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# Pleural Fluid Adenosine Deaminase in Exudative Pleural Effusion

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***Abstract***
***Background:*** *Pleural effusion is the commonest case admitted in IPD of Dept. of Respiratory Medicine/Internal Medicine. Untreated tuberculous pleural effusion (TPE) can develop into active tuberculosis so it is important to make rapid and accurate diagnosis for TPE and initiation of treatment. Adenosine deaminase level in pleural fluid is a cost effective diagnostic chemical biomarker having high sensitivity and specificity of 100% and 95% respectively for diagnosis of tubercular pleural effusion and is routinely employed as a screening tool in countries where tuberculosis is endemic.* ***Objectives of the Study:*** *The objectives of the study include 1) to estimate the pleural fluid levels of adenosine deaminase (ADA) in subjects with tuberculosis and 2) to study the diagnostic performance of ADA for tuberculosis in exudative pleural effusion.* ***Methodology:*** *A total of 80 suspected cases of tubercular pleural effusion fluid were included for diagnostic evaluation. Biochemical analysis for Protein and Glucose were performed on Automated Biochemistry Analyser and ADA was estimated by ADA-MTB kit method. Cytological examination and ADA Microbiological demonstration of AFB by ZN stain and AFB culture was done by conventional LJ method.* ***Discussion and Conclusion:*** *In this study, we found high negative predictive value of the ADA test. The sensitivity and specificity of ADA depends on the prevalence of tuberculosis in the population. With the decline in the prevalence of tuberculous pleural effusion in some areas, the positive predictive value of pleural fluid ADA also declines but the negative predictive value remains high. Therefore, the measurement of the pleural fluid ADA level is an excellent test to rule out a tuberculous aetiology of lymphocytic pleural effusions, irrespective of the rate of prevalence of the disease.*

***Key-Words:*** *tuberculosis, exudative pleural effusion, adenosine deaminase, sensitivity, specificity.*

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## I. Introduction:

Pleural effusion is the commonest case admitted in IPD of Dept. of Respiratory Medicine/Internal Medicine. Accumulation of excessive pleural fluid in the pleural space is known as pleural effusion. For the better clinical management, the diagnostic workup of pleural effusion starts with confirmation of PE due to transudate or exudate. Exudative pleural effusion is confirmed these days with the more specific marker especially Adenosine Deaminase having advantage in picking up the cases of Tubercular Origin of Exudative Pleural Effusion.

When a pleural effusion has been determined to be exudative, additional evaluation is needed to determine its cause, and amylase, glucose, pH and cell counts should be measured. The most common causes of exudative pleural effusions are bacterial pneumonia, cancer, viral infection, and pulmonary embolism. Tuberculosis is a common cause of pleural effusion especially in countries like India.[1] Untreated tuberculous pleural effusion (TPE) can develop into active tuberculosis so it is important to make rapid and accurate diagnosis for TPE and initiation of treatment. As we are aware, definitive diagnosis of tuberculosis is a difficult task, as in more than 50% of patients, pleura is the only site of infection. Adenosine Deaminase (ADA), is an enzyme which catalyses the conversion of adenosine to inosine and plays an important role in the differentiation of lymphoid cells. Adenosine deaminase level in pleural fluid is a cost effective diagnostic chemical biomarker having high sensitivity and specificity of 100% and 95% respectively for diagnosis of tubercular pleural effusion and is routinely employed as a screening tool in countries where tuberculosis is endemic.[2-6]

The combination of ADA and pleural fluid lymphocyte proportion has come to be recognized as an excellent approach for increasing the specificity of ADA test.[7] Although pleural fluid ADA is not a perfect discriminator, its level is considerably elevated in patients with TPE. Hence we have taken up this study to determine the levels of ADA in subjects with tuberculosis.

## II. Objectives:

The objectives of the study include

1. To estimate the pleural fluid levels of adenosine deaminase (ADA) in subjects with tuberculosis.
2. To study the diagnostic performance of ADA for tuberculosis in exudative pleural effusion.

## III. Materials And Methods:

**Source of Data:** A Hospital Based observational study conducted on "Pleural Fluid Adenosine Deaminase in Exudative Pleural Effusion" at Chandulal Chandrakar Memorial Medical College from March 2019 to September 2019. A total of 80 suspected cases of tubercular pleural effusion fluid were included for diagnostic evaluation.

**Laboratory Analysis:** Biochemical analysis for Protein and Glucose were performed on Automated Biochemistry Analyser and ADA was estimated by ADA-MTB kit method. Cytological examination (cell count, cell type, malignant cells) and ADA Microbiological demonstration of AFB by ZN stain and AFB culture was done by conventional LJ method. After all relevant investigations, lymphocytic exudates were segregated with >50% lymphocytic proportion of all nucleated cells. ADA level cut-off >40IU/ L were considered as tuberculous exudates which were confirmed by AFB stain and AFB culture subsequently. ADA level cut off value <40IU/L were studied for cytological examination for malignant cells and relevant investigation to confirm non-tuberculous lesion.

**Statistical Analysis:** Data were expressed as mean ± SD. The Student *t* test was used for the comparison. The results of the diagnostic tests were expressed as sensitivity, specificity, predictive values (positive and negative) and accuracy, with 95% confidence intervals (95% CI).

## IV. Results:

A Hospital Based observational study conducted on "Pleural Fluid Adenosine Deaminase in Exudative Pleural Effusion" at Chandulal Chandrakar Memorial Medical College from March 2019 to September 2019 in collaboration with TB and Chest department. A total of 80 suspected cases of tubercular pleural effusion fluid were included for diagnostic evaluation. Out of 80 subjects 62 patients were males (77.5%) and females were 18 (22.5%). The mean age in years and SD in males and females were 48.2±14.28 and 44.6±13.67 respectively.
ADA levels were measured in all the subjects, out of which we found elevated levels of ADA (>40 IU/L) in 50 subjects out of 80 and 30 subjects had normal ADA levels (<40IIU/L) (table 1).

**Table 1: Shows Distribution of Study Subjects depending on ADA cut-off 40IU/L**

| ADA levels in IU/L | Number of Subjects | Percentage |
|---|---|---|
| ADA <40IU/L | 50 | 62.5% |
| ADA >40IU/L | 30 | 37.5% |
| Total | 80 | 100% |

**Table 2: Shows Distribution of Study Subjects depending on ADA cut-off 40IU/L and Lymphocyte Exudate**

| ADA levels in IU/L | Lymphocyte Exudate >50% | Lymphocyte Exudate <50% |
|---|---|---|
| ADA <40IU/L | 24 | 26 |
| ADA >40IU/L | 29 | 01 |
| Total | 53 | 27 |

It is evident from the table 2 that 29 subjects had ADA >40IU/L and lymphocyte exudate >50% and 1 subject had <50% lymphocyte exudate <50%. 24 subjects had ADA <40IU/L and lymphocyte exudate >50% and 26 subjects had ADA <40IU/L and lymphocyte exudate <50%.

**Table 3: Shows Distribution of Study Subjects depending Pleural Fluid Protein of cut-off 3gm/dL**

| ADA levels in IU/L | Protein <3gm/dL | Protein >3gm/dL |
|---|---|---|
| ADA <40IU/L | 28 | 22 |
| ADA >40IU/L | 1 | 29 |
| Total | 29 | 51 |

It is evident from the table 3 that 29 subjects had ADA >40IU/L and Protein >3gm/dL and 1 subject had Protein <3gm/dL. 22 subjects had ADA <40IU/L and Protein >3gm/dL and 28 subjects had ADA <40IU/L and Protein <3gm/dL.

**Table 4: Shows Distribution of Study Subjects depending AFB Culture and ADA levels**

| ADA levels in IU/L | AFB culture Positive | AFB culture Negative |
|---|---|---|
| ADA <40IU/L | 3 | 47 |
| ADA >40IU/L | 28 | 02 |
| Total | 31 | 49 |

It is evident from the table 4 that 2 subjects had ADA >40IU/L and AFB culture negative and 28 subjects had AFB culture positive and ADA >40 IU/L. 3subjects had ADA <40IU/L and AFB culture positive and 47 subjects had ADA <40IU/L and AFB culture negative.

**Table 5: Diagnostic Validity of ADA for Tubercular and Non-Tubercular PE**

| | |
|---|---|
| Sensitivity | 88% |
| Specificity | 87% |
| Positive Predictive Value | 80% |
| Negative Predictive Value | 93% |

It is evident from the table 5 that the sensitivity is 88%, specificity is 87%, positive predictive value is 80% and negative predictive value is 93%.

## V. Discussion:

In our study, we evaluated the diagnostic utility of ADA in exudate pleural effusion mainly concerning to tubercular pleural effusion. We performed biochemical evaluation of pleural fluid by measuring pleural fluid protein levels in gm/dL, pleural fluid LDH in IU/L and glucose levels in mg/dL, Differential counts mainly lymphocytes and AFB culture. The pleural fluid ADA cut-off was 40IU/L. We found significantly elevated ADA levels in different types of exudative pleural effusion in comparison to transudate pleural effusion. The diagnosis of tuberculous pleural effusions can be difficult because of the low sensitivity of various diagnostic tools available till date. A lymphocytic exudate which is seen with tuberculous pleuritis, can also occur with other diseases such as malignancy and collagen vascular diseases.

Studies conducted in the past have reported the positive rate with smear testing for tubercle bacilli in pleural fluid is 11.1% and culture 33.3% and with closed pleural biopsy 96.2%. These studies have reported lower diagnostic rates for tuberculous pleural effusions.[8-10]

Pleural fluid ADA has long been used as a marker for tuberculous pleurisy. Levels of ADA in pleural fluid >40 $IU{\cdot}L^{-1}$ can indicate pleural tuberculosis with sensitivity (81–100%) and specificity (83–100%) as reported in the previous studies. The false-positive cases in the literature are mainly due to empyemas, lymphomas, malignant diseases and other aetiologies, such as parapneumonic or collagen vascular disease. Examination of those studies reveals that pleural fluids of any cell type predominance were included.[11-12]

Some other studies have also found increased ADA levels in patients with complicated parapneumonic effusions, wherein the immune response involves polymorphonuclear cells and macrophages rather than lymphocytes.[13-14]

In this study, there were no empyemas in the parapneumonic effusion group as empyemas are predominantly neutrophilic effusions. This could explain the low average ADA values found in the group of lymphocytic parapneumonic effusions. An elevated pleural fluid ADA level in countries with a high prevalence of tuberculous pleural effusions, as in Spain, has a high degree of specificity for tuberculous pleuritis, which makes it an integral part of the diagnostic work-up of lymphocyte-rich pleural effusions. In areas where the prevalence of disease is low, there is a higher likelihood of false-positive test results, and this can lead to the unnecessary administration of antituberculous therapy or a delay in making an alternative diagnosis such as malignancy. Thus, high ADA levels in lymphocytic effusions should be looked on as a screening test to guide further diagnostic tests, such as closed pleural biopsy.

In this study, we found high negative predictive value of the ADA test. The sensitivity and specificity of ADA depends on the prevalence of tuberculosis in the population. With the decline in the prevalence of tuberculous pleural effusion in some areas, the positive predictive value of pleural fluid ADA also declines but the negative predictive value remains high. Therefore, the measurement of the pleural fluid ADA level is an excellent test to rule out a tuberculous aetiology of lymphocytic pleural effusions, irrespective of the rate of prevalence of the disease.

## VI. Conclusion:

In day to day practice we come across cases of pleural effusion, usually to diagnose pleural effusion not a difficult task but still some cases require detailed examination but number of these cases are few. By doing specific tests like pleural fluid ADA we can significantly improve diagnostic yield as these tests are, easily approachable and non-invasive or minimally invasive and can significantly reduce hospitalization period. ADA estimation with cytology increases the sensitivity and specificity and predictive value for the diagnosis of tuberculosis. A cut off 40 IU/L is adequate to exclude tuberculosis. All cases of lymphocytic pleural effusion should be screened for ADA to exclude tuberculosis

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