Determination and Significance of a New Carbohydrate Antigen CA19-9 in Digestive System Cancers

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To assess the diagnostic significance of CA19-9, the serum levels in 225 healthy subjects, 201 patients with cancers, 423 patients with benign diseases and 21 pregnant women, were determined by RIA. The mean CA19-9 level of the healthy subjects was 11.2 ± 0.4 U/ml (range, 6–100 U/ml). Only 3.1% of them were above 37 U/ml. The CA19-9 levels were elevated above 37 U/ml in 7.9% of 293 patients with non-carcinomatous diseases of the digestive system. Among digestive system cancers, elevated levels were found in 18.2% of 11 patients with esophageal cancer, 42.7% of 68 patients with gastric cancer, 39.1% of 23 patients with colorectal cancer, 27.8% of 18 patients with primary hepatic cancer, 71.4% of 35 patients with biliary cancer, and 75% of 20 patients with pancreatic cancer. Most of the patients with levels above 100 U/ml had carcinomatous diseases. The CA19-9 positive rates for patients with gastric cancer and colorectal cancer were extremely low at stages I, II and III, while in patients at stage IV and in patients with recurrent cancer, a tendency for rapid increase in the positive rates and concentrations of CA19-9 was noted. Based on combination assay of CA19-9, CEA and ferritin, in comparison with the positive rates for CA19-9 alone, it was found that the rates were raised to 42.7% in gastric cancer, to 39.1% in colorectal cancer, and to 71.4% in biliary cancer, suggesting the simultaneous determination with these tumor markers may serve to elevate their usefulness.

Key Words: CA19-9, Tumor markers, Digestive system cancers, Monoclonal antibody.

Many fetal antigens or antigens associated with tumor tissues, hormones, or enzymes, have been reported as tumor markers. All of them, however, lack satisfactory organ- or disease-specificity, since they have indicated high pseudo-positive rates in benign diseases, limiting their diagnostic value. Accordingly, in the immunological and biochemical diagnosis of carcinomas, no definitive method comparable to the pathohistological diagnostic method has yet been established. The development of a serum tumor marker, excellent both in its sensitivity and specificity and usable for the early diagnosis of carcinoma, or as a parameter of the progress of carcinoma, is thus one of the most important topics in present clinical medicine.

Carbohydrate antigen CA19-9 is a large monologanglioside recognized by monoclonal antibody produced from hybridoma in mouse splenic cells immunized with the strain SW 1116 originating from the human colorectal carcinoma cultured by Koprowski et al.¹⁾ in 1979. The antigenic determinant of this antigen has been identified as sialylated lacto-N-fucopentaose II.²⁾ Recently, Del Villano et al.³⁾ established a radioimmunoassay for CA19-9, and has applied it in clinical practice. The diagnostic significance of this antigen has attracted our attention as a possible new tumor marker associated with carcinoma of the digestive organs.⁴⁻⁶⁾ In the present study, we determined the serum CA19-9 levels in patients with benign

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or malignant diseases, in pregnant woman, and in healthy subjects, by radioimmunoassay, and attempted to assess its diagnostic usefulness for carcinoma of the digestive organs.

METHODS AND SUBJECTS

1. Subjects

The subjects were inpatients or outpatients of the Third Department of Internal Medicine or the First Department of Surgery, Nihon University School of Medicine, during the past one year. Their diagnoses were established on the basis of general clinical inspections, as well as the endoscopic inspections, overall imaging diagnosis, biopsy or autopsy, including 201 cases of carcinomatous diseases, 423 cases of benign diseases, 21 cases of pregnancy, and 225 healthy subjects.

2. Methods of determination of serum CA19-9 and other tumor markers

Serum CA19-9 was determined in duplicate by a solid-state radioimmunoassay method based on the forward sandwich method, using the CA19-9 TMRIA Kit manufactured by Centcor Inc. The standard solution at each concentration, the test sera, and the control sera, were reacted with the CA19-9 monoclonal antibody coated over polystyrene beads in a thermostat trough at 37°C, and the unreacted sera were then rinsed and removed. Next, ¹²⁵I-labelled CA19-9 antibody was added and incubated with the CA19-9 antigen bonded with the solid-state beads at room temperature for 3 hours (solidified antibody-antigen-¹²⁵I-labelled antibody).

The labelled antibody in excess was rinsed 3 times and removed. The quantity of labelled antibody bonded together with the beads was calculated using a gammacounter, and the CA19-9 concentrations in the control sera and test sera were determined by comparison with the standard curve.

The samples (sera) were stored in a freezer at -40°C for the period from separation of the serum to the determination in each experiment.

In the present study, the cut-off value of serum CA19-9 was set at 37 U/ml based on the report of Del Villano et al.³⁾, and values above this were evaluated as serum CA19-9 positive.

The CEA, ferritin, alpha-fetoprotein and

Fig. 1. CA19-9 concentration in the serum of healthy subjects by age and sex.

elastase I in the serum were determined with RIA kit available on the market. The normal value of CEA was taken as below 2.5 ng/ml, of ferritin in males 16.5–281.2 ng/ml, and in females 3.3–86.3 ng/ml, of alpha-fetoprotein below 20 ng/ml and of elastase I 100–400 ng/ml.

RESULTS

1) Serum CA19-9 values in healthy subjects (Fig. 1)

The mean concentration of serum CA19-9 in 225 healthy subjects showing no abnormality not only by physical inspections, but also by ordinary clinical examinations, was 11.2 ± 10.4 U/ml (mean $\pm$ SD). The mean concentration in the 127 male subjects was 8.5 ± 4.3 U/ml, and that in the 98 female subjects, 14.4 ± 14.2 U/ml. The latter indicated a slightly higher tendency, but no statistical significance was noted.

Classification of the serum CA19-9 concentration in the healthy subjects was made by age group. The serum CA19-9 concentration in the young female group below 20 years thus revealed a higher tendency. Seven cases (3.1%) in which the serum CA19-9 value was abnormally high (over 37 U/ml) were all young females, with 6 subjects below 20 years, and 1 subject in her twenties, the highest value being 100 U/ml. The association between serum CA19-9 value and smoking and drinking habits was examined, but no significant correlation was noted.

2) Serum CA19-9 values in patients with benign

Diagnostic Significance of CA19-9

Fig. 2. CA19-9 concentration in the serum of patients with benign digestive system diseases.

diseases (Figs. 2 and 3)

The numbers of patients with benign digestive diseases whose serum CA19-9 values proved to be positive (above 37 U/ml) were 2 out of 76 (2.6%) with chronic hepatitis, 13 out of 78 (16.7%) with hepatic cirrhosis, 2 out of 8 (25.0%) with primary biliary cirrhosis, 4 out of 24 (16.0%) with cholelithiasis, and 2 out of 24 (8.3%) with pancreatitis. In patients with acute hepatitis, fulminant hepatitis, fatty liver, gastric and duodenal ulcers, and other digestive diseases, the values were all below the cut-off value.

The numbers of patients with benign and non-digestive diseases and of pregnant women whose serum CA19-9 values proved to be positive were 1 out of 21 pregnant women (4.8%), 2 patients out of 42 (4.8%) with renal insufficiency, and

Fig. 3. CA19-9 concentration in the serum of patients with benign non-digestive system diseases and pregnant woman.

13 out of 78 (16.7%) with diabetes mellitus. In patients with mastopathy and thyroidal diseases, no abnormalities above 37 U/ml were observed, although the number of cases was limited.

The mean value for acute hepatitis was 10.8 ± 6.6 U/ml (mean $\pm$ SD) (range, 6–23 U/ml), for fulminant hepatitis, 16.0 ± 4.2 U/ml (range, 13–19 U/ml), for fatty liver, 13.0 ± 8.0 U/ml (range, 6–31 U/ml), for chronic hepatitis, 13.2 ± 9.4 U/ml (range, 6–61 U/ml), for hepatic cirrhosis, 21.9 ± 21.7 U/ml (range, 6–115 U/ml), for primary biliary cirrhosis, 24.9 ± 26.5 U/ml (range, 6–77 U/ml), for cholelithiasis, 27.5 ± 43.4 U/ml (range, 6–200 U/ml), for gastric and duodenal ulcers, 10.0 ± 6.1 U/ml (range, 6–28 U/ml), for pancreatitis, 16.0 ± 10.7 U/ml (range, 6–39 U/ml), for other digestive diseases, 10.9 ± 4.7 U/ml (range, 6–23 U/ml), for pregnant women, 16.1 ± 10.2 U/ml (range, 6–45 U/ml), for renal insufficiency, 17.8 ± 11.0 U/ml (range, 6–48 U/ml), for diabetes mellitus, 22.7 ± 22.3 U/ml (range, 6–110 U/ml), for mastopathy, 13.3 ± 3.8 U/ml (range, 9–16 U/ml), and for benign thyroidal diseases including hyperthyroidism and chronic thyroiditis, 15.2 ± 43 U/ml (range, 11–20 U/ml).

Thus, among the 444 cases of benign diseases and pregnant women, the serum CA19-9 values proved positive in 39 cases (8.8%). Out of these 39 cases, higher values exceeding 100 U/ml were indicated in 3 cases, including one each with hepatic cirrhosis, cholelithiasis and diabetes

Table 1. CA19-9 in the serum of patients with cancers

Cancer Type	No. of Cases	No. Positive	Percent Positive
Esophageal	11	2	18.2
Gastric	68	29	42.7
Colorectal	23	9	39.1
Hepatic	18	5	27.8
Biliary	35	25	71.4
Pancreatic	20	15	75.0
Breast	17	2	11.8
Lung	3	2	66.7
Thyroid	4	2	50.0
Ovarian	2	1	50.0
Total	201	92	45.8

Fig. 4. CA19-9 concentration in the serum of patients with cancers.

mellitus.

3) Serum CA19-9 values in patients with cancers (Table 1 and Fig. 4)

The numbers of patients with cancers whose serum CA19-9 values proved positive were 2 out of 11 (18.2%) with esophageal cancer, 29 out of 68 (42.6%) with gastric cancer, 9 out of 23 (39.1%) with colorectal cancer, 5 out of 18 (27.8%) with primary liver cancer, 25 out of 35 (71.4%) with biliary cancer, 15 out of 20 (75%) with pancreatic cancer, 2 out of 17 (11.8%) with breast cancer, 2 out of 4 (50%) with ovarian cancer.

The highest positive rates were noted in the patients with pancreatic cancer and biliary cancer.

The distribution of serum CA19-9 in patients with cancers ranged widely from low to high levels. The mean values of serum CA19-9 in patients with cancers were as follows: 16.5 ± 15.3 U/ml (mean $\pm$ SD) in patients with esophageal cancer, 2792.7 ± 11729.0 U/ml in patients with gastric cancer, 1831.0 ± 4264.5 U/ml in patients with colorectal cancer, 72.9 ± 146.9 U/ml in patients with primary liver cancer, 5108.4 ± 11650.4 U/ml in patients with biliary cancer, 3003.3 ± 5259.5 U/ml in patients with pancreatic cancer, 14.9 ± 14.4 U/ml in patients with breast cancer, 45.3 ± 42.3 U/ml in patients with lung cancer, 61.3 ± 68.3 U/ml in patients with thyroid cancer, and 23.0 ± 22.6 U/ml in patients with ovarian cancer.

4) Relationship between clinical disease stage in cancer of the digestive system and the serum

Fig. 5. CA19-9 concentration in the serum of patients with gastric and colorectal cancers by stage of disease.

CA19-9 value (Fig. 5)

Fig. 5 shows the distribution of serum CA19-9 values in cancer of the stomach and of the colon classified by disease stage. The mean value of serum CA19-9 was 21.4 ± 17.8 U/ml (mean $\pm$ SD) at Stage I ($n=9$), 29.4 ± 26.8 U/ml at Stage II ($n=5$), 57.1 ± 132.6 U/ml at Stage III ($n=9$), and 2173.4 ± 4391.5 U/ml at Stage IV ($n=19$), while it was 853.5 ± 2215.4 U/ml in recurrent carcinoma ($n=11$). On the other hand, the serum CA19-9 positive cases classified by disease stage numbered 1 out of 9 (11.1%) at Stage I, 1 out of 5 (20.0%) at Stage II, 1 out of 9 (11.1%) at Stage III, and 13 out of 19 (68.4%) at Stage IV, while the serum CA19-9 positive cases in recurrent carcinoma numbered 4 out of 11 (36.4%). It was clarified therefore that the positive rate tended to be lower in cases at an early stage, whereas it was higher in cases at Stage IV or in recurrent carcinoma.

5) Relationship between histological classification of cancer of the digestive system and the serum CA19-9 value (Fig. 6)

Fig. 6 shows the histological classification of 73 cases of esophageal cancer, gastric cancer, and colorectal cancer, and the distribution of serum CA19-9 values in each. The mean value of serum CA19-9 was 1485.3 ± 3213.2 U/ml (mean $\pm$ SD) in 20 cases of well-differentiated adenocarcinoma, 634.6 ± 1884.8 U/ml in 14 cases of moderately differentiated adenocarcinoma, 1036.1 ± 4114.2 U/ml in 17 cases of poorly differentiated adenocarcinoma, 2517.3 ± 4047.9 U/ml in 4 cases of signet-ring cell carcinoma, 1566.7 ± 602.8 U/ml in 3 cases of mucinous adenocarcinoma, 420 U/ml in 1 case of undifferentiated carcinoma, 53.3 $\pm$ 34.0 U/ml in 3 cases of papillary adenocarcinoma, and 16.5 ± 15.3 U/ml in 11 cases of squamous

Fig. 6. CA19-9 concentration in the serum of patients with digestive system cancers by histological classification.

cell carcinoma. The serum CA19-9 values in the patients with papillary adenocarcinoma and squamous cell carcinoma thus showed a lower tendency than those of patients with carcinoma exhibiting other tissue pictures.

6) Relationship between serum CA19-9 values in patients with cancer of the digestive system, and other tumor markers (Figs. 7 and 8)

Fig. 7 gives a comparison of the positive rates for CA19-9, CEA, ferritin, alpha-fetoprotein, and elastase I, in the sera of patients with cancer of the digestive system. There were significant differences in the positive rates, as follows: in esophageal cancer, CEA was positive in 3 out of 10

(30.0%), and ferritin in 5 out of 10 (50.0%); in gastric cancer, CEA was positive in 31 out of 67 (46.3%), and ferritin in 14 out of 60 (23.3%); in colorectal cancer, CEA was positive in 10 out of 22 (45.5%), and ferritin in 5 out of 19 (26.3%), in primary liver cancer, CEA was positive in 6 out of 18 (33.3%), ferritin in 10 out of 11 (90.9%), and alpha-fetoprotein in 15 out of 18 (83.3%); in biliary cancer, CEA was positive in 19 out of 28 (67.9%), and ferritin in 18 of 24 (75.0%); in pancreatic cancer, CEA was positive in 12 out of 20 (60.0%), ferritin in 10 out of 18 (55.6%), and elastase I in 7 out of 13 (53.9%).

A significant difference in positive rates was observed between CA19-9 and ferritin ($p < 0.05$) in gastric cancer, and also between CA19-9 and ferritin ($p < 0.01$), and between CA19-9 and alpha-fetoprotein in primary liver cancer. Table 2 shows the correlation between serum CA19-9 values and other tumor markers. A significant correlation was noted between CA19-9 and CEA in gastric cancer with $r = 0.606$ ($p < 0.01$); between CA19-9 and CEA with $r = 0.846$ ($p < 0.01$), and between CA19-9 and CEA with $r = 0.632$ ($p < 0.01$) in colorectal cancer; between CA19-9 and CEA with $r = 0.564$ ($p < 0.01$) in biliary cancer; and between CA19-9 and CEA with $r = 0.562$ ($p < 0.01$) in pancreatic cancer.

Fig. 7. Comparison of the detection of tumor markers in patients with digestive system cancers.

The positive rates in which one or more of the 3 tumor markers, CA19-9, CEA and ferritin, in the sera of patients with cancer of the digestive

Table 2. Correlation between CA19-9 and other tumor markers in the serum of patients with digestive system cancers

Diagnosis	No. of Cases	Coefficient of Correlation
Esophageal Cancer		
CA19-9 & CEA	10	0.166
CA19-9 & Ferritin	10	-0.154
Gastric Cancer		
CA19-9 & CEA	65	0.606**
CA19-9 & Ferritin	58	0.211
Colorectal Cancer		
CA19-9 & CEA	22	0.846**
CA19-9 & Ferritin	19	0.632**
Biliary Cancer		
CA19-9 & CEA	28	0.564**
CA19-9 & Ferritin	24	0.25
Pancreatic Cancer		
CA19-9 & CEA	20	0.562**
CA19-9 & Ferritin	18	0.353
CA19-9 & Elastase I	12	0.138

* : $P < 0.05$ ** : $P < 0.01$

system proved to be positive on combination assay, were 39 out of 60 (65.0%) in gastric cancer, 11 out of 19 (57.9%) in colorectal cancer, 21 out of 24 (87.5%) in biliary cancer, and 17 out of 18 (94.4%) in pancreatic cancer (Fig. 8). Thus, in comparison with the positive rates for CA19-9 alone, the combination assay was able to increase the rate by 22.3% in the case of gastric cancer, by 18.8% in colorectal cancer, by 16.1% in biliary cancer and by 19.4% in pancreatic cancer.

DISCUSSION

The authors have confirmed in the present study that determination of serum CA19-9 by RIA has a satisfactory sensitivity and reproducibility, and the standard curve in linear, so that the technique can be considered an established quantitative determination method. As a result of determining the serum CA19-9 in 201 patients with carcinoma, 423 patients with benign diseases, 21 pregnant women, and 225 healthy subjects, it was found that although this antigen may sometimes turn positive at low frequencies in patients with carcinomas other than in the digestive system, or in patients with several benign diseases, it does represent a very useful marker for the diagnosis of carcinoma of the digestive system, especially pancreatic cancer or biliary cancer, by a noninvasive method. It was further clarified that combination assay with other known tumor markers, such as CEA, ferritin and elastase I, can increase the accuracy of diagnosis.

A tumor marker has been understood as "a substance produced by the cancer cell, having a qualitative or a quantitative difference from a non-cancer cell." It is therefore considered not to be produced qualitatively under ordinary circumstances, or to be produced in only a trace amount, whereas it is produced abnormally in the cancer cell.

In recent years, investigations of the whole structure of glycochains have become one of the most important topics in the study of tumor markers. In particular, when a monoclonal antibody is made out of hybridoma, it can recognize the difference in stereoscopic position of an amino acid, and the difference in the glycochain,

Fig. 8. Combination assay of 3 tumor markers in the serum of patients with digestive system cancers.

unlike conventional polyclonal antibody manufacturing methods, having the property of delicately reflecting the whole chemical structure. As mentioned above, CA19-9 is a new tumor-related antigen recognized by the monoclonal antibody found by Koprowski et al.¹⁾ It has been confirmed to exist not only in the sera of healthy subjects, but also in their body fluids, such as bile juice or pancreatic juice.⁶⁻¹⁰⁾

Del Villano et al.³⁾ determined the CA19-9 in sera obtained from 1020 healthy blood donors, and reported that the mean value was 8.4 ± 7.4 U/ml (range, 0–107 U/ml), and that only 6 cases (0.6%) presented pseudopositiveness of over 37 U/ml. They stated that the mean value of CA19-9 in male subjects did not show any significant changes with advancing age, while that in female subjects was highest in their twenties, decreasing with advancing age.

The results of the present study indicated that the mean value of serum CA19-9 in 225 healthy subjects was 11.2 ± 10.4 U/ml, and its pseudopositive rate was 3.1%. These figures were slightly higher than the mean value and pseudopositive rate for CA19-9 obtained by Del Villano et al. in healthy subjects. It was further found that the mean value of CA19-9 in female subjects was higher than that in male subjects, in their all age groups, excluding those in their forties. This tendency was particularly noticeable in younger women.

From the data obtained by several researchers^{3, 12)} as well as by the authors, the serum CA19-9 value in healthy subjects appears to be higher in young women, so that the majority of pseudopositive cases may possibly be occupied by such young women. It is considered therefore that the mean value and the pseudopositive rate of CA19-9 may vary to some extent in accordance with the age constitution and sex ratio of healthy subjects to be studied, especially the number of young women in the population.

Unlike CEA, the serum CA19-9 in healthy subjects does not show a significant relation with smoking and drinking habits, and why the CA19-9 in young women is higher than that in other age groups is not yet certain.

In order to differentiate patients with carcinoma and healthy subjects, or patients with benign diseases, based on determinations of the serum CA19-9, Del Villano et al.³⁾ decided to set the cut-off value at 37 U/ml. As has been clarified in the present study, the diseases which can elevate the serum CA19-9 are multifarious, and even within the same disease, CA19-9 is widely distributed from a low to a high value. Accordingly, if we set the cut-off value of CA19-9 at a low level, many non-cancerous diseases will be included, and pseudopositive cases will be increased reducing the rate of accurate diagnosis. On the other hand, if we set the cut-off value at a high level, the rate of diagnosis of carcinomatous diseases is elevated, but the possibility of judging cancerous diseases as pseudopositive or of overlooking them completely is elevated. Taking the mean ± 2 SD of the CA19-9 value in healthy subjects determined by the authors as a standard, its upper limit becomes 32 U/ml, but some reports¹²⁾ have set the cut-off value at 40 or 44 U/ml.

It is important to decide an appropriate cut-off value for CA19-9 as a tumor marker to have high sensitivity and specificity. At the present, the cut-off value of 37 U/ml decided by Del Villano et al. may represent an appropriate standard, since it can limit the pseudopositive rates in healthy subjects at middle or higher ages or patients with benign diseases to a rather low level. However, it is considered necessary to re-examine the cut-off value of CA19-9 based on an analysis of various background factors.

Although the serum CA19-9 in pregnant women, in patients with chronic hepatitis, hepatic cirrhosis, primary biliary cirrhosis, cholelithiasis, pancreatitis, renal insufficiency, diabetes mellitus and other benign diseases, showed positive rates of 3.6–25%, it was within the normal range in many other patients with benign digestive diseases. Among the 39 cases of benign diseases and pregnant women who were CA19-9 positive, those in whom higher values of over 100 U/ml were indicated amounted to only 3 patients including one each with hepatic cirrhosis, cholelithiasis and diabetes mellitus. In the majority of them, a mild elevation below 100 U/ml was observed. The

positive rate of serum CA19-9 in the pregnant women was as low as 4.8%, and the mean value was not so high compared with that of healthy young women. This suggests that CA19-9 may have no close relationship with the fetal character.

When CA19-9 was analyzed by Sephadex G-200 column-chromatography, it was eluted in the void volume, and was therefore presumed to be a high molecular substance.¹³⁾ Further, in view of the fact that the positive rate of CA19-9 is somewhat higher in hepatic cirrhosis than in chronic hepatitis, the former being at a more advanced state of disease, and that the positive rate in patients with renal insufficiency is low, the possibility of high molecular CA19-9 being metabolized mainly in the liver can be postulated. It has been confirmed that in the bile ingredients of patients with carcinoma and with benign diseases, CA19-9 is present at a very high concentration.^{11, 13)} Accordingly, the elevation of serum CA19-9 at attacks of cholelithiasis may be associated with impairment of bile excretion.

In the 4 cases of cholelithiasis treated by the authors in which the CA19-9 was abnormal, the determinations were made in all cases when colic and jaundice appeared, and the CA19-9 value returned immediately to the normal range when the pathological state was improved. In some patients with primary biliary cirrhosis, CA19-9 was elevated, and all the patients involved had jaundice and pruritus. Since this disease consisted of chronic non-suppurative destructive cholangitis at the interlobular bile duct of medium size (40–80 μ in diameter) or at the septal bile duct, and its basic lesions presented a pathological state of chronic intrahepatic cholestasis, often complicated with dry gland syndrome due to systemic adenopitthelial cell impairment, or with autoimmune diseases in other organs, the origin of the CA19-9 in the serum is complex. However, the main causes are presumed to be impairment of excretion of bile ingredients due to the above-mentioned lesions in the bile ducts, as well as a decrease in clearance in the liver.

The mechanism of increase in serum CA19-9 in patients with diabetes mellitus remains unclarified, but abnormal values exceeding 37 U/ml were shown in 13 of 78 patients (16.7%) treated

by the authors. In the majority of these 13 patients in whom CA19-9 was abnormal, the carbohydrate metabolism was under poor control. It may be considered therefore that an imbalance between abnormal metabolism of glucose and lipid existing in the background of patients with diabetes mellitus, may have some association with the increase in CA19-9.

According to the report of Del Villano et al.,³⁾ the positive rates of serum CA19-9 in patients with carcinoma of the digestive system were as follows: 63 out of 80 patients (79%) with pancreatic cancer, 46 out of 94 patients (49%) with primary liver cancer, 12 out of 24 patients (50%) with cancer of the stomach, and 77 out of 210 patients (37%) with cancer of the colon and rectum, while the pseudopositive rates in benign diseases including pancreatitis, inflammatory intestinal diseases, polyps, and other digestive diseases were as low as 0–2%. On the other hand, a compilation of results reported by Japanese researchers revealed that the positive rates of cancer of the digestive system were as follows^{10–14)}: 205 out of 249 patients (82.3%) with pancreatic cancer, 90 out of 144 patients (62.5%) with cancer of the bile-duct, 94 out of 300 patients (31.3%) with cancer of the stomach, 73 out of 201 patients (36.3%) with cancer of the colon and rectum, 56 out of 292 patients (19.2%) with primary liver cancer, and 3 out of 20 patients (15.0%) with esophageal cancer.

According to the results obtained by the authors, the positive rate of CA19-9 was highest (75.0%) in patients with pancreatic cancer, followed by 71.4% in patients with biliary cancer, 42.6% in patients with gastric cancer, 39.1% in patients with cancer of the colon and rectum, 27.8% in patients with primary liver cancer, and 18.2% in patients with esophageal cancer. These findings thus agree essentially with those reported by other researchers.^{3, 8–14)} It has also been confirmed that CA19-9 sometimes becomes positive not only in cancer of the digestive system, but also in lung cancer, breast cancer, ovarian cancer and thyroid cancer, although at low frequencies. It seems possible, therefore, that serum CA19-9 may turn positive not only in entodermal carcinoma, but also in

ectodermal or mesodermal carcinoma, and a clear organ-specificity seems to be unrecognizable. It was found among 26 patients with breast cancer, thyroid cancer, and ovarian cancer, however, that the serum CA19-9 value in 6 out of the 7 patients in whom elevation of the value was noted, was below 100 U/ml. The level was 150 U/ml in the other positive patient. These findings suggest that serum CA19-9 determination is very useful as an immunoserological diagnostic method for pancreatic cancer, cancer of the bile-duct, and other kinds of cancer of the digestive system.

Further, as mentioned above, there have been some cases of benign diseases where CA19-9 showed an increase, but the majority of the increased levels were below 100 U/ml, whereas in cases of carcinoma of the digestive system, many show high values, although low values have sometimes been noted. Accordingly, when the CA19-9 value is below 100 U/ml, we should consider an alternative of carcinomatous as well as benign diseases, but when high values over 100 U/ml are indicated, which continue to increase exponential-functionally, it is very important to treat the case with the possibility of cancer of the digestive system in mind.

Whether CA19-9 can be used as a marker for early diagnosis of cancer of the digestive system is an extremely important question in assessing its clinical usefulness as a tumor marker. Del Villano et al.³⁾ reported that 46% of their 164 patients with advanced colorectal adenocarcinoma, and 8% of their 25 patients with localized colorectal adenocarcinoma, showed increased CA19-9 values, but that the CA19-9 in their 21 patients with inactive colorectal adenocarcinoma who showed no clinical symptoms and were able to undergo successful tumor resection, did not exceed 37 U/ml.

Concerning CA19-9 and the classification of disease stage in stomach cancer, Ariyoshi et al.¹⁴⁾ reported that the marker level was within 37 U/ml in patients at Stage I and Stage II, and that it was positive in 42.9% of patients at Stage III, and in 50% in patients at Stage IV.

The CA19-9 positive rates among the authors' patients with stomach cancer and colorectal cancer were extremely low at Stages I, II and III,

while in patients at Stage IV and in patients with recurrent carcinoma, a tendency for rapid increase in the positive rate and concentration of CA19-9 was noted. It seems therefore that the possibility of CA19-9 serving as an influential marker for the early diagnosis of carcinoma of the digestive system should not be overemphasized. Although there have been few reports comparing CA19-9 concentrations classified according to tissue types of carcinoma of the digestive system, the CA19-9 values in patients with carcinoma of the digestive system of tissue types other than papillary adenocarcinoma and squamous cell carcinoma were widely distributed from low to high values, due partly to the influence of different stages, and a significant difference between the mean values of CA19-9 in each may not be recognizable. Since CA19-9 is a glycolipid of product from the secreting epithelium, it is essentially produced easily in adenocarcinoma, and its blood concentration is elevated with increase in the carcinoma. However, in cases of squamous cell carcinoma, as seen in esophageal cancer, the production of CA19-9 appears to be very small or none. Further, there are carcinomas which produce CA19-9 at high levels as well as at low levels, although both presenting the same tissue type of adenocarcinoma at a considerably advanced stage, suggesting that the nature of the CA19-9 production may differ in each case. Clarification of both types in detail histologically is therefore an important future task.

There are generally 2 kinds of tumor markers which can be utilized for the diagnosis of carcinoma of organs over a broad range as well as for the diagnosis of carcinoma of a specific organ. For carcinoma of the digestive system, CEA and ferritin represent the former category, while alpha-fetoprotein and elastase I represent the latter. To be more specific, CEA can be usefully employed in the diagnosis of biliary cancer, pancreatic cancer, and colorectal cancer; ferritin for primary liver cancer, biliary cancer, and pancreatic cancer; elastase I, for pancreatic cancer, and alpha-fetoprotein, for primary liver cancer. The results obtained by the authors comparing the positive rates of various tumor markers for carcinoma of the digestive system well support these findings.

In view of the fact that tumor markers of excellent specificity and sensitivity able to detect cancer-bearing organs at an early stage have yet to be established, it is more effective to use available markers in plural numbers rather than singly for the diagnosis of a carcinoma. Although contradictory reports have indicated that in carcinoma of the digestive system, CA19-9 and CEA, and CA19-9 and ferritin are significantly correlated, or are not correlated, the present authors' assessment of the relation between CA19-9 and other tumor markers classified by organ suggested that a correlation between CA19-9 and CEA was present in stomach cancer, colorectal cancer, pancreatic cancer and biliary cancer, while a correlation between CA19-9 and ferritin was noted in colorectal cancer.

Based on combination assay of CA19-9, CEA and ferritin, in comparison with the positive rates for CA19-9 alone, it was found that the rates were increased to 22.3% in stomach cancer, to 18.8% in colorectal cancer, to 16.1% in cancer of the bile-duct, and to 19.4% in pancreatic cancer, indicating that simultaneous determinations with these markers can be very helpful for the diagnosis of carcinoma. Ishida et al.¹¹⁾ found by combination assay of CA19-9, CEA and ferritin that while the positive rates on their single use were 42.0% for CA19-9, 47.7% for CEA and 31.8% for ferritin, simultaneous determination with the plural markers was useful for raising the rate of diagnosis, since there was 71.6% with more than 1 positive. The ultimate value of tumor markers rests on the extent to which an early carcinoma can be diagnosed. Single use of CA19-9 as an auxiliary for early diagnosis is not considered realistic, but combination assay with other tumor markers is expected to enhance the clinical usefulness of these markers.

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