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Adenosine deaminase in pleural effusions with special reference to tuberculous effusions

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ABSTRACT

Aim: The aim of this study is to assess the usefulness of Adenosine deaminase levels of the pleural fluid in three different groups of patients and to confirm its usefulness in the diagnosis of tuberculous effusions. **Materials and methods:** 25 consecutive patients admitted with their first episode of pleural of were included in the study. The routine investigations were history, clinical examination. Diagnosis of tuberculosis was made based on pleural fluid analysis, chest radiography and histo pathological examination of pleural tissue. After the final diagnosis was established, the patients fell into 3 groups namely Group I: 18 patients of Tuberculous effusion. Group II: 5 patients of transudate effusion. Group III: 2 patients of Malignant effusion. The exudates were separated from, transudates by pleural fluid protein content of 3 grams or over. **Results:** Mean age of the patients in tuberculosis effusion was 27.3 years. While that of transudate effusion 42.4 years and that of malignancy 50.5 years. The male to female ratios of tuberculosis patients was 13:5 and that of transudate effusion was 3:2 and malignant effusion 1:1. Out of the 25 cases 18 had tuberculous pleural effusion (72%). 5 Patients are of tansudate effusion (20%; 3 are due to congestive cardiac failure , 2 patients of cirrhosis of liver), 2 Patients had Malignant effusion(8%; I due to sq.cell carcinoma lung, 1 due to undifferentiated carcinoma of lung) . 50% of tuberculous effusions were on the left side and 50% to the right side. In transudate effusions 2 had right sided effusions, 3 had bilateral effusions. In malignant effusions one had effusion on the right side and one had effusion on the left. The A D A level in tuberculous effusions ranged from 281 U/L to 100 I U / L. 95% of patients had levels above 55 IU/L. Malignant effusions had a range from 30-35 IU/L. In transudates the A D A levels ranged from 23 to 31 I U/ L. The mean protein concentration of tuberculous effusions was 4.93 gm % and that of malignant effusions 4.5 gm %. In transudate effusions it was 1.9 gm %. The mean A D A concentration in pleural fluid was clearly much higher in tubercular effusions (66.5 IU/L) than in transudate (28.2 1U/L) and in malignant effusions 32.51U/L. Pleural fluids from all patients with tuberculosis showed lymphocytosis. **Conclusion: E**stimating ADA activity of the pleural fluid has the advantage of a high sensitivity and specificity, Hence, it is concluded that estimation of adenosine deaminase activity in pleural fluid is an easy and reliable method for diagnosing tuberculous pleural effusion.

Key words: Adenosine deaminase, Lymphocytosis, Pleural fluid.

Introduction

A pleural effusion is said to exist when fluid can be detected clinically or by standard radio graphic techniques in the pleural space. The pleural effusion develops following changes in capillary permeability, capillary hydrostatic pressure, plasma colloid osmotic pressure or lymphatic drainage. The pleural effusion should always be considered a manifestation of systemic or local disease. Generalised fluid retention or a transudate suggests a systemic cause while an exudate suggests a local cause. The diagnosis could be established by clinical assessment chest radio graphical analysis of pleural fluid, pleural biopsy and appropriate special investigations. But inspite of careful diagnostic evaluation. The aetiology of the effusion cannot be established in about 20% of patients. The treatment in such cases has largely been empirical.

Over 90% of pleural effusions are caused by one of the following diseases- congestive Heart failure, Cirrhosis of Ascites, Pleuro-pulmonary infections, malignancy and pulmonary Embolism. Traditionally the effusions are divided into exudates and transudates based on light's criteria. If the effusion is a transudate,

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no further diagnostic procedures on the pleural fluid are indicated and in the majority of cases the underlying cause can be diagnosed clinically. However if the effusion is an exudate more investigations will be needed to define the cause of pleural disease. Numerous tests are available for determining the cause of the exudate but they lack sensitivity and specificity and are not generally available. In the height of this observation, Adenosine deaminase assay has been found to be a simple and useful investigation in the diagnosis of pleural effusion by many studies.

Materials and methods

It is a clinical study in 25 consecutive patients admitted to department of general medicine .Patients with their first episode of pleural of were included in the study. The ages of the patients ranged from 16 to 70 years. The group consisted of 9 female patients and l6 male patients. The course of the effusion was established by following investigations. The routine investigations were history, clinical examination, X-ray chest, laboratory investigations, total count, differential count, ESR, blood sugar, blood urea, serum proteins A/G ratio, urine analysis montaux test. The specific tests were pleural fluid analysis, physical appearance, proteins C sugar, cell count, types of cells, X-ray chest, histopathological examination of pleural tissue.

A diagnosis of tuberculosis was made based on pleural fluid analysis, chest radiography and histo pathological examination of pleural tissue. Ultrasonogram of abdomen was done where cirrhosis is suspected. Cases of Malignancy were diagnosed based on pleural fluid analysis, chest Radiography and histopathological examination of pleural tissue. After the final diagnosis was established, the patients fell into 3 groups namely

Group I: 18 patients of Tuberculous effusion.

Group II: 5 patients of transudate effusion.

Group III: 2 patients of Malignant effusion.

The exudates were separated from, transudates by pleural fluid protein content of 3 grams or over.

Results

25 consecutive patients admitted in general medicine department.

Table 1: Age and sex distribution among different groups

Group	Mean Age	M/F ratio
Tuberculos	27.3 years	13:5
Transudate	42.4 years	3:2
Malignant	50.5 years	2:0

Table 1 shows mean age of the patients in tuberculosis effusion was 27.3 years. While that of transudate effusion 42.4 years and that of malignancy 50.5 years. The male to female ratios of tuberculosis patients was 13:5 and that of transudate effusion was 3:2 and malignant effusion 1:1.

Table 2 : Pleural effusions among different groups

Group	No. of patients	Percentage
Tuberculous	18	72%
Transudate	5	20%
Malignant	2	8%

Table 2 shows Out of the 25 cases 18 had tuberculous pleural effusion (72%). 5 Patients are of tansudate effusion (20%; 3 are due to congestive cardiac failure , 2 patients of cirrhosis of liver), 2 Patients had Malignant effusion(8%; I due to sq.cell carcinoma lung, 1 due to undifferentiated carcinoma of lung) . 50% of tuberculous effusions were on the left side and 50% to the right side. In transudate effusions 2 had right sided effusions, 3 had bilateral effusions. In malignant effusions one had effusion on the right side and one had effusion on the left.

Table 3 : ADA values among different groups

Group	Minimum	Maximum	Mean	S.D.
Tuberculous	28	100	66.5	15.3
Transudate	23	31	28.2	3.10

Malignant	35	30	32.5	2.50

Table 3 shows The A D A level in tuberculous effusions ranged from 281 U/L to 100 I U / L. 95% of patients had levels above 55 IU/L. Malignant effusions had a range from 30-35 IU/L. In transudates the A D A levels ranged from 23 to 31 I U/ L.

Table 4 : shows mean protein and ADA levels in different groups

Group	Mean protein concentration	Mean ADA activity
Tuberculos	4.93 gm%	66.5 IU/L
Transudate	1.09 gm%	28.2 IU/L
Malignant	4.05 gm%	32.5 IU/L

Table 4 shows the mean protein concentration of tuberculous effusions was 4.93 gm % and that of malignant effusions 4.5 gm %. In transudate effusions it was 1.9 gm %. The mean A D A concentration in pleural fluid was clearly much higher in tubercular effusions (66.5 IU/L) than in transudate (28.2 1U/L) and in malignant effusions 32.51U/L. Pleural fluids from all patients with tuberculosis showed lymphocytosis.

Discussion

Pleural effusion is a common clinical problem. Pleural effusions are traditionally divided into transudates and exudates based on Light's criteria. Transudates require no further diagnostic procedures on the pleural fluid since in the majority of cases the underlying cause is diagnosed clinically. However, if the effusion is an exudate more investigations will he needed to define the cause of the pleural disease. Adenosine deaminase assay is a cheap; simple and useful one among the numerous tests available for determining the cause of the exudate. In the present study, the usefulness of ADA assay in the diagnosis of pleural effusions was evaluated by determining ADA levels in three different groups of patients. Previous studies have confirmed the usefulness of ADA assay in the diagnosis of pleural exudates particularly in differentiating tuberculosis and malignant effusions, the two most common causes from each other and from other causes of pleural exudates.

Piras et al[1]found that the mean ADA concentration in tuberculous pleural effusions was 83.04 ± 25.51 IU/L. This was much higher (P less than 0.01) than pleuropulmanory malignancy (15.54 ± 6.56 IU/L). Jan Hankiewicz et al [3]have found that patients with tuberculosis showed increased activity of ADA in pleural exudates, the highest value obtained being 21.81 mu/ml in pleural exudates and 6.06 mu/m1 in serum. The pleural exudate of neoplastic origin showed a general increase in ADA activity. In pleural transudates ADA activity was comparatively the lowest. Irma Ocana et al opined that in tuberculous effusion the ADA activity (92.43 ± 29.43) was clearly higher than in all other groups (P less than 0.001). In non-tuberculous effusions like malignancy (13.47 ± 10.63) and in acellular transudates (2.29 ± 3.04) the ADA activity is always low. Tom Patterson et al[2] had similar findings. Patients with tuberculous pleurisy had a significantly higher mean ADA activity in pleural fluid than patients with malignancy (P less than 0.001) or transudates (P less than 0.001).

F. J. Maritz et al[6] had a mean ADA activity in tuberculous exudates of 92.11 ± 37.05 IU/L which was statistically different from the 23.23 ± 13.15 IU/L in secondary malignant tumours of the pleura (P less than 0.0001). Baldevraj et al reported a mean pleural ADA activity of 99.56 ± 9.78 IU/L in tuberculous effusions which again was clearly higher than in other groups (P less than 0.001) like malignancy 20.58 ± 3.04 IU/L and transudates 12.25±14 IU/L. R. Vidal et al found an average value of ADA in tuberculous pleural fluid (91.9 ± 27.9) which was higher than the values observed in other aetiologies (P less than 0.0001). Pranay Kumar sinha et al had a similar observation of ADA concentration in tuberculous pleural effusions (78.2 ± 24.3). This was much higher (P less than 0.01) than those in pleuropulmonary malignancies (14.61 ± 7.8) and hypoproteinemia (5.0 ± 2.0). R.K. Narang reported a value of 97.65 ± 15.96 1U/L in tuberculous pleural effusions which was consistently superior to that in malignant effusion (19.45 ± 4.81 TU/L) followed by transudate effusion with a mean of 8.70 ± 0.44 IU/L. Adenosine deaminase activity was significantly elevated in tuberculous effusions in comparison with malignant effusions and transudates (P less than 0.001). In the present study the mean ADA activity in tuberculous exudate was 66.5 ± 14.6 IU/L while that in malignant effusions was 32.5 ± 2.5 IU/L and in the transudate effusions the value is 28.2 ± 2.78 11.J/L. The mean higher in tuberculous effusions compared to ADA activity was significantly other two groups. The sensitivity and specificity of ADA which compared to pleural biopsy in tuberculous effusions

was determined as Sensitivity as 94.5% , Specificity 100% .Jan Hankiewicz et al and Tom Patterson et al failed to show any relationship between ADA activity in effusions and its activity in blood Maritz et al found high ratios in tuberculosis but there was a greater degree of overlap with effusions due to malignant tumours at the lower end of the scale. They saw no advantage in determining the ADA ratios in all cases. The cut off levels of ADA activity in tuberculous pleural fluid has been different in different studies. Inma Ocana et al found that none of their patients with tuberculous effusions had ADA activity less than 45 1U/L. An arbitrary value of 40 U/L for ADA in pleural fluid were chosen by Maritz et al . 7% of tuberculous patients had a value below this and none of the patients had a value less than 20 1U/L. of the patients with malignant tumours 15% had an ADA concentration more than 40 IU/L but in no case was a value above 60 IU/L was seen. So, in patients with ADA activity less than 40 IU/L tuberculosis is unlikely. With values between 40 and 60 IU/L, the likelihood of tuberculosis increases. Values above 60 IU/L especially more than 80 IU/L make the diagnosis of tuberculous effusions certain. Baldevraj et al chose a cut off value of 40 IU/L and suggested that low values less than 40 IU/L serve to exclude tuberculosis and suggest the probability of malignant effusion. None of the patients of tuberculous effusions had values below 40 IU/L . So ADA values below 40 IU/L make tuberculosis unlikely.

Vidal et al had 45 IU/L as lowest value for tuberculosis. In the present study the ADA activity in the pleural fluid for tuberculous patients was from 28 IU/L to 100 IU/L with a cut off value of 51.9 IU/L Only one patient had a value below this value. (1 out of 18). For malignant effusions the cut off value was 30 IU/L one patient having value above this value . The sensitivity of ADA activity in tuberculous effusion in diagnosing tuberculous pleural effusions is 100% as reported by Inma Ocana[4] et al. Similar values were reported by Baldev raj et al 100%. The high sensitivity and specificity of adenosine deaminase activity 94.5% and 100% found in this study goes well with the findings of Martinezet al. According to their study the ADA concentration in all panems with tuberculous effusion were well above the upper non-tuberculous value. The findings in the study were similar to those of conducted by Malchlouf et al. whose study showed a sensitivity and specificity of 9511, and 100% respectively for ADA concentration in diagnosing tuberculosis. Kaur et al in their study on the diamostic value of adenosine deaminase in pleural peritoneal and cerebrospinal fluid have shown that of no practical [10]clinical value in diagnosing tuberculosis. The findings of this present study contradicts these findings and establishes well that adenosine deaminase activity has a high sensitivity and specificity in diagnosing tuberculosis ADA activity was found to be useful in diagnosing tuberculous peritonitis in studies conducted by Nijawan et al. Dwivedi [7]et al and Soliman et al. Thus, the present study has confirmed the Value of ADA activity in pleural fluid in the diagnosis of pleural effusion in differentiating tuberculous pleural effusions from others like malignant pleural effusions and transudates. The mean value obtained in the present study for tuberculous pleural effusion was significantly different from other groups. The sensitivity of 94.5% obtained in our study was also higher compared to other methods of diagnosing tuberculous pleural effusion. But why was ADA increased only in Tuberculous effusion. This can possibly be explained by the following observations made by previous workers. Piras et al[1] opined that ADA had a crucial function in the differentiation or proliferation or both of lymphoid cells. ADA concentrations are increased in typhoid fever and tuberculosis in which host defences are mostly a function of cell mediated immunity, underlying the importance of this enzyme to rapid proliferating cells and agrees well with the negative response observed in combined immune deficiency. The increased enzymatic activity in tuberculous pleurisy further supports the view of a causal relationship between ADA and T cell response. Cellular activation could be responsible for an augmented enzymatic activity to avoid accumulation of toxic metabolites but an increased demand for energy might be an explanation. In human pathology B cell activation seems not responsible for the same phenomenon, A D A could be a new marker for delayed immunity only. Previous studies have shown that the percentage of T- lymphocyte sub-population in tuberculous pleural fluid is higher than in peripheral blood. Inma Ocana et al [5] found a high percentage of T-Lymphocytes in tuberculous effusions but this was not correlated with the enzyme level (p less than 0.10). This suggests that the activity of the enzyme may be correlated more to the maturative stage of the T-cell than to its number. Tom Patterson suggested that higher A D A activity [8]in pleural fluid may probably be due to ADA being locally synthesised by cells within the pleural cavity in tuberculoses. The high activity of T_Lymphocytes in tuberculous effusion seems a reflection of local activation of T-Lymphocytes and local cellular immune response. Above all, ADA assay is a simple rapid and least invasive method of diagnosis of tuberculous effusion particularly when it is unsettled . Estimation of A D A can be done within 2 hours. It is a non invasive procedure and can be safely done in any patient[9]. It is also found to be cost effective as the

cost of estimation of adenosine deaminase activity has only about Rs. 15/- per patient with this method. Another method gaining popularity is the enzyme based A D A estimation available as kits. These kits are convenient to use, rapider but little expensive. what ever method is used A D A estimation is very cheap when compared to other methods of confirming the diagnosis of tuberculous pleural effusions except that of showing acid fast bacilli in smear.

CONCLUSION: This study has established the superiority of estimating A D A activity of the pleural fluid to all other tests which can be used to diagnose tuberculous pleuritic as a cause of effusion. It has the advantage of a high sensitivity and specificity. It is simple to perform and can be done in any patient. With the advent of kits, it is still more simple to perform. It is a cheap and rapid procedure. Hence, it is concluded that estimation of adenosine deaminase activity in pleural fluid is an easy and reliable method for diagnosing tuberculous pleural effusion.

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