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Pleural adenosine deaminase estimation: A Potential marker to distinguish between tubercular and non-tubercular effusion

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Abstract: *Background:* Tuberculosis is a common cause of pleural effusion in countries like India where it is highly endemic. The biochemical markers are more sensitive and reliable in the diagnosis of pleural tuberculosis. *Objectives:* The present study was aimed to evaluate the diagnostic potential of pleural adenosine deaminase levels in tubercular pleural effusion. *Materials and Methods:* The study is a clinical, prospective and observational of 50 patients of pleural effusion consecutively admitted in the medical wards. Detailed history, thorough physical examination, radiological findings, haematological and biochemical findings were recorded in the proforma. Pleural aspiration was performed on all patients. Macroscopic findings, cytological, microbiological and biochemical analysis of pleural fluid were performed in all patients including pleural adenosine deaminase level. *Results:* Mean age group of tubercular effusion was 26-55 years and common in men. Out of 31 tubercular effusion patients, 29 (93.33%) were showed pleural adenosine deaminase level more than 40IU/L. pleural adenosine deaminase estimation showed 93.3% sensitivity and 90% specificity, 93.3% positive predictive value and 90% negative predictive value. Mean pleural adenosine deaminase level (IU/L) in tubercular, synpneumonic and transudative effusions were 70.36±26.48, 17.46±4.31 and 11.58±2.35 respectively. *Conclusions:* Pleural adenosine deaminase estimation seems to have the potential for being one of safe, simple, reliable and noninvasive marker which is adequately sensitive and specific in distinguishing tubercular and non tubercular effusion.

Keywords: Pleural Adenosine Deaminase, Pleural Effusions, Tuberculosis.

Introduction

Pleural effusion refers to the excessive accumulation of fluid in the pleural space. Pleural effusion is a commonly encountered medical problem in India [1]. The first step in the evaluation of a pleural effusion is a detailed history and physical examination; the importance of the history and physical examination arises from the fact that a significant percentage of pleural effusions have no definitive diagnostic features on pleural fluid analysis or pleural biopsy [2].

Diagnosis of the cause of many pleural effusions is based on the clinical setting and exclusion of other alternative causes. The next step is sampling of the pleural fluid and categorization as a transudate or exudate. Transudative pleural effusions result from systemic diseases that do not directly involve the pleura but instead produce an imbalance of Starling's forces, resulting in movement of fluid into the pleural space. The diagnostic focus for transudates call for recognition of the systemic disease. Such systemic diseases include congestive heart failure, cirrhosis with ascites, and the nephritic syndrome. Exudative pleural effusions result from local or systemic diseases that directly injure the pleural surface. The diagnostic focus for exudative effusions is to recognize the responsible intrapleural disease. TB is the most common cause of pleural effusion worldwide (30-60%) [3]. It is important to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion [4].

The stepwise diagnosis of TB pleural effusion is subsequently the same as for any other exudative pleural effusion. An initial diagnostic thoracocentesis is always indicated. Definitive diagnosis of Tubercular pleural effusion can be difficult to make because of low sensitivity and specificity of noninvasive

diagnostic tools. Results of pleural fluid staining for Acid Fast Bacilli (AFB) are virtually always negative and pleural fluid cultures for mycobacterium are positive in < 25% of cases [5]. The diagnosis of pleural tuberculosis has been greatly improved by the use of biochemical markers, which are faster and can be more sensitive [6]. Therefore, we selected pleural fluid adenosine deaminase (ADA) as one of the biochemical marker to study the basis for a treatment decision, particularly in the diagnosis of tuberculosis, due to its high sensitivity.

Material and Methods

Source of Data: The present study was conducted in the Department of Medicine, Al-Ameen Medical College, Vijayapur and Shri B. M. Patil Medical College, Hospital & Research Centre, BLDE University, Vijayapur. The patients with pleural effusions admitted in the medical wards were included. Consecutive 50 cases of pleural effusion were studied of which cases were tuberculosis effusions and cases of non-tubercular effusions. All patients in this study were belonged to lower socio economic status.

Inclusion Criteria: Patients with pleural effusion diagnosed clinically and radiologically were included.

Exclusion Criteria: Patients were excluded from the study, with emphysema and co-existent lung malignancy.

Study Design: After a detailed history, clinical examination and investigations, the 50 cases of pleural effusion were divided into following 4 groups:

- *Group I (Tuberculous effusion):* The diagnosis of tubercular pleural effusion was based on factors like clinical features, X-ray evidence of parenchymal infiltrates, sputum AFB positivity, pleural fluid AFB positivity, pleural fluid features, pleural biopsy for evidence of granuloma and montoux test. There were 31 cases suggestive of tuberculous pleural effusion.
- *Group II (Synpneumonic effusion):* The diagnosis of synpnemonic effusion was based on clinical features like fever, cough with expectorant, signs of consolidation, chest X-ray, sputum Gramstain and culture sensitivity and response to antimicrobial therapy. There were 9 cases of synpneumonic pleural effusions.
- *Group III (Transudative effusion):* The diagnosis of transudative pleural effusion was based on the presence of systemic disease predisposing for transudative effusion and pleural fluid characteristics. There were 11 cases of transudative effusion.
- *Group IV (Malignant effusion):* The diagnosis of malignant pleural effusion was based on presence of malignant cells in pleural fluid, and/or positive histopathological evidence of mesothelioma. There were no cases of malignant effusion.

Pleural fluid Adenosine deaminase (ADA) estimation: Pleural fluid ADA level was measured in all above study groups of pleural effusion patients by Giusti and Galanti method. The ADA was measured by following formula:

$$\text{Total ADA activity in U/L} = \frac{\text{Abs.T - Abs.SB}}{\text{Abs.S - Abs.B}} \times 50$$

Statistical Analysis: Continuous variables are presented as mean ±SD and frequency variables as percentages. Chi - square test was performed for statistical significance. P value of <0.05 was considered for statistical significance.

Results

Figure 1 showed the commonest type of pleural effusion is tuberculosis (62%) > transudative (20%) > synpneumonic (18%).

Table 1 showed that 86% (43) were male and 14% (7) were female pleural effusion cases. In which 52% (26) male and 10% (5) female of tubercular pleural effusion cases, 16% (8) male and 2% (1) female cases of synpneumonic pleural effusion and 18% (9) male and 2% (1) female cases of transudative pleural effusion were present. Table 1 also showed that pleural effusion were more common in male than female and tubercular pleural effusion was more common in male than female. Pleural effusion was more common in age group of 26-55 years.

Fig-1: Distribution of type of pleural effusion (n=50)

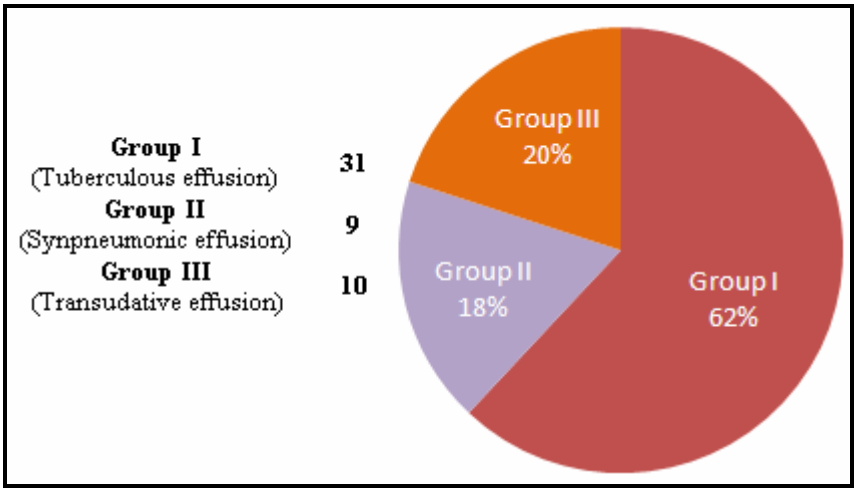


Table-1: Age and sex wise distribution of patients of plural effusion (n=50)

Age (years)	Number of cases						Total (n=50)	Percentage (%)
	Group I (Tuberculous effusion		Group II (Synpneumonic effusion)		Group III (Transudative effusion)			
	Male	Female	Male	Female	Male	Female		
20-30	15	2	4	1	4	1	27	54
31-40	5	3	3	-	4	-	15	30
41-50	3	-	1	-	1	-	5	10
51-60	1	-	-	-	-	-	1	2
61-70	2	-	-	-	-	-	2	4
Total	26	5	8	1	9	1	50	100

Table-2: Distribution of the presenting symptoms in patients (n=50)

Symptoms	No. of cases	Percentage (%)
Fever	49	98
Breathlessness	48	90
Chest pain	40	80
Cough	30	60
Weight loss	30	60
Loss of appetite	25	50
Haemoptysis	5	10
Distension of abdomen	5	10
Swelling of feet	5	10
Puffiness of face	4	8

Table 2 depicted the most common presenting symptom were fever, breathlessness, chest pain and cough followed by the weight loss, loss of appetite. In patients having transudative effusion of different causes abdominal distension, swelling of feet, puffiness face were noted.

The mean pleural fluid glucose level (mg/dL) in tubercular, synpneumonic and transudative were 52.11±10.89, 40.05±8.23 and 100.55±22.67 respectively. Glucose levels were found to be low in the synpneumonic pleural effusions (Table 3).

The mean pleural fluid protein level (gm/dL) in tubercular, synpneumonic and transudative were 4.17±0.56, 3.78±0.45 and 2.47±0.04 respectively. Protein was found to be

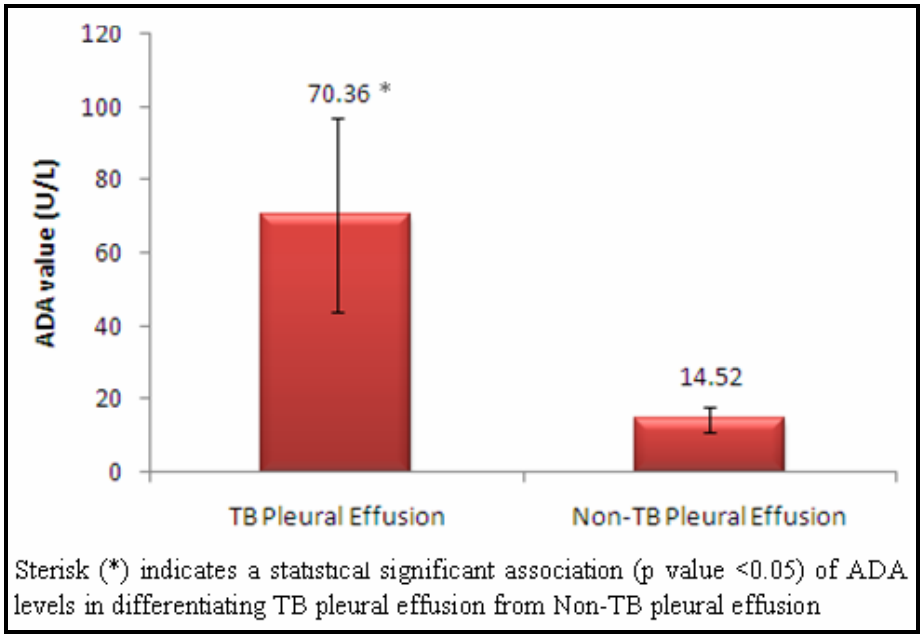
significantly high in TB Pleural Effusion (Table 3). The Mean ADA (IU/L) level in pleural fluid in tubercular, synpneumonic and transudative effusions were 70.36±26.48, 17.46±4.31 and 11.58±2.35 respectively (Table 3).

Mean ADA in TB Pleural Effusion was 70.36U/L and in Non-TB Pleural Effusion was 14.52U/L in present study (Figure 2).

Table-3: Showing estimated mean ± SD values of pleural fluid glucose, protein and adenosine deaminase (ADA) level in patients (n=50)

Type of pleural effusion	Pleural fluid glucose (mg/dL)	Pleural fluid protein (gm/dL)	Pleural adenosine deaminase-ADA (IU/L)
Group I (Tuberculous effusion)	52.11±10.89	4.17±0.56	70.36±26.48
Group II (Synpneumonic effusion)	40.05±8.23	3.78±0.45	17.46±4.31
Group III (Transudative effusion)	100.55±22.67	2.47±0.04	11.58±2.35

Fig-2: Comparison between tubercular (TB) and non-tubercular (Non-TB) pleural effusion with respect to ADA level



Discussion

The most frequent cause of pleural effusion in India is tuberculosis [1]. But at times pleural effusion can be a presentation of various other diseases. Even after extensive investigations some pleural effusions remain undiagnosed. Routine investigations of pleural fluid can sometimes helps in etiological diagnosis. The commonest exudative effusion in this study was tuberculosis (62%) followed by transudative effusion (20%) and synpneumonic effusion (18%). There were no cases of malignant effusion. In India tubercular effusion is the commonest cause of all exudative effusions. This was similar to the observation in another study from India by Maldhure et al [7] where they showed that the tubercular effusions constitute 66% of the effusions, malignancy 15%, and parapneumonic effusion 4.8%. This observation is different from that of the West countries where the incidence of

parapneumonic effusion and malignant effusion are much higher compared to that of tubercular effusion. This is consistent with the fact that India has a high prevalence of tuberculosis in the general population.

In this prospective study of 50 patients, the incidence of pleural effusion was seen in male (86%) as compared to female (14%), the ratio was 7.3:1. In comparison, the sex distributions in some of the previous studies are: Burgess LJ [8] - 58% males and 42 % females, Luis Valdes et al [9]- 56.6% males and 43.3% females. The mean age group in cases of tuberculous pleural effusion was 35.41±12.58 years, consistent with Luis Valdes et al [9] (34 years) and S.K.Sharma et al [10] (33 years). In one recent series from Qatar, Ibrahim WH et al [11] reported the mean age of 100 patients with tuberculous pleuritis was 31.5 years. Denise Duprat Neves et al [12], the mean age in patients with TB (mean = 33.76; SD = 13.96 years old) was significant lower ($p < 0.0001$) than in NTB group (mean = 49.29; SD = 18.01 years old).

The commonest presenting complaints of pleural effusion were fever (98%), breathlessness (90%), chest pain (80%) followed by cough (60%), loss of weight (60%), loss of appetite (50%), haemoptysis (50%). These findings are compatible with the studies done earlier by Moudgil et al [13]. The symptoms most commonly reported in published series by Morehead RS et al [14] are: cough (71-94%), fever (71-100%), chest pain (78-82%) and dyspnea.

Pleural fluid glucose was seen predominantly in patients with transudative effusion. The majority of pleural fluid glucose levels were between 40-100 mg/dL in tubercular effusions, consistent with the earlier observation by Light [15]. Only 3% of tuberculous effusions had sugars less than 40 mg%. The mean pleural fluid protein level in cases of exudative 4.17±0.56gm/dL and in cases of transudative effusion 2.47±0.04gm/dL.

According to the literature pleural fluid adenosine deaminase (ADA) has got a good discriminative value in differentiating tuberculous effusions from malignant effusion. Although a pleural fluid ADA above 70 IU/L is diagnostic of tuberculosis [16]. It has to be considered if the pleural fluid ADA is between 40 IU/L and 70 IU/L. An ADA level less than 40IU/L rules out pleural tuberculosis. In our study out of 31 patients with tuberculosis pleural fluid ADA was done in them and 29 (93.54%) of them had a level more than 40IU/L but 2 (6.45 %) showed a level of less than 40IU/L. Studies done in the West countries demonstrate pleural fluid ADA more than 70 IU/L (Valdes and Burgess et al) our study showed a mean of 70.36 IU/L [8-9]. The mean ADA were high in the 2 Indian studies done by Rajendra Prasad et al [17] and Gilhotra et al [18] with the mean ADA level ranging between 76.8 IU (+23.8) to 95.8 (+57.5).

We determined the sensitivity and specificity of ADA in patients of tuberculosis. Using a cut off of greater 40 IU/L we got a sensitivity and specificity of 98% and 100% respectively and Positive predictive value 93.3% and Negative predictive value 90% in differentiating tuberculous (TB) and non-tuberculous (Non-TB) pleural effusions. This is more consistent with the observation made by Valdes et al [9]. Spain 47 IU/L cut off value sensitivity 100%, specificity 95%, positive predictive value 85%, negative predictive value 100% with mean ADA 107.5. In this study there was a statistical significant association (p value <0.05) of ADA levels in differentiating TB pleural effusion from Non-TB pleural effusion (Figure 2).

Conclusion

Tuberculosis was the commonest cause of pleural effusion. In this study there was a statistical significant association (p value <0.05) of ADA levels in differentiating TB pleural effusion from Non-TB pleural effusion. Thus pleural adenosine deaminase estimation seems to have the potential for being one of safe, simple, reliable and noninvasive marker which is adequately sensitive and specific in distinguishing tubercular and non tubercular effusion.

References

1. San Jose ME, Alvarez D, Valdes L, Sarandeses A, Valle JM, Penela P. Utility of tumour markers in the diagnosis of neoplastic pleural effusion. *Clin Chim Acta.* 1997; 265:193-205.
2. Chinchkar NJ, Talwar D, Jain SK. A stepwise approach to the etiologic diagnosis of pleural effusion in respiratory intensive care unit and short-term evaluation of treatment. *Lung India.* 2015; 32:107-115.
3. Baumann MH, Nolan R, Petrini M, Lee YCG, Light RW, Schneider E. Pleural tuberculosis in the United States: incidence and drug resistance. *Chest.* 2007; 131:1125-1132.
4. Light RW, Lazarus AA, McKay S, Gilbert R. Update on tuberculous pleural effusion. *Respirol.* 2010; 15:451-458.
5. Light RW. Pleural diseases. 3rd edition. *William and Wilkins, Baltimore*, 1995; 154-155.
6. Oliveira HG, Rossatto ER, Prolla JC. Pleural fluid adenosine deaminase and lymphocyte proportion: clinical usefulness in the diagnosis of tuberculosis. *Cytopathol.* 1994; 5:27-32.
7. Maldhure BR, Bedarkar SP, Kulkarni HR, Papinwar SP. Pleural biopsy and adenosine deaminase in pleural fluid for the diagnosis of tubercular pleural effusion. *Indian J Tuberculosis.* 1994; 41:161-165.
8. Burgess LJ, Maritz FJ, Le Roux I, Taljaard JJ. Use of Adenosine Deaminase as a diagnostic tool for tuberculous pleurisy. *Thorax.* 1995; 50:672-674.
9. Valdes L, Alvarez D, Jose ES, Juanatey JRG, Pose A, Valle JM, et al. Value of ADA in the diagnosis of TB pleural effusions in young patients in a region of high prevalence of tuberculosis. *Thorax.* 1995; 50:600-603.
10. Sharma SK, Suresh V, Mohan A, Kaur P, Saha P, Kumar A, et al. A prospective study of sensitivity and specificity of adenosine deaminase in a diagnosis of tubercular pleural effusion. *Indian J Chest Dis Allied Sci.* 2001; 43:149-155.
11. Ibrahim WH, Ghadban W, Khinji A, Yasina R, Soubb H, Al-Khalb AL , et al. Does pleural tuberculosis disease pattern differ among developed and developing countries. *Respir Med.* 2005; 99:1038-1045.
12. Neves DD, Dias RM, Ledo AJ. Dacunha. Predictive model for the diagnosis of tuberculous pleural effusion. *Braz J Infect Dis.* 2007; 11:83-88.
13. Moudgil H, Sridhar G, Leitch AG. Reactivation disease: the commonest form of tuberculous pleural effusion in Edinburgh, 1980-1991. *Respir Med.* 1994; 88:301-304.
14. Morehead RS. Tuberculosis of the pleura. *Southern Med J.* 1998; 91:630-634.
15. Light RW. Clinical manifestations and useful tests. Pleural diseases. 4th edition, *Lippincott Williams and Wilkins*; 2001.
16. Light RW, Erozan YS, Ball WC. Cells in Pleural fluid: their value in differential diagnosis. *Arch Intern Med.* 1973; 132:854-860.
17. Prasad R, Tripathi R, Mukerji K. Adenosine deaminase activity in pleural fluid. *Indian J Chest Dis Allied Sci.* 1992; 34:123-126.
18. Gilhotra R, Seghal S, Gindal SK. Pleural biopsy and adenosine deaminaseenzyme activity in effusions of different etiologies. *Lung India.* 1989; 3:122-124.

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