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Original Research Article

Evaluation of adenosine deaminase activity in serum and pleural fluid of pulmonary tuberculosis patients with pleural effusion

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ABSTRACT

Background: In endemic regions, a high adenosine deaminase (ADA) activity in lymphocyte predominant exudate is a valuable adjunct in diagnostic evaluation and treatment initiation in tuberculous pleural effusion. Tuberculosis is highly endemic in India, requiring prompt diagnosis, effective treatment and control of the disease. The present study was aimed to evaluate the serum and pleural fluid ADA activities in pulmonary tuberculosis patients with pleural effusion.
Methods: This study includes a total of 240 subjects; 40 pulmonary tuberculosis patients (PTB), 40 PTB with pleural effusion (PE), 40 PTB treated for one month, 40 healthy controls, 40 transudative PE patients and 40 nontuberculous exudative PE patients, between 20-70 years of age. ADA activity was estimated by the Guisti-Galanti method along with routine parameters in all study subjects.
Results: Serum ADA activity was significantly higher ($p<0.001$) in PTB with PE (37.68±12.42U/L) than healthy controls (12.15±5.38U/L), transudative PE (22.43±9.12U/L), nontuberculous exudative PE (16.92±4.98U/L) and treated PTB (19.39±4.54U/L). Pleural fluid ADA activity was significantly higher ($p<0.0001$) in PTB with PE (78.94±36.75U/L) than in transudative PE (11.25±3.12U/L) and nontuberculous exudative PE (17.56±10.42U/L). ADA activity was significantly higher ($p<0.001$) in pleural fluid than serum in PTB with PE. Lymphocyte percentage was significantly higher ($p<0.001$) in pleural fluid (86.57±9.64) than peripheral blood (37.48±8.49) in PTB with PE.
Conclusions: The pleural fluid ADA activities were elevated in lymphocyte predominant exudates of PTB patients with PE from endemic regions, prompting treatment initiation in high suspicion cases with elevated ADA activity.

Keywords: Adenosine deaminase, Pulmonary tuberculosis, Pleuritis, Tuberculous pleural effusion

INTRODUCTION

Tuberculosis is one of the oldest diseases known to affect humans. Tuberculosis is caused by bacteria belonging to *Mycobacterium tuberculosis* complex. Tuberculosis is one of the top ten causes of death worldwide.[1] Tuberculosis causes morbidity in approximately 10 million people each year. For the past 5 years, tuberculosis has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS.[2]

As per the Global TB report 2017 the estimated incidence of tuberculosis in India was approximately 2.8 million, accounting for about a quarter of the world's tuberculosis cases. India has the highest burden of the disease with tuberculosis causing two deaths every three minutes. The most common presentation of tuberculosis in India is pulmonary tuberculosis, affecting lungs in >85% of the cases.[3] Tuberculosis is transmitted from person to person by the airborne spread of infectious agents in the form of droplets while coughing.

Pulmonary tuberculosis is the most common cause of pleural effusion in India.[4] Pleural effusion in pulmonary tuberculosis can occur as the sequel to a primary infection of 6-12weeks duration or as the reactivation of latent infection.[5] It is primarily a hypersensitivity reaction to the tuberculous protein and very few bacilli that enter the pleural space.[6] The pleural effusion results from the combination of the increased pleural fluid formation and the decreased pleural fluid removal from the pleural space. The pleural fluid in tuberculous pleural effusion is invariably an exudate with the pleural fluid protein concentration frequently exceeding 5g/dL.[7,8] The pleural fluid glucose concentration is usually similar to that of the serum concentration or may be reduced in some cases. The pleural fluid lactate dehydrogenase (LDH) activity is higher than serum activity in most cases. Tuberculous pleural effusions are predominantly lymphocytic with lymphocyte percentage usually ranging from 50-85% in the pleural fluid.[9,10] The presence of exudative pleural fluid with high protein concentration and lymphocyte predominance suggests tuberculous pleural effusion. The presence of high neutrophil percentage usually indicates the presence of acute infections like empyema. Absence of malignant cells in the pleural fluid rules out malignant pathology.

The definitive diagnosis of tuberculosis depends on the demonstration of the bacilli by microscopy and isolation by acid fast bacilli (AFB) stain and culture of the diagnostic specimen sent to the laboratory.[11] The isolation and identification of mycobacterium from the patient's specimen by smear or culture is specific but not sensitive. The culture of mycobacterium in routine Lowenstein-Jensen culture medium takes 6weeks. Due to low bacillary load in tuberculous pleural effusion, demonstration and isolation of mycobacterium is difficult. The results of pleural fluid culture are positive in less than 25% of the cases. The conventional diagnostic methods delay diagnosis as they are laborious, time consuming and more invasive needing patient cooperation. Relatively new techniques like adenosine deaminase (ADA), lysozyme, interferon-γ, polymerase chain reaction (PCR) were introduced. PCR technique is fairly expensive, has relatively low sensitivity in body fluids and stays positive even in treated patients. Interferon gamma assay is less affordable for routine use in developing countries. Pleural fluid lysozyme activity elevates in tuberculosis and nontuberculous infections.

Serum ADA activity was initially used as diagnostic marker for lung cancer and has been found to be useful in the diagnosis of tuberculous pleural effusion. The estimation of ADA activity in biological fluids is a simple procedure that does not require sophisticated instrumentation or highly experienced personnel. The estimation of serum ADA activity in pleural fluid is a reliable marker of tuberculosis in endemic areas with high suspicion of the disease.[12] According to an algorithm for diagnostic evaluation of suspected tuberculous pleural effusion published in lung, a patient should be treated for TB without pleural biopsy in the case of a lymphocytic exudate, negative cytology, and elevated ADA, in an area of moderate to high incidence of TB.[3,13] ADA plays an important role in the proliferation, differentiation and activation of T-lymphocytes.[14] ADA also plays a crucial role in the maturation of monocytes to macrophages.[15] The serum ADA activity is elevated in tuberculosis due to high lymphocyte turnover during the active disease. The pleural fluid ADA activity is generally two times more elevated than the serum ADA activity due to high lymphocyte percentage in tuberculous pleural effusion.[16] The serum ADA activity decreases significantly after one month of effective treatment.[17] Prompt diagnosis followed by proper treatment of tuberculosis, prevents death, limits ill-health and further transmission of infection to others. With this background, the present study was undertaken to evaluate serum and pleural fluid ADA activities in pulmonary tuberculosis patients with pleural effusion.

METHODS

This prospective observational study was conducted in the department of Biochemistry, Siddhartha Medical College and Government General Hospital, Vijayawada. This study was conducted after obtaining the approval from the Institutional ethical committee. A total of 240 age and sex matched subjects belonging to 20-70years of age were included in this study. This study included 120 controls organized into three groups namely group A with 40 apparently healthy individuals, group B with 40 transudative pleural effusion patients (due to congestive cardiac failure, hepatic failure and hypo-albuminemia) and group C with 40 non-tuberculous exudative pleural effusion patients (due to malignancy, empyema, chylothorax, sarcoidosis and rheumatoid arthritis). This study included 120 tuberculosis patients as cases, organised into three groups namely group D with 40 pulmonary tuberculosis patients without pleural effusion, group E with 40 pulmonary tuberculous patients with pleural effusion and group F with 40 pulmonary tuberculosis patients treated for 1 month with anti-tubercular treatment.

All the subjects included in this study were explained in detail about the study in their local language and written informed consent was obtained from all of them. Patients suffering with other cell-mediated immune response diseases like typhoid fever, infectious mononucleosis, leukaemia, viral hepatitis, active cirrhosis, rheumatoid arthritis, leprosy, HIV, brucellosis and coccidiomycosis were excluded from the study. Pregnant and lactating women were not included in the study. Persons on drugs that affect ADA activity like interferon alpha, deoxycoformycin, ribavirin and viramidine were also excluded from the study.

After taking detailed clinical history, a thorough physical examination and routine laboratory investigations were performed in all the study subjects. The diagnosis of

tuberculosis was established by clinical evaluation, chest X-ray, sputum smear and pleural fluid for AFB by Ziehl-Neelsen staining, sputum or pleural fluid culture for *Mycobacterium tuberculosis* in Lowenstein-Jensen medium, histo-pathological examination of pleural biopsy, total and differential counts of pleural fluid and other laboratory investigations. The aetiology of the transudative and non-tuberculous exudative pleural effusions was made out by clinical examination, ECG, ultrasonography and other relevant laboratory investigations.

A venous blood sample of 5ml was collected under aseptic conditions in lying down position from the anterior cubital vein of all the study subjects. The serum was separated from the blood by centrifugation at 2500rpm for 10minutes. Pleural tap was performed under aseptic conditions to collect 5ml of pleural fluid sample from the pleural effusion patients. The pleural fluid samples were centrifuged immediately after collection and the supernatants were used for analysis. The serum and pleural fluid samples were stored at 2-4°C until analysis which was done on the same day of sample collection.

The serum and pleural fluid total lactate dehydrogenase activity was analysed by the method of King J.[18] The serum and pleural fluid total glucose was estimated by the method of Trinder P.[19] The serum and pleural fluid total protein was estimated by Biuret's method.[20] Based on light's criteria, effusions with pleural fluid/serum ratios of protein >0.5 and LDH >0.6 were considered exudative.[21] The serum and pleural fluid Adenosine deaminase activity was analysed by the spectrophotometric method of Giusti et al.[22] Adenosine deaminase hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with a phenol and hypochlorite in an alkaline medium to form a blue indophenol complex with sodium nitroprusside acting as a catalyst. Intensity of the blue colour formed is directly proportional to the amount of ADA activity present in the sample.

Statistical analysis

The results were statistically analysed by Microsoft office Excel software. The results of continuous variables were expressed as mean ±standard deviation (SD). The categorical variables were expressed in numbers. The significance of difference between two groups for a parameter was assessed by submitting the data to unpaired student `t' test. A 'p' value <0.05 was considered as statistically significant.

RESULTS

A total of 240 age and sex matched study subjects between 20-70 years were included in this study. They were organized into six groups as shown in the Table 1.

Table 1: Categorization of study subjects into six groups.

Groups	Category	Sample size
Group A	Apparently healthy controls	40
Group B	Transudative pleural effusion patients	40
Group C	Nontuberculous exudative pleural effusion patients	40
Group D	Pulmonary tuberculosis patients without pleural effusion	40
Group E	Pulmonary tuberculosis patients with pleural effusion	40
Group F	Pulmonary tuberculosis patients treated for 1 month with anti-tubercular treatment	40

The mean age for cases was 32 years with the male to female ratio 3:1. The mean age for controls was 36 years with male to female ratio of 3:1. The mean ±SD of serum ADA activity in group A (healthy controls) was 12.15±5.38U/L, group B (patients with transudative pleural effusion) was 22.43±9.12U/L, group C (patients with nontuberculous exudative pleural effusion) was 16.92±4.98U/L, group D (pulmonary tuberculosis patients without pleural effusion) was 36.52±10.69U/L, group E (pulmonary tuberculosis patients with pleural effusion) was 37.68±12.42U/L and group F (pulmonary tuberculosis patients treated for 1 month) was 19.39±4.54U/L. The serum ADA activity in groups D and E was higher than that of groups A, B, C and F with statistically significance of p <0.001 (Figure 1).

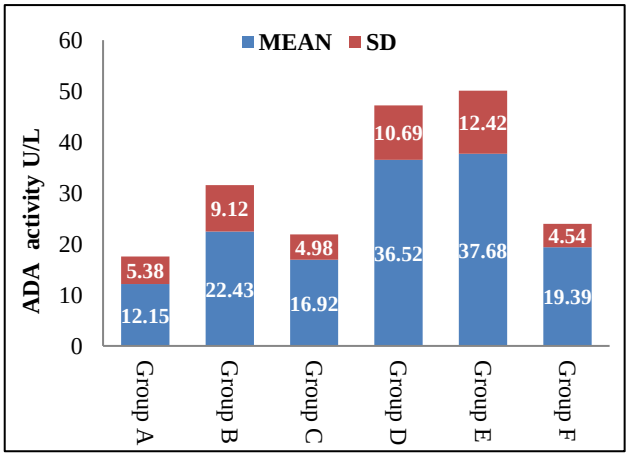

Figure 1: Comparison of serum ADA activity between groups.

The mean±SD of pleural fluid ADA activity in group B was 11.25±3.12U/L, group C was 17.56±10.42U/L and group E was 78.94±36.75U/L. The pleural fluid ADA activity in group E was higher than that of groups B and C; and the differences were statistically significant with p<0.0001 (Figure 2).

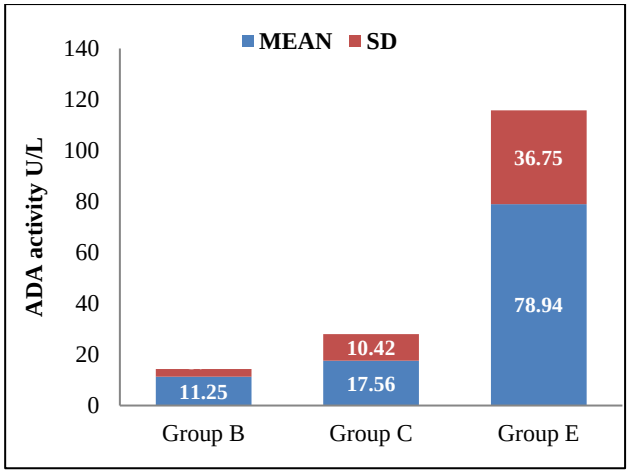

Figure 2: Comparison of pleural fluid ADA activity among groups.

The mean±SD of serum LDH activity in group A was 102.48±31.65U/L, group B was 106.26±39.42U/L, group C was 112.62±42.36 U/L, group D was 115.44±37.58U/L, group E was 120.39±41.25U/L and group F was 107.26±32.69U/L. The serum LDH activity in groups D and E were slightly elevated than other groups but no statistical significance has been observed. The pleural fluid LDH activity of group E with a mean ±SD of 292.35±121.52U/L was significantly higher ($p<0.001$) than that of Group B with a mean±SD of 113.79±48.82U/L and Group C with a mean±SD of 155.78±66.32U/L.

The mean±SD of serum glucose concentration in group A was 92.45±12.47mg/dL, group B was 97.84±21.69mg/dL, group C was 111.52±28.48mg/dL, Group D was 112.86±26.23mg/dL, group E was 110.67±34.26mg/dL and group F was 96.52±13.92.

The serum glucose concentration in groups A, B and F was lower than groups C, D and E and the difference was not statistically significant. The pleural fluid glucose concentration in group E with mean ±SD of 79.49±37.28mg/dL was significantly lower than in group B (119.40±24.18mg/dL) with statistical significance of $p<0.001$. The pleural fluid glucose concentration in group E was less than group C (81.96±31.42mg/dL) with no statistical significance.

Table 2: Mean±SD of biochemical parameters.

Variable	Specimen	Group A	Group B	Group C	Group D	Group E	Group F
ADA (U/L)	Serum	12.15±5.38	22.43±9.12	16.92±4.98	36.52±10.69	37.68±12.42*	19.39±4.54
	Pleural fluid	-	11.25±3.12	17.56±10.42	-	78.94±36.75**	-
LDH (U/L)	Serum	102.48±31.65	106.26±39.42	112.62±42.36	115.44±37.58	120.39±41.25	107.26±32.69
	Pleural F fluid	-	113.79±48.82	155.78±66.32	-	292.35±121.52	-
Glucose (mg/dL)	Serum	92.45±12.47	97.84±21.69	111.52±28.48	112.86±26.23	110.67±34.26	96.52±13.92
	Pleural fluid	-	119.40±24.18	81.96±31.42	-	79.49±37.28	-
Total protein (g/dL)	Serum	6.74±0.59	6.21±0.65	7.14±0.75	6.64±0.42	6.89±0.73	6.90±0.67
	Pleural fluid	-	1.98±0.83	3.99±0.72	-	4.14±0.89	-

There was no statistically significant difference in the mean±SD of serum protein concentrations (g/dL) in group A (6.74±0.59), group B (6.21±0.65), group C (7.14±0.75), group D (6.64±0.42), group E (6.89±0.73) and group F (6.90±0.67).

The pleural fluid protein concentrations in group E (4.14±0.89g/dL) was higher than in group B (1.98±0.83g/dL) and the difference was statistically significant with $p<0.001$. The pleural fluid protein concentration in group E was higher than group C (3.99±0.72g/dL) with no statistical significance. The mean±SD of the above biochemical parameters was shown in Table 2.

The pleural fluid/serum ratios of protein were >0.5 and LDH was >0.6 in group E patients meeting the light's criteria for differentiation of the pleural fluid as exudate. The mean±SD of percentage of lymphocytes estimated in peripheral blood and pleural fluid of group E or pulmonary tuberculosis with pleural effusion was 37.48±8.49 and 86.57±9.64 respectively and the difference was statistically significant with a $p<0.001$.

The pleural fluid ADA activity was significantly higher than serum ADA activity in group E with a $p<0.001$. (Figure 3) group E patients showed high ADA activity in exudative lymphocytic pleural effusion fluid

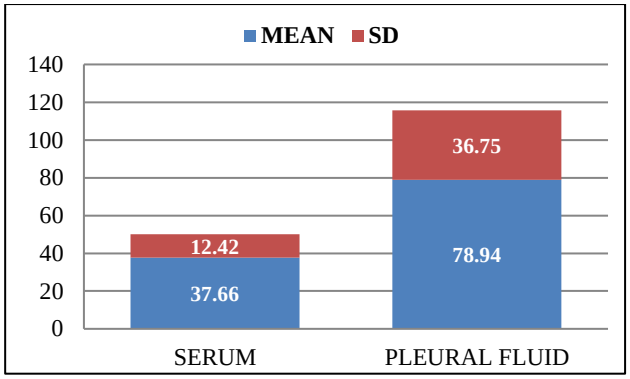

Figure 3: Comparison of serum and plerual fluid ADA activity in pulmonary tuberculosis patients with pleural effusion.

DISCUSSION

The diagnosis of tuberculous pleural effusion is challenging with 45-96% of cases being sputum negative for AFB stain and culture. In present study, 72.5% of (29 out of 40) pulmonary tuberculosis patients with pleural effusion were sputum negative for AFB stain and culture. The definitive diagnosis of paucibacillary tuberculous pleural effusion by direct examination of pleural fluid obtained by thoracentesis reveals AFB in less than 10% of the cases.[23] In present study, 12.5% of (5 out of 40) cases revealed AFB by direct examination of pleural fluid. Thoracentesis shows an exudative lymphocytic pleural effusion in more than 90% cases of tuberculous pleural effusion, thereby distinguishing them from parapneumonic and malignant pleural effusions.[24] In present study, all the 40 cases of pulmonary tuberculosis with pleural effusion (100%) had exudative lymphocytic pleural effusion.

In present study, the serum ADA activity was increased in pulmonary tuberculosis patients when compared to healthy controls and the difference was statistically significant ($p < 0.001$). This was in conformance with the work of researchers Rao et al, Amniafshar S et al, Verma M et al, and Lakshmi et al.[25-28] The serum ADA activity >30U/L and pleural fluid ADA activity >40U/L were considered as the diagnostic cut off values in pulmonary tuberculosis with pleural effusion.[29] In present study, the serum ADA activity was significantly increased ($p<0.001$) in pulmonary tuberculosis patients with pleural effusion when compared to healthy controls, transudative pleural effusion and exudative pleural effusion in conformance with study of Sonone et al.[30]

In present study, the pleural fluid ADA activity in pulmonary tuberculosis patients with pleural effusion was significantly increased ($p<0.001$) when compared to transudative and non-tuberculous exudative pleural effusion controls which was in agreement with Sonone et al, Devkota et al, Gupta BK et al, and Lee et al.[30-33] The pleural fluid ADA level rarely exceeds the cut off limit of >40U/L in nontuberculous lymphocytic effusions.[34] In present study, the pleural fluid ADA levels were >40U/L in all 40 cases of pulmonary tuberculosis with pleural effusion. In present study, the pleural fluid ADA levels were significantly higher than serum ADA levels in pulmonary tuberculosis patients with pleural effusion ($p <0.001$) which was in conformance with studies of Sharma SK et al, and Piras et al.[35,36] In present study, the serum ADA activity in treated pulmonary tuberculosis patients was significantly decreased ($p<0.001$) when compared to pulmonary tuberculosis patients, which was in conformance with Shibagaki T et al, indicating the role of pleural fluid ADA activity as prognostic marker of the disease.[37]

CONCLUSION

The serum and pleural fluid ADA activities were elevated, with pleural fluid ADA activity elevated more than that of the serum in pulmonary tuberculosis patients with pleural effusion. The serum ADA activity was decreased in pulmonary tuberculosis patients treated for one month with antitubercular treatment. The estimation of pleural fluid ADA activity in exudative lymphocytic pleural effusions can be used as a reliable marker in endemic regions for initiation of antitubercular treatment. The effective treatment response can be monitored by estimating serum ADA activity, one month after the treatment initiation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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