USEFULNESS OF SERUM CA125 MEASUREMENT FOR MONITORING PERICARDIAL EFFUSION

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To investigate the clinical significance of carbohydrate antigen 125 (CA125), an antigen related to ovarian cancer, in patients with pericardial effusion, we examined the relationship between serum levels of CA125 and the presence or severity of pericardial effusion. Fifty-seven patients (25 with heart failure, 22 with pericardial metastasis, 4 with hypothyroidism, 4 with renal failure, and 2 with other diseases) in whom pericardial effusion was confirmed by echocardiography or autopsy, were used as subjects. Thirty-seven of these patients (65%) tested positive for CA125 in the serum. Of these, no significant differences in serum levels of CA125 were found between patients with benign and those with malignant underlying diseases or between those with, or without, pericarditis. However, CA125 values were higher in the patients with larger pericardial effusions and the serum level decreased when the pericardial effusion reduced. In some cases, the serum level normalized before the effusion resolved. Pericardial drainage was performed on 6 patients with cardiac tamponade. Four of these 6 patients had high serum CA125 levels and recurrent pericardial effusion. The other 2 patients had normal serum CA125 levels and no recurrence of effusion. An immunohistological study showed that a positive stain of pericardial tissues reacting to CA125 antibodies correlated to higher serum and pericardial fluid levels of CA125 than the levels of groups staining negative to the antibody. These results suggest that CA125 can be useful in assessing the status and clinical course of this disease.

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CARBOHYDRATE antigen 125 (CA125) is an antigen related to ovarian cancer that was discovered by Bast et al in 1981 and is reported to have a high degree of correlation to non-mucinous ovarian cancer. In 1983, Kabawat et al performed an immunohistochemical study showing the CA125 antigen present in tissues related to the coelomic epithelium, i.e., the pleura, the peritoneum, the Mullerian duct, and the amnion. Several reports have described the distribution of CA125 within these tissues. Inflammation of any of these tissues may lead to elevation of serum CA125 levels.

There are some reports on CA125 in patients with ascites and the relationship of CA125 to changes in this disease. However, there are no reports on CA125 in patients with pericardial effusion. Pericardial effusion is clinically infrequent, yet it is important to assess not only the presence of

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Fig. 1. Comparison of serum CA125 levels between patients classified by the type of effusion (exudate or transudate) and by the underlying disease (benign or malignant).

Fig. 2. Comparison of the extent of the pericardial effusion and the serum CA125 level. EFS: echo free space

Fig. 3. Serum CA125 level as a function of pericardial effusion. The level normalized before the pericardial effusion disappeared.

Effusion but also its status, especially to help decide the necessity of cardiac drainage. This is similar to the use of the erythrocyte sediment rate as a gauge of the activity of pulmonary tuberculosis with pleural effusion, and the efficacy of therapy. In this study, we measured CA125 levels in serum and pericardial fluid in patients with pericardial effusion confirmed by echocardiography or autopsy to investigate the clinical significance of CA125 in this disease group.

SUBJECTS AND METHODS
Fifty-seven patients, whose pericardial effusion was detected at autopsy or by echocardiography, were used as subjects. There were 20 males and 37 females with a mean

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age of 61±6 years. Twenty-five of the subjects had heart failure, 22 had pericardial metastasis, 4 had hypothyroidism, 4 had renal failure, and 2 had other diseases. Of the patients with heart failure, 10 had old myocardial infarction, 5 had valvular heart disease, 5 had pericarditis, 3 had dilated cardiomyopathy, 1 had atrioventricular block, and 1 had sick sinus syndrome. Of the patients with pericardial metastasis, 13 had lung cancer, 3 had pancreatic cancer, 2 had malignant lymphoma, 2 had hepatoma, and 2 had gastrointestinal cancer. Twenty additional healthy individuals (8 males and 12 females; mean age: 65±13 years) formed the control group.

Blood samples were centrifuged at 3,000 rpm for 30 min and the serum thus obtained was stored at 70 °C until it was assayed. The CA125 concentration was determined by an immunoradiometric method using a commercially available CA125 RIA Diagnostic Kit (Centor Co. USA). Immunohistochemical staining of the pericardium for CA125 was performed with an ORIS-HISH kit, using formalin-fixed, paraffin embedded sections. Echocardiographic examination was undertaken with the subject in the supine position holding their breath after quiet expiration. A Toshiba medical SSH-40A or SSH-270A Duplex ultrasound instrument was used. The size of the echo free space was determined by B-mode echocardiography to measure the amount of pericardial effusion. The degree was measured by M-mode echocardiography in diastole by varying the gain control.

In 32 patients, pericardial effusion was confirmed by echocardiography and its severity was compared to serum CA125 levels. In 13 of these patients, continued serum CA125 levels were measured and the timecourse was noted, until the pericardial effusion decreased.

The six patients with cardiac tamponade underwent drainage enabling us to investigate whether serum CA125 levels were re-
related to changes in the pericardial volume. The pericardial fluid was also classified as an exudate or transudate and serum CA125 values were compared between these two groups.

In 19 patients, the CA125 level in pericardial fluid, obtained at the time of therapeutic paracentesis, was compared with that in the serum. In 17 patients, the pericardium was obtained at autopsy and the pericardial tissues were stained for CA125. The presence or absence of staining was determined by 3 pathologists. An evaluation was made to determine whether CA125 levels of the serum and pericardial fluid were related to the presence or absence of staining. For negative controls, serial sections were obtained by substituting the primary antibody with nonimmune serum.

The paired or unpaired Student's t-test was used to evaluate the significance of differences between each group. Data are given as the mean ± SD and p < 0.05 was accepted as indicating statistical significance.

RESULTS

The upper limit of serum CA125 levels in healthy individuals was previously determined to be 35 μ/ml. Serum CA125 levels were < 35 μ/ml in all 20 control subjects, but were higher than this level in 37 (65%) of the 57 test subjects. Serum CA125 levels > 35 μ/ml were found in 60% of the subjects with heart failure, in 73% with pericardial metastasis, in 50% with hypothyroidism, and in 50% with renal failure. Hypothyroidism and renal failure thus had the lowest rate (i.e., 2 out of 4 or 50% of the patients).

There were no significant differences in CA125 serum levels between groups with malignant and those with benign underlying diseases (163 ± 32 vs. 154 ± 28 μ/ml) or between groups whose fluids were classified as exudates or transudates (172 ± 33 vs. 205 ± 44 μ/ml)(Fig. 1). The serum CA125 level was higher in patients with large effusions (diastolic echo free space ≥ 8 mm) as compared to those with small effusions (diastolic echo free space < 8 mm)(Fig. 2).

The CA125 levels decreased along with reduction of effusion and, in some cases, normalized before the effusion disappeared on echocardiographic images (Fig. 3). A representative case is shown in Fig. 4. The first panel shows pericardial effusion in the echocardiogram on admission of a 19-year-old
male with dyspnea. The middle panel shows increased pericardial effusion at later examination with an increase in the CA125 level from 164 to 376 μ/ml. Constrictive pericarditis was diagnosed on the basis of the clinical course. His symptoms improved after pericardectomy. The lower panel of Fig. 4 shows decreased pericardial effusion accompanied by a decrease in the CA125 level to 37 μ/ml.

Two of the 6 patients with cardiac tamponade had normal levels of serum CA125 (24 and 14 μ/ml) after pericardiocentesis and no recurrence of pericardial effusion. The remaining 4 patients had high serum levels of CA125 (164, 324, 179, and 121 μ/ml) and recurrence of pericardial effusion. The pericardial fluid levels of CA125 were significantly higher than serum levels (406±110 vs 147±30 μ/ml, p<0.05)(Fig. 5) based on 19 patients.

Anti-CA125 antibody staining of the pericardium is shown in Fig. 6. Positive staining of epithelial cells in the pericardium is shown on the left side of Fig. 6 and a stain testing negative is shown on the right side. Control sections were not stained with nonimmune serum. Serum CA125 levels tended to be higher in patients with a CA125-positive pericardium (59%) than in those in whom the pericardium was negative for CA125 (322±138 vs 196±40 μ/ml). The CA125 concentration in the pericardial fluid was significantly higher in the CA125-positive group than in the CA125-negative group (564±154 vs 75±25 μ/ml p<0.05)(Fig. 7).

DISCUSSION

Mitsuhashi reported that high CA125 levels were found only in subjects with malignancies. In the present study, 65% of patients with pericardial effusion had high CA125 levels while none of the control patients tested positive. However, no significant relationship was found between the CA125 level and the characteristics of the pericardial effusion or the nature of the underlying disease. These results indicate that CA125 is related to the presence of pericardial effusion.

Serum CA125 levels were high in patients with large effusions, and decreased as effusion decreased. In some cases, the CA125 level became normal before the effusion disappeared. In patients with cardiac tamponade, recurrence of the effusion was related to high serum CA125 levels. The levels increased at the time of recurrence. After surgery, both the degree of the pericardial effusion and the CA125 level decreased as the patient improved. These results indicate that the CA125 level is related to the severity of the pericarditis.

The mechanism of the change of the serum CA125 levels was studied in cases of pleural effusion and was assumed to function as follows. CA125, which exists in the pleural mesothelial cells, activates those cells during stagnation of the pleural exudate resulting from progression of pleuritis, liver cirrhosis, heart failure, or uremia. CA125 is then released to the pleural exudate. When the repair mechanism of inflammation begins to act, fibrin and exudate materials are precipitated on the surface of the pleura, which inhibits the activation of the pleural mesothelial cells. The active mesothelial cells then separate into the pleural exudate. Thus, reduction of the serum CA125 level corresponds to repair from inflammation, despite stagnation of the pericardial exudate.

Immunohistochemical analysis showed that some epithelial cells in the pericardium stained positive for CA125. CA125 values in the pericardial fluid were higher in patients positive for CA125 as compared to those negative for the antigen, suggesting that the antigen is produced and secreted by the pericardium, not merely filtered out by it. These findings indicate that monitoring of the serum CA125 level in patients with pericardial effusion can be of value and shows that high serum CA125 levels may indicate pericarditis.

CONCLUSION

The CA125 level is related to both the presence and the severity of a pericardial effusion. CA125 is a useful indicator to assess the status and clinical course of this disease.

REFERENCES


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