Adenosine Deaminase and Carcinoembryonic Antigen in Pericardial Effusion Diagnosis, Especially in Suspected Tuberculous Pericarditis

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Background Adenosine deaminase (ADA) and carcinoembryonic antigen (CEA) have been measured in pleural fluid to help distinguish malignant from benign effusions, especially in tuberculosis pleurisy. We investigated ADA and CEA levels in patients with moderate to large pericardial effusions of different etiologies.

Methods and Results We performed diagnostic and therapeutic pericardiostomy with drainage and biopsy. We measured ADA and CEA levels in the pericardial fluid in 26 patients with moderate to large pericardial effusion and 19 control patients. Patients were included in a prospective protocol from August 1991 to August 1993. Patients were grouped as follows: group 1, 9 patients with tuberculous pericarditis (TP) confirmed by bacteriologic culture or histology of pericardial biopsy; group 2, 5 patients with clinically strongly suspected TP; group 3, 12 patients with malignancy (8) and acute pericarditis (4); group 4, 19 control patients without pericardial disease. We treated patients with TP with isoniazid, rifampin, and either streptomycin or ethambutol for 12 months and pyrazinamide for 2 months. We observed for symptoms and signs of recurrent pericarditis or constrictive pericarditis on follow-up. In group 1 the ADA activity was significantly higher (101 ± 14 U/L) than that in group 3 (22 ± 5 U/L) or that in group 4 (17 ± 2 U/L) (P < .05). There was no significant difference between ADA activity in group 1 (101 ± 14 U/L) and that in group 2 (100 ± 26 U/L). With a cutoff value for ADA activity of 40 U/L, sensitivity was 93% and specificity 97% in the diagnosis of TP. In benign diseases, the CEA level was significantly lower (1.0 ± 0.3 ng/mL) than that in malignant diseases (135.1 ± 79.7 ng/mL) (P < .05). With a cutoff value for CEA level of 5 ng/mL, sensitivity was 75% and specificity 100% in the diagnosis of malignant pericarditis. Follow-up study (mean, 12.9, 19.8, and 11.8 months in groups 1, 2, and 3, respectively, showed no symptoms or signs of constrictive pericarditis, except for 1 patient.

Conclusions Pericardial fluid ADA and CEA are useful for the differential diagnosis of pericardial effusion of various causes. They also have great value in early diagnosis of TP, particularly when the results of other clinical and laboratory tests are negative. (Circulation. 1994;89:2728-2735.)

Key Words • adenosine deaminase • carcinoembryonic antigen • tuberculous pericarditis

The discovery that more than 50% of the white blood cells in an exudative pleural effusion are small lymphocytes is important diagnostically because it means that the patient probably has a malignant disease or tuberculosis.1 Several studies have concluded that measurement of the carcinoembryonic antigen (CEA) level in pleural fluid is useful in establishing the diagnosis of malignant pleural effusion.2,3 Measurement of the adenosine deaminase (ADA) level in pleural fluid is diagnostically useful because ADA levels tend to be higher in tuberculous pleural effusions than in other exudates.2-6 It is difficult to establish a definitive bacteriologic diagnosis of tuberculous pericarditis because of several factors. The most difficult diagnostic case involves the patient with pericarditis in whom the PPD (purified protein derivative) test is positive but no tubercle bacilli are demonstrated in the pericardial fluid by histologic examination of the pericardium or elsewhere in the body in the absence of another cause of pericarditis. A few articles about the use of ADA assay in the diagnosis of tuberculous pericarditis have been reported,7-9 but comparison of the use of ADA assay in confirmed tuberculous pericarditis with that in clinically suspected tuberculous pericarditis has not yet been reported. Therefore, we investigated ADA and CEA levels in patients with moderate to large pericardial effusions of different etiologies.

Methods

Patients

In a systemic prospective protocol from August 1991 to August 1993, we measured the ADA and CEA levels in the pericardial fluid of 26 patients with pericarditis with moderate to large pericardial effusion on echocardiography for diagnostic and therapeutic pericardiostomy and biopsy. Moderate effusion was defined as echocardiographic evidence of anterior and posterior pericardial effusion and when the distance of the pericardial space was more than 15 mm on subcostal view during diastole. All patients gave written informed consent for participation in the study, which was approved by the Ethics Committee of the Inha University Hospital.
Patients were grouped according to the diagnosis as follows: group 1, 9 patients with tuberculous pericarditis confirmed by demonstration of Mycobacterium tuberculosis by culture of pericardial fluid or pericardial tissue or caseous necrosis or granulomas on pericardial biopsy; group 2, 5 patients with clinically strongly suspected tuberculous pericarditis; group 3, 12 patients with acute pericarditis (4) or malignancy (7 with lung cancer and 1 with cervical cancer) by histologic examination; group 4, 19 control individuals without pericardial disease from whom pericardial fluid was obtained during cardiac surgery. We considered group 2 to be severely ill patients with (1) a hemorrhagic pericardial effusion, (2) a positive tuberculin skin test, (3) absence of a prodromal syndrome of an upper respiratory tract infection within the preceding weeks, (4) a negative workup for other causes of pericarditis, and (5) clinical improvement after initiation of antituberculosis chemotherapy after 10 to 14 days of admission.10-12

Study Protocol

We performed diagnostic and therapeutic pericardiostomy with drainage and biopsy in all the patients of groups 1, 2, and 3. We checked total proteins, glucose, red blood cell and white blood cell counts, differential cell count, lactate dehydrogenase, acid fast bacilli stained by the Ziehl-Neelsen method and cultured in Ogawa media and ordinary bacteria smears and cultures, cytology, and ADA and CEA from pericardial fluid of all the patients of groups 1, 2, and 3. Three sputum samples were stained by the Ziehl-Neelsen method and cultured in Ogawa media. Pathologists were blinded to the patients' ADA and CEA levels. The determination of ADA activity in the pericardial fluid was carried out by the method of Galanti and Giusti13 in samples stored at −20°C for a period of less than 1 week. This is a calorimetric method based on measurement of CO2 formation of ammonia, which is produced when ADA acts on excess adenosine. CEA was measured with radioimmunoassay kits available commercially (CEA RIA BEAD, Dinabott).2,3 We also routinely checked serum ADA and CEA levels in patients of groups 1, 2, and 3 since May 1992. We did not perform a PPD skin test early in 6 patients of group 1, but after then we routinely performed a PPD skin test in groups 1, 2, and 3. Five of 12 patients in group 3 were admitted to Korea Cancer Center Hospital (cancer referral center in Korea). We did not get information about the PPD skin test and differential cell count of pericardial fluid in 5 patients. A positive tuberculin skin test is defined as when the measured diameter of induration is more than 10 mm after injection (5 TU) 48 to 72 hours later. We started antituberculosis chemotherapy consisting of a four-drug regimen, such as isoniazid, rifampin, and either streptomycin or ethambutol for 12 months and pyrazinamide for 2 months in group 1 and 2 patients. We observed symptoms and signs of recurrent pericarditis and constrictive pericarditis by (1) history and physical examination (specific symptoms and signs sought in each case: dyspnea on exertion, jugular venous distention, ankle edema, hepatomegaly, and ascites), (2) posteroanterior and lateral chest radiography (a radiologist was asked to comment on the presence or absence of cardiomegaly and pericardial calcification), and (3) M-mode and two-dimensional echocardiograms. Echocardiography was performed with commercially available scanners (Aloka SSD-880). Echocardiograms were examined for evidence of pericardial thickening or effusion and for wall motion abnormalities associated with the constrictive pericardial process. Echocardiographic criterion for thickened pericardium was the presence of multiple continuous parallel pericardial echoes with no reduction of echo density in the more posterior portion of parallel echoes. Flat endocardial motion was present when the distance from the left ventricular endocardial echo and the crystal artifact increased by less than 1 mm during diastole after the rapid filling phase and before atrial systole.14 Abnormal interventricular septal motion was described when brisk anterior and then posterior displacement of the interventricular septum was present, beginning 40 to 120 milliseconds after end systole.15 Abnormal interventricular septal systolic motion was defined as the absence of posterior systolic motion in the absence of left bundle branch block, right ventricular volume overload, or recent open heart surgery.16 In addition, the ejection fraction was calculated from the two-dimensional echocardiogram.

Technique of Operation

Subxiphoid drainage was performed under general or local anesthesia. A midline incision was made from the xiphosternal junction to 10 cm below the tip of the xiphoid, and the linear alba was divided. A plain was developed behind the xiphoid, and the xiphoid then was lifted anteriorly while being separated from the rectus sheath on each side.17 Dissection of the prepericardial tissue revealed the lower part of the anterior pericardium. A 2×3-cm2 biopsy specimen was taken under direct vision from the lower aspect of the anterior pericardium. The pericardial cavity decompressed, and samples of the drained fluid were collected for routine laboratory tests and cytologic examination as indicated. The pericardial cavity was digitally explored, the presence of tumor or adhesion assessed, and gentle digital lysis of adhesions and opening of loculations was performed as needed to enhance satisfactory drainage. For continuous postoperative drainage, one or two chest tubes were inserted in the pericardial cavity through the created defect.18

Statistical Analysis

One-way ANOVA with Tukey's multiple range and nonparametric tests (Kruskal-Wallis) were used to compare the means of pericardial fluid ADA (f-ADA) among the four groups. The Pearson rank correlation coefficient was used to compare f-ADA and lymphocyte percentage, f-ADA, and absolute lymphocyte count. The Spearman rank correlation coefficient was used to compare pericardial fluid CEA and serum CEA. CEA levels <1.0 ng/mL and >500 ng/mL were regarded as 1.0 ng/mL and 500 ng/mL, respectively. The Wilcoxon rank sum test was used to compare pericardial fluid CEA between malignant and benign diseases.

Results

Clinical Features

The most common symptoms of tuberculous pericarditis in 14 patients (groups 1 and 2) were dyspnea (100%), cough (57%), weight loss (36%), and anorexia (36%). The most common physical findings were enlarged cardiac silhouette (100%), jugular vein distention (71%), fever (64%), pleural effusion (57%), and hepatomegaly (57%). The mean age was 62 years in group 1, 66 in group 2, and 48 in group 3 patients with acute pericarditis. The mean duration of pericardial symptoms was 34 days in group 1, 23 days in group 2, and 7.5 days in group 3 patients with acute pericarditis. In 4 patients with acute pericarditis, other causes were ruled out except for idiopathic or viral pericarditis by clinical history, physical examination, and laboratory tests. They showed a negative Mantoux test (except for one patient) and prodromal syndrome of an upper respiratory infection—like fever and general malaise within the preceding weeks. Chest pain also was present. Eight patients with malignant pericarditis were confirmed by histologic examination. (See Table.)

Diagnosis

The mean diameter of the PPD skin test in tuberculous pericardial effusion was 19±4 mm (mean±SEM) and was significantly (P<.05) larger than that in nontu-
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PSD indicates pericardial symptom duration; PPD, purified protein derivative; s, serum; ADA, adenosine deaminase; f, pericardial fluid; CEA, carcinoembryonic antigen; WBC, white blood cell; L, lymphocyte; AL, absolute lymphocyte; P-H, pericardial tissue histology; P-B, pericardial fluid bacteriology; H, hemorrhagic; SS, serosanguineous; and EF, ejection fraction.

Tuberculous pericardial effusions (12±4 mm). The color of pericardial fluid of tuberculous pericarditis was hemorrhagic in 11 (79%) among 14 patients. Bacteriologic culture was positive in 1 of 14 patients with tuberculous pericarditis, but histologic diagnosis was positive in 9 (64%) of 14 patients. (See Table.)

**Adenosine Deaminase Level**

The mean ADA concentration was 101±14 U/L in group 1, 100±26 U/L in group 2, 22±5 U/L in group 3, and 17±2 U/L in group 4. Distribution of the ADA activity in the pericardial fluid in each group is shown in Fig 1. The mean ADA concentration in serum was 32±2 U/L in group 1, 28±4 U/L in group 2, 19±4 U/L in group 3, and 21±5 U/L in 6 patients of group 4. The ADA activity in the pericardial fluid was significantly higher in group 1 than that in group 3 or group 4 (P<.05). There was no significant difference in the ADA activity between the pericardial fluid in groups 1 and 2.

Fig 2 shows the correlation between lymphocyte percentage and ADA levels in the pericardial fluid of
various causes, and there was not a significant correlation between them ($r=.40$). There was also not a significant correlation between ADA levels and absolute lymphocyte count ($r=.12$). There was threefold higher ADA levels in pericardial fluid than in serum in groups 1 and 2 compared with in group 3. There was no significant difference in ADA activity between the sera of various causes. With a cutoff value for ADA activity in pericardial fluid of 40 U/L, sensitivity was 93% and specificity 97% in the diagnosis of tuberculous pericarditis.

**Carcinoembryonic Antigen**

The mean CEA level in serum of benign diseases was $2.0\pm0.6$ ng/mL and was significantly ($P<.05$) lower than that in malignant diseases ($21.5\pm17.9$ ng/mL). The mean CEA level in pericardial fluid of benign diseases was $1.0\pm0.3$ ng/mL and was significantly ($P<.05$) lower than that in malignant disease ($135.1\pm79.7$ ng/mL) (Fig 3). Fig 4 shows the Spearman correlation between serum CEA and pericardial fluid CEA level in various causes, and there was a significant correlation between...
them \( r = 0.68 \). With a cutoff value for CEA level in pericardial fluid of 5 ng/mL, sensitivity was 75% and specificity 100% in diagnosing malignant pericarditis.

**Follow-up**

Thirteen patients with tuberculous pericarditis showed a good response to antituberculosis chemotherapy (case No. 1 in group 2 did not show such response). Dyspnea, cough, sinus tachycardia, fever, and hepatomegaly subsided rapidly, but one patient showed a continued jugular venous pressure elevation and hepatomegaly after 8 weeks of chemotherapy (pericardiectomy was performed and the patient's state improved, although the operator could not remove pericardial calcification completely). Histology showed dense fibrosis with extensive dystrophic calcification. Four patients with acute pericarditis in group 3 showed clinical and serological improvement without antituberculosis chemotherapy. After hospital discharge, the patients were followed up in the outpatient clinic every 2 months during the first 6 months, at 3-month intervals during the second 6 months, and subsequently at 6 months. Follow-up of group 1 patients ranged from 2 to 26 months (mean, 12.9 months), group 2 patients from 8 to 26 months (mean, 19.8 months), and group 3 patients from 2 to 23 months (mean, 11.8 months). No patient gave a history of recurrent pericarditis. No patient had pericardial calcification on chest x-ray examination except for one case (No. 1 in group 2). Echocardiographic abnormalities were few: pericardial thickening and brisk anterior and then posterior displacement of the interventricular septum after end systole in one case (No. 1 in group 2, Fig 5) and mitral regurgitant valve lesion in one case (No. 3 in group 3). Wall motion and ejection fraction were normal in all patients. The mean ejection fraction was 70±1% in group 1, 74±2% in group 2, and 72±4% in group 3. Pericardial effusion was absent in all patients except three (Nos. 8 and 9 in group 1 and No. 3 in group 3). Minimal pericardial effusion was present in these patients but decreased to some extent compared with the amount at hospital discharge. One patient (No. 3 in group 3; Fig 6) showed a high ADA level (75 U/L), but other clinical features did not reveal tuberculous pericarditis. We closely observed that patient every week and included an echocardiographic examination. The other patient (No. 4 in group 3) showed a strong positive PPD test, but other clinical features did not reveal tuberculous pericarditis. These two patients showed a good recovery course. Only one patient died (No. 6 in group 1); he had shown a good recovery course until last follow-up (March 1993), then died of metastasis of unknown origin (lung metastasis).

**Discussion**

There is considerable urgency in establishing the correct diagnosis so that appropriate treatment can be started. However, it is difficult to establish a definitive bacteriologic diagnosis of tuberculous pericarditis. The probability of obtaining a definitive diagnosis is greatest when pericardial fluid and a pericardial biopsy specimen are examined early in the effusive stage. However, it must be emphasized that a normal pericardial biopsy result does not exclude tuberculous pericarditis because in some patients, the examination of the entire pericardium removed at pericardiectomy or autopsy is required to demonstrate clear-cut evidence of tuberculosis. Moreover, constrictive pericarditis ultimately develops in almost all patients with untreated tuberculous pericarditis and in about half or less of patients who receive antituberculosis chemotherapy.

We believe that it may be necessary to make a presumptive clinical diagnosis of tuberculous pericarditis in strongly suspected patients living in endemic areas. In the era before antituberculosis therapy, tuberculous pericarditis was rapidly fatal, with an early mortality rate greater than 80%. Since the introduction of early chemotherapy, mortality from acute tuberculous pericarditis has fallen to less than 50%. However, it is very difficult to identify patients with tuberculous pericarditis. The most difficult diagnostic case involves the patient with pericarditis in whom tuberculous pericarditis is clinically strongly suspected but no tubercle bacilli are
Adenosine deaminase is an enzyme of purine catabolism that catalyzes the pathway from adenosine to inosine. Its level is 10 times higher in lymphocytes than in erythrocytes, particularly in T-lymphocytes with variations according to cellular differentiation. Few studies about the use of ADA assay in the diagnosis of tuberculous pericarditis have been conducted. The number of patients with tuberculous pericarditis was low. Several articles reported that measurement of CEA levels in pleural fluid is useful in distinguishing pleural effusions due to malignancies from those of tuberculous origin. Therefore, we investigated ADA and CEA levels in patients with moderate to large pericardial effusions of different etiologies.

Our study showed very low yield (0%) of sputum cultures, even though 2 patients had previous pulmonary tuberculosis. Our study showed only 1 patient (9%) confirmed by bacteriologic diagnosis among 14 patients with tuberculous pericarditis but 9 patients (64%) proven by pericardial biopsy among 14 patients. Patients with tuberculous pericarditis were much older compared with patients with idiopathic or viral pericarditis. In our study the most common symptoms of tuberculosis were dyspnea, cough, and weight loss. Our tuberculous pericarditis patients had a long duration of pericardial symptoms, and the pericardial fluid was hemorrhagic in 79%. These findings are similar to those reported in other studies. All patients in group 2 demonstrated significantly larger-diameter PPD skin tests compared with those in group 3. ADA activity in tuberculous pleural effusion varied from 43±4 to 102±9

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**Fig 6.** Echocardiograms recorded 3 months after pericardiotomy and drainage. Top: Parasternal long-axis view. Abnormal systolic or diastolic motion of interventricular septum is not observed. Pericardial thickening is absent. Bottom: Subcostal view. Minimal loculated pericardial effusion is shown, but the amount decreased on follow-up. PE indicates pericardial effusion; RV, right ventricle; VS, ventricular septum; LV, left ventricle; and PW, posterior wall of the left ventricle.
U/L. Ocana et al.57 reported that in the group of 48 patients with tuberculous pleurisy the mean enzyme activity was 92 U/L, whereas for other etiological groups the mean activity varied from 2 to 20 U/L. Sensitivity was 100% and specificity 97% when the cutoff value was 50 U/L. In nontuberculous effusions, ADA activity was always low. In patients with tuberculous pericarditis, the results were similar.8 The ADA activity of our patients with tuberculous pericarditis was similar to the mean values found in previous studies of tuberculous pleural or pericardial effusions.2-5,8 The mean enzyme activity in the pericardial fluid of the other groups of subjects also was similar to that of patients in the earlier studies with nontuberculous pleural or pericardial effusions.2-5,8 Our study showed that when the cutoff value for ADA was 40 U/L, sensitivity was 93% and specificity 97% in the diagnosis of tuberculous pericarditis. Our study showed that a parallel correlation did not exist between the number or percentage of lymphocytes in tuberculous pericardial effusions and their levels of ADA activity. Ocana et al.57 also showed that a parallel correlation does not exist between the number of T-lymphocytes in tuberculous effusions and their levels of ADA activity, even though Bagana et al.25 reported that the levels of ADA activity and the percentage of CD4 T cells in pleural exudates showed a positive correlation. In our study, the markedly higher concentrations of ADA activity in tuberculous pericardial fluid than in serum and no significant difference in ADA activity between the serum of various causes suggest a local production of ADA in the pericardial effusion. This may be related to local inflammatory processes within pericardial effusion and pericardial membrane, as shown in other studies.5,26

Various tumor markers and biochemical parameters have been measured in pleural fluid to help distinguish malignant from benign effusions,2-3 of which CEA has been used most widely as a tumor marker of serous effusions. In the current study, pericardial fluid CEA levels in patients with malignant diseases were significantly higher than those in patients with benign diseases, and positivity rate at a cutoff level of 5 ng/mL was 75% for patients with malignant diseases. These results are similar to those reported in other studies.2-3 Interestingly, there were no patients with acute pericarditis showing CEA levels >5 ng/mL and ADA levels >40 U/L (except for one patient) in their pericardial fluids.

It remains uncertain whether antituberculous drug therapy will prevent the development of constrictive pericarditis. Follow-up study showed that 13 patients with tuberculous pericarditis showed no symptoms or signs of constrictive pericarditis (except for one patient), in contrast to 25% to 54% in previous studies.7,11 The reasons for this are believed to be early and effective new antituberculosis chemotherapy and therapeutic removal of pericardial fluid in patients with tuberculous pericarditis. Since the introduction of early chemotherapy, mortality from acute tuberculous pericarditis has fallen to less than 50%. Long et al.55 reported that when pericardiectomy was not required for the relief of cardiac compression in the acute phase of tuberculous pericarditis, the long-term outcome with medical therapy alone was excellent. Hageman et al.56 emphasized that in tuberculosis of the pericardium, early chemotherapy appeared to be of paramount importance for a medical cure because the number of patients with given duration of symptoms before chemotherapy was correlated with the number of patients surviving for 5 years. Sagista-Sauleda et al.57 reported that they were unable to identify a specific interval between the onset of symptoms and the start of therapy, separating the patients who required pericardiectomy from those who did not, but also pointed out the delay in obtaining the correct diagnosis (average, 5.2 weeks from admission). We started antituberculosis therapy within 10 to 14 days of admission. Therapeutic removal of pericardial fluid might reduce the incidence of progression into constrictive pericarditis in patients with moderate to large tuberculous pericardial effusions. We treated our patients with a combination of isoniazid, rifampin, and either streptomycin or ethambutol for 12 months and pyrazinamide for 2 months, unlike methods used in previous studies.7,11

Conclusions

Pericardial fluid ADA and CEA are useful for the differential diagnosis of pericardial effusion of various causes because of their high specificity and sensitivity. They also have great value in the early diagnosis of tuberculous pericarditis, particularly when the results of other clinical and laboratory tests are negative.

Acknowledgments

We are indebted to Min Seon Lim, MD, and to Ju Rae Cho for secretarial assistance.

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Circulation. 1994;89:2728-2735
doi: 10.1161/01.CIR.89.6.2728

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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