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A CLINICAL STUDY OF OUTCOME OF PLEURAL FLUID ADA NAGATIVE TUBERCULOUS PLEURAL EFFUSION

Respiratory Medicine

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ABSTRACT

Aims: To study the outcome of patients with pleural effusion in whom ADA of pleural fluid is less than 40 but clinically suspicious of Tuberculous in a high Tuberculosis prevalence area. **Method:** This is a prospective observational study done at AMC MET medical college on 18 patients presented with lymphocytic exudative pleural effusion with Pleural fluid ADA negative (less than 40 IU/L) where other causes of exudative effusion were ruled out and patient diagnosed as clinically Tuberculous Pleural Effusion. Such patients were given Antitubercular drugs for 6 months and were followed up for 9 months. **Results:** All the patients having exudative pleural effusion after all inconclusive investigations, Antitubercular drugs were given to all 18 (100%) study patients, all the patients showed improvement over period of 6 months. **Conclusion:** Antitubercular treatment leads to early recovery and reduced mortality in high tuberculosis prevalence area in patients having low ADA levels(40IU/L) and positive constitutional symptoms after ruling out all other causes of exudative pleural effusion.

KEYWORDS

Exudative pleural effusion, pleural fluid ADA

INTRODUCTION

Tuberculosis (TB) is a contagious, infectious disease, due to Mycobacterium tuberculosis that has always been a permanent challenge over the course of human history, because of its severe social implications. About total number of 3000 cases per million of population in the world suffer from pleural disease[1]. About one-third of tuberculosis patients showed extra-pulmonary tuberculosis (EPTB), while a quarter of them developed Tuberculous Pleural Effusion (TPE) [2]. TPE is the second most common extra pulmonary manifestations of tuberculosis proceeded by tubercular lymphadenitis[3] and is the most common cause of pleural effusion in areas where tuberculosis is endemic.

Conventional diagnostic tests for pleural fluid Tuberculosis include microscopic examination of the pleural fluid for acid-fast bacilli, molecular test such as CBNAAT, Mycobacterial culture of pleural fluid and sputum or pleural tissue for histopathological examination for granulomatous inflammation. Molecular methods such as Xpert MTB/RIF show poor performance for the diagnosis of pleural effusion especially in acute setting. [4,5] The yield of pleural fluid culture for mycobacteria is low at about 36% and also time consuming.[6] Further invasive surgery as pleural biopsy can be used to detect caseating granuloma, but it is also less sensitive as in some case; the poor preservation of tumor cells and the small sample size, the low cytological examination rate (about 60%) in the detection of malignant pleural effusion has become a long-term clinical problem[7]. Thoracoscopic biopsy is a high-performance diagnostic method for both tuberculous pleural effusion and malignant pleural effusion, but its invasiveness limits clinical application.[7] These tests have limitations for clinical use and also time consuming; Therefore, serum biomarkers, including adenosine deaminase (ADA), lactate dehydrogenase (LDH), C-reaction protein (CRP) and many inflammatory cytokines are used for diagnosis. although Pleural fluid Adenosine deaminase (ADA) level is use as a means of cost effectiveness, ease of performance and rapid non-invasive test for faster diagnosis and higher sensitivity[8]. The Light's criteria is an early standard established for the classification of exudates or transudates effusion, which involves the ratio of serum protein and PF-protein; serum LDH (S-LDH) and PF-LDH.[9]

Adenosine deaminase (ADA), an enzyme produced from lymphocytes and involved in purine metabolism, has been extensively studied as a biochemical marker in pleural fluid during investigation for Tuberculous pleural effusion (TPE)[10]. ADA represents the sum of two isoenzymes (ADA1 and ADA2). Analysis and determination of these isoenzymes have shown that increases in ADA with tuberculous pleurisy are due to increases in ADA2 and that the ADA1/ADA2 ratio[10]. High levels of ADA in the lymphocytic pleural effusion have been also reported in the fungal infections such as coccidioidomycosis and histoplasmosis, also seen in the malignancies and collagen vascular diseases e.g., rheumatoid arthritis and systemic lupus erythematosus[10]. Almost all patients with TPE have a pleural fluid ADA level above 40 U/L, which is the most widely accepted cut off value for the diagnosis of TPE. [11]Higher the level, the greater the chance of the patient having TPE and vice versa [12]

In some cases of exudative pleural effusion, where all the investigation are inconclusive; clinician comes in dilemma of diagnosis, in such cases antitubercular drugs can be started if patient seems to have clinically suspicious TPE in high Tuberculosis prevalence area and presented with constitutional symptoms of tuberculous, delay in diagnosis may cause worsening of outcome and increase in mortality.

METHODOLOGY

This prospective study was conducted in Respiratory Medicine Department at AMC MET Medical college, Ahmedabad. The approval of the Institutional Review Board was obtained prior to the initiation of study. Written informed consent was taken from all patients before including them into the study according to inclusion and exclusion criteria.

Total 489 patients with pleural effusion underwent thoracentesis; all patients underwent all routine serological and pleural fluid investigations. The routine study of pleural fluid included the following: Routine and microscopic examination (protein, glucose); ADA; cytology; aerobic and anaerobic culture and CBNAAT. As per light's criteria 343 patients have exudative pleural effusion patients and 146 patients have transudative pleural effusion. Among the exudative pleural effusion; 168 patients have pleural fluid ADA >40 U/L which were diagnosed as TPE, rest of 79 patients with pleural fluid ADA>40 U/L and 69 patients with pleural fluid ADA <40IU/L having other underlying known etiology like malignant pleural effusion, empyema

thoracic and other causes of pleural effusion like para pneumonic, pancreatic, chylothorax, fungal infection etc. 9 patients with exudative TPE with PF ADA >40 IU/L were diagnosed with TPE by presence of mycobacteria in pleural fluid or proven via biopsy. Total 325 patients out of 343 exudative pleural effusion had a definitive pleural effusion diagnosis (fig.1); only 18 patients of exudative pleural effusion with low ADA <40 with other tests were unconclusive and clinically strongly suspicious of tuberculosis were included in our study as per inclusion criteria as per listed below:

Inclusion Criteria:
All patients with age group more than 18 years and willing for thoracentesis. Patients with pleural effusion who meets light's criteria for exudative pleural effusion with PF ADA <40/IU/L and presence of constitutional symptoms of TPE

Exclusion Criteria:
Patients who gave negative consent were excluded from study

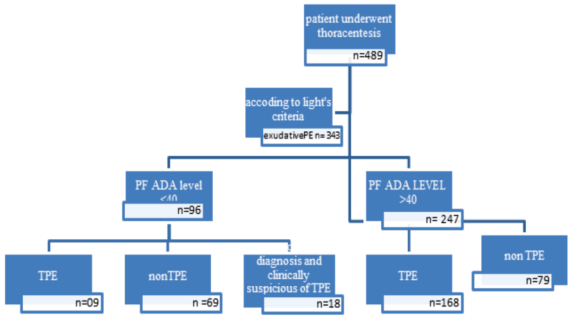

Fig:1 Total Nomber Of Pleural Effusion Patients With Underlying Etiology

18 patients having all the constitutional symptoms of tuberculosis like dyspnea on excersion, dry cough, low grade fever, chest pain, anorexia and weight loss with uncertain diagnosis even after all routine investigations including thoracoscopy (thoracoscopy not done in patients with minimal effusion or in patients who gave negative consent for it); with Radiological investigation like CT scan and 2D echo (as needed). Antitubercular drugs (2 months of HRZE, 4 months of HRE) had been given such patient to treat as clinically diagnosed tuberculous pleural effusion as all patients living in high tuberculosis prevalence area with strongly suspicious of TPE. All patients were closely followed up for 6-9 months to look for radiological and clinical improvement.

RESULT

In this study, total 18 patients were included, amongst them incidence of pleural effusion was higher in male (56%) compared to female (44%). Male:Female ratio was 5:4. Mean age of study patients who developed pleural effusion was 34.66 years. In current study, Commonest presenting symptoms were dry cough (76%) and dyspnea (71.4%) followed by anorexia (66%) and chest pain (62%). In present study, Diabetes was commonest observed comorbidity (16.66%) followed by Hypertension (11.11%) and IHD (5.5%). Commonest chest xray finding observed was moderate pleural effusion on right side of hemithorax (27.77%) followed by left side moderate effusion (22.2%), Bilateral Moderate PE (11.11%) and Mild Right PE (5.56%), Gross right and left PE (5.56%). In present study, patients have mean PF ADA 17.16. In our observation, All the patients (100%) improved after giving antituberculous drug for 6 months.

VARIABLE	PATIENTS (n=18)
DEMOGRAPHIC DATA	
MEAN AGE Male Female	34.66 ±50 10 (56%) 08(46%)
Male:Female	5:4
COMORBIDITIES:	
Diabetes	3(16.66%)
Hypertension	2(11.11%)
IHD	1(5.55%)
Clinical Presentation:	
Cough	16(76%)
Dyspnoea	15(71.4%)
Chest pain	13(62%)
Anorexia Blood Ix:	14(66.6%)
Mean WBC, cells/µL	5500(2700-10,400)
Mean CRP,mg/L	24.22(0.76-128.03)
Mean S.ALBUMIN g/dl Chest Xray:(site and amount)	34.8(23.3-40.6)
MODERATE RIGHT PE	5(27.77%)
GROSS RIGHT PE	1(5.55%)
MILD LEFT PE	1(5.55%)
MODERATE LEFT PE	4(22.22%)
GROSS LEFT PE	1(5.55%)
BILATERAL MODERATE PE	2(11.11%)
MEAN PF ADA	17.16
IMPROVEMENT AFTER GIVING AKT	18(100%)
CURED AFTER GIVING AKT	18(100%)
RELAPSED AFTER AKT	0(0%)

DISCUSSION

ADA is generally readily accessible, and together with lymphocyte predominance justifies treatment initiation in patients with a high pre-test probability. The diagnostic usefulness of ADA depends not only on its sensitivity and specificity, but also on the local prevalence of TB. [14]

So many studies had been done in past about the sensitivity and specificity of PF ADA. However, false-negative and false-positive results remain problematic.Study done by Alberto GraciaZamalloa et al have concluded that diagnostic accuracy of ADA and lymphocytic proportion useful for the TPE in low to intermediate prevalence scenarios whereas its value is still questioned in area with high prevalance[15]. But sometimes in population with a high prevalance of tuberculosis clinician encounter with such cases of exudative PE; where all the test were inconclusive including PF ADA and patient is strongly suspicious of TPE. This study is tuned for patients having Clinically diagnosed tuberculous Pleural effusion in whom none of test of Pleural fluid is conclusive for any diagnosis. For our knowledge no study had been done in past for these categories. We looked for the outcome of patients; both clinical and radiological improvement after giving antitubercular drugs in these types of patients. In this study all patients clinically and radiologically improved after treatment with antituberculous drugs.

CONCLUSION

In this study we can conclude that the possibility of TPE should be considered in patient with a clinically suspected low ADA value Tuberculous PE. If this diagnosis is not made with any of tests but patient is strongly suspected to have TPE then antituberculous drugs can be started in these patients. This will prevent likelihood of subsequent development of multidrug resistance tuberculosis (MDR TB). So, initiation of Antituberculous drug will leads to not only improvement but also reduced the risk of subsequent development of future adverse events in term of relapse or MDR TB as we aim to ensure better TB cures that will advance global health and TB free India.

Study Limitation:
this study has some limitations; this study is performed in a single hospital. Second, the study included a small number of patients, thus limited the relevant scope of our study; requires further prospective studies that cover large sample size and more comprehensive parameters.

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