Study Of Diagnostic Efficacy Of Adenosine Deaminase (ADA) Levels In Tubercular Pleural Effusion

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Abstracts: Background**:** Pleural effusion due to tuberculosis is common in countries like India where it is highly endemic, however the organism is seldom detectable from plural fluid. The diagnosis of pleural tuberculosis has been greatly improved by the use of biochemical markers. Activity of adenosine deaminase (ADA) in the pleural fluid is one of the best providing reliable basis for a treatment decision, particularly in excluding the diagnosis of tuberculosis, due to its high Sensitivity. The present study was aimed to evaluate the diagnostic use of Adenosine Deaminase (ADA) levels in pleural effusion due to TB. Methodology: The study is a clinical, prospective and observational study of 50 Patients of Pleural Effusion consecutively admitted in Department of Medicine, Ashwini rural Medical College and hospital, Kumbhari from Jan 2013 to Dec 2013. Macroscopic findings, cytological study, microbiological and biochemical analysis of pleural fluid were performed, including ADA levels. Results: Mean age group was 37 years and common in men. In our study, out of 32 patients with tuberculosis pleural fluid ADA was done in them and 29 (90.63%) of them had a level more than 40IU/L. Using a cut off of greater 40IU/L we got a sensitivity and specificity of 93% and 90% respectively and Positive predictive value 93% and Negative predictive value 90%. Conclusion: All patients with TB Pleural effusion had elevated ADA levels and there was a statistical significant association (p value <0.05) of ADA levels in differentiating TB pleural effusion from Non-TB pleural effusion. [Golwalkar J.K NJIRM 2016; 7(3):12 - 16]

Key Words: TB Pleural Effusion, Adenosine Deaminase, Mycobacterium tuberculosis.

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Introduction: A Pleural fluid accumulates when pleural fluid formation exceeds pleural fluid absorption. Normally, fluid enters the pleural space from the capillaries in the parietal pleura and is removed via the lymphatics situated in the parietal pleura. [1,2] Fluid can also enter the pleural space from the interstitial spaces of the lung via the visceral pleura or from the peritoneal cavity via small holes in the diaphragm. The lymphatics have the capacity to absorb twenty times more fluid than is normally formed. 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. [3]

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. 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%). In the United States, tuberculous pleural effusion (TPE) accounts for 2 to 5% of all pleural effusions, approximately 1000 cases per year, and is the one of the most common extrapulmonary manifestation of tuberculosis.[4]

It is important to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion. [5]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 less than 25% of cases.[6] The diagnosis of pleural tuberculosis has been greatly improved by the use of biochemical markers, which are faster and can be more sensitive. The pleural fluid activity of adenosine deaminase (ADA) is one of the best, providing reliable basis for a treatment decision, particularly in excluding the diagnosis of tuberculosis, due to its high sensitivity.[7]

Material and Methods: This study was performed at the Department of Medicine, Ashwini Rural Medical College Hospital and Research Centre (ARMCH&RC), Solapur, from Jan 2013 to Dec 2013. Which comprised of fifty patients of pleural effusion those age more than 14 years and had Clinical and radiological evidence of pleural effusion. Present study excluded that patient with age more than 65 years, those who have not given consent and pleural effusion due to trauma. Study also collected the detailed history, thorough physical examination, radiological findings, haematological, biochemical and plural aspiration findings. Macroscopic findings, cytological, microbiological and biochemical analysis of pleural fluid were performed in all patients. To differentiate transudate from exudate, the ratio of pleural fluid and serum protein; the ratio of pleural fluid and serum LDH were calculated. Pleural fluid Adenosine deaminase level was measured by Giusti and Galanti method.

After a detailed history, clinical examination and investigations, the 50 cases of pleural effusion were divided into 4 groups in which Group 1 had 30 cases of Tubercular pleural effusion, Group 2 had 7 cases of Transudative pleural effusion, 8 cases of malignant pleural effusion in Group 3 and 5 cases of Synpneumonic pleural effusion in Group 4.

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: A In this study, 62% were male and 38% were female in which 55%of tubercular pleural effusion, 15%cases of transudative pleural effusion, 18%cases of malignant pleural effusion and 12%cases of Synpneumonic pleural effusion were present. Pleural effusion was more common in male than female and tubercular pleural effusion was also more common in male than female. Pleural effusion was more common in age group of 26-55 years. (Table 1)

Table 1: Age & Sex wise distribution of patients of plural effusion

Age (Years)	No. Of Cases		Total	Percentage
	Male	Female		
15-25	06	0 5	11	22
26-35	10	0 6	16	32
36-45	05	0 3	09	18
46-55	06	0 3	09	18
56-65	02	03	05	10
Total	31	1 9	50	100

The most common presenting complaints were chest pain (80%) and cough (76.7%) followed by fever (73.3%), breathlessness (66.7%), weight loss (63.3%) and loss of appetite (66.7%). (Table 2)

Table 2: Distribution of presenting symptoms in TB Pleural effusion

Symptoms	No. Of Cases (%)
Fever	22 (73.3)
Cough	23 (76.7)
Chest pain	24 (80)
Breathlessness	20 (66.7)
Loss of appetite	20 (66.7)
Loss of weight	19 (63.3)

The average Hb in Tubercular effusion, Malignant, Transudative and Synpneumonic pleural effusion was 9.88, 8.03, 8.11 & 11.31 % respectively. Total Leukocyte count: The average total counts in Tubercular, Malignant, Transudative and Synpneumonic was pleural effusion 7651, 8120, 6433& 12289 cells/mm^3 respectively. The average ESR value in Tubercular, Malignant, Transudative, Synpneumonic pleural effusion 71, 48, 16.4 & 40.22 mm/hr respectively. ESR was significantly elevated in exudates. (Table 3)

Table 3: Haematology investigation finding

Type of effusion	Hb (gm %)	Total leukocyte	ESR
	Mean±SD	Count Mean ± SD	Mean±SD
Tubercular	9.88 ± 0.72	7651 ± 907	71 ± 12.55
Malignant	8.03 ± 0.88	8120 ± 1302	48 ± 12.43
Transudative	8.11 ± 1.0	6433 ± 1489	16.4 ± 5.09
Synpneumonic	11.31 ± 0.86	12289 ± 1455	40.22 ± 11.2

The mean pleural Fluid cell count and SD in Tubercular, Malignant, Transudative and Synpneumonic are 1102 ± 392, 598 ± 167, 128 ± 27 and 1319 ± 541 respectably. (Table 4)

Table 4: Cell count & Cell type in Pleural effusion

Type of effusion	Cell count	Cell type predominant	Malignant cells
Tubercular	1102 ± 392	Lymphocytes	-
Malignant	598 ± 167	Lymphocytes	Positive in 8 cases
Transudative	128 ± 27	Monocytes & Lymphocytes	-
Synpneumonic	1319 ± 541	Polymorphocytes	-

The mean pleural Fluid sugar level in Tubercular, Malignant, Transudative and Synpneumonic are 52.74± 10.26, 63.55± 8.08, 105.11± 22.32 and 38.78± 9.05. Sugars were found to be low in the Synpneumonic pleural effusions. (Table 5)

Table 5: Glucose, Protein & ADA level in Pleural effusion

Type of effusion	Pleural fluid Sugar (mg) Mean±SD	Protein (gm) Mean±SD	ADA (IU/L) Mean± SD
Tubercular	52.74±10.26	4.39±0.68	123.51±56.21
Malignant	63.55±8.08	3.44±0.39	30.32±5.33
Transudative	105.11±22.32	2.23±0.58	27.67±5.15
Synpneumonic	38.78±9.05	3.93±0.29	28.22±9.11

The mean pleural Fluid protein level in Tubercular, Malignant, Transudative and Synpneumonic are 4.39± 0.68, 3.44± 0.39, 2.23± 0.58 and 3.93± 0.29 respectably. Protein was found to be significantly high in TB Pleural Effusion. The Mean ADA (IU/L) level in pleural Fluid in Tubercular, Malignant, Transudative and Synpneumonic 123.51± 56.21, 30.32±5.33, 27.67±5.15, and 28.22± 9.11 respectively.

Discussion: Exudative Lymphocytic pleural effusions are commonly encountered in clinical practice but they often constitute difficult diagnostic problems. Adenosine Deaminase is an enzyme in the purine salvage pathway required for converting Adenosine to Inosine. Its levels are ten times higher in lymphocytes than in erythrocytes and particularly in T-lymphocytes.

TB Pleural effusion is the manifestation of delayed hypersensitivity to *Mycobacterium tuberculosis* antigen and is characterised by the presence of activated T Lymphocytes and macrophages in the pleural space. Elevated levels of ADA in TB Pleural effusion have been noted by several authors. These observations were reproduced and further confirmed in our study. In this prospective study of 50 patients with pleural effusion, the mean age was 37 years and two thirds were men which is consist with other previous studies[8-10].

In current study patients with TB were younger (31 years) than the patients with malignancy which is consistent with Luis Valdes et al (34 years)[9], S.K.Sharma et al (33 years) [11] and Ibrahim WH et al(31.5 years)[12].

The commonest exudative effusion in this study was tuberculosis followed by malignant effusion and synpneumonic effusion. This is similar to the observation in another study from India by Maldhure et al 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.

The most common symptom encountered by out TB patients in the present study 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.

In our study we demonstrated that massive effusion was most commonly seen in malignant effusion group, similar to that observed by Maher et al (55%) [15]. Large effusions were less commonly seen in the other observed etiologies.

Understandably the majority of Synpneumonic effusions had cell counts greater than 10,000 mm3 consistent with Light's observation et al[16]. Tuberculous effusions in our study had a total count greater than 10,000/mm3 similar to Light's[17] observation. Our result was similar to the study done by Valdes L et al[18] where they had encountered neutrophil predominant tuberculous effusion in only 6.7% of patients and only one malignant effusion had neutrophil predominant effusion (3%).

Low pleural fluid glucose was seen predominantly in patients with Synpneumonic effusion. The majority of pleural fluid glucose levels were between 40-100mg/dl in tubercular effusions, consistent with the earlier observation by Light.[17]

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[19]. 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 32 patients with tuberculosis pleural fluid ADA was done in them and 29 (90.63%) of them had a level more than 40IU/L. Studies done in the West countries demonstrate pleural fluid ADA more than 70 IU/L (Valdes et al and Burgess et al) [20,21], our study showed a mean of 123.51 IU/L. The mean ADA were high in the 2 Indian studies done by Rajendra Prasad et al [22] and Gilhotra et al[23] with the mean ADA level ranging between76.8 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 40IU/L we got a sensitivity and specificity of 93% and 90% respectively and Positive predictive value 93% and Negative predictive value 90%. This is more consistent with the observation made by Valdes et al [20]. In this study there was a statistical significant association of ADA levels in differentiating TB pleural effusion from Non-TB pleural effusion (p value <0.05).

Conclusion: All patients with TB Pleural effusion had elevated ADA levels in Pleural fluid. 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 fluid ADA estimation seems to have the potential for being one of reliable test for the diagnosis of TB pleural Effusion which is adequately sensitive and specific and at the same time inexpensive and easy to perform.

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