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Increased Serum CA 72-4 Levels in Patients With Gastrointestinal Carcinoma

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Abstract: This study is an evaluation of serum levels in the tumor markers CA 19-9 and CA 72-4 in gastric cancer patients in preoperative, postoperative and follow-up periods. These tumor markers were measured in 35 patients with primary gastric carcinoma (28 advanced stage, 7 early stage), 27 with benign gastric disease and 20 healthy control subjects. Serum CA 72-4 levels were found to have increased (>6.7kU/l) in 16 (14 with advanced stage, 2 with early stage) patients with primary gastric carcinoma. Serum CA 19-9 levels were elevated (>22kU/l) in 9 patients with primary gastric carcinoma (8 with advanced stage, 1 with early stage) and 3 of patients with benign gastric disease, respectively. Only 19 out of 35 patients had follow-up periods of approximately 15 months. During the follow-up period, while all of these 19 cases had lower CA 19-9 levels, only 10 of them had higher CA 72-4 levels than the cut-off points. The sensitivity and specifity of CA 72-4 were determined to be 45% and 100%, respectively. The positive and negative predictive values for CA 72-4 were 100% and 71%, respectively. Specificity and sensitivity of CA 19-9 were 89% and 25%, respectively. Positive and negative predictive values for CA 19-9 were 69% and 62%, respectively.

The findings suggest that serum CA 72-4 may be a useful marker in gastric carcinoma, and its measurement in combination with CA 19-9 may be useful in the clinical management of gastric carcinoma.

Key Words: CA 72-4, CA19-9, Gastrointestenol korsinom

Introduction

Gastric cancer in Chile, Japan, and Iceland have the highest incidence of gastric cancer. The United states has experienced a rapid decline in stomach cancer deaths, from a rate of 30 per 100,000 in 1930 to 8 per 100,000 today (1, 2). Tumor markers, which may be oncofetal or tissue-affected antigens, hormones or enzymes, have been described for a variety of malignancies. Tumor markers are most useful in evaluating the progression of disease status after the initial therapy and in the monitoring of subsequent treatment modalities. CA 19-9 is a carbohydrate antigen identified as a glycolipid–that is, sialylated lacto-N-fucopentaose II ganglioside, which is a sialylated derivative of the Lewis blood group antigen. It is synthesized by normal human pancreatic and biliary ductular cells and by gastric, colonic, endometrial, and salivary epithelia (3). In recent years, a new tumor-associated glycoprotein antigen, TAG-72, has been identified. This antigen is known as CA 72-4, a newly found marker for carcinomas of the gastrointestinal tract and of the ovary. This oncofetal antigen, a high-molecular-weight mucin glycoprotein, is detectable in the sera of patients with a variety of gastrointestinal adenocarcinomas (4).

Most studies on tumor markers in gastric carcinoma have determined tumor markers only in the preoperative period. Very few iongitudinal follow-up studies have been done. In the present study, we aimed to investigate serum levels of CA 19-9 and CA 72-4 in gastric cancer patients both in preoperative and postoperative periods, to reveal the relationship between these tumor markers and the disease stage, and to investigate the courses of the disease and of the tumor markers CA 19-9 and CA 72-4 in the postoperative period.

Materials and Methods

Thirty-five patients (23 men, 12 women) who had undergone surgery for primary gastric adenocarcinomas were assessed. Each patient's disease was classified according to tumor node metastasis (TNM) system (5), with the following stages: I (n=2), II (n=5), III (n=10)

Table 1. Characteristics of the patients and control subjects.

	Gastric cancer	Benign	Control
Sex			
Male	23	15	12
Female	12	12	8
Age(Years)	59±7.4	39±8.8	33±6.4

Table 2. Serum CA 72-4 and CA 19-9 levels above cutoff points in patients with benign and malignant gastric disease, and healty controls.

	Malignant (n=35)		Beningn (n=27)	Control (n=290)
	Stage(I+II) n=7	Stage(III+IV) n=28		
CA 72-4 >6.7kU/L	2	14	0	0
CA 19-9 >22kU/L	1	8	3	0

Table 3. Serum Levels of CA 72-4 19-9 the Study Groups in Between Disease

	CA 72-4 kU/L (Mean±SD)	CA 19-9 kU/L (Mean±SD)
Control	2.2±0.8	11.7±4.1
Benign	2.1±0.8	13.1±6.2
Early Cancer	3.9±3.0*	15.0±8.0*
Late Cancer	14.1±11.8**	21.1±11.4***

*No significant difference between early cancer vs benign groups and control groups for CA 72-4 or CA 19-9.
**p<0.0001 v.s. benign and controls groups; p<0.01 v.s. early cancer
***p<0.01 v.s. benign and p>0.05 v.s. early cancer and p<0.001 v.s. control

and IV (n=18). Patients in stages I and II had early gastric cancer involving the mucosa and submucosa only, and those in stages III and IV had advanced gastric cancer involving the muscularis and serosa. Twenty-seven patients (15 men, 12 women) with endoscopically and histopathologically diagnosed benign gastric disease (ulcer, gastritis) were evaluated. Additionally, 20 healthy volunteers (8 women, 12 men) with no medical complaints were used as the control group.

Follow-ups were conducted on 19 of the patients for an average postoperative period of 15 months (ranging from 8 to 24). Outpatient visits were scheduled every three months for the first year and every six months thereafter. During each visit, the patient was evaluated by physical examination, standard biochemical and hematological blood profiles, chest radiographs, upper gastrointestinal endoscopic assessment, and ultrasonography of the abdomen and pelvis.

Blood samples were taken preoperatively, between two and seven days postoperatively, and during each visit. All samples were aliquated and stored at -70˚C until assays were performed. 1000µl of conjugate and antibody-POD conjugate solution mixture was added to a tube containing 50µL of serum sample and incubated for 150 min, and tube contents were aspirated and the tubes were rinsed twice with Enzymun-test® washing solution within 5 minutes. Then, 1000µL substrate chromogen solution (phosphate / citrate 100 mmol/L, 3.2 mmol/L H_2O_2) was added and incubated for 30 min and the absorbance was measured at 405 nm, and the results were obtained by standard absorbance curve. CA 72-4 assay was made with a commercial kit (Enzymun-test® CA 72-4, Cat. No: 1490 486, Boehringer Mannheim, Germany). CA 19-9 assay was made with a commercial kit (GI-MA, Chemiluminescent enzymun immunoassay, Cat No: LK GIZ, USA) with Immulite Automated Analyzer and designed for the qualitative measurement of CA 19-9 in serum.

Statistical analysis: Data are given as mean±standard deviation. For statistical analysis, Mann-Whitney U test and X^2 was used. Specificity and sensitivity were calculated for each tumor marker. A p value of lower than 0.05 was considered to be statistically significant.

Results

Serum samples from 35 patients with primary gastric carcinoma and 27 patients with benign gastric disease were evaluated for CA 72-4 and CA 19-9. The characteristics of the patients are given in Table 1. Table 2 shows the incidence of positive results for CA 72-4 and CA 19-9 in benign and malignant gastric disease. Serum CA 72-4 levels increased in 16 (45.7%) of 35 patients with primary gastric carcinoma. In contrast, none of the 27 patients with benign gastric disease had positive CA 72-4 levels (p<0.001). Serum CA 19-9 levels increased in 9 (26.3%) and 3 (10.7%) patients with malignant and benign diseases, respectively (p<0.5). Correlation of the serum levels of tumor markers with the clinical stage of malignant disease was also performed. As shown in Table 2, positive serum CA 72-4 levels were found in 14 of 28

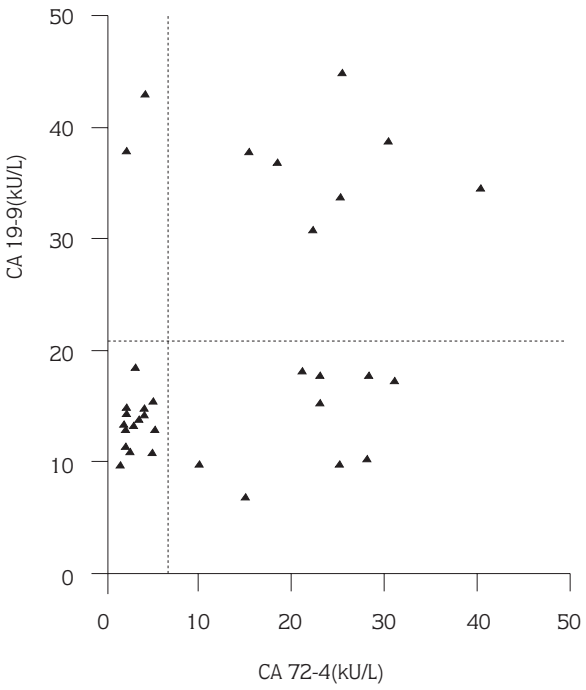

Figure 1. Serum CA 72-4 and CA 19-9 levels in patients with gastric carcinoma.

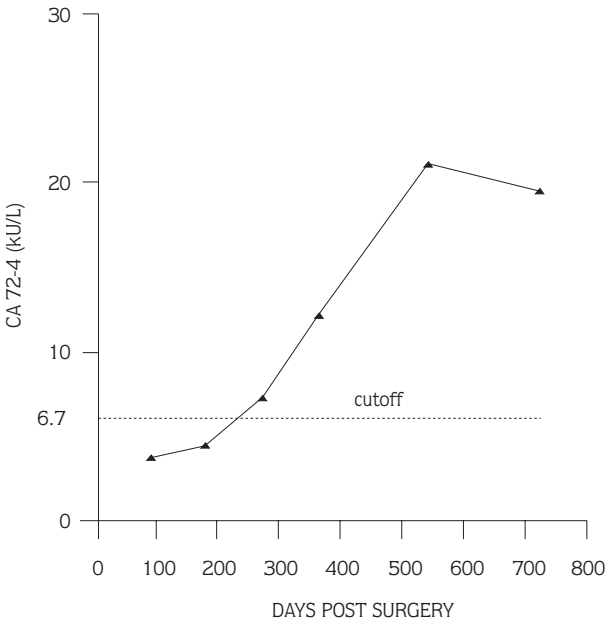

Figure 2. Longitudinal postsurgical evaluation of serum CA 72-4 in patients with gastric carccinoma.

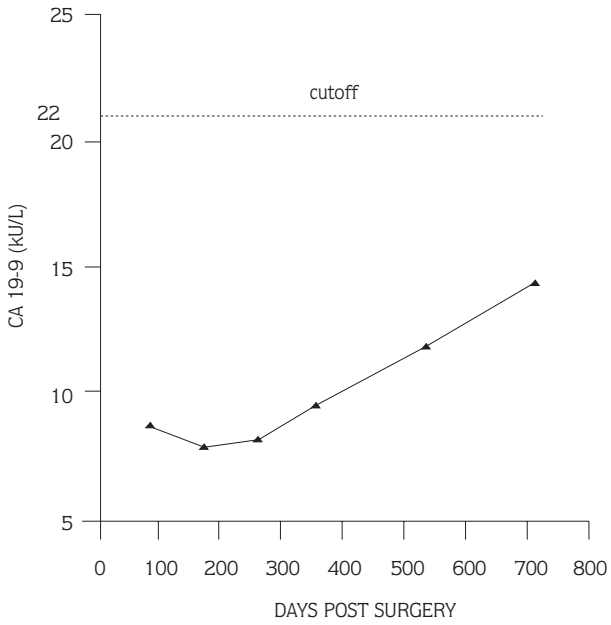

Figure 3. Longitudinal postsurgical evaluation of serum CA 19-9 in patients with gastric carinoma.

patients (50%) with advanced gastric carcinoma. Likewise, there was a predominant increase of serum CA 19-9 was also predominantly increased in the sera of 8 (28.5%) of 28 patients with advanced stage gastric carcinoma.

Figure 1 illustrates CA 72-4 and/or CA 19-9 in the sera of 35 patients with gastric carcinoma. The mean levels and ranges of serum tumor markers in patients with benign gastric disease and early and late gastric carcinoma are shown in Table 3. No correlation was detected between patients with benign gastric disease and healthy controls in terms of serum CA 72-4 and serum CA 19-9 values. There was no statistically significant difference. Serum CA 72-4 and CA 19-9 levels were significantly higher in the advanced stage group than in the benign disease group, control group and early cancer group ($p<0.0001$, $p<0.01$ for CA 72-4; $p<0.01$, $p<0.001$ for CA 19-9 respectively). There was a trend towards higher values in the advanced gastric cancer group than in those with benign disease or early gastric cancer.

Following curative surgery for primary gastric carcinoma, follow-ups wereconducted on 19 patients were for a mean postoperative time of 15 months (range 8-24 months). Recurrence was seen in 10 patients whose serum CA 72-4 levels were significantly above the cutoff point (Figure 2). Conversely, in all 19 patients on follow up, CA 19-9 levels were below the cutoff point (Figure 3).

The sensitivity and specifity of CA 72-4 were found to be 45% and 100%, respectively. Positive and negative predictive values were 100% and 71%. The specificity and sentivity of CA 19-9 were 89% and 25%, respectively. The positive and negative predictive values were 69% and 62%, respectively.

Discussion

One problem encountered in the diagnosis and postoperative follow-up of patients with gastric cancer involves tumor markers. It is generally agreed that the conventional tumor markers, such as CEA, CA 19-9, and CA 125, are all unreliable in the detection and clinical management of gastric cancer. An ideal tumor marker detecting gastric cancer has not yet been found. More recent studies have shown that measurements of the new serum marker CA 72-4 are useful and correlate well with disease stage and activity (6-9). The CA 72-4 antigen is distinct from CEA and has recently been purified and characterized as a mucin-like molecule on the basis of its high molecular weight, resistance to chondroitinase digestion, density determination, the presence of blood group-related oligosaccharides, and sensitivity to shearing into lower molecular weight forms (10). CA 72-4 expression was not found in nonepithelial tumors (including melanomas, sarcomas, tumor of neural crest derivation, leukemia and lymphoma); very low levels of expression of CA 72-4 have been found in some malignant mesotheliomas (11). CA 19-9 is a molecule that might actually play a role in the adhesion of cancer cells to endothelial cells (12, 13). Serum CA 19-9 levels rise in neoplasm of the gastrointestinal system, pancreas, and biliary tract, as well as in inflammatory and destructive diseases of the biliary tract (14, 15).

The present study indicates that the measurement of serum CA 72-4 levels may be an important component in the diagnosis and clinical follow-up of patients with malignant gastric disease. The sensitivity and specificity of CA 72-4 were found to be 45% and 100%, respectively. These findings were in accordance with studies by Joypaul et al. (4), Guadagni et al. (6), and, Ohuchi et al. (16). There was a significant difference between patients in advanced stages of the disease and fhose in early stages. These observations suggest that serum levels of CA 72-4 closely reflect the aim of clinical staging of the disease, which was elucidate the roles that the tumor markers play in the biology of human gastric carcinoma. CA 19-9 was positive in nine patients. No statistically significant difference was seen between advanced and early stages with respect to CA 72-4 and CA 19-9. The specificity and sensitivity of these markers were 89% and 25%, respectively. One important application of any serum marker is the measurement of the serum tumor antigen in predicting the clinical course of malignant disease, particularly in the diagnosis of recurrence. Ten out of 19 patients had higher serum CA 72-4 values than the cutoff point during follow-up. This condition shows that CA 72-4 is a specific marker in the follow-up of gastric carcinoma. The findings of the present study demonstrate that the measurement of CA 72-4 is an important marker both in the diagnosis and follow-up of patients with malignant gastric disease. In our study, when compared with CA 19-9 a higher percentage of patients with gastric cancer had positive CA 72-4 serum levels that had positive CA-19 serum levels. In addition, the specificity of serum CA 72-4 was better than that of CA 19-9. According to the results of our study, the CA 72-4 serum marker is present in a considerable number of patients where CA 19-9 cannot be detected at the time of diagnosis and/or at the time of recurrence in gastric carcinoma patients.

Studies of greater scope are needed to confirm the reliability of CA 72-4 as a marker for gastric cancer. A combination of CA 72-4 level measurement and other postoperative surveillance techniques may be useful in the detection of recurrence.

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