İzmir Göğüs Hastanesi Dergisi 2020;34(1):20-6
doi:10.5222/IGH.2020.1812

Özgün Araştırma / *Research Article*

Are Patients With Tuberculous Pleurisy With Low ADA Levels Different from Those With High ADA Levels?

Düşük ADA Düzeyi Olan Tüberküloz Plörezili Hastalar, Yüksek ADA Düzeyi Olanlardan Farklı mıdır?

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Cite as: Büyükşirin M, Anar C, Yüksel Yavuz M, Güldaval F, Alıcı İO. Are patients with tuberculosis pleurisy with low ADA levels different from those with high ADA levels? İzmir Göğüs Hastanesi Dergisi. 2020;34(1):20-6.

ABSTRACT

Objective: We aimed to compare the patients with low andhigh ADA levels in terms of their clinical, radiological and cytopathological features.
Method: Tuberculous pleural effusion (TPE) patients who underwent thoracentesis were retrospectively reviewed. The pleural fluid profiles were compared between patients with low and high ADA levels.
Results: A total of 138 patients consisting of 43 women and 95 men, who were diagnosed with tuberculous pleurisy with a mean age of 36, were included in the present study. Anystatistically significant differences were not detected among the patients who had low and high pleural fluid ADA levels in terms of age, gender, clinical symptoms, amounts ofpleural fluid (low, median, massive), its characteristics (free, loculated, empyema), and its cytology (lymphocytic, neutrophilic, mixed).However, it was determined that parenchymal involvement was higher at a statistically significant level in those who had increasedpleural fluid ADA values (≥40 IU/L), and those who had low ADA values of the pleural thickening (<40 IU/L) (p: 0.011; 0.016, respectively).
Conclusion: It should be kept in mind that clinical, radiological and histopathological findings of patients with tuberculous pleurisy may not differ according to ADA level.

Keywords: tuberculosis, pleural fluid, ADA

ÖZ

Amaç: Bu çalışmada düşük ADA düzeyi olan TPE'lu hastalar ile yüksek ADA düzeyine sahip olan hastaları klinik, radyolojik, sitopatolojik özellikleri yönünden karşılaştırılması amaçlandı.
Yöntem: Torasentez yapılan tüberküloz plevral efüzyon (TPE) hastaları retrospektif olarak incelendi. Plevral sıvı profilleri düşük ADA seviyeleri ile yüksek ADA seviyeleri arasında karşılaştırıldı.
Bulgular: Çalışmaya 95 erkek, 43 kadın ve median yaş ortalaması 36 olan tüberküloz plörezi tanısı konan 138 hasta dahil edildi. Hastaların çeşitli klinik, sitopatolojik, mikrobiyolojik ve radyolojik özellikleri tabloda gösterilmiştir. Plevral sıvı ADA değeri düşük ve yüksek olan hastalar arasında yaş, cinsiyet, klinik, plevral sıvı miktarı (az, orta, masif), karakteri (serbest, loküle, ampiyem) ve sitolojisi (lenfosittik, nötrofilik, mix) yönünden istatistiksel olarak anlamlı fark saptanmadı. Ancak plevral sıvı ADA değeri (≥ 40 IU/L) yüksek olanlarda parenkimal tutulumun, plevral kalınlaşmanın ADA değeri (< 40 IU/L) düşük olanlara göre istatistiksel olarak anlamlı düzeyde daha fazla olduğu bulundu (sırasıyla p: 0,011, 0,016).
Sonuç: Tüberküloz plörezili hastaların klinik, radyolojik ve histopatolojik bulgularının ADA düzeyine göre farklılık göstermeyebileceği akılda tutulmalıdır.

Anahtar kelimeler: tüberküloz, plörezi, ADA

Alındığı tarih: 31 Temmuz 2019
Kabul tarihi: 9 Ağustos 2019
Yayınlandığı tarih: 30 Nisan 2020

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INTRODUCTION

Tuberculouspleural effusion (TPE) is the most common form of extrapulmonary tuberculosis and requires differential diagnosis in exudative pleural effusions. The diagnosis of TPE has improved significantly with the use of biochemical markers, such as adenosine deaminase (ADA), in combination with microbiological or histological methods, especially in areas with moderate to high TB prevalence [1-3]. In areas with high tuberculosis prevalence, adenosine deaminase (ADA) measurement for pleural tuberculosis is a cheap, minimally invasive, fast and easily accessible popular test with 95% sensitivity and 90% specificity. For patients suspected of pleural tuberculosis due to these benefits, ADA testing is the preferred screening method compared to other diagnostic tools [4,5].

TPE is typically characterized by lymphocytic predominance and high ADA levels [6]. These characteristics are helpful in the presumptive differential diagnosis of TPE, PPE, and MPE [7]. Also, measurement of ADA can be valuable in avoiding inappropriate antituberculosis treatment in patients diagnosed as lymphocytic PE without Mycobacterium tuberculosis infectio [7,8]. However, TPE occasionally displays neutrophilic predominance similar to how PPE does, and the ADA levels in PPE cases frequently exceed the threshold value for a diagnosis of TPE. In addition, sometimes ADA levels in TPE may be low [6,7,9].

In this study, we aimed to compare the patients with low and high ADA levels in terms of their clinical, radiological and cytopathological features.

MATERIALS and METHODS

Subjects and Study design

We retrospectively reviewed all TPE patients who underwent diagnostic thoracentesis at Izmir Dr. Suat Seren Chest Diseases and Surgery Training and ResearchHospital, Turkey, from January 2012 to December 2017. Turkey is an area with an intermediate prevalence of active TB. In the 2015 Global Tuberculosis Report, the prevalence andand incidence rates were 0.22% and 0.18%, respectively [10]. A diagnosis of TPE was confirmed when one of the following criteria was met: (1) a positive culture for Mycobacterium tuberculosis (MTB) in pleural fluid, pleural tissue, sputum, or bronchial aspirate; (2) pathologically chronic granulomatous inflammation with either a positive MTB polymerase chain reaction, positive acid-fast bacilli (AFB) smear, caseous necrosis in pleural biopsy tissue; or (3) chronic granulomatous inflammation per sedetected in the pleural biopsy and pleural effusion that was resolved with anti-TB treatment [11].

Academic Board approval was obtained from the training planning board of T.R. Izmir University of Health Sciences Suat Seren Chest Diseases and Surgery Research Center with protocol number 48865165-302.14.02.

Incidence of tuberculosis is one of the factors that determine the diagnostic value of ADA. ADA elevation alone may not provide sufficient data for low incidence sites. In such areas, a negative ADA value is more meaningful for exclusion of the disease. In a region with high incidence of tuberculosis, in patients under 40 years of age, and in the presence of lymphocyte-rich exudative pleural fluid, the ADA value above 40 U/L greatly confirms the diagnosis of TP and provides an indication for treatment. An ADA value that is below 35 IU/L excludes nearly completely the diagnosis of tuberculosis in patients demonstrating only occasionallylymphocyte-rich pleural fluid, in an area with lower incidence of TB [11]. On the other hand, a pleural ADA value that is higher than 70 U/L has very high sensitivity and specificity with an approximate diagnostic value [13,14]. In the present study, the patients who were included in the study were divided into two groups according to ADA levels (ADA≥40 U/L,

ADA<40U/L) in line with the literature.

The demographic data of the patients were examined from the records. Those who had fever, pleuritic chest pain that was associated with chills, and shortness of breath were recorded as those having clinical symptoms that mimicked pneumonia. Whereas, those who had symptoms such as weight loss, loss of appetite, weakness, and a chronic cough, were evaluated separately. The fluid levels of the patients were determined according to a posterior anterior chest X-ray. If the fluid closed only the sinus, it was encoded as "low"; if it reached the hilus, it was encoded as "median"; and if it exceeded the hilus, it was encoded as "massive" amounts of fluid Aside from the amount of fluid, the character of the fluid was evaluated as "free", "loculated" or "empyema". After the treatment at the 4th and/or 6th month, the presence of pleural thickening was encoded with a chest X-ray orwith computed tomography. The values above 10mm were considered as pleural thickening.

The presence or absence ofparenchymal involvement, was evaluated with a chest radiography and/or thorax CT. CT findings considered to be suggestive of active pulmonary involvement in the presence ofcentrilobular nodules with or without branching opacities pulmonary consolidation in the upper lung zones, and cavitary lesions [5].

Data regarding the demographic and serial pleural fluid profiles [total leukocyte and differential leukocyte counts, pH, protein, glucose, lactate dehydrogenase (LDH), and ADA] were collected from patients in each group. Pleural fluid samples obtained during thoracocentesis were collected into 5 ml sterile heparinised tubes for routine biochemical and microbiological analysis. Additional samples of pleural fluid were inoculated into separate tubes containing ethylenediaminetetraacetic acid, centrifuged at 4°C, and the supernatant was frozen at - 80°C for further analyses. The pleural fluid ADA activity was measured in a routine clinical setting using an automated calorimetric assay kit (Roche-HITACHI- cobasc 501).

Neutrophilic effusion was defined as effusion with 50% neutrophils in the differential leukocyte count.

Statistical Analysis

SPSS for Windows® 20.0 was used for statistical analyses. Descriptive statistics were expressed as mean ± standard deviation or median (25%-75%) for continuous variables, and as frequency (%) for categorical variables. Pearson's chi-squared test was used to determine the association between categorical variables. The Independent samples T-test or the Mann-Whitney U test were used to compare descriptive values of continuous variables between the two groups. The value of $p<0.05$ was assumed to be statistically significant.

RESULTS

A total of 138 patients consisting of 43 women and 95 men with a mean age of 36, who were diagnosed with tuberculous pleurisy, were included in the present study. The clinical, cytopathological, microbiological and radiological characteristics of the patients are given in Table 1.

Anystatistically significant differences were not detected among the patients who had low and high pleural fluid ADA levels in terms of age, gender, clinical symptoms, pleural fluid amounts (low, median, massive), its characteristics (free, loculated, empyema), and its cytology (lymphocytic, neutrophilic, mixed).However, it was determined that parenchymal involvement was higher at a statistically significant level in those who had high pleural fluid ADA values (≥40 IU/L), and those who had low ADA values of pleural thickening (<40 IU/L) (p: 0.011; 0.016, respectively) (Table 2).

Table 1. Demographic, clinical, cytopathological, microbiological and radiological features of patients.

Features	
Age; median (25-75)	36 (27-52)
Gender (Male: Female)	95:43
Pleural fluid amount; n (%)	
Little	19 (13,8)
Middle	62 (44,9)
Massive	57 (41,3)
Pleural fluid character; n (%)	
Free liquid	98 (71)
Lokulated	38 (27,5)
Empyema	2 (1,4)
Pneumonic symptom; n(%)	48 (34,8)
Pleural fluid cytology; n(%)	
Lymphocytic	107 (77,5)
Neutrophilic	15 (10,9)
Mix	16 (11,6)
Pleural biopsy (N:131); n(%)	
NG	57 (41,3)
Non-NG	74 (53,7)
Pulmonary involvement; n(%)	38 (27,5)
Pleural thickening; n(%)	83 (60,1)
TB culture (N=120); n(%)	14 (10,1)

NG: necrotizing granulomatous; TB: tuberculosis

It was found that the patients who had high pleural fluid ADA levels also had lower pleural fluid glucose, and serum albumin levels, but higher pleural fluid LDH values (p:0.035; 0.002; 0.001, respectively) (Table 3).

DISCUSSION

In our study, although anydifferences were not detected between the pleural fluid ADA levels and age, gender, clinical and histopathological characteristics of the patients who had tuberculous pleurisy, it was determined that the pulmonary involvement and pleural thickening levels were higher in patients who had tuberculous pleurisy with elevated ADA values.

An association between age, and ADA values has been reported previously with much higher levels of pleural fluid ADA among younger patients with TPE [15-17]. We did not find significant age-related differences in ADA values

Table 2. Comparison of various features of patients with low and low pleural fluid ADA.

Various features	ADA<40 U/L	ADA≥40 U/L	p
n(%)	75 (54.3)	63 (45.7)	0,755*
Age; median (25-75)	38 (28-58)	38 (23-61)	0,816†
Gender (M:F)	51:24	44:19	0,797†
Pleural fluid amount; n(%)			
Little	9 (12)	10 (15.9)	
Middle	34 (45.3)	28 (44.4)	
Massive	32 (42.7)	25 (39.7)	0,440†
Pleural fluid character; n(%)			
Free Fluid	50 (66.7)	48 (76.7)	
Lokulated	24 (32)	14 (22.2)	
Empyema	1 (1.3)	1 (1.6)	0,697†
Pneumonic syptom; n(%)	25 (33.3)	23 (36.5)	0,166†
Pleural fluid cytology; n(%)			
Lymphocytic	54 (72)	53 (84.1)	
Neutrophilic	9 (12)	6 (9.5)	
Mix	12 (16)	4 (6.3)	0,529†
Pleural biopsy; n(%)			
NG	30/71 (42.3)	27/60 (44.6)	
Non-NG	41/71 (57.7)	33/60 (54.4)	0,011†
Pulmonary involvement; n(%)	14 (18.7)	24 (38.1)	0,016†
Pleural thickening; n(%)	31 (49.2)	52 (69.3)	0,092†
TB culture; n(%)	5/68 (7.4)	9/52 (17.3)	

NG: necrotizing granulomatous; TB:tuberculosis
**Mann-Whitney U test for non-parametric continuous variables; †Pearson Chi-square test for categorical variables*

Table 3. Comparison of various pleural effusions and serum parameters of patients with low and high pleural fluid ADA levels.

Features	ADA<40 U/L	ADA≥40 U/L	p
Serum			
Leukocyte	8000 (6750-9225)	7950 (6350-9725)	0,878*
Neutrophils	5472±1960	9658±2779	0,443‡
Lymphocytes	1400 (1000-1700)	1220 (800-1800)	0,334*
Eosinophils	100 (77-200)	100 (0-200)	0,527*
Protein	7,10 (6,50-7,50)	7,05 (6,55-7,5)	0,984*
Albumin	3,66±0,84	3,38±0,87	0,035‡
LDH	195 (171-221)	223 (176-266)	0,077*
Glucose	86 (67-98)	97 (86-109)	0,362*
Pleural fluid			
pH	7,36 (7,29-7,39)	7,31 (7,23-7,39)	0,108*
Protein	5,09±0,63	5,06±0,74	0,773‡
Albumin	2,9 (2,6-3,2)	2,80 (2,50-3,30)	0,097*
LDH	476 (318-626)	762 (452-1045)	<0,001*
Glucose	86 (67-98)	70 (42-87)	0,002*
ADA	29 (23-33)	53 (43-66)	na
LDH/ADA	19,1±9,2	15,7±9,6	0,036‡

ADA: Adenozin deaminaz; LDH: Laktat dehidrojenaz; na: not applicable
**Mann-Whitney U test for non-parametric continuous variables; ‡Independent samples T-test for parametric continuous variables*

(ADA<40U/L, ≥40U/L). Furthermore, we did not identify any correlation between ADA values and clinical symptoms. In another study, the patients with TPE were found to have a shorter history of fever, and in particular, chest pain, which is a more specific symptom of the pleural involvement in polymorphonuclear leukocyte group of TPE.

TPE patients may show neutrophilic predominance, especially during the first two weeks following the onset of symptoms. Some studies confirmed that this neutrophilic predominance usually shifts to lymphocytic predominance within a week [18,19]. We did not find any difference between levels of ADA and lymphocytic, neutrophilic, mixed TPE. It was found that total ADA levels were not affected by the predominant type of pleural fluid leukocytes in TPE. Low ADA levels can occur in both lymphocytic and neutrophilic TPE, as shown in the current study. The low ADA levels in lymphocytic TPE may be somewhat different from those in neutrophilic TPE, which usually appears in the early stages of the disease, in terms of the host immune response. The present study therefore confirmed that low ADA levels, even in lymphocytic exudates, could not exclude the possibility of TPE. Thus, even where there is a lymphocytic exudate with low ADA levels, if clinical suspicion exists, especially in patients with risk factors for low ADA levels, further examination must be done. Consequently, a follow-up thoracentesis may provide useful information for clinical decision-making in suspected atypical TPE cases with neutrophilic exudates or low ADA levels as shown in some studies [19,20]. In our study, ADA measurements were performed atdifferent time points.

In the present study, 38 patients (27.5%) had findings of pulmonary involvement on chest CT and/or chest radiographs. Furthermore, when ADA values were high, pulmonary involvement was more frequent (p:0.011) as shown in another study 5, where pulmonary involvement was seen in 42 of the 60 patients, with centrilobular nodular patterns in 37, consolidation in 22 patients, and in 17 patients, both findings were identified. For these patients, the centrilobular nodular pattern was more common than consolidation, and

all ADA values were >40 IU/l with a mean of 87.9 IU/l 5. In our study, the features of parenchymal involvement were not mentioned because some of the patients did not have a tomography scan. It would not be appropriate to specify the features of parenchymal involvement solely by a chest radiography.

Some studies reported that residual pleural thickening of ≥10 mm could cause significant clinical symptoms in patients with TB pleural effusion, with incidences varying from 26.0% to 50.4% 21,22. Therefore, it is very important to clinically decrease the incidence and degree of residual pleural thickening, and re-expand the trapped lung as early as possible. In our study, residual pleural thickening was seen in60% of the patients. We found this high frequency of pleural thickening becausepleural thickening was evaluated in patients either at the 4th month, at the end of the 6th month, or at the end of the first year. There was no standardization on this issue because it was a retrospective study.

The main limitation of this study was itsretrospective design. Some clinical data were lacking or were not reflected in the medical charts. Another potential limitation is that the reference standard used for diagnosing a significant percentage of TPE patients was based on a combination of clinical (consistent signs and symptoms, and exclusion of other causes), analytical (high pleural fluid ADA) and follow-up data. Therefore, patients with undiagnosed pleural tuberculosis, especially pleura- confined tuberculosis, were not enrolled because the sensitivity of the diagnostic tools were low for these conditions. Another limitation was that ADA is generally divided in two molecular forms, ADA1 and ADA2, however, in the present study, ADA was not divided into ADA1 and ADA2, so these factors could not be evaluated separately. In addition, we did not do a follow-up thoracentesis.Only the first pleural fluid profiles were used for the statistical analysis in patients and a second thoracenteses was not done. Pleural fluid samples collected for the second time might be helpful in the clinical decision-making and management of pleural effusions of uncertain origin. Another limitation was the presence of underlying diseases, such as diabetes mellitus, which may change a patient's immune status. We did not record underlying diseases of the patients.

In conclusion, there were no differences between the pleural fluid ADA levels and age, gender, clinical and histopathological characteristics of the patients. Also ıt was determined that the pulmonary involvement and pleural thickening levels were higher in patients who had tuberculous pleurisy with elevated ADA values. It should be kept in mind that clinical, radiological and histopathological findings of patients with tuberculous pleurisy may not vary according to ADA levels.

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