# **Research Article**

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# A clinical study of diagnostic efficacy of adenosine deaminase levels in tubercular pleural effusion

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## **ABSTRACT**

**Background:** Tuberculosis is a common cause of pleural effusion in countries like India where it is highly endemic. However, the organism mycobacterium tuberculosis is seldom detectable in pleural fluid. The diagnosis of pleural tuberculosis has been greatly improved by the use of biochemical markers. The pleural fluid activity of adenosine deaminase (ADA) is one of the best providing reliable bases 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 efficacy of ADA levels in tubercular pleural effusion.

**Methods:** The study is a clinical, prospective and observational study of 50 Patients of pleural effusion consecutively admitted in Government Medical College and Hospital, Kannouj from Dec 2008 to Dec 2009. Macroscopic findings, cytological, microbiological and biochemical analysis of pleural fluid were performed, including ADA levels in all patients.

**Results:** Mean age group was 31 years and common in men. In our study, out of 30 patients with tuberculosis pleural fluid ADA was done in them and 28 (93.33%) of them had a level more than 40IU/L. Using a cut off of greater 40IU/L we got a sensitivity and specificity of 93.3% and 90% respectively and positive predictive value 93.3% and Negative predictive value 90%.

**Conclusions:** 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.

Keywords: TB pleural effusion, ADA, Mycobacterium tuberculosis

### 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<sup>1</sup>. 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.<sup>2</sup> 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.

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.<sup>3</sup>

It is important to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion. 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.<sup>5</sup> 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.<sup>6</sup>

# **METHODS**

This study was performed at the Department of Medicine, Government Medical College and hospital, Kannouj from Dec 2008 through Dec 2009. Which comprised of fifty patients of pleural effusion those patients that age more than 14 years and had Clinical and Radiological evidence of Pleural Effusion. Present study excluded that patient who's had age more than 65 years, 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  $\pm SD$  and frequency variables as percentages. Chi - square test was performed for statistical significance. P value of <0.05 was considered for statistical significance.

#### RESULTS

In this study, 72% were male and 28% were female pleural effusion were studied in which 24 60% of tubercular pleural effusion, 14% cases of transudative pleural effusion, 16% cases of malignant pleural effusion and 10% cases of synpneumonic pleural effusion were present. Figure 2 showed that pleural effusion were 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).

The most common presenting complaints were cough (73.33%) and chest pain (76.66%). followed by fever (70.00%), breathlessness (63.33%), weight loss (60%) and loss of appetite (60%) (Table 2).

The average Hb in tubercular effusion, malignant, transudative and synpneumonic pleural effusion was 9.616, 8.412, 8.6 & 11.76 % respectively. Total leukocyte count: the average total counts in tubercular, malignant, transudative and synpneumonic was pleural effusion 7792, 8026, 6770 & 12440 cells/mm<sup>3</sup> respectively (Table 3).

The average ESR value in tubercular, malignant, transudative, synpneumonic pleural effusion 68, 45, 15.7 & 41.6 mm/hr respectively. ESR was significantly elevated in exudates.

The mean pleural fluid cell count and SD in tubercular, malignant, transudative and synpneumonic are  $1061\pm410$ ,  $574\pm190$ ,  $139\pm31$  and  $1332\pm571$  respectably.

The mean pleural fluid sugar level in tubercular, malignant, transudative and synpneumonic are 53.16±10.92, 64.37±8.86, 103.85±26.14 and 39.6±9.39. Sugars were found to be low in the synpneumonic pleural effusions.

Table 1: Age & sex wise distribution of patients of plural effusion.

Age (years)	No. of cases		Total	Percentage
	Male	Female		
15-25	08	03	11	22
26-35	09	05	14	28
36-45	08	02	10	20
46-55	08	02	10	20
56-65	03	02	05	10
Total	36	14	50	100

Table 2: Distribution of presenting symptoms in TB Pleural effusion.

Symptoms	No. of cases (%)
Fever	21(70)
Cough	22(73.33)
Chest pain	23(76.66)
Breathlessness	19(63.33)
Loss of appetite	18(60.00)
Loss of weight	18(60.00)

Table 3: Haematology investigation finding.

Type of effusion	Hb (gm %) Mean±SD	Total leukocyte count Mean±SD	ESR Mean±SD
Tubercular	9.616±0.817	7792±928	68±13.09
Malignant	8.412±0.955	8026±1335	45±13.16
Transudative	8.6±1.49	6770±1545	15.7±5.61
Synpneumonic	11.76±0.97	12440±1507	41.6±10.8

Table 4: Cell count & cell type in pleural effusion.

Type of effusion	Cell count	Cell type predominant	Malignan t cells
Tubercular	1061± 410	Lymphocytes	-
Malignant	574± 190	Lymphocytes	Positive in 8 cases
Transudative	139±31	Monocytes & Lymphocytes	-
Synpneumonic	1332±5 71	Polymorphocy tes	-

The mean pleural Fluid protein level in tubercular, malignant, transudative and synpneumonic are 4.83±0.75, 3.56±0.47, 2.42±0.63 and 4.08±0.33 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 24.02±57, 45,31, 75±5.51, 27.14±5.78 and 28.0±9.46 respectably.

Mean ADA in TB Pleural Effusion was 100.55 and in Non-TB Pleural Effusion were 30.78 in present study.

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	53.16±10.92	4.83±0.75	124.02±57.45
Malignant	64.37±8.86	3.56±0.47	31.75±5.51
Transudative	103.85±26.14	2.42±0.63	27.14±5.78
Synpneumonic	39.6±9.39	4.08±0.33	28.0±9.46

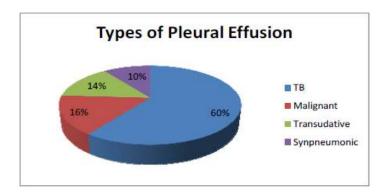


Figure 1: Type of pleural effusion.

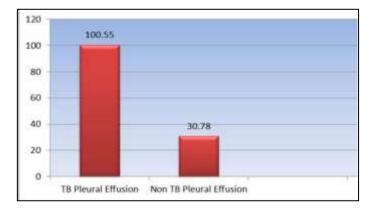


Figure 2: Distribution of mean ADA in tubercular and nontubercular pleural effusion.

## **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 36 years and two thirds were men which were consist with other previous studies.<sup>7-9</sup>

In current study, three most common causes of exudative effusion were tuberculosis, malignancy and Synpneumonic effusions. The patients with TB were younger (31 years) than the patients with malignancy which was consistent with Luis Valdes et al (34 years), S. K. Sharma et al (33 years) and Ibrahim WH et al (31.5 years).

The commonest exudative effusion in this study was tuberculosis (60%) followed by malignant effusion (16%) and synpneumonic effusion (10%). 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 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 our TB patients were fever (76%) followed by cough (73%) and chest pain (70%). These findings are compatible with the studies done earlier by Moudgil et al.  $^{12}$ 

The symptoms most commonly reported in published series by Morehead RS et al are: cough (71-94%), fever (71-100%), chest pain (78-82%) and dyspnea.<sup>13</sup>

In our study we demonstrated that massive effusion was most commonly seen in malignant effusion group (50%) similar to that observed, by Maher et al (55%). 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. Ten percent of tuberculous effusions in our study had a total count greater than 10,000/mm³ similar to Light's observation. Ninety percent of TB effusions and most of malignant effusions had lymphocyte predominance. Our result was similar to the study done by Valdes L et al, where they had encountered neutrophil predominant tuberculous effusion in only 6.7% of patients and only one malignant effusion had neutrophil predominant effusion (3%). To

Low pleural fluid glucose was seen predominantly in patients with synpneumonic effusion.

The majority of pleural fluid glucose levels were between 40-100 mg/dl in tubercular effusions, consistent with the earlier observation by Light. Only 3% of tuberculous effusions had sugars less than 40 mg%.

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. 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 30 patients with tuberculosis pleural fluid ADA was done in them and 28 (93.33%) of them had a level more than 40IU/L but 2 (6.66 %) 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 100.55 IU/L. The mean ADA were high in the 2 Indian studies done by Rajendra Prasad et al<sup>21</sup> and Gilhotra et al with the mean ADA level ranging between 76.8 IU (+23.8) to 95.8 (+57.5). <sup>22</sup>

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 93.3% and 90% respectively and Positive predictive value 93.3% and Negative predictive value 90%. This is more consistent with the observation made by Valdes et al. Spain 47 IU/L cut off value sensitivity 100%, specificity 95%, positive predictive value 85%, negative predictive value 100% with mean ADA 107.5. All our malignant effusions had pleural fluid ADA less than 40 IU/L with a mean of 32.92 IU/L.

All the other Indian studies also showed a similar finding, where the average pleural fluid ADA among malignant effusions were 7 to 18 IU/L. 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.

### **CONCLUSIONS**

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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Ethical approval: The study was approved by the

institutional ethics committee

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