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The diagnostic value of adenosine deaminase activity in sputum in pulmonary tuberculosis

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Abstract This study was carried out in Atatürk Chest Diseases and Surgery Center. It's aim to determine and compare sputum adenosine deaminase (ADA) activity in pulmonary tuberculosis (tb), lung cancer and chronic obstructive pulmonary disease (COPD) patients in order to assess its diagnostic value. Patients and method: Eighty-four patients (25 tb, 30 lung cancer and 29 COPD) were included in the study. ADA activity in sputum and serum was measured. Sputum ADA activities of tb patients were significantly higher than the other two groups ($P < 0.05$). Sputum/serum ADA ratios were similar in all groups. Sputum ADA activities between 150 and 200 U/L were the measurements with the best test performance according to the ROC curve. Sensitivity, specificity, positive predictive value, and negative predictive value were 44.0, 86.4, 57.8, 78.4% for 150 U/L and 32.0, 96.6, 80.0, 77.0% for 200 U/L, respectively. Area under the curve was 0.663. Because of low sensitivity, routine determination of ADA activity in sputum for the diagnosis of pulmonary tb is not recommended. However, it can be helpful in the diagnosis of smear-negative cases who are strongly suspected of tb.

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Keywords pulmonary tuberculosis; sputum; serum; adenosine deaminase.

INTRODUCTION

Successful treatment of tb largely depends on early diagnosis and the most important diagnostic method is to detect the bacilli bacteriologically. However, as this is not always possible, new methods are being developed and used (1).

Adenosine deaminase (ADA) is an enzyme catalyzing the hydrolytic and irreversible deamination of adenosine to inosine and deoxyadenosine to deoxyinosine. ADA is used for the diagnosis of pleural tb and there are studies showing high levels of ADA in sera and bronchoalveolar lavage (BAL) fluids of tb patients (2–9). However only a few studies have focused on ADA activity in materials obtained by non-invasive methods, such as sputum (10). We, therefore, measured and compared sputum and serum ADA activities in pulmonary tuberculosis (tb), lung cancer and chronic obstructive pulmonary disease (COPD) patients in order to assess this test's diagnostic value.

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MATERIALS AND METHODS

Eighty-four patients (25 with pulmonary tb, 30 with lung cancer and 29 with COPD) who were followed up in Atatürk Chest Diseases and Surgery Center were included in the study. Twenty-two of the tb patients were smear- and culture-positive and the remaining three were smear-negative, and culture-positive.

Early morning sputum and 5 cc venous blood were obtained from all patients. Blood samples were centrifuged at 3500 rpm for 10 min to separate the sera.

Sputum samples were homogenized with 70 milli-mol phosphate buffer (pH: 6.0) containing 0.5 mol NaCl (1 ml sputum + 5 ml buffer). They were centrifuged at 5000 rpm for 30 min and ADA activity of the supernatant was measured by Guisti method. Results were corrected by multiplying with the dilution coefficient. All measurements were done on the same day samples were obtained.

A serum ADA activity between 14 and 20 U/l was considered normal. Enzyme activities in three groups were

compared by one-way ANOVA and when a significant difference was found, pair-wise post hoc comparisons were carried out using Tukey's honestly significant test. When the study population was divided into tb and non-tb groups, *t*-test was used. Correlation between serum and sputum values was assessed by Pearson correlation test. Specificity, sensitivity, positive predictive value, negative predictive value and area under the curve were calculated using ROC curve.

RESULTS

Number of patients, mean ages, sex distribution, sputum ADA, serum ADA measurements and sputum/serum ADA (ADA ratio) of the groups are shown in Table I.

Mean age of tb group was significantly lower than the other two groups ($P < 0.001$). Other demographic characteristics were similar in all groups.

Sputum ADA activities in the tb group were significantly higher than the other two groups ($P < 0.01$ for lung cancer group, $P < 0.05$ for COPD). There was a significant difference in serum ADA activities between tb and cancer groups ($P < 0.05$). ADA activities in sera were similar in tb- and cancer-COPD comparisons ($P > 0.05$). Sputum/serum ADA ratios were similar in all groups ($P > 0.05$).

ADA activity in serum and sputum in tb group was significantly higher than the non-tb groups ($P < 0.05$). Ratios were similar.

When we tried to set a cut-off point for sputum ADA activities of tb and non-tb groups, values between 150 and 200 U/l were the ones with the best specificity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 44.0, 86.4, 58.8, 78.4% for 150 U/l and, 32.0, 96.6, 80.0, 77.0% for 200 U/l, respectively. AUC for ADA activity in sputum was calculated as 0.66 (Table 2). This value was significantly higher than 0.5 ($P < 0.05$).

There was no correlation between ADA activities in sputum and serum of tb group (P: 0.681). However, there was a significant correlation in non-tb group (P: 0.0047).

Distribution of ADA activities in sputum is shown in Fig. 1.

DISCUSSION

ADA is an enzyme that takes part in lymphoid cell differentiation and monocyte, macrophage maturation. Its activity is high in lymphocytes and monocytes and it has two isoenzymes designated A_1 and A_2 (11). High ADA activity in pleural fluid is valuable for the diagnosis of tb pleurisy in countries with high tb prevalence (2).

High ADA activity in pleural effusions of patients with other diseases as lymphoproliferative disorders, bronchogenic cancer, pulmonary embolism, systemic lupus erythematosus, rheumatoid arthritis, empyema, liver diseases, mesothelioma, parapneumonic and idiopathic fluid lower the specificity. Additionally, ADA levels can be initially low in tb effusions and may rise in repeated measurements (5).

ADA activity in BAL fluid of patients with pulmonary tb was higher than patients with malignancies (8,9). However, serum ADA activity was similar in two groups (8). In the diagnosis of tb, sputum smear and culture are routinely used and are reliable. Sophisticated methods like BACTEC, polymerase chain reaction (PCR), nucleic acid

Table I. Number of patients, sex distribution, mean ages, sputum and serum ADA activities and sputum/serum ADA ratios of the patients

Groups	*n*	Male	Female	Age (mean ± SD)	Sputum ADA (IU/l) (mean ± SD)	Serum ADA (IU/l) (mean ± SD)	ADA ratio (mean ± SD)
Tb	25	23	2	38.8 ± 15.5	161.8 ± 143.4	27.5 ± 11	6.8 ± 8.2
Neoplasm	30	30	—	60.1 ± 10	74.5 ± 51.6	18.4 ± 7.5	5.1 ± 3.5
COPD	29	22	7	61.2 ± 10.2	89.2 ± 85.6	23.9 ± 24	4.3 ± 3.5
Non-tb (COPD+Neoplasm)	59	52	7	60.6 ± 10	81.7 ± 70.2	21.1 ± 12.1	4.7 ± 5.2

Table 2. Sensitivity, specificity, PPV, NPV and AUC values for ADA activity in sputum of tb and non-tb groups

Cut-off (IU/l)	Sensitivity (%)	Specificity (%)	PPV (%)	PPV (%)	AUC
150	44	86.4	58.8	78.4	
200	32	96.6	80	77	0.66

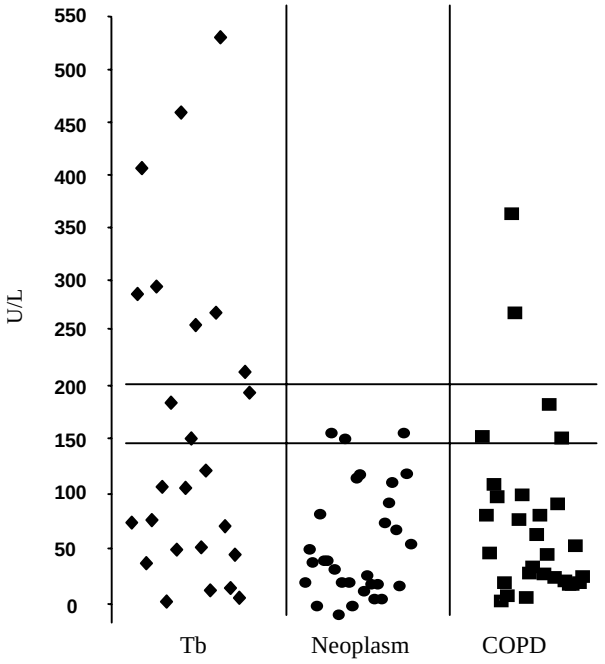

Fig 1. Sputum ADA activities of the study groups.

probe and biochemical analysis such as tuberculostearic acid may increase diagnostic yield (12).

ADA levels have so far been measured in materials obtained by invasive methods such as BAL and thoracentesis and only a few studies have depended on non-invasive methods.

Dimakou and colleagues found significantly higher ADA activity in sputums of 22 tb patients than 13 lung cancer patients. Sensitivity was 60%, specificity was 92% with a cut-off level of 15 U/l (10).

Sputum ADA activity of the tb group was significantly higher than other groups in our study. We obtained the best specificity values with cut-off points between 150 and 200 U/l. As in Dimakou and colleagues' study, we found low sensitivity values with moderate specificities. We have included COPD patients as well as lung cancer patients as controls. However, when we excluded COPD group, similar results were obtained (with a cut-off point of 150 U/l, sensitivity was 44%, specificity 90%, and AUC 0.678).

It must be noted that two of the three smear-negative patients had sputum ADA levels of 150 U/l.

ADA activity in sputum of our tb patients was strikingly higher than those observed by Dimakou and colleagues. This can be explained by the standard dilution and multiplication of the result by the dilution coefficient (6).

Because of low sensitivity, these results are insufficient to recommend ADA activity in sputum as a diagnostic method for pulmonary tb. But, since sputum is a material that can be obtained by non-invasive methods, in smear-negative patients who are strongly suspected to have pulmonary tb, the determination of ADA activity in sputum can be helpful. Further studies on new methods to diagnose tb in smear-negative patients are needed.

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