Significance of adenosine deaminase in diagnosing tuberculous pleural effusion

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ABSTRACT

Tuberculosis (TB) is a major public health problem in developing countries including Nepal. One of the common presentations of TB is pleural effusion. The diagnosis of tubercular pleural effusion can be difficult because of the low rate of detecting tubercule bacilli by direct stain and culture of pleural fluid for acid-fast bacilli (AFB). Pleural biopsy can be useful but is invasive and requires experts. In this context, pleural fluid Adenosine Deaminase (ADA) level has been proposed as easy, cheap and highly sensitive test for diagnosis of TB pleural effusion. The present study was undertaken to define the role of pleural fluid ADA value in accurate diagnosis of TB pleural effusion. A Prospective analysis of 100 patients admitted in Nepal Medical College and teaching Hospital with pleural effusion was done. Pleural fluid ADA level was evaluated in all patients, and significance of pleural fluid ADA level in TB pleural effusion was studied. It was found that mean ADA level in pleural fluid was 105.8 $\pm$ 67.23 U/L in cases of TB, as compared to 16.83 $\pm$ 8.91 U/L in malignancy, 44.53 $\pm$ 32.84 U/L in parapneumonic effusion and 15.94 $\pm$ 4.88 U/L in patients with miscellaneous diagnosis. For a cut-off value of 42.19 U/L for diagnosis of TB pleural effusion, sensitivity was found to be 90.8% and specificity 82.8%. Almost all patients diagnosed to have TB pleural effusion responded completely to anti-tubercular treatment. So, we concluded that pleural fluid ADA analysis could be easy, cheap and highly sensitive and specific test for diagnosis of TB pleural effusion.

Keywords: Tuberculosis, pleural effusion, tubercular pleural effusion, ADA.

INTRODUCTION

Tuberculosis (TB) is one of the major public health issues in developing countries like ours. Pleurisy with effusion as a complication of primary pulmonary tuberculosis occurs in children and adolescents, but can also occur in older patients with classic reactivation of tuberculosis.[1]

The initial event in the pathogenesis of primary TB pleural effusion is the rupture of subpleural caseous focus in the lung.[2] Tuberculous pleural effusion is thought to result from a delayed hypersensitivity reaction in response to the presence of mycobacterial antigens in the pleural space that follows this rupture.[3] The accumulation of fluid in pleural cavity results due to increased capillary permeability as well as due to impairment of lymphatic clearance of exudative fluid from pleural cavity due to occlusion of pleural stomata.

The diagnosis of tuberculous pleural effusion can be difficult because of the low sensitivity of various diagnostic methods. Lymphocytic exudate seen in tuberculous pleural effusion also can occur in other diseases such as malignancy and collagen vascular diseases. Mycobacterium tuberculosis in pleural fluid is scanty and rarely observed on direct examination by AFB staining. Cultures for AFB in TB pleural effusion are positive in only 20 to 30% of pleural fluid samples and in 50 to 80% of pleural biopsy specimens.[4] The sensitivity of polymerase chain reaction for active disease is 78%.[5] The cutaneous response to purified protein derivative (Mantoux test) may also be negative in one third of the patients.[6]

In this context, attempts have been made to identify markers which allow more rapid and accurate diagnosis. One such marker is adenosine deaminase (ADA), which has been proposed to be a useful diagnostic marker for tuberculous disease in pleura, pericardium, and peritoneum.[7] Several reports have suggested that an elevated pleural fluid ADA level predicts tuberculous pleurisy with a sensitivity of 90 to 100% and a specificity of 89 to 100%.[8]

ADA is an enzyme in the purine salvage pathway that catalyses conversion of adenosine and deoxyadenosine to inosine and deoxyinosine with the release of ammonia.[9] Its distribution in the human organ is ubiquitous, but its physiologic role is especially important in lymphoid tissue.[10] ADA is a predominant T lymphocyte enzyme,[11] with variation according to cellular differentiation,[12] and its plasma

Table-1: Sings and symptoms patients

Clinical features	Percentage/ number (n=100)
H/O smoking	31
Fever	58
Cough	59
Shortness of breath	65
Chest pain	59
Hemoptysis	10
Others	15

activity is high in diseases where cellular immunity is stimulated. It is well known that tuberculosis is one of these diseases. The ADA activity is raised in lymphocytic pleural effusions of tuberculous origin only. We do not know why the enzyme level is not increased in other lymphocytic effusions. ADA analysis is a sensitive marker of tuberculous pleural effusion, even in HIV patients with very low CD4 counts.

In this work, pleural fluid ADA value was correlated in patients provisionally diagnosed to have TB pleural effusion. Patients diagnosed to have TB from relevant clinical findings and elevated pleural fluid ADA level were put on standard anti-tubercular treatment and response noted at the end of treatment.

MATERIALS AND METHODS

A Prospective analysis of 100 patients (53 males and 47 females) admitted in Nepal Medical College and Teaching Hospital with pleural effusion from January 2007 to December 2011 was done. A detailed history, a thorough physical examination were performed, and chest X-ray films of all patients were obtained. A standard diagnostic thoracocentesis was performed. Pleural fluid thus obtained was analysed for total count, differential count, total protein, Lactate Dehydrogenase (LDH), ADA and culture and sensitivity for pyogenic pathogens. Further, cytological examination, AFB staining and Gram's staining of the fluid sediment were also done. Mantoux test of patients provisionally diagnosed to have TB was also done.

Pleural effusion was classified as either exudative or trasudative on basis of Light's criteria. Patients with relevant clinical history and examination findings with exudative pleural fluid supported by Mantoux test as well as all those patients with ADA value >40 U/L were provisionally diagnosed to have TB pleural effusion and standard ATT regimen was started. Such patients were reviewed at 2 and 6 months interval on out-patient department (OPD) basis. Clinical as well as laboratory improvement of patients were assessed by history, clinical examination as well as repeated chest X-ray. Patients with clinical and laboratory evaluation not compatible with TB were considered for alternative diagnosis, investigated as required to reach a final diagnosis and treated accordingly.

Table-2: Mean ADA level in pleural fluid (U/L)

Diagnosis	Mean ADA level in pleural fluid U/L
Tuberculosis	105.8 $\pm$ 67.23
Malignancy	16.83 $\pm$ 8.91
Pneumonia	44.53 $\pm$ 32.84
Others	15.94 $\pm$ 4.88

RESULTS

Mean age of patients was 42.2 $\pm$ 19.48 years, with the minimum being 15 years and maximum being 83 years. The signs and symptoms elicited in patients are as shown in the Table-1.

Of 100 patients with pleural effusion, 67 were finally diagnosed to be due to tuberculosis, 11 were diagnosed to be due to malignancy, 13 due to pneumonia leading to parapneumonic effusion, 5 due to congestive heart failure and 4 due to nephrotic syndrome.

Mean ADA level in pleural fluid was 105.8 $\pm$ 67.23U/L in cases of TB, 16.83 $\pm$ 8.91U/L in malignancy, 44.53 $\pm$ 32.84U/L in parapneumonic effusion and 15.94 $\pm$ 4.88 U/L in others (Table-2). Graphical representation of Pleural ADA values in different diseases was showed in Fig. 1.

Analyzing pleural fluid by Light's criteria, all cases with TB, malignancy and pneumonia had exudative effusion, all cases with CHF had transudative effusion whereas 50% of cases of nephrotic syndrome had

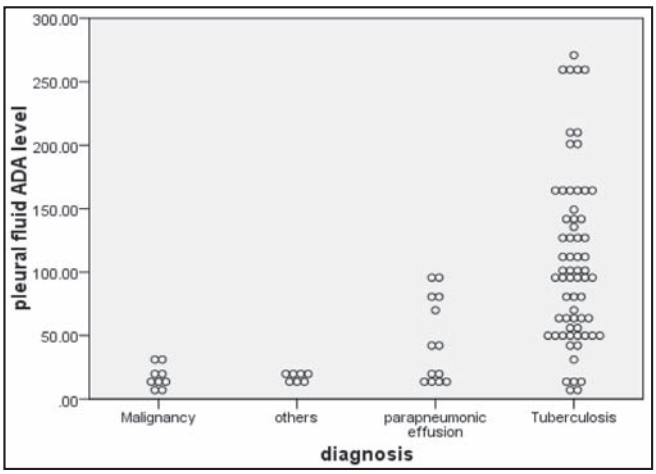

Fig. 1. Graphical representation of Pleural ADA values in different diseases

exudative and 50% had transudative effusion. Of all cases diagnosed as TB (67 cases), 41.79 % (28 cases) had mantoux test positive (Induration more than 10 mm) whereas none of the cases were positive for AFB. Of all cases diagnosed as malignancy (11 cases), 18.18% (2 cases) had positive pleural fluid cytology for malignant cells (Fig. 2). All cases provisionally diagnosed as TB (67 cases) were put on anti-tubercular treatment as per DOTS, of which 3 cases were lost follow up, 1 didnot respond to treatment and the remaining 63 cases were cured.

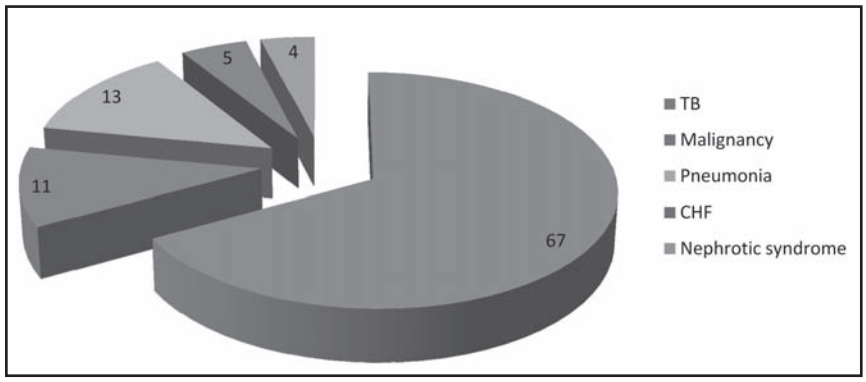

Fig. 2. Report of final diagnosis

Among cases with pleural fluid ADA value more than 40 U/L, all cases were of tuberculosis except 7 cases of parapneumonic effusion. The values of ADA in pleural fluid in different diseases is showed in Table-3.

DISCUSSION

In this study, tuberculosis accounted for 67% of cases of pleural effusion. As expected all cases of TB pleural effusion were exudative which is explained by the pathogenesis of formation of effusion in TB.

Considering pleural fluid ADA level in different conditions, mean ADA level was very high in TB pleural effusion (105.8 ± 67.23 U/L) as compared to 44.53 ± 32.84 in parapneumonic effusion, 16.83 ±_8.91 in malignancy and 15.94 ± 4.88 in cases with miscellaneous diagnosis.

Similar findings have been found in several previous studies. Ocaña *et al* found mean pleural fluid ADA level to be 92.43 ± 29.43 U/L in TB pleural effusion.[13] Valdes *et al* found pleural fluid ADA level in TB pleural effusion to be 111.1 ± 36.6 U/L.[14] Valdes *et al* found pleural fluid ADA level in TB pleural effusion to be 127.5 ± 2.9.[15]

Thus, high ADA value in pleural fluid can diagnose TB with high accuracy. Using ROC curve, the cut-off value from our study was 42.19 U/L with sensitivity 90.8% and specificity 82.8%. For ADA level >90 U/L the specificity was 100%.

Table-3: Pleural fluid ADA level in different diseases.

Diagnosis	Pleural fluid ADA level U/L		
	< 40	40-70	>70
Tuberculosis	6	18	41
Malignancy	9	0	0
Parapneumonic effusion	6	2	5
Others	7	0	0

Several studies have defined several cut-off values for diagnosis of TB pleural effusion ranging from 40 to 70 U/L. Our study also shows that there are no other causes of pleural effusion for ADA level >40 U/L than TB, except for few cases due to parapneumonic effusion. Ocaña *et al* found 97% sensitivity and 100% specificity for value more than 45 U/L. Bañales *et al* found ADA level of >70 U/L to be 98% sensitive and 96% specific.[16] DE Oliveira *et al* found ADA level of >40 U/l to be 90.7% sensitive and 97.7% specific.[17]

Abnormally high levels of pleural fluid ADA level in all patients with TB pleural effusion indicated pleural fluid ADA could be a good diagnostic marker for TB pleural effusion. In our study, patients diagnosed as TB, depending on relevant clinical history and high ADA level in pleural fluid, were put on standard ATT regimen and almost all were cured. This observation provides evidence in support of using pleural fluid ADA level as a diagnostic marker for TB pleural effusion.

It is difficult to diagnose TB pleural effusion by other conventional methods, as it has also been shown in our study that only 41.79% of cases diagnosed to have TB pleural effusion were Mantoux positive, and none of the cases were positive for AFB staining. Previous literatures have also mentioned AFB detection rate to be low from pleural fluid sample. The other method considered for diagnosing TB pleural effusion is pleural biopsy which is invasive blind procedure and requires high expertise as well.

In conclusion, determination of ADA is a cheap and easy test, that we now consider in the early routine evaluation of patients with pleural effusions, particularly if diagnosis of tuberculosis is suspected and in places where prevalence of the disease is still high as is in our country. By using ADA as a marker for the diagnosis of tuberculous pleural effusion, the accurate diagnosis can be made in more than 95 percent of cases and it helps avoid invasive test like pleural biopsy as well.

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