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Significance of serum tumor markers CA50 and CEA in gastric cancer

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Abstract

AIM: Cancer antigen 50 (CA50) and Carcinoembryonic antigen (CEA) are well-described human tumor-associated antigens, utilized clinically in management of gastrointestinal cancer cases. In this study, we compared these markers in sera from patients with malignant and benign digestive tract diseases.

METHODS: Using a side-phase radioimmunoassay, CA50 and CEA serum levels were measured in 33 control subjects and 86 patients with either gastric cancer (n = 34), gastric ulcer (n = 27) or chronic atrophic gastritis (n = 25). Carcinoma of the stomach was found in the antrum (n = 22), the body (n = 3) and the fundus (n = 9), and according to histopathological findings was divided into adenocarcinoma (n = 21), squamous cancer (n = 4) and undetermined (n = 9). Gastric ulcer, when present, appeared in the antrum (n = 18), the body (n = 3) and the fundus (n = 9). Chronicatrophic Gastritis cases were all associated with intestinal metaplasia.

RESULTS: The normal ranges established for CA50 and CEA in the control group were 16.26-6.14 kU/L and 3.12-1.03 μg/L respectively. In patients with gastric cancer, serum levels of CA50 (112.67 ± 38.36 kU/L) and CEA (10.28 ± 3.76 μg/L) were elevated significantly (P < 0.01), the former being < 22 kU/L in 18 of 34 patients (53%; range: 5-550 kU/L) and the latter being < 5 μg/L in 19 of 34 patients (55.8%; range: 0.5-17.4 μg/L). A statistically significant correlation was found between the levels of CA50 and CEA (r = 0.648, P < 0.01). The serum levels of CA50 (46.4 kU/L *vs* 25.9 kU/L, P < 0.01) and CEA (6.85 μg/L *vs* 2.43 μg/L, P < 0.01) were much lower in patients with gastric ulcer or chronic atrophic gastritis (P < 0.05).

CONCLUSION: CA50 and CEA are indicators for advanced gastric cancer, and postoperatively their serum levels may decrease considerably. Overall, there is such a close correlation between these two factors that in clinical practice they might be of great value for the diagnosis of gastric cancer.

Key words: Gastroesophageal reflux/diagnosis; Esophagitis/diagnosis; Hydrogen-ion concentration

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INTRODUCTION

Cancer antigen 50 (CA50) is a monoclonal antibody raised against another human colorectal carcinoma cell line COLO 205[1,2]. It reacts with an epitope present on two carbohydrate moieties, the sialylated Lewis blood group antigen and the sialosyl-lactoetraose, lacking the fucosyl residue of the sialylated Lewis antigen[1,3]. Normally, the sialylated Lewis is the dominant CA50 ganglioside in epithelial carcinomas[4]. The sialosyl-lactoetraose has been found in small amounts in various carcinomas, defined as Lewis[5]. The CA50 is expressed on cell surfaces as glycolipids and glycoproteins. In serum, the antigen is associated with a high molecular weight carbohydrate-rich mucin fraction[6]. The CA50 level is high in many patients with digestive tract malignancies. The highest frequencies of elevated level are found in ovarian cancer patients (70%) and biliary cancer patients (60%), but elevated values have also been found in patients with colorectal, gastric and liver cancer[1]. Increased serum concentrations of CA50 have also been observed in some benign diseases.

Carcinoembryonic antigen (CEA) is an oncofetal protein originally described in 1965, which has become one of the most commonly used serum tumor markers and is frequently elevated in patients with colonic, pancreatic, lung, and breast cancers[7]. The extent of elevation of CEA in colon cancer is related to the patient's overall tumor burden[2,8]. However, the usefulness of CEA is limited by the marker's overall low sensitivity in patients with minimal disease extent and by effects of smoking and benign gastrointestinal diseases on its specificity[1,9]. Nonetheless, CEA is a marker approved for monitoring the recurrence of colon cancer. It has also been proposed for a similar purpose for other gastrointestinal tract cancers and breast and lung cancers.

In the present study, the serum levels of CA50 and CEA were determined in patients with digestive tract diseases and those with digestive tract cancers.

Table 1 Serum Cancer antigen 50 and Carcinoembryonic antigen in gastric diseases (mean ± SD)

Group	CA50, kU/L	CEA, μg/L
Gastric cancer	112.67 ± 38.36[b]	10.28 ± 3.76[b]
Gastric ulcer	21.42 ± 9.57[a]	4.48 ± 1.09
Atrophic gastritis	20.82 ± 8.95[a]	4.52 ± 1.45
Controls	16.26 ± 6.14	3.12 ± 1.03

[b]$P < 0.01$ *vs* controls and benign gastric diseases; [a]$P < 0.05$ *vs* controls.

MATERIALS AND METHODS

Materials

The study consisted of: 34 patients with gastric cancer in an advanced stage, including 12 women and 22 men with a mean age of 38.2 years (s: 10.4); 27 patients with gastric ulcer in active stage, including 11 women and 16 men with a mean age of 39.4 years (s: 9.3); 25 patients with chronic atrophic gastritis associated with intestinal metaplasia (IM), including 11 women and 14 men with a mean age of 41.2 years (s: 10.6). Carcinoma of the stomach was found in the antrum (n = 22), the body (n = 3) and the fundus (n = 9), and was classified by histopathological results as adenocarcinoma (n = 21), squamous cancer (n = 4) and undetermined (n = 9). Gastric ulcer, when present, was in the antrum (n = 18), in the body (n = 3) and in the fundus (n = 9). The study also included 33 healthy subjects, including 9 women and 24 men with a mean age of 38.6 years (s: 9.7) who served as controls. Four mL of fasting blood were collected and the serum was immediately separated by centrifugation, frozen and stored at -20 ℃ until use in analysis.

Methods

Commercially available solid radioimmunoassay (RIA) was used for quantitative determination of the serum CA50 concentrations, as previously described in detail[10]. The recommended cut-off value of 22 kU/L was used. CEA assays were performed using a solid-phase two-site immunoradiometric assay (The general Hospital of Chinese PLA, Beijing, China)[11]. The samples reacted with beads dual-coated with a capture monoclonal antibody directed against one CEA antigenic site and with a radiolabelled marker monoclonal antibody. The radioactivity bound was measured with a gamma counter and was proportional to the concentration of CEA in the test sample. The recommended cut-off value was 5 μg/L. Both coefficients of variation (CV) were controlled to less than 10%. The smallest amount of tumor markers detectable with 95% confidence was 1 kU/L for CA50 and 0.1 μg/L for CEA.

Statistical analysis

The levels of the tumor markers are given as mean ± SD. The unpaired Student's t-test was used for comparison of the data for controls and patients. Correlations were calculated on the values of CA50 and CEA with linear regression analysis. $P < 0.05$ was considered significant.

RESULTS

The values of CA50 and CEA in the series of patients are summarized in Table 1. In patients with gastric cancer, the CA50 level was elevated in 18 of 34 patients (53%; range: 5-1550 kU/L). Benign gastric diseases were also associated with an increased concentration in 2 of 27 patients with gastric ulcer (7.4%; range: 5-276 kU/L) and in 3 of 25 patients with chronic atrophic gastritis (12%; range: 5-285 kU/L), whereas none of the normal subjects had an increased CA50 concentration. The CEA level was elevated in 19 of 34 patients with gastric cancer (55.8%; range: 0.5-17.4 μg/L) and in 2 of 27 patients with gastric ulcer (7.4%; range: 0.1-8.6 μg/L) and in 2 of 5 of patients with chronic atrophic gastritis (8%; range: 0.2-8.7 μg/L), whereas none of the normal subjects had an increased CEA concentration.

A statistically significant correlation was found between the CA50 and CEA levels (r = 0.648, $P < 0.01$) in patients with gastric cancer. The postoperative serum levels of CA50 (46.4 ± 25.9 kU/L, $P < 0.01$) and CEA (6.85 ± 2.43 μg/L, $P < 0.01$) were much lower post-operative (n = 21) than pre-operative. However, changes in the levels of CA50 ($P < 0.05$) and CEA ($P > 0.05$) were also observed in patients with gastric ulcer or chronic atrophic gastritis.

DISCUSSION

The results show that fasting serum CA50 and CEA levels are changed in gastric cancer. Both CA50 and CEA values are indicators for advanced gastric cancer, and after surgery, the values of CA50 and CEA may decrease. Overall, there was a good correlation between the CA50 and CEA levels. In clinical practice, the greatest value of CA50 and CEA is in the diagnosis of gastric cancer. We have not calculated the sensitivities and specificities of the CA50 and CEA tests in this study, but when we used cut-off values based on normal subjects, as expected, a good correlation was found between the serum concentrations of CA50 and CEA; although, some patients showed a clear difference in the serum levels. Both markers are usually elevated in the same patients, and a combination of the tests would therefore be of no benefit[2-4,12].

Originally, the broader reactivity of the CA50 antibody was thought to be an advantage for Lewis-negative subjects, who normally do not express sialyated Lewis but may synthesize sialosyllactotetraose[1]. However, concentrations of CA50 and CEA in the membrane fraction tended to be higher in normal tissue than in carcinoma, whereas the cytosol-to-membrane ratio was significantly higher in carcinoma. For CA50 and CEA, the phenotypic pattern of malignant transformation seems to involve a different intracellular distribution rather than a quantitative change. CEA, a most popular and useful tumor marker for cancer of digestive organs, is frequently positive in sera of colorectal cancer patients who had no subjective complaint or physical sign. This experience supported employment of CEA as a routine screening test for colorectal cancer[6-8,13].

CA50 and carbohydrate antigen 19-9 (CA19-9) perform best for the diagnosis of pancreatic cancer. SOC analysis has confirmed previous data, showing only a marginal difference between the markers in this disease. Both tests have shown higher sensitivity than CEA[6]. The histologic type of a cancer may have limited relevance in cancer screening, although known carcinogenic exposures seem to have some specificity in inducing some particular histologic gastric cancer types. However, marker specificity for certain histologic cancer types may be more important from the diagnostic viewpoint. The markers or their combinations studied here show no significant association with any histologic cancer type, with the exception of the combination of CEA and CA50 for adenocarcinomas[2].

The measurement of CA50 in serum and pleural fluid by immunoradiometric assay was presented in 45 (27 malignancy and 18 tuberculosis) patients with pleural effusion. The mean CA50 level in malignant effusion (89.26 ± 122.32 kU/L) was significantly higher than that in tuberculous effusion (5.18 ± 8.65 kU/L) ($P < 0.01$). CA50 levels of pleural fluid above an arbitrary level of 20 U/mL were found in 78% of malignant fluids and in 6% of tuberculous fluids. The serum CA50 value from 27 patients with malignant effusion (58.67 ± 85.85 kU/L) was also higher than that from 18 patients with tuberculous effusion (6.18 ± 8.37 kU/L) ($P < 0.01$). Serum CA50 levels above the same level were found in 58% of patients with malignant fluid and in 6% of patients with tuberculous fluid. The results suggest that the measurement of CA50 in pleural effusion may be helpful in the differential diagnosis between tuberculous and malignant effusions[12].

A new cell line (BRC-230) was established from a surgical speci-

men of primary ductal infiltrating breast carcinoma. The epithelial nature of this cell line was confirmed by ultrastructural analysis and demonstrated the retention of structural properties characteristic of the original tumor. The BRC-230 cell line was then shown to induce tumors in athymic Crl: nu/nu (CD-1)BR nude mice. It possessed an abnormal karyotype with a model chromosome number between 60-61 with eight recurrent marker chromosomes, and it presented a doubling time of 30.5 h. Scatchard analysis demonstrated that both primary tumor and BRC-230 cells are estrogen and progesterone receptor negative. Immunoenzymatic and radioimmunoassays show a production of marker antigens (CEA, TPA, CA125, CA15-3, CA19-9) that are similar in the patient's serum and BRC-230 cells. The *in vitro* drug sensitivity assay of the cell line and of the parental tumor tissue shows overlapping results to all tested anti-blastic drugs. BRC-230 cells are resistant to 4-idroperoxy-cyclophosphamide, idarubicinol, mitoxantrone, etoposide, 4'-epidoxorubicin, and doxorubicin, showing a multiple drug resistance phenotype. Amplification or rearrangement of HER2/neu, Ha-ras, and C-myc genes is observed neither in the original tumor nor in BRC-230 cells; the *mdr-1* gene is also present in a single copy. The authors concluded from these studies that the BRC-230 cell line maintains the same characteristics as the original tumor and may provide us with a good model to study *in vitro* the biology of drug resistance of breast cancer[13].

Significant increases in the serum levels of CA125 and CA19-9 were observed over one month prior to the removal of an ovarian adenofibroma, and the serum levels of CA125 and CA19-9 decreased rapidly after surgery. The surface of the tumor at surgery showed marked inflammation, probably induced by the necrosis produced by torsion. Pathologically, most of the tumor was necrotic, and histoimmunochemical staining of the viable cells was weak for CA125 but intense for CA19-9. Clinicopathological observations suggested that CA125 and CA19-9 might be stimulated in the cells by inflammation or that originally existing CA125 and CA19-9 were released from the tumor cells following the cell necrosis[14].

Most of the recently developed tumor antigens detected by monoclonal antibodies are sugar chains and frequently associated with blood group substance. Using immunohistochemical studies, we evaluated the clinical usefulness and significance of the serum assay of CA-50 classified as a type Ⅰ sugar chain, sialyl SSEA-1 as a type Ⅱ sugar chain, and ST-439 with an undetermined structure, as well as their clinicopathological significance. In addition, the value of measurement of CA19-9, ST-439, and SLX in pure pancreatic juice (PPJ) was investigated. Furthermore, the clinical usefulness of K-ras mutation at codon 12 in PPJ was studied. The incidence of serum CA19-9 among tumor markers was highest in pancreatic cancer (81%), but relatively high in benign diseases. On the other hand, both serological and immunohistological studies showed that sialyl SSEA-1 and ST-439 were highly specific for the tumor, whereas they appeared in serum or tumor with less frequently than CA19-9 or CA50 carrying the type Ⅰ sugar chain. The accuracy of the tumor markers (CA19-9, sialyl SSEA-1, and ST-439) for pancreatic cancer was almost equal to and even higher than (77% to 80%) that of CEA (69%). However, a highly positive correlation between sialyl SSEA-1 and ST-439 was revealed as well as among type Ⅰ sugar chains in malignant diseases. These data suggest that a combination assay with CA19-9 or a similar tumor marker, sialyl SSEA-1 or ST-439, and CEA would be appropriate for the screening of pancreatic cancer. When the cut-off value was set as the x- ± 2s of the controls, significantly elevated concentrations of CA19-9 in PPJ were found in the secretory phase in 90% of the patients with pancreatic cancer and 66% of the patients with chronic pancreatitis. Although increased concentrations of CA19-9 in PPJ have no cancer specificity, measurement of CA19-9 in PPJ can be used as a sensitive marker for some pancreatic disorders. On the other hand, concentrations of ST-439 and SLX in PPJ are significantly increased only in pancreatic cancer, and their positive rates are 50% and 40%, respectively. While they have a high tumor-specificity, their positive rates are not as high as initially expected[15].

The immunohistochemical expression of CA19-9, epithelial membrane antigen (EMA), and CEA was studied in 103 tissue samples of gallbladder cancer and 25 samples of non-tumoral gallbladder lesions. CA19-9 and EMA were positive in > 90% of cancers and in none of the non-tumorous lesions. Dupan-2 expression was observed in 100% of the non-tumorous lesions and 78% of the cancers. CEA expression was observed in 12% of the non-tumorous lesions and 89% of the cancers. The magnitude of immunohistochemical staining was moderate or intense for all antibodies, except Dupan-2. No differences were observed in the location of positive staining in superficial or deep parts of the tumor. In these lesions, the positive staining was cytoplasmic with a granular and irregular pattern; on the contrary, in the non-tumorous lesions, staining was seen in the apical parts of the cell. The calculated sensitivity, specificity and positive predictive value for CEA were 89%, 88% and 96% respectively. If future studies disclose a good correlation between serological and immunohistochemical detection of this antigen, its determination would be potentially useful in clinical settings[16].

Our results indicate that serum CA50 and CEA markers are different between malignant and benign stomach diseases. CA50 and CEA can be indicators of advanced gastric cancer, and after surgery the CA50 and CEA levels may decrease. Overall, there is a good correlation between the CA50 and CEA levels. In clinical practice, the greatest value of CA50 and CEA lies in the diagnosis of gastric cancer.

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