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Diagnostic value of ADA in Non Tuberculous Lymphocytic Pleural Effusions

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Abstract

Adenosine deaminase (ADA) is of help in tuberculous pleural effusions, there is no doubt about this fact. Cases of rise in this enzyme is evident in non-tubercular patients also. But it is also raised in non-tubercular patients with effusion in pleura also. This study was meticulously planned to find the link of ADA with the non-tubercular pleural effusion cases. Altogether, 100 cases of nontuberculous lymphocytic pleural effusion. The patients 'fluid samples were collected in a consecutive. Out of them malignancy accounted for 40cases, idiopathic effusions 22, parapneumonic effusions 21, coronary bypass cases effusions 7, cases of miscellaneous exudative effusions 10.The cut-off level of ADA in blood for tuberculosis (30 U·L) in 2 of the 40 cases 5% The negative predictive value of ADA for the diagnosis of pleural effusion was 87% (35 of 40) in the group of lymphocytic pleural effusions. In five of these seven patients ADA1 and ADA2 were measured, and in all these cases (100%) ADA1/ADAp correctly classified these lymphocytic effusions as nontuberculous (ratio <0.42). This prospective study provides additional evidence that adenosine deaminase levels in nontuberculous lymphocytic pleural effusions seldom exceed the cut-off set for tuberculous effusions. The pleural fluid adenosine deaminase levels were significantly higher in different types of exudative effusions than in transudates. An adenosine deaminase level <40 IU·L−1 virtually excluded a diagnosis of tuberculosis in lymphocytic pleural effusions. Adenosine deaminase1/adenosine deaminase correctly classified all nontuberculous lymphocytic pleural effusions with high adenosine deaminase levels.

Keywords: ADA, non-tubercular patients, parapneumonic effusions, adenosine deaminase levels

Introduction

Adenosine deaminase-pleural effusion tuberculosis

Diagnostic problem of tuberculous pleuritis (TP) is emphasized as tuberculosis is a frequent pathology and due to the difficulties of its diagnostic confirmation. The pleural fluid of TP is usually predominantly lymphocytic[1]. In fact, pleural fluid lymphocyte percentages >85% are very suggestive of the diagnosis 1. In one series of 49 patients with TP only five (10%) had <50% lymphocytes in pleural fluid 2. Only in acute TP can an increase in neutrophils be found 3. However, if serial thoracenteses are performed, the differential white blood cell count.Thiswill reveal a change to predominantly small lymphocytes. Other causes of lymphocytic pleural effusions include malignancies, collagen vascular disease, chylothorax, and post-coronary artery bypass graft (CABG) pleural effusion 4.Pleural fluid adenosine deaminase (ADA) is a useful biochemical marker of TP and provides a reliable basis for a treatment decision, particularly in areas where the disease is prevalent. However, the elevation may be limited in the early stages of the disease, and in addition, high levels of ADA can also be found in patients with neutrophilic effusions such as parapneumonic effusions or empyema 5.It has been shown recently that ADA levels in nontuberculous lymphocytic pleural effusions seldom exceed the cut-off set for tuberculous effusions 6. The purpose of this prospective study is to further assess the ADA levels in a larger series of nontuberculous lymphocytic pleural effusions.

Materials and Methods

All patients included in this study signed an informed consent that had been approved by the institutional review board. Lymphocytic effusions were defined as effusions with a lymphocyte count >50% of the total nucleated cells, as conventionally defined 7.Altogether, 410 pleural fluid samples were consecutively selected from all nontuberculous lymphocytic pleural fluids collected from patients who underwent thoracentesis at Muzaffarnagar Medical College, Muzaffarnagar between June 1 2023, and November 1, 2024. Diagnostic confirmation in tuberculous pleural effusions was obtained through the identification of mycobacteria in pleural fluid and/or biopsy or by the presence of necrotizing granulomas. The diagnoses of the pleural fluid samples are listed in Table 1⇓. All patients underwent a thorough and uniform diagnostic work-up by two independent investigators. The definitions for the diagnosis of the effusions have been previously published 8. A post-CABG effusion developed within the first 3 months after coronary artery bypass surgery with or without heart valve replacement, with no other identifiable causes (e.g. congestive heart failure, chylothorax, or infection). A pleural effusion was categorized as malignant if pleural fluid cytology or pleural biopsy findings were positive for malignancy or if the patient had known metastatic malignancy with no other explanation for the effusion. A parapneumonic effusion developed in a patient with fever, pulmonary infiltrates, and complete response to antibiotic treatment. All other exudative effusions were included in the miscellaneous exudate group. An idiopathic pleural effusion was identified as one for which a cause was not determined despite an initial work-up that included repeated thoracenteses and pleural biopsy. In six patients (7.9%), the effusion resolved spontaneously during the initial work-up. The remaining 70 patients were followed up until resolution for a mean of 26 months (range 10–72, median 21) and no patient has developed tuberculosis. Total ADA was determined by the Blake-Berman method 9, which had the same diagnostic properties as the Giusti-Galanti method in a meta-analysis of 2,251 cases 10. ADA1, one of the two isoenzymes that account for the pleural activity of ADA, was determined by the Carilaos-Gakis method. In this study, the laboratory cut-off of ADA for tuberculous pleural effusion was >40 IU·L−1 8 and the cut-off for ADA1/ADAp was <0.42

Etiologies of lymphocytic pleural effusions

The routine study of the pleural fluid included the following: pH, biochemical testing of pleura/serum (proteins, lactate dehydrogenase

(LDH), glucose, cholesterol, triglycerides, albumin, and ADA), hemogram, cytology and microbiological testing (Gram, Ziehl, aerobic and anaerobic cultures, and a mycobacterial culture). The reasons for performing a closed pleural biopsy were as follows: suspected malignant pleural effusions, suspected granulomatous diseases (tuberculosis, connective disorders, and others), and unexplained exudate. When the diagnosis was uncertain after thoracentesis or closed pleural biopsy, the effusion persisted and the symptoms increased or malignancy was still suspected, the patient was referred for thoracoscopy and/or thoracotomy. A summary of the procedures used in the diagnostic work-up is shown in Table 2⇓.

Statistical analysis

Results are expressed as mean ± SD unless otherwise stated. The statistical analyses applied included the Chi-squared test with Fisher's or Yates correction, to analyze the dependence between qualitative variables, the nonparametric Mann-Whitney U-test, for continuous variables with non-normal distribution and unpaired t-tests for those with normal distribution. Distributions were considered normal or non-normal as defined by the Shapiro-Wilks test.

Results

The ADA levels in the malignant effusions (15.57±10.60), parapneumonic effusions (15.89±10.62), post-CABG effusions (15.17±10.54), miscellaneous exudative effusions (16.84±7.58) and idiopathic effusions (13.57±8.59) were all significantly higher when compared with the transudative group (9.55±4.50, $p<0.01$, fig. 1⇓). The ADA level reached the diagnostic cut-off for tuberculosis (40 IU·L−1) in seven of the 410 cases (1.71%, fig. 1⇓). Two patients had bronchogenic carcinomas, two had complicated parapneumonic effusions, one had a diagnosis of lymphoma, one had a mesothelioma and one case was idiopathic. In five of these patients ADA1 and ADA2 were measured and in all these cases (100%) ADA1/ADAp correctly classified these lymphocytic effusions as nontuberculous (ratio<0.42). In this series, an ADA level <40 IU·L−1 excluded tuberculosis in lymphocytic pleural effusions in 99% (403 of 407) of cases.

Table 1 Diagnostic work-up data for patients with lymphocytic effusions

Closed pleural biopsy	Chest CT	Fiberoptic bronchoscopy	Lung scintigraphy	Thoracoscopy/thoracotomy		Closed pleural biopsy	Chest CT
Malignant	207	106	83	15	3	Malignant	207
Idiopathic	71	60	8	15	5	Idiopathic	71
Parapneumonic	2	7	6	1	0	Parapneumonic	2
Post-CABG	1	0	0	0	1	Post-CABG	1
Miscellaneous	7	10	5	2	0	Miscellaneous	7
Transudates	3	0	0	1	0	Transudates	3
Tuberculosis	69	8	6	0	1	Tuberculosis	69

Data are presented as patients n
Ct: Computed Tomography
CABG: Coronary Artery Bypass Grafting

Table 2 Aetiologies of lymphocytic pleural effusions

Diagnoses	Patients n
Malignant pleural effusions	221
Lung	138
Lymphoma	7
Mesothelioma	10
Others	66
Idiopathic	76
Parapneumonic	35
Post-CABG	6
Miscellaneous exudates	21
Trauma	7
Rheumatoid arthritis	5
Chylothorax	3
Post-transplantation	2
Pancreatitis	2
Pulmonary embolism	2
Transudates	51
Congestive heart failure	36
Hepatic cirrhosis	9
Renal failure	6
Tuberculosis	76

Table 3⇓ shows the hematological and biochemical analyses of the pleural fluid samples. There was no strong correlation between the ADA levels and the various hematological and biochemical parameters.

Table 3 Hematological and biochemical analysis of pleural fluids in diagnoses subgroups

Variable	Malignant	Other exudates	Idiopathic	Post-CABG	Parapneumonic	Transudates
pH	7.35±0.09*	7.38±0.04	7.37±0.05*	7.40±0.02	7.36±0.07*	7.40±0.07
Glucose mg·dL−1	112.1±44.5*	111.4±36.8*	120.6±33.9*	168.7±78.8	121.3±57.7	139.4±57.6
Protein mg·dL−1	4.4±1.0*	5.3±4.2*	4.0±1.0*	4.1±0.8*	4.4±1.1*	2.4±1.6
Cholesterol mg·dL−1	84.8±29.7*	84.6±29.1*	79.0±32.3*	80.0±27.6*	93.5±42.7*	34.3±20.2
LDH IU·L−1	740.3±808.5*	403.5±287.6*	372.9±271.8*	195.5±81.5	490.6±333.0*	177.2±83.1
WBC µL	2685±5153	2487±2887	1847±1539	815±321	2615±3013	1787±4871
Neutrophil %	13.75±10.61	15.45±7.96	12.78±8.80	9.07±6.49	12.30±8.70	15.00±10.69

Data are presented as MEAN±SD
CABG: coronary artery bypass grafting
LDH: lactate dehydrogenase
WBC: white blood cell
$p<0.05$ compared with the transudate group

Discussion

The diagnostic utility of ADA in lymphocytic pleural effusions has been evaluated. This prospective study provides additional evidence that ADA levels in nontuberculous lymphocytic pleural effusions seldom exceed the cut-off set for tuberculous effusions. Low ADA levels in lymphocytic pleural effusions virtually exclude the diagnosis of tuberculosis. The pleural fluid ADA levels were significantly higher in different types of exudative effusions than in transudates. ADA1/ADAp correctly classified all nontuberculous lymphocytic pleural effusions with high ADA levels.The diagnosis of tuberculous pleural effusions can be difficult because of the low sensitivity of the various diagnostic tools. A lymphocytic exudate which is seen with tuberculous pleuritis, can also occur with other diseases such as malignancy and collagen vascular diseases. Regarding the sensitivity of diagnostic methods for tuberculous pleurisy, the positive rate with smear testing for tubercle bacilli in pleural fluid is 11.1% in the present authors' experience 8, with culturing 33.3% and with closed pleural biopsy 96.2%. However, other groups have reported lower diagnostic rates for tuberculous pleural effusions 11, 12.Pleural fluid ADA has long been used as a marker for tuberculous pleurisy. Levels of ADA in pleural fluid >40 IU·L−1 can indicate pleural tuberculosis with sensitivity (81–100%) and specificity (83–100%) 13–15. The false-positive cases in the literature are mainly due to empyema, lymphomas, malignant diseases and other etiologies, such as parapneumonic or collagen vascular disease 14, 16. Examination of those studies reveals that pleural fluids of any cell type predominance were included. As in this study, previous reports 17, 18 have found increased ADA levels in patients with complicated parapneumonic effusions, wherein the immune response involves polymorphonuclear cells and macrophages rather than lymphocytes.In this study, there were no empyema in the parapneumonic effusion group as empyema are predominantly neutrophilic effusions. This could explain the low average ADA values found in the group of lymphocytic parapneumonic effusions.This study assesses the usefulness of ADA measurement in lymphocytic effusions. This practice resembles clinical decision making where tuberculosis is most commonly suspected only in lymphocytic effusions. By restricting this study to lymphocytic pleural effusion, false-positives were rare (<2%). An elevated pleural fluid ADA level in countries with a high prevalence of tuberculous pleural effusions, as in Spain, has a high degree of specificity for tuberculous pleuritis, which makes it an integral part of the diagnostic work-up of lymphocyte-rich pleural effusions. In areas where the prevalence of disease is low, there is a higher likelihood of false-positive test results, and this can lead to the unnecessary administration of antituberculosis therapy or a delay in making an alternative diagnosis such as malignancy. Thus far, high ADA levels in lymphocytic effusions should be looked on as a screening test to guide further diagnostic tests, such as closed pleural biopsy.In this study, the negative predictive value of the ADA test was very high. The sensitivity and specificity of ADA depends on the prevalence of tuberculosis in the population. With the decline in the prevalence of tuberculous pleural effusion in some areas, the positive predictive value of pleural fluid ADA also declines but the negative predictive value remains high. Therefore, the measurement of the pleural fluid ADA level is an excellent test to rule out a tuberculous etiology of lymphocytic pleural effusions, irrespective of the rate of prevalence of the disease. This study is larger than the prospective study of Lee et al. 6, but the results presented by these investigators are similar. The present study included a higher number of malignant and parapneumonic pleural effusions and a lower number of post-CABG effusions, which may more closely resemble the patient population in most pleural units. Moreover, all idiopathic pleural effusions were included in this study, so that the conclusions can be applied to patients with lymphocytic pleural effusions seen in clinical practice.

Summary

In view of the rigorous diagnostic criteria for pleural tuberculosis, some cases may have been expected to be missed, particularly when considering that one of the patients with an

unknown diagnosis had an elevated ADA. Thus far, the median follow-up among these patients with idiopathic effusions is 21 months and none of them have developed tuberculosis. Nonetheless, it is very unlikely that the current authors' major conclusions would be affected by the diagnostic pitfall, if any, in this group of patients. The present results are in agreement with those of Ferrer et al. 19, with 15.6% of idiopathic effusions in this study. In the study by Ferrer et al. 19, none of the patients developed tuberculosis during the follow-up period. In the current study, only one patient with an idiopathic effusion had a high ADA level (63 IU·L−1) but ADA1/ADAp correctly classified this patient as having a nontuberculous effusion. In this particular case, pleural effusion resolved spontaneously without relapses after 47 months of follow-up.ADA represents the sum of two isoenzymes (ADA1 and ADA2). ADA1 is ubiquitous in all cells, including lymphocytes and monocytes, whereas ADA2 is found only in monocytes. 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/ADAp ratio improves performance in terms of sensitivity, specificity and efficacy (100%, 92–97%, and 98%, respectively) in correcting all false-negative and false-positive results except 1–9% of non lymphoproliferative malignancies. The findings of the present study support the use of ADA isoenzymes in cases of suspected nontuberculous lymphocytic pleural effusions with an elevated ADA.

In conclusion, an elevated level of adenosine deaminase activity is seldom found in nontuberculous lymphocytic pleural effusions. An adenosine deaminase level <40 IU·L−1 virtually excludes tuberculosis in lymphocytic pleural effusions. Adenosine deaminase1/adenosine deaminase ratio improves the performance of adenosine deaminase activity in cases of false-positive findings.

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