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Original Research Article

Diagnostic Accuracy of Tuberculous Pleural Effusion by Combining Adenosine Deaminase Assay and Lymphocyte/ Neutrophil Ratio in Pleural Fluid

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Abstract

Background: Pleural effusion can be caused by various etiological conditions, commonest being tuberculosis. Histopathological examination, microbiological examination in addition with biochemical analysis of pleural fluid can help in determination of tuberculous pleural effusion. Estimation of Adenosine Deaminase (ADA) levels and lymphocyte / neutrophil ratio in the pleural fluid can help in the early diagnosis.

Material and methods: We studied 208 patients with pleural effusion. In our prospective study of 3 years we analyzed ADA levels along with lymphocyte/ neutrophil ratio in pleural fluid and total counts in the peripheral blood in both patients having tuberculous pleural effusion and non-tuberculous pleural effusion.

Results: Tuberculous pleural effusion cases showed the predominance in the lower age group when compared to non-tuberculous effusion cases. Both of them showed the male predominance. ADA levels in tuberculous pleural effusions ranged from 46.5IU/L to 210IU/L and non tuberculous pleural effusions ranged from 10.1IU/L to 48.4IU/L showing high ADA levels in tuberculous pleural effusions. Lymphocyte predominance was noted in tuberculous effusion where as neutrophil predominance was noted in non tuberculous effusion cases. There was no variability in the total count of leukocytes in peripheral smear.

Conclusion: Assessing ADA levels combined with lymphocyte/neutrophil ratio in the pleural fluid can increase the accuracy in diagnosing tuberculous pleural effusion.

Keywords: Tuberculosis; Pleural Effusion; Adenosine Deaminase; Lymphocyte Predominance.

Introduction

Tuberculosis is one of the deadly communicable disease in developing countries. Worldwide India has highest burden and accounts for quarter of global tuberculosis cases. It is one of the common cause for developing pleural effusion, but the diagnosis is difficult due to its paucibacillary nature [1].

Tuberculosis is caused by Mycobacterium tuberculosis bacteria which triggers an immune response involving CD4+T cells, macrophages and cytokines (especially γ-interferon, Interleukin-1 and Interleukin-2). Increased levels of ADA activity in pleural fluid is seen particularly in tuberculosis. However, the ADA activity in pleural fluid is also increased in other diseases like lymphomas and cancerous effusions. Assessing the ADA activity and lymphocyte/neutrophil ratio can help in accurate diagnosis of tuberculous pleural effusions. Other sensitive methods for determination of Tuberculous pleural effusion is assay of γ-Interferon, released by the CD4+T cells. Though this method is sensitive it cannot be utilized in routine clinical practice due to its high cost. Another method is polymerase chain reaction to identify the DNA of Mycobacterium tuberculosis. But this test is less sensitive as it depends on the concentration of bacteria.

In our study we tried to analyze the ADA levels and lymphocyte/neutrophil ratio in pleural effusion cases and their efficacy in diagnosing tuberculous pleural effusions.

Materials and Methods

We conducted study on 208 patients having pleural effusions, who were admitted in the pulmonary medicine department, Rajiv Gandhi university of medical sciences, general hospital in Ongole during the period from April 2015 to April 2018 . The patients were divided into two groupsi.e, patients having tuberculous pleural effusions and non tuberculous pleural effusions.

Inclusion criteria: The cases included in our study were diagnosed to be tuberculosis either on culture/pleural biopsy/ positive sputum culture/ clinical features compatible with tuberculosis and with response to anti tuberculous drugs. Patients with Para pneumonic effusions due to pneumonia, lung abscess or bronchiectasis diagnosed by presence of purulent pleural effusion, pleural fluid positive for microorganisms and pleural effusions responding to antibiotic treatment were included. Malignant pleural effusions were diagnosed on cytological examination.

Exclusion criteria: Patients diagnosed with heart failure, cirrhosis of liver, renal failure and nephrotic syndrome having transudative effusions.

Clinical details like age and sex of the patient were noted. ADA levels in pleural fluid was estimated by spectrophotometric method. Cytological examination of pleural fluid was conducted and lymphocyte neutrophil ratio was noted. Pleural effusion with lymphocyte predominance was defined asone with lymphocyte /neutrophil ratio more than 0.75 or lymphocytes more than 75% [2]. This was correlated with ADA levels.

Table 1: Age distribution in tuberculous and non tuberculous pleural effusion cases

Age groups	Tuberculous pleural effusion (n=110)	Non tuberculous pleural effusion (n=98)
10 – 20 years	8 (7.2%)	5 (5.1%)
21 – 30 years	25 (22.7%)	20 (20.4%)
31 – 40 years	18 (16.4%)	18 (18.4%)
41 – 50 years	18 (16.4%)	18 (18.4%)
51 – 60 years	21 (19.1%)	15 (15.3%)
60 years	20 (18.2%)	22 (22.4%)

Results

208 patients with pleural effusion were included in our study. Cases were divided into tuberculous and non-tuberculous groups. 110 patients were diagnosed to have tuberculous pleural effusion and 98 patients were diagnosed to have non tuberculosis pleural effusion.

Patients were divided into different age groups. Maximum number of patients having tuberculous effusions were in the age group of 21–30 years (22.7%) when compared to patients having non-tuberculous pleural effusion, which were found maximum in the age group of more than 60 years (22.4%) (Table 1). Both the groups showed male predominance than females (Table 2).

ADA levels in both groups were noted. Non tuberculous pleural effusion cases showed ADA level ranging from 10.1IU/L to 48.4IU/L in the pleural fluid. Maximum number of cases were with in the range of 21 – 30 IU/L (58.2%) (Table 3).

Tuberculous pleural effusion cases showed ADA levels ranging from 46.5IU/L to 210 IU/L. Maximum number of cases were within the range of 71-80 IU/L (33.6%) (Table 3).

Table 2: Gender distribution in tuberculous and non tuberculous pleural effusion cases

	Tuberculous pleural effusion (n=110)	Non tuberculous pleural effusion (n=98)
Male	86 (78.2%)	69 (70.4%)
Female	24 (21.8%)	29 (29.6%)

Table 3: ADA levels in pleural fluid in Tuberculous and non tuberculous pleural effusion cases

ADA levels in IU/L	Tuberculous pleural effusion (n=110)	Non tuberculous pleural effusion (n=98)
10 – 20	-	35 (35.7%)
21 – 30	-	57 (58.2%)
31 – 40	-	4 (4.1%)
41 – 50	3 (2.7%)	2 (2.0)
51 – 60	6 (5.5%)	-
61 – 70	28 (25.4%)	-
71 – 80	37 (33.6%)	-
81 – 90	16 (14.5%)	-
91 – 100	7 (6.4%)	-
>100	13 (11.8%)	-

All the cases of tuberculous pleural effusion showed lymphocyte predominance, whereas non tuberculous pleural effusion showed granulocyte predominance.

In our study cut off value of ADA levels in tuberculous pleural effusion was above 46.5 IU/L. But 2 cases of non tuberculous pleural effusion showed ADA levels more than 40IU/L. In these two cases cytological examination of the pleural fluid showed granulocyte predominance (Table 4). Thus the accuracy of diagnosis of pleural effusion can be increased by combined assessment of ADA levels and lymphocyte/neutrophil ratio.

In all the tuberculous pleural effusion cases total count of leukocytes in peripheral blood were with in normal range. In non tuberculous pleural effusion cases only 2 cases showed increase in leukocyte count and remaining all the cases showed total leukocyte count with in the normal range.

Table 4: comparision of Lymphocyte/neutrophil ratio in tuberculous and non-tuberculous pleural effusion with ADA levels between 41 – 50 IU/L

	ADA levels	Lymphocyte/ neutrophil ratio
Tuberculous pleural effusion	46.5	80/20
	48.3	85/15
	48.2	90/10
Non tuberculous pleural effusion	48.4	40/60
	45.2	50/50

Discussion

In developing countries, most common cause of pleural effusion is tuberculosis, but is difficult to diagnose due to its paucibacillary nature. Tuberculosis is caused by bacterial species, Mycobacterium tuberculosis, which belongs to family Mycobacteriaceae [3]. Though Robert Koch has isolated this bacteria in 1882 and effective treatment is available, still tuberculosis is one of the most deadly communicable disease. According to World Health Organization (WHO), the incidence of pulmonary tuberculosis in some regions is very high as 1000 cases per 100,000 persons [4]. Although majority of patients have pulmonary tuberculosis, 25% of adults have extrapulmonary tuberculosis at initial presentation involving pleura and lymph nodes [5].

Pleural effusion is manifestation of mycobacterial infection in the pleural space, acquired from the initial parenchymal lesions which results in an immunological response causing increased formation of pleural fluid and decreased removal of pleural fluid [6].

Clinical presentation of patients with tuberculous pleural effusion will be as acute febrile illness with pleuritic chest pain and non productive cough. Other manifestations are chills, night sweats, dyspnea, weight loss and weakness. In our study maximum patients with tuberculous pleural effusion were of lower age group (21–30 years) when compared to non- tuberculous pleural effusions, where maximum patients were in the age group of above 60 years. Our study coincided with study done by Shaban Mohamed Ramadan et al who showed that mean age of tuberculous patients (28±10.4) was lesser than non tuberculous effusions (48.4±13.3). In the current study, patients with both tuberculous and non tuberculous pleural effusions showed male predominance which did not coincide with study done by Shaban Mohamed Ramaden et al. who showed male predominance in tuberculous pleural effusion and female predominance in non tuberculous patients [7].

Pulmonary tuberculosis triggers an immune response involving CD4+T cells, macrophages and cytokines referred by these cells (γ-interferon, interleukin-1, interleukin-2). Pleural fluid examination reveal lymphocyte predominant effusion. Though the initial first few days effusion may show neutrophil predominance, later lymphocytes dominate [8]. But in these cases peripheral white blood cell count will not show an elevation. In our study all the cases of tuberculous pleural effusion showed lymphocyte predominance which coincided with the studies

done by Lesley J Burgers et al. [9].But the peripheral film showed total leukocyte count with in normal range. Our study correlated with the study done by Onyenekwu CP et al. [10].

Assessing ADA levels in pleural fluid can be useful in the patients suspicious of tuberculosis. Adenosine Deaminase activity is elevated in tuberculous patients due toincreased levels of ADA isoenzyme ADA_2. This isoenzyme ADA_2 is found in macrophages and monocytes. Different studies have shown the cut off value range of ADA level in pleural fluid to be between 40 to 60IU/L for tuberculous pleural effusion [11]. In our study cut offvalue of ADA levels in tuberculous patients was 46.5 IU/L.

New diagnostic tools for detection of tuberculosis is interferon gamma release assay (IGRAs) which detects the T cell immune response to the tuberculous antigens which includes Culture filtrate protein (CFP-10), Early Secretary Antigen Target (ESAT-6) and a third antigen TB7.7. These antigens are more specific for the diagnosis of tuberculosis [12]. Though these tests are highly efficient in detecting tuberculous infection, due to their high price, they cannot be used in routine clinical practice.

Conclusion

Assessing ADA activity in the pleural fluid is fast diagnostic tool which is of low cost, easy and simple test. It can be considered as appropriate test in the routine study of the patient with pleural effusion. Diagnostic accuracy of tuberculous pleural effusion can be increased by assessing ADA activity along with lymphocyte/neutrophil ratio in pleural fluid. High levels of ADA activity with lymphocyte predominant pleural effusion suggests tuberculous pleural effusion and justifies treatment for Tuberculosis.

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