Role of adenosine deaminase in monitoring tubercular pleural effusion

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ABSTRACT

Background: Tuberculosis is a common cause of pleural effusion especially in countries like India. ADA (adenosine deaminase) is predominantly an enzyme, that catalyses the conversion of adenosine to ionosine. Usually patients with tuberculous pleural effusion have ADA level >40 U/L.

Methods: This is a prospective, observational study conducted in Department of Pulmonary Medicine, Gauhati Medical College and Hospital, Guwahati from September 2016 to September 2017. 45 patients with pleural fluid ADA levels >40 U/L were selected with diagnosis of tubercular pleural effusion. Pleural fluid was analysed for cytological, biochemical and microbiological parameters along with ADA and malignant cell cytology. Anti-tubercular treatment (ATT) was started and pleural fluid ADA level were repeated after 15 days of ATT.

Results: Pleural fluid ADA levels before the start of ATT intake and after 15 days of ATT intake were statistically analysed. Among 45 patients, 38 were male and 7 females. Mean age of the patients was 45.42±16.43 years. Mean pleural fluid ADA level before starting ATT was 64.49±31.78 U/L. After 15 days of ATT intake mean pleural fluid ADA level was 36.11±10.42 U/L, p value was statistically significant (p<0.05).

Conclusions: Pleural fluid ADA significantly decreased after 15 days of initiation of anti-tubercular treatment. Pleural fluid ADA can be a useful tool as a follow up biomarker in cases of tubercular pleural effusion.

Keywords: Pleural fluid, Tubercular pleural effusion, ADA, ATT

INTRODUCTION

Pleural effusion is excess pleural fluid that accumulates in the pleural cavity, the fluid filled space that surrounds the lungs. This excess pleural fluid can impair breathing by limiting the expansion of the lungs. Pleural fluid is an ultrafiltrate of plasma, usually there is less than 10ml of fluid in each pleural cavity. Tuberculosis is a common cause of pleural effusion especially in countries like India. The tuberculous pleural effusion is thought to result from rupture of a subpleural caseous focus in the lung into the pleural space.¹ It appears that delayed hypersensitivity plays a large role in the pathogenesis of tuberculous pleural effusion.

Tubercular pleural effusion manifests as an acute illness, with approx one third of patients being symptomatic for less than 1 week & two thirds for less than 1 month.² The most common presenting symptoms are nonproductive cough and pleuritic chest pain. Other symptoms include fever, night sweats, weight loss, malaise and dyspnoea varying in severity according to the size of effusion. The reliability of the early diagnosis of pleural TB has been greatly improved by the use of biochemical markers such as ADA, interferon-gamma and lysozyme.³,⁴ The determination of the ADA level in the suspected pleural fluid appears to be the most promising marker because of the ease, rapidity and cost-effectiveness of the ADA assay.
ADA is predominantly T-lymphocytic enzyme, that catalyses the conversion of adenosine to ionsine. There are two molecular forms of ADA- ADA 1 and ADA 2. ADA 1 is found in all cells, but has its greatest activity in lymphocytes and monocytes. ADA 2 is found only in monocytes, and most of the ADA in tuberculous pleural fluid is ADA2, whereas most of the ADA in other pleural fluids is ADA 1. Also the use of the ratio of ADA 1 to ADA total of less than 0.42 slightly increase the sensitivity and specificity of the test in diagnosing tuberculous pleuritis.

In an early study, Ocana et al measured the pleural fluid ADA levels in 221 pleural or peritoneal effusions. All patients with a pleural fluid ADA level above 70 U/L had TB, whereas no patient with a pleural fluid ADA level below 40 U/L had tuberculous pleuritis. In patients with lymphocytic pleural effusion, demonstration of an ADA level above 40 U/L is strongly suggestive of the diagnosis of tuberculous pleurisy. Liang et al performed a meta-analysis of 63 articles evaluating the diagnostic usefulness of ADA that included 2,796 patients with tuberculous pleuritis and 5,297 patients with other diseases. They reported that the mean sensitivity was 0.92, the mean specificity was 0.90, the mean positive likelihood ratio was 9.03 and the mean negative likelihood ratio was 0.10.

With ATT, the patient's symptoms and radiologic abnormalities gradually abate. The average patient becomes afebrile within 2 weeks, but temperature elevations may persist for as long as 2 months. The mean duration for complete resorption of the pleural Fluid is approximately 6 weeks, but it can be as long as 12 weeks.

With this aim, the present study has been planned to evaluate the utility of pleural fluid ADA as a follow up biomarker in tubercular pleural effusion and to assess its level before starting and after 15 days of starting of ATT during follow up.

METHODS

This is a prospective single centered, observational study conducted in Department of Pulmonary Medicine, Gauhati Medical College and Hospital, Guwahati from 1st September 2016 to 1st September 2017 after taking approval from Institutional Ethical Committee.

**Inclusion criteria**
- Age above 14 year.
- Exudative, lymphocytic predominant effusion with ADA levels >40 U/L.

**Exclusion criteria**
- Age less than 14 years
- Those who were not willing to participate.

A total of 45 patients with exudative, lymphocytic predominant effusion with ADA levels >40 U/L were selected with diagnosis of Tubercular pleural effusion. Pleural fluid was analysed for cytological, biochemical and microbiological parameters along with ADA and malignant cell cytology. ATT was started and pleural fluid ADA level was repeated after 15 days of ATT. The entire data was analysed using descriptive statistics.

**RESULTS**

Pleural fluid ADA levels before the start of ATT intake and after 15 days of ATT intake were statistically analysed. Among 45 patients, 38 were male and 7 females. Mean age of the patients was 45.42±16.43 years (Table 1).

**Table 1: Demography of patients.**

| No. of patients | Mean age (in years) | Standard deviation (SD) |
|-----------------|---------------------|-------------------------|
| Total           | 45                  | 45.42                   | 16.43                   |
| Male            | 38                  | 57.86                   | 6.99                    |
| Female          | 07                  | 43.13                   | 16.70                   |

**Table 2: Mean ADA level before and after 15 days of ATT intake.**

| Mean ADA (before starting of ATT) | Mean ADA (after 15 days of ATT intake) | P value  |
|-----------------------------------|----------------------------------------|----------|
| Total                            | 64.49                                  | 36.11    | 0.0001 |
| Male                             | 70.86                                  | 39.43    | 0.0001 |
| Female                           | 63.31                                  | 35.50    | 0.0460 |

Mean pleural fluid ADA level before starting ATT was 64.49±31.78 U/L. After 15 days of ATT intake mean Pleural fluid ADA level was 36.11±10.42 U/L (Table 2). P value was calculated and was statistically significant (p<0.05).

**DISCUSSION**

In our study of 45 patients with lymphocytic, exudative pleural effusion, 38 were male and 7 were females. Mean age of the patients was 45.42±16.43 years. Mean Pleural fluid ADA level before starting ATT was 64.49±31.78 U/L. After 15 days of initiation of ATT, mean Pleural fluid ADA level was 36.11±10.42 U/L. There was a significant decrease in pleural fluid level after 15 days of initiation of ATT, with p value <0.05 (statistically significant).

In a study by Valdés et al on 254 patients with tubercular pleural effusion, 99.6% had ADA more than 47 U/L and in another group of 303 patients in a high TB prevalence population with exudative effusions, 58% had TB with a lymphocytic predominant effusion and ADA more than 50 U/L. The diagnostic usefulness of ADA depends...
not only on its sensitivity and specificity, but also on the local prevalence of TB. In populations with a high prevalence of TB and clinical suspicion of TB effusion, elevated ADA level might be considered as a confirmatory test justifying treatment initiation.

Previously, studies have been conducted using serum ADA for monitoring response to treatment in patients suffering from tuberculosis. Malempati UD et al evaluated the effective treatment response to ATT by estimating the serum ADA activity, one month after the treatment initiation. Before the initiation of ATT, 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 anti-tubercular treatment.

In another study, Rao et al evaluated the serum adenosine deaminase activity during the course of pulmonary tuberculosis treatment. The values of serum adenosine deaminase were significantly higher in the study group than in the control group. After the first month of treatment of pulmonary tuberculosis, there was no significant change (p>0.05) in serum ADA when compared to initial reading, but after the second month & sixth month of treatment there was a significant decrease in the serum ADA values (p<0.05).

Similar results were found in a study by Kartaloglu et al which showed a slight elevation of serum ADA in the first month, but it decreased during treatment in parallel with the effectiveness.

A study by Unsal et al revealed gradual decrease in serum ADA from 30.1±11.7U/L to 24.8±15.6 after first month of treatment and after second month 22.0±10.6 in limited lesion cases. In extended lesion cases before treatment ADA values was 31.3±18.3, first and second month values were 27.5±13.0 and 27.1±12.2 U/L respectively.

The diagnostic accuracy of ADA can be improved by measuring different ADA isoenzymes. ADA-2 is increased in TB effusions, while ADA-1 is increased in other bacterial empyema, and distinguishing between these two principal isoenzymes can increase the specificity of ADA for diagnosing TB. Use of the ADA-2 isoenzyme measurement increased the specificity for TB from 91% to 96% and 92.1% to 98.6%, in two different studies.

Although it has been suggested that ADA might be a less sensitive marker of TB in immune-compromised patients, there is currently little evidence to support this view. Baba et al demonstrated that ADA is a reliable marker of pleural TB in HIV-positive patients, even for those with low CD4 counts, while another study by Chung et al confirmed that ADA is an accurate marker in renal transplant recipients.

**CONCLUSION**

The gold standard for the diagnosis of tuberculous pleuritis remains the detection of M. tuberculosis in pleural fluid or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with AFB. In high burden settings, however, the diagnosis is frequently inferred in patients who presents with a lymphocytic predominant exudate with a high ADA level, which is a valuable adjunct in the diagnostic evaluation. ADA is generally readily accessible, and together with lymphocyte predominance justifies treatment initiation in patients with a high pre-test probability. The role of other biomarkers is less well described.

In our study pleural fluid ADA significantly decreased after 15 days of ATT intake. Pleural fluid ADA can be useful as a follow up biomarker in cases of tubercular pleural effusion. More such larger prospective studies needs to be conducted in order to validate and assess if any direct co-relation exists between the level of adenosine deaminase (ADA), before and after starting anti-tubercular treatment in patients with tubercular pleural effusion.

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