram staining, Z-N Staining, cultures). The patients of pleural effusion fulfilling Light's criteria [5] (pleural fluid protein/ serum protein >0.5; fluid LDH/serum LDH > 0.6) for exudative effusion were included in the study. ADA was measured in pleural fluid by colorimetric method. Pleural biopsy was done in selected cases of tuberculosis and malignancy by Abraham's punch biopsy needle.

Presence of one or more of the following criteria [5] was used to label a case as tuberculous: (1) Smear or culture positive for M. tuberculosis; (2) Caseating granulomas on histopathology; (3) radiological findings consistent with TB; and (4) clinical and radiological improvement in 2 months of empiric anti-tubercular treatment.

RESULTS

A total of 232 cases of pleural effusion were evaluated, of which 169 (72.85%) were found to be exudative pleural effusion. Overall male: Female ratio was 2.2:1. Among exudative effusions, there were 76 (45%) cases of TB, 32 (19%) of malignancy and 50 (29.6%) of parapneumonic effusion whereas 11 (6.5%) cases remained undiagnosed. Tuberculosis was diagnosed in 63 (83%) cases by history, sputum results and pleural fluid investigations; rest 13 (17%) patients were diagnosed by pleural biopsy. Patients with TB effusion had median age 32.6 +/- 17.3 years while those with patients with malignant pleural effusion had median age 58.8 +/- 16.1 years.

Median ± SD value of ADA for tubercular pleural effusion, malignant pleural effusion and parapneumonic effusion were 62.37 ± 22.63, 24.12 ± 10.88, and 34.55 ± 20.45 U/l respectively. Our study showed that 68 of 76 cases (89.5%) of patients with tubercular pleural effusion had ADA ≥ 40 U/l while only 3 (9.3%) out of 32 cases of malignant pleural effusion had ADA ≥ 40 U/l. (Figure 1) Pleural fluid ADA ≥ 40 U/L yielded a sensitivity of 89.47% and specificity of 72.04% while positive predictive value was 72.34% and a negative predictive value was 89.33% for diagnosis of TB. Serum ADA levels of more than 100 IU/l were seen in tuberculosis only. (Table no.1) (Figure no.1)

DISCUSSION

Pleural effusion is a common clinical problem. A wide variety of diseases can cause pleural effusion, tuberculosis, malignancy, pneumonia and CHF being the commonest ones. As many as 15-20% cases of effusion remain undiagnosed despite the use of available investigations. Tuberculosis is among the commonest causes of pleural effusion, especially in countries like India [5]. Up to 2/3rd untreated tubercular pleural effusion can develop active tuberculosis [6], thus early and accurate diagnosis and treatment is necessary. Diagnosis of a patient of pleural effusion principally depends on pleural fluid investigations. Definitive diagnosis of pleural tuberculosis is sometimes difficult, as in more than 50% of patients, pleura is the only site of infection [5]. Different Tuberculin tests are nonspecific and finding can be false negative in more than one third of the cases [7]. Ziehl-Neelson staining may be positive in only 15-25% cases because bacterial load is very less in effusion. For the same reasons the yield of pleural fluid culture for mycobacterium tuberculosis is also low (< 20) [8]. Closed pleural biopsy can give positive results in up to 80% cases. Thoracoscopy is almost always positive but it is not readily available in every centres. Thus we need a rapid diagnostic test for tubercular pleural effusion which can differentiate it from other causes of lymphocytic exudates especially malignant pleural effusion.

Adenosine deaminase (ADA) is an enzyme that catalyzes the conversion of adenosine to inosine. Pleural fluid ADA estimation is fast and relatively inexpensive. In present study, median ADA level in tuberculosis cases was 62.37+/- 22.63 U/L. Similar values were found in other studies also [10, 11] (Table no. 2). Previous studies showed that less than 3% of patients suffering from non-tuberculous lymphocytic pleural effusions have reported ADA levels over the diagnostic cut-off of 40 U/l [12]. The second commonest cause for elevated ADA in present study was parapneumonic effusion, which was similar to other studies (11-33%) (Figure no 1). However, parapneumonic effusion is usually neutrophilic while tubercular pleural effusion is lymphocytic hence diagnostic dilemma is not there [3].

We found that more than 89% of tubercular pleural effusion

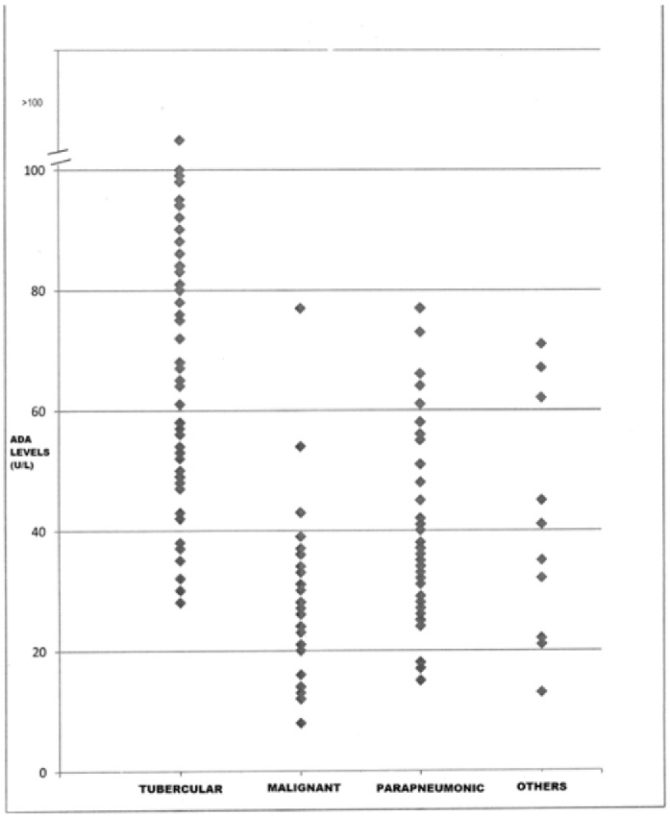
Table 1. Sensitivity, Specificity, Positive and Negative Predictive Values of pleural fluid ADA at different cut off values to diagnose tubercular pleural effusion

ADA Cut off value	Tubercular (total-76)	Non-tubercular (total- 93)	Sensitivity	Specificity	PPV	NPV
>= 40	68	26	89.47	72.04	72.34	89.33
>50	60	17	78.95	81.72	77.92	82.60
>60	48	12	63.16	87.1	80.0	74.31
>70	38	5	50.0	94.62	88.37	69.84

Table 2. Comparison of our study with other Indian studies.

	Authors	ADA cut off (U/L)	Sens.	Spec.	PPV	NPV	Mean /Range
1	Present study (2014)	40	89.47	72.04	72.34	89.33	62.37+-22.63
2	Mehta AA et al. (2013)	40	85.7	80.8	75	89.5	64.11+-32.33
3	Bharat et al. (2010)	40	92	90	92.86	90	67.34+-22.85
4	Sushmita et al. (2010)	40	97	93	94	97	114.1+-67.36
5	Sharma et al. (2010)	35	83.3	66.6	-	-	95.8+-57.5
	Verma SK et al. (2007)	36	100	77.7	-	-	36- 229.7

Fig. 2. Pleural fluid Adenosine Deaminase (ADA) levels in various etiologies.



cases had ADA > 40U/l; whereas less than 10% of those with malignancy had ADA > 40. In case of malignant pleural effusion our findings co- relate with most of the authors. Uppermost range of ADA level in malignancy was 76.3 IU/L. Patients with tubercular effusion had median age 32.6 +/- 17.3 years while those with patients with malignant pleural effusion had median age 58.8 +/- 16.1 years. Median ± SD value of ADA for tubercular pleural effusion and malignant pleural effusion were 62.37 ± 22.63 and 24.12 ± 10.88 respectively. This difference in median age of tubercular and cancer patients may be the reason for difference in medial ADA level in both the groups but we found no significant difference in median ADA level in young age group (<50 years) and elderly age group (=/> 50 years) among tubercular effusion patients (64.22+/- 17.78 vs 61.56+/- 20.44).The most widely accepted cut- off level of ADA for the diagnosis of tubercular pleural effusion is 40 U/l [13]. Sensitivity and specificity in our study was similar to other previously published Indian studies [14- 17] (Table no.2). If we increase cut off value for ADA to =/> 70 U/l, it increased specificity of the test to 94.62%, but sensitivity fell to 50% (Table No. 1). Serum ADA level more than 100 IU/L observed only in cases of tubercular pleural effusion and it can rule out other diagnoses of lymphocyte pleural effusion such as malignancy and collagen vascular diseases (i.e. rheumatoid arthritis and systemic erythematosus). In present study, 13 patients of tubercular pleural effusion were diagnosed with the help of pleural biopsy. In all these patients, ADA level was more that the usual cut-off level of 40u/l. In a few studies [12, 18], it was proposed to skip the pleural biopsy for the diagnosis of tuberculous pleurisy in a subset of patients with lymphocytic exudative pleural effusion with a high ADA level, those who are younger than 35 years of age and to prescribe anti-tuberculosis treatment. Thus a higher ADA level can obviate the need of pleural biopsy to diagnose tubercular pleural effusion in appropriate settings. The follow- up was done of all the patients diagnosed with tubercular pleural effusion until complete recovery with anti-tuberculosis treatment of 6-8 months duration.

CONCLUSION

We conclude, from present study and other related studies that estimation of ADA level in pleural fluid is extremely helpful in establishing the etiology of tubercular pleural effusion and to rule out other diagnosis especially malignancy. Pleural fluid ADA should be utilized for differentiating TB effusions from those of non-tubercular etiology. Moreover it can obviate the need for pleural biopsy for the diagnosis of tuberculous pleuritis in patients younger than 35 years of age.

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