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STUDY OF ADENOSINE DEAMINASE LEVEL IN BRONCHOALVEOLAR LAVAGE FLUID AND ITS CORRELATION WITH GENXPERT IN SPUTUM NEGATIVE SUSPECTED PULMONARY TUBERCULOSIS AND SUSPECTED LUNG MALIGNANCY.

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ABSTRACT Tuberculosis (TB) has been one of the health problems in the world. Diagnosis of pulmonary tuberculosis based on finding of AFB in the sputum has several limitations. So we decided to evaluate ADA activity in BAL fluid and correlate it with BAL GenXpert result and we used suspected lung malignancy patients as control. Total 33 patients - 17 suspected TB, 16 suspected lung malignancy were enrolled in study and subjected to bronchoscopy and BAL fluid was submitted for ADA level and GenXpert for TB.Increased BAL level was well correlared with GenXpert positivity in suspected TB group.

KEY WORDS : Adenosine deaminase (ADA); Bronchoalveolar lavage (BAL);Tuberculosis

Introduction:

Tuberculosis is the most important cause of death from infectious diseases and major public health problem in India. Multidrug resistance in tuberculosis and its association with AIDS have further aggravated the problem. It has wide range of clinical presentation from totally asymptomatic to respiratory failure. . Radiologically, TB can present with different patterns of abnormality, mimicking other pulmonary diseases. The gold standard for TB diagnosis is growth of Mycobacterium in specimen culture but its sensitivity is low and it is time-consuming. Hence, it is necessary to find faster methods with higher sensitivity. As an alternative noninvasive means of establishing diagnosis of tuberculosis several biomarkers like adenosine deaminase (ADA), interferon gamma (IFN-γ), and a variety of tumor markers and cytokines have been proposed. ADA is used as a useful surrogate marker of TB pleuritis, pericarditis, and peritonitis. However, its diagnostic value in bronchoalveolar lavage fluid (BALF) in the diagnosis of pulmonary TB remains ambiguous due to lack of properly designed studies.[1-5] The aim of the present study was to evaluate the efficacy of BALF ADA activity and its correlation with GenXpert for diagnosing pulmonary TB and distinguishing it from other pulmonary diseases.

ADA is an enzyme of purine metabolism. It causes deamination of deoxyadenosine and adenosine to deoxyinosine and inosine respectively. It has important role in lymphocyte activity and maturation.There are three subtypes of ADA - ADA1, ADA1+CP, ADA2. Normal serum has ADA_{1+CP} and ADA_2. ADA1 is found in most body cells, particularly lymphocytes and macrophages.ADA activity is raised in various body fluids of patients with Tb like serum, pleural, pericardial, peritoneal or CSF. Hence detecting ADA activity in blood, pleural effusion, ascitic fluid or BALF may be useful as rapid diagnostic tool replacing time consuming culture.

Material & Method:

We performed a prospective study that included 17 suspected adult TB patients with acid-fast bacillus (AFB)-negative sputum smears and 16 non who were subjected to bronchoscopy for diagnostic evaluations of pulmonary diseases between August 2020 and July 2021 at GCS Medical College and Hospital. Written informed consent was obtained from all patients before doing the bronchoscopy. BAL fluid was obtained from a pulmonary lobe with the most involvement seen on chest X-ray and a right middle pulmonary lobe in patients with a diffuse involvement. , BAL was performed in the target bronchus leading to the lesion according to imaging studies; 50 ml of normal saline was instilled and aspirated into a trap. Repeated instillations of 50 ml normal saline up to a total of 100–150 ml, or collection of 50 ml of retrieved fluid, was considered adequate lavage. . The choice of other sampling techniques such as bronchial brushing, endobronchial biopsy, and transbronchial biopsy were utilized depending on bronchoscopy finding. BALF was centrifuged at 6000 rpm for 10 min and the ADA activity of the supernatant was measured.The pellet was then processed for GenXpert analysis. Bronchoscopic biopsy of visible lesion was taken in 11 patients of suspected malignancy.

Result:

Table 1: Demographic information of enrolled patient in study

Suspected TB (n=17)			Suspected Malignancy (n=16)		
Male	Female	Mean Age (Yrs.)	Male	Female	Mean Age (Yrs.)
15	02	46.2	13	03	50.8

Table 2: BALF ADA value and its correlation with GenXpert result in two subgroup:

Suspected TB (n=17)				Suspected Malignancy (n=16)			
ADA>3.5IU/lit		ADA<=3.5IU/lit		ADA>3.5IU/lit		ADA<=3.5IU/lit	
13		4		2		14	
GenXpert positive	GenXpert negative	GenXpert positive	GenXpert negative	GenXpert positive	GenXpert negative	GenXpert positive	GenXpert negative
12	1	0	4	0	2	0	14

Out of total 33 patients enrolled in study in suspected TB subgroup (n=17) ADA was positive (>3.5IU/lit) in 13 patients (76.47%) and negative (<=3.5IU/lit) in 4 patients (23.53%). Out of 13 ADA positive patients 12 patients (92.3%,)were GenXpert result positive and out of 4 ADA negative patients all (100%) were GenXpert negative, while in Suspected Malignancy subgroup(n=16) ADA was positive in 2 patients and negative in 14 patients. All patients in this subgroup all were GenXpert negative($p<0.001$). Of 11 patients whose biopsy was taken all had confirmed malignancy.

Discussion:

ADA activity has been used as a valuable marker for differentiating tuberculous pleural effusion from other causes of exudative pleural effusions.6,7Porcel et al. emphasized the diagnostic utility of pleural fluid ADA activity in 2193 patients with different etiologies of pleural effusions. Patients with TB pleuritis had significantly higher ADA activities than patients

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with non-TB effusions. However, differential diagnoses of exudative pleural effusions are narrow when comparing with parenchymal lung diseases, as in our patients. Many studies have reported that ADA activity in BALF of patients with pulmonary TB is higher than in comparators like malignancy. However, Reechaipichitkul et al. reported that BALF ADA of pulmonary TB patients was not significantly different from the other groups.

In the diagnosis of TB pleural effusion using ADA activity, there is also false-positivity that is caused by both solid and hematologic malignancies, bacterial infection, and connective tissue diseases. Many etiologies also caused false-positive BALF ADA activities, giving ADA 3 U/l. ADA is produced not only by mononuclear cells and lymphocytes, but also by many different cell types, including neutrophils and red blood cells. Therefore, we believe that in any organs, local ADA would be high when affected not only by TB, but also by these etiologies. Unfortunately, to date, ADA2, which is secreted only by monocytes and macrophages and is believed to be a more efficient diagnostic marker of TB pleuritis than total ADA activity, has not been studied in BALF and this awaits further research[8,9].

Orphanidou et al., reported ADA activity was significantly higher in patients with extensive disease than in those with limited disease. In contrast, ADA activity did not correlate with the presence of BALF smear, culture, and granuloma formation. In pleural effusion, ADA expressed high activity in TB pleuritis, which occasionally identified organisms or granulomas. Thus, the extent of the lesions would have more influence on ADA production than the organism loads and granulomatous reactions. V. Boonsarngsuk et al has reported the sensitivity of TB PCR in BALF in our study was quite low. When the differential diagnosis leaves only TB and solid tumor, BALF ADA is a useful tool. In addition, the combination of BALF ADA 3 U/l and TB PCR had marked additive diagnostic value.

Similarly no study was found which had done comparison and correlation between positive BALF ADA result and GenXpert in suspected tuberculous and suspected malignancy. In conclusion increased BALF ADA was well correlated with positive GenXpert level in suspected sputum negative clinical pulmonary Tuberculosis.Considering this as a pilot study further study is required.

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