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A STUDY OF ROLE OF PLEURAL FLUID ADENOSINE DEAMINASE IN THE DIAGNOSIS OF TUBERCULOUS PLEURAL EFFUSION

Respiratory Medicine

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ABSTRACT

Introduction: An excessive or abnormal accumulation of fluid in the pleural space is referred to as a pleural effusion. Tuberculosis is the most common cause of effusion in developing countries like India. Because of the simplicity, rapidity and cost-effectiveness of the ADA assay, early diagnosis of Tuberculous Pleural Effusion has been substantially improved by the use of biochemical markers such as adenosine deaminase (ADA). In present study, we discussed the role of pleural fluid ADA (PF ADA) level in the diagnosis of tuberculous pleural effusion. Methodology: Patients with pleural effusion attending GMERS Medical College, Sola, Ahmedabad, were taken for the study after relevant investigations. PF ADA level was estimated by enzymatic kinetic method and its role evaluated. ADA >40 U/L was considered diagnostic of tuberculosis.**Results:** Of the 56 patients, 41 (73.21%) are male and 15 (27.78%) are female. The mean age is 39 years. Among 56, 49 had TB pleural effusion (group 1) and 7 due to other causes (group 2). The mean ADA value was 81.33 in group 1 compared to 22.57 in group 2. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PFADA was 87.75%, 85.71%, 97.72% and 50% respectively. Out of 49 cases in group 1, all responded to antituberculous therapy. **Conclusion:** It is concluded that ADA estimation in pleural fluid is not only simple, inexpensive and rapid but also fairly specific and sensitive method for diagnosing tuberculous etiology in patients of pleural disease. ADA activity in the pleural fluid can be a diagnostic biomarker and for this reason ADA estimation in pleural fluid can be used as a routine investigation.

KEYWORDS

Tuberculosis, Pleural effusion, Adenosine deaminase

INTRODUCTION:

Since exudative lymphocytic pleural effusion is typically curable, the diagnosis of tuberculous pleural effusion (TPE) is crucial. (1, 2)Other differential diagnoses of exudative lymphocytic pleural effusions are malignancy, fungal infection, melioidosis, sarcoidosis, and connective tissue diseases. (3, 4)Tuberculous Pleural effusion (TPE) is diagnosed by demonstration of tubercular bacilli in pleural fluid or granuloma in pleural biopsy specimen(5) ,although the diagnosis can be challenging due to the limited sensitivity of acid-fast staining and culture for Mycobacterium tuberculosis in pleural fluid.(6) because the yield of pleural fluid culture for mycobacteria is about 36%.(7) Since pleural biopsy is more challenging than pleural aspiration, various parameters have been developed and evaluated as an alternative to pleural biopsy.(8)

Due to affordability, rapidity, high accuracy and sensitivity of up to 100% for the diagnosis of TPE, PFADA has emerged as a crucial diagnostic tool in the evaluation of exudative pleural effusion(9). 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. Its activity is high in diseases in which cellular immunity is stimulated (5). Different cut off values of ADA ranging from 30–100 IU/L have been used in various studies, with differing sensitivities and specificities (10).

When the sub pleural focus ruptures, TB antigen enters the body and causes a delayed hypersensitivity reaction, leading to pleural TB. The proliferating activated macrophages enter the pleural space and produce ADA. According to research, TB causes an increase in ADA in tubercular pleuritic that is greater than that of other exudative fluids (11, 12).

MATERIAL AND METHOD:

This prospective study was done by department of Respiratory medicine, GMERS medical college, Sola, Ahmedabad. All the patients with pleural effusion aged 18 and above, between September 2021 and August 2022, were studied. Informed consent was obtained before beginning the study. A detailed history, thorough physical examination, and a chest radiograph were taken of each patient. A standard diagnostic and therapeutic (when needed) thoracocentesis was performed. Pleural fluid was sent for conventional diagnosis, including Pleural fluid differential cell count, protein, sugar, gram staining, AFB staining, aerobic culture and cytology. Ten milliliters of additional pleural fluid was sent for ADA assay, using enzymatic kinetic method. ADA level cut off of > 40IU/ L were considered as tuberculous exudates.

The study protocol was approved by the institutional ethics committee of GMERS medical college, Sola, Ahmedabad.

STATISTICAL ANALYSIS:

After compiling the data in Microsoft excels 2016, the chi-square test was applied to compare the categorically variable data.

RESULT:

Among fifty six pleuritis patients, 41 (73.21%) were male and 15 (26.78%) were female. The patients were between the ages of 18- 75 years and mean age was 38.57 years. The ADA level in pleural effusion ranged from 14-243 U/L and the mean level was 73.85 U/L. The level in Tubercular effusion was between 15 U/L to 243 U/L and the mean was 81.33 U/L while in non tubercular ranged from 15 U/L to 50 U/L and the mean was 22.57 U/L ($p < 0.0000001$). Using the cut off value of 40 U/L, the overall sensitivity and specificity of ADA was 87.75% and 85.71 % respectively. The agreement between ADA findings and the clinical findings was statistically significant ($p<0.0000001$). The positive predictive value (PPV) and the negative predictive value (NPV) were 97.72%and 50 % respectively. (Table 1)

Table 1:

Pleural fluid ADA	Tuberculous	Non-tuberculous
>40 U/L	43	1
< 40 U/L	6	6

Sensitivity of ADA = 43/ 43+6 x 100= 87.75 %
Specificity of ADA = 6/ 6+1 x100 = 85.71%
Positive Predictive Value = 43/44x100= 97.72%
Negative Predictive Value= 6/12x100= 50%

Clinical and pleural fluid profiles of patients: (Table 2)

Patient characteristics	Tuberculosis	Malignancy	Inflammation
No. of patients	49	6	1

Age(year)	35.57	63.16	38
Male : female ratio	37:12	3:3	1:0
Leukocytes(cells/microL)	1023.81	407.5	100
Lymphocytes (%)	51.83	63.3	20
Proteins (gm/dl)	4.97	4.7	2.3

DISCUSSION:

Pleural effusions are commonly seen in clinical practice; however they can pose challenging diagnostic issues. Tuberculosis is a common cause of pleural effusion (13) especially in countries like India. Additionally, the prevalence of TB is rising globally (14). Malignancy and tuberculous effusions are the two most common causes (15). Although lymphocytic predominant fluid is usually seen in tubercular pleural effusion but all lymphocytic predominant fluid can't be tubercular, it could be malignant. So there is a need to differentiate among various causes of pleural effusion. Because bacterial load is less so pleural fluid culture for mycobacterium tuberculosis is also low so pleural fluid ADA estimation is quick and relatively inexpensive.

Adenosine deaminase, which is mostly present in T lymphocytes and macrophages, is thought to be a marker of cell mediated immunity (16).ADA is essential for the development of lymphoid cells and is most active in lymphoid tissues. There are 2 isoenzymes, ADA1 and ADA2, with ADA2 found only in monocytes and macrophages. The high total level of ADA in tuberculous pleural effusion is due largely to high ADA2 activity (17). The standard ADA determination measures ADA activity and not the absolute amount of enzyme present. ADA activity may be dependent more on the pathologic stimulus e.g. TB and rapidity of T lymphocyte proliferation, and not on amount of lymphocytes present.

The study was carried out in fifty six pleuritis patients. Present study confirms that ADA level in tubercular pleural effusion is increased and in non tubercular pleural effusion ADA level did not exceed to 50 IU/L. The mean ADA of tubercular effusion was 81.33 U/L while in non tubercular the mean was 22.57 U/L ($p < 0.001$). Using the cut off value of 40 U/L, the overall sensitivity and specificity of ADA was 87.75% and 85.71 % respectively. The positive predictive value (PPV) and the negative predictive value (NPV) were 97.72%and 50 % respectively (Table 1). The result shows the low NPV of ADA in the diagnosis of Tuberculous pleuritis. The measurement of ADA levels is a useful test with good sensitivity and specificity. (18, 19)

Burgess (20) showed ADA activity in tuberculous effusion was higher than in any other diagnostic group. At a level of 50 U/L the sensitivity and specificity for the identification of tuberculosis was 90% and 89% respectively.

So we can say that estimation of ADA level in pleural fluid is extremely helpful in establishing the etiology of tubercular pleural effusion and to rule out other diagnosis especially of other diseases in which lymphocyte predominance of pleural effusion is seen such as malignancy and collagen vascular diseases.

Limitation of the study:

Number of patients studied is small. So definitive criteria can't be established on this sample size.

CONCLUSION:

Patients with tuberculous pleural effusion tend to have high levels of ADA in their pleural fluid. To diagnose TPE, measuring ADA levels offers a quick and easy alternative to pleural needle biopsy. In addition, ADA level analysis is less expensive and time –consuming than other diagnostic tests. Patient morbidity rises as a result of the delay in diagnosis.

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