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Research Article

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Diagnostic Value of Pleural Fluid Adenosine Deaminase In Patients With Pleural Tuberculosis

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Abstract

Background and Objectives

Extra-pulmonary tuberculosis occurs in about 10-20% of patients with tuberculosis. It most commonly manifests as tuberculous lymphadenitis or pleural effusion. Pleural fluid Adenosine deaminase (ADA) activity considered as a useful biomarker for detecting pleural tuberculosis. The purpose of this study was to evaluate the diagnostic accuracy of pleural fluid adenosine deaminase level in patients with pleural tuberculosis.

Methods

In this study, 113 patients with exudative pleural effusion with unknown underlying diagnosis, were enrolled. Physical examination, chest CT, ADA level of pleural fluid, direct thoracoscopic examination, and biopsy of pleura were obtained for all individuals. ADA level and thoracoscipoc appearance of the lesions was then compaierd among the patients with regard to the pleural biopsy report as the diagnostic goldstandard.

Results

The diagnosis of tuberculous pleurisy was established in 40 individuals based on the pathology reports. The mean ADA level of the TB and the non-TB group was 39.90±22.93 IU/L and 30.74±38.27 IU/L, respectively (P-value=0.167). Sensitivity, specificity, positive predictive value, and negative predictive value of ADA test were 35%, 86.30%, 58.33%, and 70.79%, respectively.

Conclusion

Based insuffiecient sensitivity and specificity of ADA, in patients with unexplained exudative pleural effusion especially in those with a high suspicion of tuberculous pleurisy, despite the low level of ADA, direct thoracoscopic pleural evaluation with obtaining multiple biopsies of pleura is highly recommended.

Keywords: Pleural Effusion, Thoracoscopy, Tuberculosis, Diagnostic Accuracy, Extra-pulmonary tuberculosis, Adenosine deaminase

Introduction

Tuberculosis is a chronic bacterial infection caused by Mycobacterium tuberculosis. It remains a disease with a high rate of mortality in the world especially in developing and low-income countries [1]. Extra-pulmonary tuberculosis occurs in about 10% -20% of patients and the most common forms of involvement are tuberculous Lymphadenitis and tuberculous pleural effusion [2].

Pleural tuberculosis (TB) which is the topic of this study, is characterized by symptoms such as chest pain, cough, and fever. Chest Radiography of these patients shows a small to moderate unilateral pleural effusion which is lymphocyte dominant in serologic evaluations. The condition also could be bilateral within the minority of cases [1, 3]. The prevalence of tuberculosis among all patients with pleural effusion is between 4-22%, and pleura is involved in 3-23% of patients with tuberculosis [4, 5].

Different diagnostic methods have been used to diagnose pleural tuberculosis, including thoracentesis, measurement of serum and pleural fluid adenosine deaminase (ADA) level, pleural biopsy, and thoracoscopy assisted pleural examination and biopsy [3].

Measuring ADA activity in pleural fluid is an easy, inexpensive, fast, and useful way for diagnosing TB in endemic areas, such as South Africa, Asia, Brazil, Spain, and Eastern Europe [6-8]. Based on literature a cut-off point of 40 U/L of ADA activity in a lymphocyte dominant pleural fluid is diagnostic for pleural TB. But the validity of the test is not generally accepted by consensus [9-11].

With the advancement in endoscopic techniques and video equipment, thoracoscopy has been suggested as a diagnostic and therapeutic modality in patients with pleural tuberculosis, and become more popular among the physicians. Thoracoscopic findings of these patients include caseous necrosis, miliary nodules, exudative pleural effusion, and pleural adhesion or fibrotic septa [12-14].

Considering the important role of ADA in the diagnosis of pleural tuberculosis, evaluating the correlation between pleural ADA level and thoracoscopic findings of pleural tuberculosis seems necessary [15, 16].

This study aims to determine the correlation of the pleural fluid ADA activity and its diagnostic accuracy in histologically confirmed cases of pleural tuberculosis.

Materials and Methods

In this cross-sectional study, 113 patients from those who referred to the cardiothoracic surgery department of Tabriz University of Medical Science with unexplained exudative pleural effusion were enrolled. The study population was measured by GPOWER software with a confidence interval of 95% and a test power of 80%. All patients had a pleural effusion with unknown etiology and candidated for thoracoscopy and biopsy. Patients were excluded from the study in case of transudative pleural effusion, post-traumatic effusion, known pulmonary disorders, history of pulmonary or pleural malignancies, and history of radiotherapy on the thoracic cavity.

All patients underwent thoracoscopic study with direct evaluation of the pleural cavity. Multiple pleural biopsies and pleural fluid specimen for ADA analysis were obtained. All tissue samples were evaluated by a certain pathologist and ADA was measured using ADA Reagent Kit in an acredited laboratory of the affiliated university. The ADA level of greater than or equal to 40 U/L considered as diagnostic for TB. According to the pathologic reports, patients were divided into two TB and non-TB groups. The demographic data, examination and thoracoscopic findings, as well as ADA levels were compared between two groups.

Data were collected and analyzed by IBM SPSS statistic for windows version 23.0. (IBM Corp., Armonk, N.Y., USA). Descriptive data were reported using mean, standard deviation, relative, and absolute frequencies. Chi2, paired sample t-test, independent t-test. and repeated measure ANOVA were used for analytical comparison of the variables between the groups as needed. The p-value of less than 0.05 was considered statistically significant. Sensitivity and specificity were calculated based on patient-level analysis of gathered data using confusion matrix and relying on pathologic results as the gold standard diagnostic test.

Ethical Consideration

The study was approved by the ethics committee of Tabriz University of Medical Science under the approval number of 5/d/8716-94/5-6/3. All diagnostic and therapeutic interventions were performed regarding the routine management of patients; no additional intervention or cost was imposed on participants in this study. Patients' data were recorded as encoded variables without mentioning the name of any participant. None of the patients' personal information was included in this research.

Informed consent was obtained from each participant; nevertheless, patients were excluded from the study in cases they were reluctant to participate in the study.

Results

Of the total 113 patients, 73 (58.4%) were male, and 40 (32.0%) were female, and 42 (33.6%) were smokers. The mean age of the patients was 49.77 ± 18.71 years.

The diagnosis of TB was confirmed in 40 patients according to the histopathologic reports. These patients were stratiffied as the case group (known as group A), and the other 73 with a diagnosis of non-tuberculous pleural effusion were considered as the control group (known as group B).

As depicted in Table-1 dyspnea, cough, and pleuritic chest pain were the dominant symptoms of patients at the time of admission with a frequency of 66.37%, 48.67%, and 40.7% respectively. The frequency of fever and weight loss were30.97%, and 28.31%, respectively among the patients. Table-1 also demonstrates demographic data of individuals separately for each study groups.

Table1: Demographic Data of Studied Individuals

		In Group A	In Group B	Total	P-value
Number of Patients		40	73	113	-
Age (years)		43.32 ± 17.31	53.31 ± 18.61	49.77 ± 18.71	0.006
Gender	Male	24	49	73	0.453
	Female	16	24	40	
Smoking	Smoker	14	28	42	0.957
	Non-smoker	26	45	71	
Signs and Symptoms	Cough	30 (75%)	25 (34.2%)	55 (48.6%)	0.045
	Pleuritic Chest Pain	36 (90%)	10 (13.7%)	46 (40.7%)	0.000
	Dyspnea	39 (97.5%)	36 (49.3%)	75 (66.3%)	0.19
	Weight Loss	7 (17.5%)	25 (34.2%)	32 (28.3%)	0.000
	Fever	20 (50%)	15 (20.5%)	35 (30.9%)	0.036

Regarding the thoracoscopic examination, pleural effusion, pleural adhesion band, miliary nodules, and caseous necrosis were found in 100%, 67.5%, 70%, and 60%, of the group A respectively (Table-2). Among the control group (group B), pleural effusions, thickening of pleura and miliary nodules were the dominant manifestations with a frequency of 100%, 46.57%, and 30.13% respectively (Table-2). The underlying cause of pleural effusion among the patients in control group was: metastasis (23.28%), mesothelioma (5.47%), inflammation (32.87%), fibrosis (36.98%), and fungal infection (1. 36%) as depicted in Table-2. The mean ADA level was 39.90 ± 22.13 IU/L in group A and 30.74 ± 38.27 IU/L within group B individuals which did not differ statistically significantly between the two study groups (p=0.167).

Table 2: Surgical And Paraclinical Findings of Patients

		In Group A	In Group B	Total
Number of Patients		40	73	113
CT-Scan Findings	Pleural Effusion	40 (100%)	73 (100%)	113 (100%)
	Pleural Effusion + Pleural Thickening	17 (42.5%)	22 (30.!%)	39 (34.5%)
Thoracoscopic Findings	Pleural Effusion	40 (100%)	73 (100%)	113 (100%)
	Solitary Nodule	1 (2.5%)	0 (0.0%)	1 (1.3%)
	Miliary Nodules	28 (70%)	22 (30.1%)	50 (44.2%)
	Caseous Necrosis	24 (60%)	0 (0.0%)	24 (21.2%)
	Adhesion Bands	27 (67.5%)	0 (0.0%)	27 (23.9%)
	Pleural Thickening	12 (30%)	34 (46.5%)	46 (40.7%)
	Edema	7 (17.5%)	0 (0.0%)	7 (6.2%)
Histologically Confirmed Diagnosis	Tuberculosis	40 (100%)	0 (0.0%)	40 (35.4%)
	Metastasis	0 (0.0%)	17 (23.2%)	17 (15%)
	Mesothelioma	0 (0.0%)	4 (5.4%)	4 (3.5%)
	Inflammatory	0 (0.0%)	24 (32.8%)	24 (21.2%)
	Fibrosis	0 (0.0%)	27 (36.9%)	27 (23.9%)
	Fungal Infection	0 (0.0%)	1 (1.3%)	1 (0.8%)

As delineated in Table-3, 35% of patients in group A has ADA level of greater than 40 (as a diagnostic cut-off for TB) compared to 13.7% in group B (p>0.05). Bar chart for these amounts is also illustrated in figure-1.Sensitivity, specificity, positive predictive value, and negative predictive value of ADA test were measured 35%, 86.30%, 58.33%, and 70.79% respectively (Table-4). Figure-2 demonstrates the ROC curve of ADA test measures.

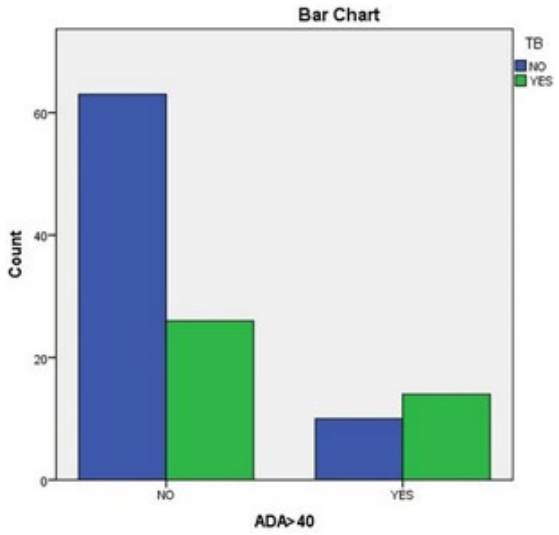

Figure 1: Frequency of patients with ADA activity level of greater than 40 in each TB-positive and TB-Negative groups (ADA: Adenosine deaminase, TB: Tuberculosis)

Table 3: Measured ADA level of the patients

ADA Level	Group A	Group B	Total	P-value
≥ 40	14 (35%)	10 (13.7%)	24 (21.2%)	0.993
< 40	26 (65%)	63 (86.3%)	89 (78.7%)	

Table 4: Characteristics of the ADA test and its diagnostic power for diagnosing TB (CI: Confidence Interval, TB: Tuberculosis)

	Value	95% CI
Sensitivity1	35.00%	20.63% to 51.68%
Specificity	86.30%	76.25% to 93.23%
Positive Predictive Value	58.33%	40.67% to 74.4.09%
Negative Predictive Value	73.00%	65.47% to 75.59%

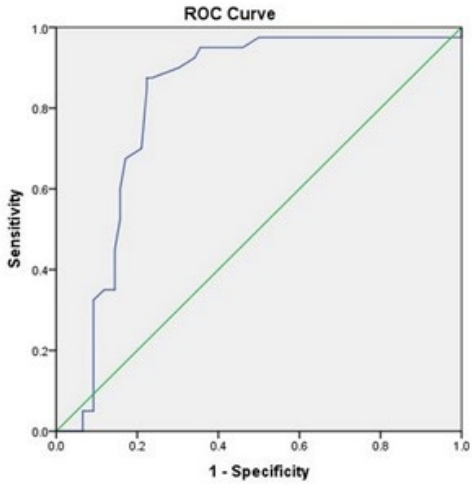

Figure 2: ROC Curve For Sensitivity and Specificity of ADA biomarker (ADA: Adenosine deaminase)

Discussion

In this study, 113 patients (73 males and 40 females) with unexplained pleural effusion were evaluated for probable pleural tuberculosis by using thoracoscopic examination and biopsy. Meanwhile, the ADA level was measured for all individuals regardless of pathologic findings. The diagnosis of pleural TB established only in 40 individuals according to the histopathologic reports. The ADA level among these tuberculous pleurisy patients was 39.90 ± 22.13 IU/L compared to a level of 30.74 ± 38.27 IU/L in non-tuberculous individuals, which was not statistically significant. Based on our results, the ADA test yield a sensitivity, specificity, positive predictive value, and negative predictive value of 35%, 86.30%, 58.33%, and 70.79% respectively.

In a study performed by Van et al., the causes of pleural effusion were evaluated among 95 patients in Netherland. According to their results, they have found tuberculous pleurisy just in five patients, among them the high ADA activity was only detected in four individuals. On the other hand, the underlying pathologies other than TB could raise the ADA activity based on their study. The authors conclude that the high ADA activity level in a country with low tuberculosis incidence is not accurate enough to establish the diagnosis of tuberculous pleurisy [17].

Tian et al. found a sensitivity and specificity of 84.4% and 91.8% for ADA in diagnosing tuberculous pleurisy by evaluating 190 patients with pleural effusion. The cause of pleural effusion was TB in 141 patients of their study population [18]. The difference between the results of our study compared to the recently mentioned research is explainable by the high overall incidence of TB in the country in which Tian et al., performed their study.

Valdes et al., in their study, revealed that measuring pleural ADA level is a useful parameter for the diagnosis of tuberculous pleurisy by evaluating 405 patients with pleural effusion. All 91 cases of pleural TB in their study showed an ADA level of greater than 47 IU/L, compared to the elevation just in 5% of non-tuberculous patients [15].

Zemlin et al. demonstrated that measuring the ADA2 isoenzyme is more accurate, and it is superior to ADA in diagnosing tuberculous pleurisy by performing a study on 951 pleural fluid samples, including 387 patients with TB. They suggested that measuring ADA2 level is better to use as a routine test among patients with pleural effusion in endemic areas for TB [11].

Technically, the predictive value of an indicator such as ADA does not only depend on its sensitivity and specificity, but also the incidence of the disease in the study region is also effective [19, 20]. The inconsistency between the results might have happened due to the variable prevalence of TB and different sample sizes in which the mentioned studies were performed.

The strength of this study was the use of pathlogical confirmation for the diagnosis of the underlying cause of the pleural effusion in the studied patients. The patients with the diagnosis other than pleural tuberculosis was also considered as a reliable corntol group for calculating the diagnostic accuracy of the applied method. Somehow, the shortness of the study sample size was a weakness of our study. Howere, it should be considered that the overall prevalence of the TB within the population in which the study takes place may alter the results of the study; then, it should also be considered as a limitation of the study.

By comparing our results with previous studies, it can be concluded that the sensitivity, specificity, and accuracy of this test are not suffiecient enough; so, ADA is not utterly useful in diagnosis of pleural TB. Therefore, in patients with pleural effusion with undetermined origin and in patients with a high level of suspicion of TB infection, despite the low ADA level, thoracoscopic evaluation of pleural cavity with obtaining multiple biopsies of pleura would be more appropriate.

Also, in cases with high ADA level and lack of proper response to TB treatments, for further investigation and rule out the other diagnosis, thoracoscopy and pleural biopsy could be beneficial. However, further studies with larger sample size are suggested.

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None

Authors' Contributions

F.R., M.S., S.B.R. and S.P. conceived of the presented idea. F.R. and M.S. diagnosed the disease and selected the patients. F.R., M.S. and S.B.R. provided the management methods, F.R. and S.P. collected the data sets, S.P. acquired additional data from the database. F.R. and S.P. wrote the manuscript. S.P. analyzed the data, M.S. and S.B.R. made a revision on the manuscript. M.S. supervised the whole project.

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