Factors Influencing Pleural Adenosine Deaminase Level in Patients With Tuberculous Pleurisy

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Abstract: *Background:* Adenosine deaminase (ADA) activity is useful for diagnosing tuberculous (TB) pleurisy in regions with a high prevalence of tuberculosis. However, some cases of TB pleural effusion show decreased ADA activity. Therefore, we evaluated factors influencing pleural ADA levels in patients with TB pleurisy. *Methods:* We retrospectively evaluated 182 patients with TB pleural effusion who were admitted to Gyeongsang National University Hospital from January 2004 to September 2008. Patients were dichotomized into 2 groups: a low-ADA (<40 IU/L) group (n = 22) and a high-ADA (≥40 IU/L) group (n = 160). Age, sex, ADA level of pleural effusion, smoking status, history of tuberculosis and comorbid diseases were evaluated in each group. *Results:* The median age of the patients was 50.5 years, with a male to female ratio of 1.72:1. Patients with a low-ADA level were significantly older than those with a high ADA level (66.9 ± 12.0 versus 49.4 ± 21.2 years, $P < 0.001$). A history of tuberculosis and hypertension was more common in the low-ADA group than in the high-ADA group (31.8% versus 15.0%, $P = 0.049$ and 36.4% versus 16.9%, $P = 0.03$, respectively). A multivariate analysis revealed that older age and current smoking were predictive of TB pleurisy with a low ADA level (odds ratios, 1.053 and 4.848; $P = 0.002$ and 0.028, respectively). *Conclusions:* Physicians should be careful when interpreting pleural ADA levels in elderly patients and/or current smokers for the diagnosis of TB pleurisy.

Key Indexing Terms: Tuberculosis; Pleural effusion; ADA; Age; Smoking. **[Am J Med Sci 2014;348(5):362–365.]**

Diagnosing tuberculosis in pleural fluid poses many problems. The positivity rates of direct pleural fluid testing for acid-fast bacilli have a low sensitivity of <10%.[1–3] Low sensitivity (20%–30%) and a delay in the results of *Mycobacterium tuberculosis* culture of the fluid are also problems.[4] The combination of pleural biopsy culture and a histopathological examination has a higher sensitivity than do other methods (50%–80%), but a pleural biopsy is more invasive.[1,4]

Adenosine deaminase (ADA) analysis is a test with a better yield and lower cost.[3,5–7] Because Piras et al reported that ADA activity in pleural fluid is markedly higher in patients with tuberculous (TB) pleurisy than in those with non-TB pleurisy, the pleural fluid ADA level has been used for the differential diagnosis of TB pleurisy. ADA has been investigated by many researchers and is used in the diagnosis of TB pleurisy.[8–10] ADA is a purine catabolic enzyme that catalyzes the pathway from adenosine to inosine.[1] Its physiological role is particularly important in lymphoid tissue. The ADA level is 10 times higher in lymphocytes than that in erythrocytes, and particularly in T lymphocytes, with variations according to cellular differentiation.[11] However, TB pleurisy is suspected clinically in some cases, but the ADA level is low, causing difficulty in its diagnosis and treatment delays. Thus, we identified factors affecting the pleural ADA level.

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PATIENTS AND METHODS

Study Population

The subjects were 182 patients who were admitted to the Respiratory Department of Gyeongsang National University Hospital for pleurisy and diagnosed with TB pleurisy from January 2004 to September 2008. According to their pleural fluid ADA activity, we divided the subjects into a low-ADA group (n = 22) and a high-ADA group (n = 160). The cut-off value of pleural fluid ADA was 40 IU/L. The ADA activity of pleural fluid was colorimetrically estimated by the method of Galanti and Giusti.[12] Clinical characteristics were compared between the 2 groups, and factors associated with a low ADA level were assessed through a retrospective review of medical records.

Diagnosis of Tuberculous Pleurisy

Measurement of the biochemical properties, differential cell count, ADA level, as well as direct examination by Zeihl-Nielsen staining, and culture and polymerase chain reaction (PCR) assays for *M tuberculosis* in pleural fluid were performed routinely. A pleural needle biopsy was performed under local anesthesia based on the physician's decision. The confirmative diagnostic criteria of TB pleurisy were as follows: (1) demonstration of *M tuberculosis* in the sputum, pleural effusion or a pleural biopsy specimen; (2) demonstration of TB granuloma unless Ziehl-Nielsen staining or PCR was positive in a pleural biopsy specimen and (3) positive PCR result for *M tuberculosis* in pleural effusion. Additionally, a probable diagnostic criterion of TB pleurisy in the high-ADA group included: (4) demonstration of an elevated ADA level ≥40 IU/L in lymphocyte-dominant exudative pleural effusion with evidence of clinical improvement after antituberculosis chemotherapy.

Statistical Analysis

Continuous variables, including age and the ADA level in the pleural effusion, were compared using independent *t* test. Comparisons of categorical variables, including sex, history of tuberculosis, smoking status and the presence of comorbid disease, were performed using Pearson's χ^2 test. The multivariate binary logistic regression method was used to investigate factors for predicting low-ADA TB pleurisy. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A $P < 0.05$ was

considered to indicate statistical significance. Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS, Inc, Chicago, IL).

RESULTS

Demographic and Baseline Characteristics

A total of 182 patients composed of 115 male (63.2%; mean age: 48.3 ± 19.7 years) and 67 female (36.8%; mean age: 57.1 ± 22.1 years) patients were included, of which 136 (74.7%) did not have a comorbid disease. However, 18 patients (9.9%) (M:F = 12:6) had diabetes and 35 (19.2%) (M:F = 15:20) had hypertension. A total of 160 patients were included in the high-ADA group (ADA activity ≥40 IU/L) with a mean age of 49.4 ± 21.1 years (M:F = 99:61), whereas the low-ADA group had 22 patients with an ADA activity <40 IU/L and a mean age of 66.9 ± 12.0 years (M:F = 16:6) (Table 1). The mean ADA level of the high-ADA group was 90.0 ± 29.6 IU/L, whereas that of the low-ADA group was 18.7 ± 10.9 IU/L. The numbers of patients diagnosed by the 1st, 2nd and 3rd criteria were 65 (40.6%), 16 (10.0%) and 5 (3.1%) in the high-ADA group and 8 (36.4%), 13 (59.1%) and 1 (4.5%) in the low-ADA group, respectively. The number of patients in the high-ADA group diagnosed by the 4th criterion was 74 (46.3%).

Clinical Characteristics

Patients with a low ADA level were significantly older than those with a high ADA level ($P < 0.001$) (Table 1). The correlation between ADA activity and age at the time of diagnosis had a correlation coefficient of −0.254 ($P < 0.001$). A scatter diagram is shown in Figure 1.

Among the 182 patients, 92 were never smokers (50.5%), 30 were former smokers (16.5%), 58 were current smokers (31.9%) and 2 had an unknown smoking status (1.1%). The low-ADA group comprised 6 (27.3%) never smokers, 5 (22.7%) former smokers and 11 (50.0%) current smokers, whereas the high-ADA group had 86 (54.4%) never smokers, 25 (15.8%) former smokers, 47 (29.7%) current smokers and 2 (1.25%) with an unknown smoking status (Table 1). The average ADA level of current smokers was 70.7 ± 31.7 IU/L, whereas that of never smokers was 89.3 ± 36.2 IU/L ($P = 0.001$). However, the differences between the average ADA values of never smokers and former smokers ($P = 0.190$) and between current smokers and former smokers ($P = 0.401$) were not significant.

Among the 182 patients, 31 (17.0%) had a history of tuberculosis. A history of tuberculosis was significantly more common in the low-ADA group than in the high-ADA group (31.8% versus 15.0%, $P = 0.049$) (Table 1). The mean ADA activity of the group without a history of tuberculosis was 85.0 ± 34.5 IU/L, whereas that of the group with a history of tuberculosis was 51.6 ± 39.1 IU/L ($P = 0.001$). There were more patients with hypertension in the low-ADA group than in the high-ADA group (36.4% versus 16.9%, $P = 0.03$) (Table 1).

Predictors for Low-ADA Tuberculous Pleurisy

Old age (OR, 1.053; 95% CI, 1.020–1.088) and current smoking (OR, 4.848; 95% CI, 1.182–19.881) were the 2 independent predictors of low-ADA TB pleurisy after adjusting for confounding variables, including age, sex, smoking status, history of tuberculosis, diabetes and hypertension (Table 2).

DISCUSSION

The present retrospective analysis investigated the demographic and clinical differences between the high- and low-ADA groups, as well as predictive factors of low ADA level in patients with TB pleurisy. The low-ADA group was older in age and comprised more patients who were current smokers, had a more history of tuberculosis and had accompanying hypertension. After adjusting for confounding variables, old age and current smoking were significant predictors of TB pleurisy with a low ADA level.

Tuberculosis is a leading cause of death from infectious disease.[13] According to the World Health Organization, 9 million people developed tuberculosis in 2004. Of those, 3.9 million were cases of active tuberculosis, and 741,000 were coinfected with human immunodeficiency virus.[14] Despite rapid industrial development over the past several decades, tuberculosis remains a serious problem in South Korea. According to a recent report, 46,969 new patients with tuberculosis occurred in South Korea during 2005, an incidence of 97.3/100,000.[15]

Tuberculosis is the principal cause of exudative pleural effusion, and TB pleurisy is the extrapulmonary form most commonly observed in adults. Tuberculous pleural effusion results mostly in a lymphocyte-dominant exudate and increased ADA activity. Banales et al[16] reported in their study of 218 patients that when the cutoff of ADA activity is 70 IU/L, the sensitivity was 98% and the specificity was 96%. Jung et al[17] reported a sensitivity of 96% and a specificity of 100% with a cutoff of 40 IU/L. The meta-analysis of 11 studies that included 2,251 patients and used different cut-off values of

TABLE 1. Baseline characteristics of the study populations

	Low-ADA group	High-ADA group	*P*
Age, mean ± SD (yr)	66.9 ± 12.0	49.4 ± 21.2	<0.001
Male:female	16 (72.7):6 (27.3)	99 (61.9):61 (38.1)	0.322
ADA level, mean ± SD (IU/L)	18.7 ± 10.9	90.0 ± 29.6	<0.001
Smoking status			0.055
Current smoker	11 (50.0)	47 (29.7)	
Former smoker	5 (22.7)	25 (15.8)	
Never smoker	6 (27.3)	86 (54.4)	
History of tuberculosis	7 (31.8)	24 (15.0)	0.049
Diabetes	4 (18.2)	14 (8.8)	0.165
Hypertension	8 (36.4)	27 (16.9)	0.030

SD, standard deviation; ADA, adenosine deaminase.