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Original Article

Is Adenosine Deaminase in Pleural Fluid a Useful Marker for Differentiating Tuberculosis from Lung Cancer or Mesothelioma in Japan, a Country with Intermediate Incidence of Tuberculosis?

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The objective of this study was to evaluate the utility of the determination of adenosine deaminase (ADA) level in pleural fluid for the differential diagnosis between tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE) in Japan, a country with intermediate incidence of tuberculosis (TB). We retrospectively reviewed the clinical records of 435 patients with pleural effusion and investigated their pleural ADA levels as determined by an auto analyzer. ROC analysis was also performed. The study included patients with MPE (n = 188), TPE (n = 124), benign nontuberculous pleural effusion (n = 94), and pleural effusion of unknown etiology (n = 29). The median ADA level in the TPE group was 70.8 U/L, which was significantly higher than that in any other groups ($p < 0.05$). The area under the curve (AUC) in ROC analysis was 0.895. With a cut-off level for ADA of 36 U/L, the sensitivity, specificity, positive predictive value, and negative predictive value were 85.5%, 86.5%, 69.7%, and 93.6%, respectively. As many as 9% of patients with lung cancer and 15% of those with mesothelioma were false-positive with this ADA cutoff setting. Although the ADA activity in pleural fluid can help in the diagnosis of TPE, it should be noted that some cases of lung cancer or mesothelioma show high ADA activity in geographical regions with intermediate incidence of TB, in contrast to high prevalence areas.

Key words: pleural effusion, adenosine deaminase, tuberculosis, lung cancer, mesothelioma

Malignant diseases and tuberculosis (TB) are major causes of pleural effusion, and such pleural effusions are usually exudative [1–3]. Massive pleural effusion causes severe dyspnea due to progressive respiratory failure, and markedly affects the prognosis of patients with either malignant disease or TB. Therefore, patients with pleural effusion need to be promptly and accurately diagnosed and immediately treated. However, differentiating tuberculous pleural effusion (TPE) from malignant pleural effusion (MPE)

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can be a critical problem.

Pleural fluid cytology is the simplest, most definitive method for diagnosing MPE. The diagnostic yield is dependent on factors such as the extent of disease and the nature of the primary malignancy [2]. Therefore, previous studies have shown a large variation in diagnostic yields ranging from 60–90% [2]. The diagnostic yield of cytology for mesothelioma is 30% [1].

The diagnosis of TPE is usually made from histological confirmation of granulomas in pleural biopsy specimens and/or detection of *Mycobacterium tuberculosis* (*M. tuberculosis*) from pleural tissue or pleural fluid. However, the sensitivity of these methods is not sufficiently high even if histological examination of a pleural biopsy specimen and culture of a pleural fluid are combined [4, 5]. Although repeating these diagnostic procedures could yield more positive results, such an approach would place patients at higher risk of complications and cost more. Accordingly, a reliable clinical marker providing rapid and accurate diagnosis of TPE or MPE is urgently required [6–8].

An elevated level of adenosine deaminase (ADA) in pleural fluid has been reported to predict TPE with a sensitivity of 90% to 100% and specificity of 89% to 100%, although such reports have been performed mainly in geographical regions with a high prevalence of TB [3, 9–14]. Although the ADA activity in pleural fluid is frequently measured in Japan, a country with intermediate prevalence of TB [15, 16], the utility of this method for Japanese patients remains unclear. In this study, we retrospectively reviewed patients with pleural effusion in our hospital and investigated the utility of determination of ADA activity for differential diagnosis between TPE and MPE.

Materials and Methods

This study was approved by the Institutional Review Board of the Yamaguchi-Ube Medical Center. Clinical records of 724 consecutive patients undergoing thoracocentesis for pleural effusion at Yamaguchi-Ube Medical Center between January 1995 and December 2008 were retrospectively reviewed. Informed consent was received from all patients before thoracocentesis. The ADA activity was measured in pleural fluid of 435 patients by an auto analyzer using commercially available kits (Nittobo Medical, Tokyo, Japan). The utility of the measurement of ADA activity in pleural effusion was evaluated for these 435 patients.

Diagnostic criteria for pleural effusions. TPE was diagnosed by confirming one of the following: isolation of *M. tuberculosis* from pleural fluid or pleural tissue; detection of granulomas in the pleural tissue with positive staining for acid fast bacilli (AFB); or detection of granulomas in pleural tissue with observation of clinical response to antituberculous treatment. MPE was diagnosed either by cytological observation of malignant cells in pleural fluid or histological confirmation of malignancy in a pleural biopsy specimen. MPE was also diagnosed after exclusion of other diseases, if patients had widely disseminated cancer and the pleural effusion was strongly suspected to be caused by the cancer [6, 7, 17].

Statistical analysis. Group comparisons were made using the nonparametric Kruskal-Wallis test. The discriminating quality of ADA was evaluated independently using receiver operating characteristic (ROC) curve analysis [18]. The quality of the biological markers was assessed based on the area under the curve (AUC). For each ROC curve, a cut-off point was determined as the value of the parameter that maximized the sum of specificity and sensitivity, weighting their significance equally.

Results

Characteristics of the reviewed cases. The patients consisted of 333 men and 102 women, and the mean age was 69 years. The most frequent cause of pleural effusion was MPE (n = 188, 43.0%), followed by TPE (n = 124, 28.4%), parapneumonic pleural effusion (n = 23, 5.3%), heart failure (n = 16, 3.7%), asbestos-related pleural effusion (n = 12, 2.7%), bacterial pleuritis (n = 11, 2.5%), fibrous pleuritis (n = 7, 1.6%), rheumatoid pleuritis (n = 7, 1.6%), empyema (n = 4, 0.9%), renal failure (n = 3, 0.7%), Meigs' syndrome (n = 2, 0.5%), nontuberculous mycobacterium (n=2, 0.5%), pneumothorax (n = 2, 0.5%), traumatic pleural effusion (n=2, 0.5%), aneurysm (n = 1, 0.2%), angitis (n = 1, 0.2%), liver cirrhosis (n = 1, 0.2%), malnutrition (n = 1, 0.2%), and pancreatitis (n = 1, 0.2%). In 29 cases (6.6%), the cause

of the effusion could not be identified.

The most common tumor, responsible for 78.7% of MPE, was lung cancer, followed by mesothelioma (10.6%), breast cancer (2.7%), lymphoma (2.1%), colon cancer (1.1%), gastric cancer (1.1%), hepatoma (1.1%), prostate cancer (0.5%), thymus cancer (0.5%), and uterus cancer (0.5%). In 2 cases (1.1%), the primary sites were unknown.

ADA levels in pleural effusion. The median values of ADA were 70.8 U/L (10.3–182.6 U/L) in patients with TPE, 19.0 U/L (1.7–193.4 U/L) in those with MPE, 17.8 U/L (1.6–500 U/L) in those with non-tuberculous/non-malignant pleural effusion, and 22.8 U/L (10.7–70.5 U/L) in those without identified causes (Fig. 1). ADA levels in pleural effusion were significantly higher in patients with TPE than in patients of the other groups ($p < 0.05$).

Diagnostic utility for tuberculous pleural effusion. In order to differentiate patients with TPE from those with effusions due to other causes, the diagnostic value of the ADA level in pleural fluid was assessed using a ROC analysis (Fig. 2). The area under the curve was 0.895. At the defined cutoff value of 36 U/L, the sensitivity, specificity, positive predictive value, and negative predictive value were 85.5%, 86.5%, 69.7% and 93.6%, respectively.

ADA levels in nontuberculous pleural effusion. Of the 435 patients with pleural effusion, 152 patients (34.8%) had a pleural ADA level over 36 U/L. Of those, 106 patients had TPE and 46 had nontuberculous pleural effusion, which consisted of 18 patients with MPE, 5 with pneumonic effusions, 5 with rheumatoid arthritis, 3 with asbestos pleurisy, 3 with empyema, 3 with bacterial pleuritis, 2 with nontuberculous mycobacteria infection, 1 with aneurysm, 1 with Meigs syndrome, and 5 with effusions without identified cause.

With regard to the ADA level of MPE (Fig. 3), 13 of 148 patients with lung cancer (8.8%), 3 of 20 with mesothelioma (15%), 1 with lymphoma and 1 with hepatoma had pleural effusions with an ADA level over 36 U/L. In particular, ADA levels in pleural fluid were over 100 U/L in 2 patients with lung cancer and 1 with mesothelioma.

Discussion

Pleural fluid cytology is the simplest, most definitive method for diagnosis of MPE. The diagnostic yield is dependent on factors such as the stage of disease and the nature of the primary malignancy. Malignant effusion can be diagnosed with one pleural fluid cytology specimen for 60% of cases of carcinoma but only 30% of cases of mesothelioma [1, 2]. Differential diagnosis between MPE and TPE

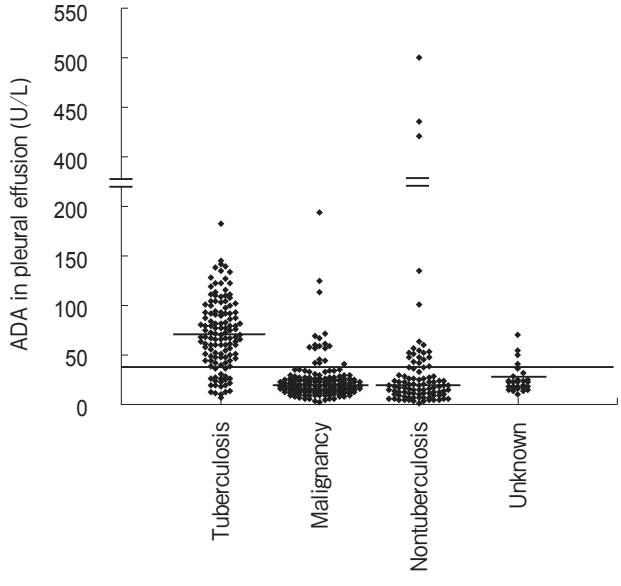

Fig. 1 ADA levels in 435 patients with various etiologies. The horizontal bars represent group medians.

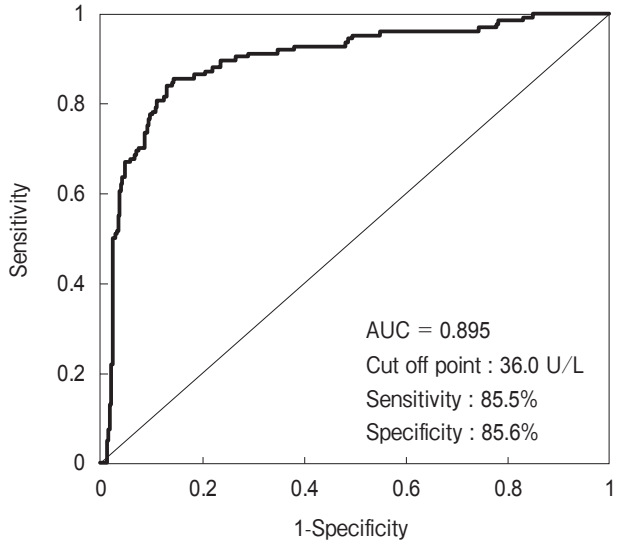

Fig. 2 An ROC curve showing the sensitivity and 1-specificity values at various cutoff values for ADA levels in pleural fluid.

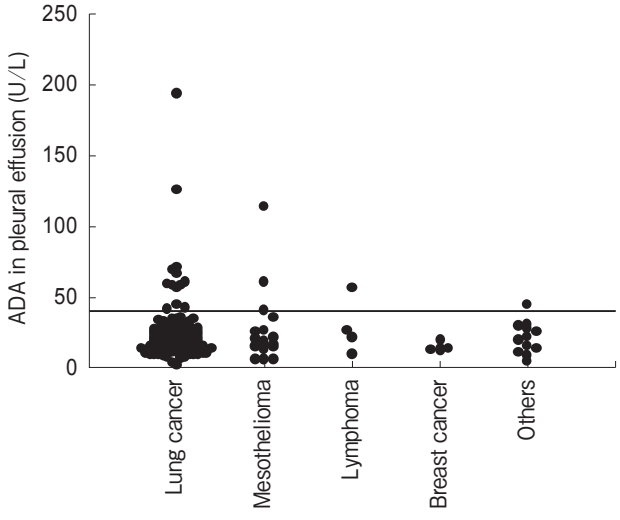

Fig. 3 ADA levels in patients with malignant pleural effusions.

becomes a more critical problem when the pleural fluid cytology shows negative results.

ADA is present in most cells of the organism and is associated with the proliferation and differentiation of lymphocytes, especially T lymphocytes. The concentration of ADA in these lymphocytes is inversely proportional to their degrees of differentiation [9]. ADA has gained increasing attention as a diagnostic tool, especially in countries where the prevalence of TB is high [9–14]. It achieves a high sensitivity (90% to 100%) and is inexpensive and easy to measure. It is also used in Japan, although the prevalence of TB is not particular high in that country [15, 16]. In Japan, the TB notification (incidence) rate fell 20 per 100,000 in 2007 and continued to decline, reaching 19.4 in 2008 [16]. Our study shows that the sensitivity of pleural fluid ADA for TPE was 85% in a Japanese cohort, which is lower than that in area with a high prevalence of TB.

Our study also showed that the ADA levels in nontuberculous pleural effusions exceeded the cutoff value for TPE in Japan more frequently than in areas with a high incidence of TB. The most common underlying disease with pleural effusion was malignancy (43%), which included lung cancer (79% of malignancy) and mesothelioma (8% of malignancy). Nine percent of lung cancer patients and 15% of mesothelioma patients showed higher levels of ADA in pleural effusion than the cutoff set for tuberculous effusion. High levels of ADA have already been reported in nontuberculous conditions associated with pleural fluid lymphocytosis, including malignant conditions (*e.g.*, adenocarcinoma, mesothelioma, leukemia, and lymphomas) and collagen vascular disease (*e.g.*, rheumatoid pleuritis and systemic lupus erythematosus) [9, 19]. To our knowledge, however, the previous reports have been mainly case reports, while this study has shown the frequency of patients with a high level of pleural fluid ADA in malignant pleural effusions by a larger scale analysis.

At least 50% of the cases of TB pleural effusion are present as a primary disease without TB involvement in other organs [20]. The patients with early stage mesothelioma and some with peripheral lung cancer show only pleural effusions before forming obvious mass lesions. Although mesothelioma is currently rare in Japan, the incidence is rapidly increasing [21, 22]. Since mesothelioma in the early stage may be curable by surgery, accurate and prompt diagnosis of mesothelioma is very important [23]. Accordingly, other useful markers together with ADA are necessary for diagnosis of pleural effusion. A higher rate of false-positive results can lead to the unnecessary administration of antituberculous therapy or delay in making a precise diagnosis. Indeed, 2 patients with mesothelioma in this series were initially treated with antituberculous drugs, and so the diagnosis of the cause of pleural effusions was delayed. Their first cytology tests were negative, and the levels of ADA in their pleural effusions were high. Several months' treatment could not improve the effusion and the pleurae grew thicker, and finally pleural biopsies revealed the diagnosis of mesothelioma.

The significance of a high level of ADA in the pleural fluid of malignant effusion is not clear yet. It might be associated with the parapneumonic effusion caused by lung cancer-induced obstructive pneumonia or with the activity of lymphocytes during the immune reaction against tumors. In this series, a high level of pleural fluid ADA did not affect the survival of patients with malignant pleural effusion (data not shown). In practice, a high level of ADA in pleural fluid may lead to treatment for TPE, as was the case in our mesothelioma patients. It may occur that patients with lung cancer or mesothelioma are infected with TB concurrently.

In conclusion, although the determination of the level of ADA in pleural fluid can contribute to the

diagnosis of TPE, ADA should be used carefully for the differential diagnosis between TPE and MPE in Japan, especially in the cases in which pleural effusion is the sole manifestation.

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