

## Original Article



# Pleural fluid cytology, biochemistry and adenosine deaminase level study in differentiating tubercular and non tubercular causes of pleural effusion

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### Abstract

**Background:** Adenosine deaminase (ADA) level in pleural fluid study has gained popularity for quick diagnosis and treatment of tuberculous pleural effusion in tuberculosis burdened countries. Studies have confirmed high sensitivity and specificity across the world. Pleural fluid cytology, biochemistry and malignant cell examinations are already in use and widely available. **Objectives:** Diagnostic approach to quickly differentiate between tubercular and non tubercular pleural effusions by analyzing cytology, biochemistry and ADA level. **Materials & Methods:** This study was carried out on 85 patients who were admitted or visited outpatient department with pleural effusion. The pleural fluid study was including measurement of ADA level was done. **Results:** 41 cases were diagnosed as tubercular pleural effusion. Among the low ADA group, 9 cases were diagnosed as malignant pleural effusion with positive malignant cell and 13 cases were transudative effusion. 7 cases were diagnosed as parapneumonic effusion with exudative fluid, neutrophilic cell distribution and mixed ADA activity. **Conclusion:** ADA was found positive with a mean value of 88.3 U/L in tubercular pleural effusions. Non tubercular pleural effusion showed low ADA level. However the cytological and biochemical examination of pleural fluid was also found to be important in differentiating tubercular from non tubercular causes.

**Keywords:** Adenosine deaminase, Malignant pleural effusion, Tuberculosis, Tubercular pleural effusion.

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### Introduction

Tuberculosis (TB) is one of the commonest infectious disease burdens of developing countries. Bangladesh is ranked sixth in the world of tuberculosis with around 300000 new cases per year.<sup>1</sup> TB usually affects lung but extra pulmonary TB is also common and occurs at around 4% of all TB cases.<sup>2</sup> Among the extra pulmonary TB cases tuberculous pleural effusion (TPE) is the most common form.<sup>3</sup> Diagnosis of pulmonary TB is done by sputum for Acid Fast Bacilli (AFB). But the diagnosis of TPE is challenging as percentage of finding AFB in pleural fluid or typical histopathology of pleural biopsy is very low and AFB culture is time consuming, though they are gold standard.<sup>4</sup> Also the expertise and centre doing pleural biopsies lacking in high incidence areas of TB in our country. ELISA, PCR and TB interferon tests are very expensive as well. Pleural TB occurs as a result of a TB antigen entering the

pleural space, usually through the rupture of a subpleural focus, followed by a local, delayed hypersensitivity reaction mediated by CD4+ T lymphocytes and macrophages. The activated macrophages enter the pleural cavity, producing adenosine deaminase during its proliferation process.<sup>5</sup> ADA has been proposed and used widely to be a useful marker for TPE. Different studies across the world have confirmed high sensitivity and specificity of ADA level for diagnosis of TPE especially high incidence areas for TB. The test is less invasive, cheap and readily available.<sup>6</sup> Accuracy can be improved by including the cytology and biochemistry of pleural in terms of exudative nature and lymphocyte predominance.<sup>7</sup> Pleural effusion is common clinical scenario in tertiary level hospitals. Other than TPE, non tuberculous pleural effusion as malignant pleural effusion, parapneumonic effusion and transudative effusion are common cases.

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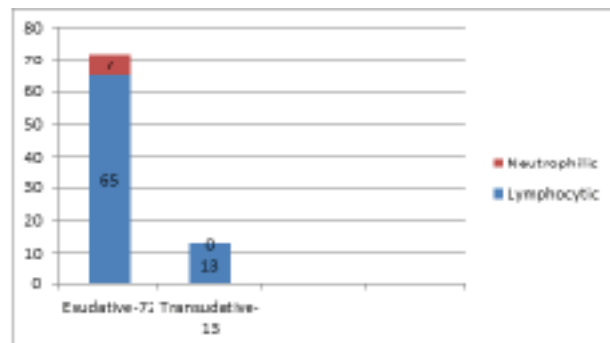
Pleural fluid aspiration is very safe, less expensive and can be done at bedside. By detailed clinical history along with study of cytology, biochemistry, malignant cell and ADA level of pleural fluid, early differentiation of TPE from non tuberculous causes is possible in a cost effective manner.

**Materials and Methods**

This study was carried out on 85 patients who attended with pleural effusion in Khwaja Yunus Ali Medical College and Hospital (KYAMCH) from March 2017 to October 2017. After taking detailed clinical history, physical examinations and appropriate investigations they were diagnosed to have pleural effusion. Then they were admitted in inpatient department of Medicine and further investigations and pleural fluid aspiration were done. Pleural fluids of these patients were studied for cytology, biochemistry, ADA level and malignant cell examination. Whenever necessary other investigations such as ultrasound, echocardiogram, CT scan etc. were done. The pleural fluid studies were classified as exudative or transudative by biochemical examination and lymphocytic or neutrophilic by cytological examination. For ADA study, commercially available kit was used and the cut off value for pleural fluid was 35 U/L. These results were matched as exudative with lymphocytic or exudative with neutrophilic effusion with high or normal ADA level and transudative with lymphocytic with high or normal ADA level. None of these cases revealed transudative with neutrophilic result. In respective cases with suspicious clinical history, age and CXR findings, malignant cell examination of the fluid were also included. Pleural fluid study having exudative with lymphocytic pattern with ADA level above the cut off were diagnosed and treated as TPE. Other findings were classified as para pneumonic effusion or MPE or transudative effusion due to other systemic causes.

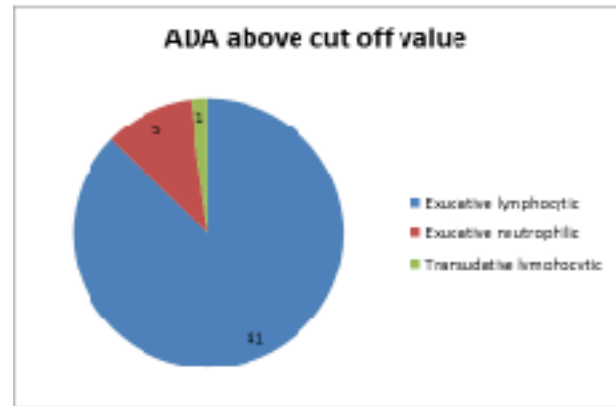
**Results**

Out 85 cases, 72 were exudative among which 65 were exudative with lymphocytic and 7 were exudative with neutrophilic distribution. All the rest 13 cases were transudative with lymphocytic distribution and no case was found to be transudative with neutrophilic distribution. Fluid examinations for malignant cell were done in 35 cases among which 9 cases turned out positive for malignant cell of different category and were diagnosed as MPE.



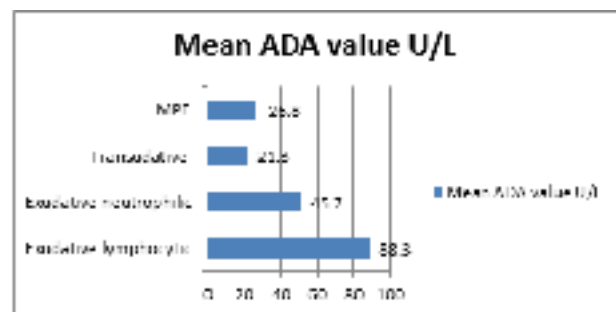
**Figure 1:** Cytological and Biochemical differentiation of study case (n-85).

In a total 47 cases, ADA was found higher than cut off value ranging from 39-229 U/L. Among these cases with higher ADA level, 41 cases were exudative lymphocytic distribution and 5 cases with exudative neutrophilic distribution. There was only 1 case with transudative lymphocytic distribution with ADA just above the cut off value with 39U/L and was taken as inconclusive result. Out of 9 malignant pleural effusion cases, only two cases showed ADA level above cut off value of 45 U/L and 49 U/L.



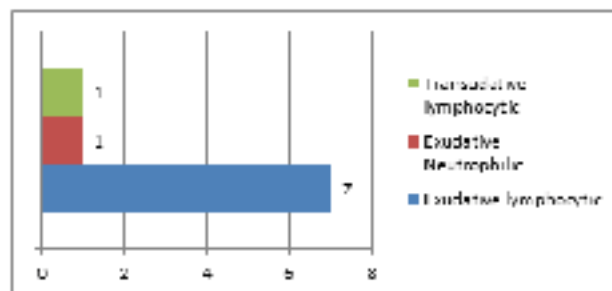
**Figure 2:** Cases distribution with ADA above cut off value.

In cases with TPE mean value was 88.4 U/L (range 45-229 U/L), in transudative cases mean value was 21.3 (range 12-39 U/L) and in MPE mean value was 26.8 U/L (range 13-45 U/L). These data shows that most of the cases with TPE have much higher value than the cut off value given for the supplied kit. The mean ADA for exudative neutrophilic cases was 45.7 U/L, slightly higher than the cut of value.



**Figure 3:** Mean ADA value in differentiated pattern.

Among the MPE cases, 7 were exudative lymphocytic, 1 was exudative neutrophilic and 1 was transudative lymphocytic. However in 15 cases the findings were exudative with lymphocytic distribution with a normal ADA level but negative for malignant cell. They were inconclusive for diagnosis and referred for further investigations as CT scan of chest and or pleural biopsy.



**Figure 4:** Findings of malignant pleural effusion

Total 41 cases were diagnosed to have TPE and treatment with follow up was done accordingly. The rest 5 cases were diagnosed to have parapneumonic effusion along other 2 cases with normal ADA. The transudative cases with normal ADA were further investigated for the actual cause. Lastly 9 cases were diagnosed with MPE and were referred to Cancer center of KYAMCH.

## Discussion

In this study we have used pleural fluid ADA level as an excellent surrogate marker for diagnosis of TPE. But at the same time it is evident from result that ADA level alone is not enough to make an accurate diagnosis. However the accuracy may be increased by studying the cytology and biochemistry in terms of differential count and protein level of the fluid. With this regard, this study also helps to determine the non tubercular causes of pleural effusion as transudative causes, MPE and parapneumonic effusion. Another interesting finding was there were few exudative cases with normal ADA or negative malignant cell where further costly and invasive investigations were awaited before a diagnosis. Study showed ADA activity in tuberculous effusion was higher than in any other diagnostic group.<sup>8</sup> ADA level at 50U/L the sensitivity and specificity for the identification of tuberculosis was 90% and 89% respectively. Another study investigated 10 patients with tuberculosis pleurisy and 76 patients with pleural effusions of other etiology.<sup>9</sup> The ADA activity in the tuberculous patients was significantly higher than in the other groups. Value of ADA activity along with its isoenzymes in TPE was studied against MPE as control and found that TPE had a much higher ADA level than MPE.<sup>10</sup> Our study findings is also similar as ADA activity and mean ADA was highest in TPE group and lower in MPE and transudative group. The mean ADA level of cases suggestive of parapneumonic effusion needs further large scale study to come to a conclusion.

It is also evident that the mean ADA level that reached the diagnostic cut-off set for tuberculous effusions is much higher than that of the malignant group of patients.<sup>11</sup> In TPE group mean was 85.3 U/L, where in malignant group no one ADA level exceeds 40 U/L. Our study also has similar result with a mean of 88.3 U/L in TPE group and 26.8 in MPE group. So an exudative effusion with a normal ADA level should be investigated further to exclude MPE. All cases with transudative pleural effusions had lymphocytic cell distribution and showed very low ADA activity in our study which is expected as well. Adenosine Deaminase Levels in

nontuberculous lymphocytic pleural effusions was studied and the level exceeded the diagnostic cutoff for TB in very few cases though effusion ADA levels cannot be assumed from total or differential leukocyte counts.<sup>12</sup>

## Conclusion

The method of ADA estimation is easy, simple and doesn't require expensive equipment and it takes only 2 hours and it is also cheap. Bangladesh is a TB burden country. But most of the hospitals and clinics in our country do not have the ADA facility. We must try to provide them ADA measurement kit do that their diagnostic accuracy can be improved further. At least referral system should be practiced so that the collected fluid can be sent for ADA level measurement.

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