Original Research

Role of adenosine deaminase in diagnosis of exudative type of pleural effusion

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Abstract

Background: The diagnosis of tubercular pleural effusion remains a common clinical challenge. At least 50% of cases of tubercular pleural effusion present as primary disease without involvement of other organs.

Objectives: Estimation and comparison of Adenosine Deaminase (ADA) levels in exudative pleural effusions with special reference to tubercular aetiology.

Materials and Methods: Sixty patients of pleural effusions of various aetiologies formed the sample of the study. Pleural fluid analysis was done and clinical profile of each patient was taken. Total patients were divided into 6 groups consists of Tubercular pleural effusion (39), parapneumonic effusion (10), emphyema (5), malignant pleural effusion (3), pancreatic pleural effusion (2) and amoebic pleural effusion (1).

Results: Incidence of tubercular pleural effusion is 65% followed by parapneumonic effusions 16.6%. Males (68.3%) are more prone to incidence of tubercular pleural effusion.

Conclusion: Pleural fluid Adenosine deaminase (ADA levels are highly sensitive for tuberculous pleural effusions. ADA is diagnostic even in HIV positive patients with tubercular pleural effusion. ADA levels easily differentiate tuberculous pleural effusion from parapneumonic, malignant, pancreatic, and amoebic pleural effusions.

KEY WORDS: Adenosine Deaminase (ADA), Tubercular pleural effusion, Para pneumonic effusion, Empyema

Introduction

The global incidence of tuberculosis has sharply increased. Tuberculosis (TB) is an important cause of lymphocytic effusions along with malignancy, lymphoma, collagen vascular diseases, and chylothorax. More than 90% TB effusions show a lymphocytic predominance. The diagnosis of tubercular pleural effusion remains a common clinical challenge. At least 50% of cases of TB pleural effusion present as primary disease without TB involvement of other organs. Tuberculin testing is neither sensitive nor specific.[1]

The traditional answer to the problem is to perform a needle biopsy for both histological study and culture which can lead to diagnosis of tuberculosis patients 86% of the time.[2] These procedures combined with cultures of pleural fluid and sputum, have been reported to provide microbiological confirmation of *Mycobacterium tuberculosis* as often as 90% of the time.[3] Four relatively new techniques have been reported to help make the diagnosis of TB patients: Adenosine deaminase, lysozyme, interferon gamma, and PCR. Surprisingly, PCR has a relatively low sensitivity in pleural fluid (0.42–0.81) and is fairly expensive.[4,5,6]

The sensitivity of elevated interferon level appears better (0.89–0.99).[7,8] ADA is an enzyme of purine catabolism leading to hydrolytic deamination of adenosine to inosine and ammonia. ADA has shown promising results in diagnosis of tuberculous pleural, peritoneal and pericardial effusion, and tuberculous meningitis.[9-15]

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The present study aimed to evaluate and compare the adenosine deaminase levels in exudative pleural effusions of various aetiologies.

Materials and Methods

The present study includes patients presenting with signs and symptoms suggestive of pleural effusion and undergoing pleural fluid analysis in MNR Medical College and Hospital, Sangareddy from October 2013 to October 2015. A total of 60 subjects were included in this study.

Total patients were divided into 6 groups consists of

1. Tubercular pleural effusion (39)
2. parapneumonic effusion (10)
3. emphyema (5)
4. malignant pleural effusion (3)
5. pancreatic pleural effusion (2) and
6. amoebic pleural effusion (1)

Inclusion criteria
Patients with exudative pleural effusion were included.

Exclusion criteria
Patients with transudative pleural effusion were excluded.

Diagnostic criteria
LIGHT'S criteria

- Pleural fluid protein to serum protein ratio > 0.5
- Pleural fluid LDH to serum LDH > 0.6
- Pleural fluid LDH greater than 2/3 rd of the upper limit of normal serum LDH

Parameters studied
Blood analysis, chest X-ray, sputum analysis, instead of sputum fluid analysis - pleural fluid analysis, USG- abdomen, bronchoscopy, and HIV test.

Results

The present study includes 60 cases. Among which 65% are tubercular pleural effusion, 16.6% are parapneumonic effusion, 8.8% are emphyema, 5% are malignant pleural effusion, 3.33% are pancreatic pleural effusion, and 1.6% are amoebic pleural effusion.

The incidence of tubercular pleural effusion is highest in the present study (65%) followed by para pneumonic effusion (16.6%), empyema (8.3%), malignant pleural effusion (5%), pancreatic pleural effusion (3.3%), and amoebic pleural effusion (1.6%) (Figure 1).

In the present study the incidence of pleural effusion was highest in the age group of 30–39 years. Tuberculous pleural effusions were common between 30 and 39 years. Para pneumonic effusions were common between 30 and 39 years. Empyema was common between 30 and 49 years. Malignant effusion was common between 60 and 89 years. Pancreatic effusions and amoebic pleural effusions were common between 40 and 49 years. (Table 1) In present study, the incidence of pleural effusion was higher in males than females. There were 41 (68.3%) males and 19 (31.7%) females.

In the present study, the commonest symptom was fever (75%), followed by breathlessness (70%), cough (57%), and chest pain (47%). The commonest symptom in tubercular pleural effusion is fever (72%). The commonest symptom in para pneumonic effusion is fever (90%). The commonest symptom in Empyema is breathlessness (100%).

Out of 60 cases of pleural effusion, there were 10 cases of HIV with tubercular pleural effusion. 60% of patients with HIV with tubercular pleural effusion had fever, 70% had cough, 60% had breathlessness, and 40% had history of loss of weight.

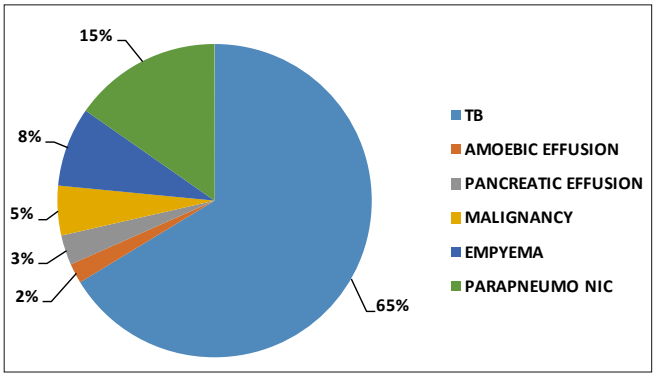

Figure 1: Incidence of various types of pleural effusion

Table 1: Incidence of age in various types of pleural effusion

Age (Yrs.)	Total cases (%)	Group I *n* = 39 (%)	Group II *n* = 10 (%)	Group III *n* = 5 (%)	Group IV *n* = 3 (%)	Group V *n* = 2 (%)	Group VI *n* = 1 (%)
20-29	11(18.3)	10(25.6)	1(10)	-	-	-	-
30-39	18(28.3)	12(30.7)	4(40)	2(40)	-	-	-
40-49	14(23.3)	8(20.5)	1(10)	2(40)	-	2(100)	2(100)
50-59	10(16.6)	8(20.5)	2(20)	-	-	-	-
60-69	4(6.4)	-	2(20)	-	2(66.6)	-	-
70-79	1(1.6)	-	-	1(20)	-	-	-
80-89	2(3.3)	1(2.5)	-	-	1(33.3)	-	-

Table 2: The pleural fluid cell count/mm^3 in different types of pleural effusion

	Total cases (%)	Group I *n* = 39 (%)	Group II *n* = 10 (%)	Group III *n* = 5 (%)	Group IV *n* = 3 (%)	Group V *n* = 2 (%)	Group VI *n* = 1 (%)
0-100	5(8.3)	4(10.2)	1(10)	-	-	-	
100-200	10(16.6)	7(17.9)	-	-	-	2(100)	1(100)
201-300	5(8.3)	2(5.1)	3(30)	-	-	-	-
301-400	6(10)	4(10.2)	1(10)	-	-	-	-
401-500	16(26.6)	11(28.2)	3(30)	-	1(33.3)	-	-
501-600	8(13.3)	7(17.9)	1(10)	-	2(66.4)	-	-
601-700	4(6.6)	3(7.6)	1(10)	-	-	-	-
701-800	1(1.6)	1(2.5)	-	-	-	-	-
801-1000	-	-	-	-	-	-	-
1000-5000	4(6.7)	-	-	5(80)	-	-	-
5000-25000	1(6.6)	-	-	1(20)	-	-	-

Table 3: Variation of pleural fluid protein

Pleural fluid protein (gm %)	Total cases (%)	Group I *n* = 39(%)	Group II *n* = 10(%)	Group III *n* = 5 (%)	Group IV *n* = 3 (%)	Group V *n* = 2(%)	Group VI *n* = 1(%)
3.0-3.5	6(10)	3(8)	2(20)	-	-	-	1(100)
3.5-4.0	16(27)	6(15.3)	6(60)	2(40)	1(33.3)	1(50)	-
>4.0	38(63)	30(77)	2(20)	3(60)	3(66.6)	1(50)	-

In the present study, all patients of tuberculosis, malignant, and amoebic effusion had lymphocytes as the predominant cells in that pleural fluid. All patients of Para pneumonic effusion, empyema, and pancreatic pleural effusion had a neutrophilic response in their pleural fluid (Table 2).

The majority of patients with tubercular pleural effusions i.e., 33 (84.6%) had pleural fluid sugars >60 mg%. The majority of para pneumonic effusion i.e., 5 (50%) had pleural fluid sugars >60 mg%. In Empyema group, 3 (60%) patients had pleural fluid sugars less than 45 mgs%. In malignant, pancreatic, and amoebic pleural effusion all patient had pleural fluid levels >60 mgs%.

In the present study 10 (17%) of the patients were positive for HIV. In the tuberculous pleural effusion group, 10 (26%) of patients were HIV positive. All the patients with para pneumonic, empyema, malignant, pancreatic, and amoebic pleural effusions were negative for HIV.

All the patients of Tuberculous pleural effusion i.e., 39 (65%) had their Pleural fluid Adenosine Deaminase (ADA-PF) levels between 48 and 242 U/L. A total 17 patients of tuberculous pleural effusion had their ADA-PF levels between 71 and 100 U/L. All the patients of para pneumonic effusion had their ADA-PF levels below 40 U/L except 2 cases. Those 2 patients had ADA-PF levels between 41 and 50 U/L (Table 4).

Among 39 patients of tuberculous pleural effusion, 10 were HIV positive and 29 were HIV negative patients. However, there was no significant difference in the pleural fluid percentage of leucocytes (P value 0.1026), proteins (*p* value 0.166), glucose (*P* value 0.7719) between HIV positive and HIV negative. The ADA-PF levels among HIV positive patients (103.5 U/L) did not differ from the ADA-PF level among the HIV negative patients (115.5 + 45.8U/L). Statistically there is no difference between HIV positive and HIV negative patients (*p*-value 0.4729) in ADA levels.

The smear for AFB was negative in all cases of pleural effusion. Gram stain showed positive in 4 cases all belonging to empyema group. Two smear showed gram +ve cocci in chains and 2 smears showed gram –ve bacilli. The pleural fluid culture was positive in 3 cases all belonging to empyema group.

Two specimens showed growth of streptococcus pneumoniae and other one specimen showed *Klebsiella pneumonia*. The sputum for AFB was done in all the patients. Smear was positive for AFB in 4 cases. Sputum test for gram stain was done in all the patients and it found in 4 patients, all belonging to para pneumonic effusion. Two smears showed gram +ve cocci and 2 smears showed gram –ve bacilli. Sputum culture are positive in 4 cases all belonging to para pneumonic effusion. Two specimens showed growth of *Streptococcus pneumoniae*. FNAC was done in 2 patients who had mass lesions in the x-ray. Two patients FNAC was suggestive of adenocarcinoma.

Discussion

Three major meta-analyses, based on 75 studies including a total of 14,505 patients, have been performed over the last decade, and these have demonstrated a uniformly high diagnostic performance of pleural ADA for TPE.[16,17,18] One of the major concerns regarding the sensitivity of ADA was its

Table 4: Pleural fluid adenosine deaminase (ADA-PF) levels in tuberculous pleural effusion

Pleural fluid ADA (U/L)	Total cases	Group I *n* = 39	Group II n = 10	Group III *n* = 5	Group IV *n* = 3	Group V *n* = 2	Group VI *n* = 1
1-10	1					1	
11-20							
21-30	4		2			1	1
31-40	7		6		1		
41-50	5	1	2		2		
51-60	1	1					
61-70	3	3					
71-80	5	5					
81-90	6	6					
91-100	6	6					
101-110	2	2					
111-120	1	1					
121-130	4	3		1			
131-140	3	2		1			
141-150	3	2		1			
151-160	2	1		1			
161-170	2	2					
171-180							
181-190	1	2					
191-200	2	2					
201-250	1	1					
>250	1			1			

Table 5: Comparison of ADA values of present study with previous studies in India and foreign country.

Investigator	Country	Year	Cut off	Sensitivity	Specificity	PPV	NPV
Reechapichitkul et at	Thailand	2001	48	80	80.5	71.4	86.8
Mo-Lung chen et al	China	2004	55	87.3	91.8	82.1	92.4
Bharat et al	India	2010	40	92	90	92.8	90
Sushmita et al	India	2010	40	97	93	4	97
Sharma et al	India	2010	35	83.3	66.6	-	-
Perlat et al	Albania	2011	40	89	28.8	54.5	685
Present study	India	2014	45	100	71.42	86.56	100

reliability in immune-compromised patients; however, more recent studies have demonstrated that ADA is a reliable marker of tuberculous pleurisy in HIV-positive patients, even in those with a low CD4 T-cell count.[20,21] On the other hand, ADA levels in pleural fluid are also elevated in renal transplant recipients with tuberculous pleurisy.

To date, almost all the studies performed concerning the diagnostic value of ADA for TPE were reported from intermediate-to-high prevalence areas, so acceptance of this test was not universal and remained contentious in countries with lower prevalence. Given this, it was considered desirable that further studies be carried out in areas of low TPE prevalence in order to confirm the suitability of this biomarker in these areas.[19]

Almost all research workers have shown sensitivity and specificity of 80% to 100% for the value of ADA in pleural fluid using different cut-off levels. Several studies have suggested that an elevated pleural fluid ADA level predicts tuberculous pleuritis with a sensitivity of 80–100% and a specificity of 80–92% when the Giusti method is used (20). The reported cut-off value for ADA (total) varies from 40 to 55 U/L[12-15] (Table 5).

Conclusion

Pleural fluid Adenosine Deaminase (ADA) levels are highly sensitive for tuberculous pleural effusions. ADA is diagnostic even in HIV positive patients with tubercular pleural effusion. ADA levels easily differentiate tuberculous pleural effusion from para pneumonic, malignant, pancreatic, and amoebic pleural effusions.

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